RISK-BASED EVIDENCE FOR ANIMAL HEALTH POLICY

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RISK-BASED EVIDENCE FOR ANIMAL HEALTH POLICY

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EDITORIAL
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Editorial: Risk-Based Evidence for Animal Health Policy

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Editorial on the Research Topic

Risk-Based Evidence for Animal Health Policy

Infectious animal and zoonotic diseases are important and immediate global disease threats which exhaust resources and place demands on both national and international global animal and human health institutions and infrastructures. These diseases create challenges for industry stakeholders and policy-makers because of their pandemic potential and resultant widespread economic and social disruption. The current pandemic of the coronavirus SARS-CoV-2 (disease name COVID-19), which was first detected in the wet markets of Wuhan, Hubei Province, China, offers a contemporary example on which we might reflect about the lessons learned from this Research Topic—in particular, the importance of transparent data sharing and the development of risk-based evidence for policy-making for zoonotic disease outbreak preparedness and control. COVID-19 has now been detected in 188 international locations despite the closure of the wet markets and imposition of movement restrictions and other interventions to reduce risks of onward transmission. Risk management decisions in different countries [such as the imposition and subsequent release of social distance policies (1) and the introduction of compulsory mask-wearing (2)] are not purely (public health) science-based. The political, cultural, and societal dimensions of the pandemic have highlighted sharply the need to "remedy… disciplinary silos" (3) through holistic interdisciplinary approaches to understand the complex trade-offs and unintended consequences of disease control policies.

In this Research Topic, we wanted to explore the development of a robust and fit-for-purpose evidence base for animal (and public) health and the different mechanisms used to ensure its effective delivery to policy-makers in order to better anticipate and respond appropriately to existing and emerging animal and zoonotic disease risks. The response to the call for papers yielded 17 accepted papers with 112 contributing authors and the Research Topic has been accessed more than 25,000 times highlighting the importance and timely nature of these contributions. In this editorial, we identify 5 key lessons learned from these contributions and consider the future for risk-based policy-making for animal and public health.

IMPROVE UNDERSTANDING AND COMMUNICATION OF CONCEPTS OF RISK AND UNCERTAINTY TO DIFFERENT STAKEHOLDER AUDIENCES

Policy and decision-making is not based on scientific evidence alone, but also influenced by political will, existing governance structures, public opinion, and other exogenous factors. Researchers need to engage with all of these facets in a holistic way, but this is challenging to do in the context of traditional research environments. More reflects on these difficulties and highlights the need for a commitment to integrate "policy relevance to the research focus from the outset, to engage with policy-makers and other stakeholders throughout, to use platforms to facilitate science-policy dialogue, and to disseminate research findings appropriately." He articulates the need and demand for interdisciplinary approaches—and in particular, input from the social sciences, which stems from the recognition that science, itself, is not value-free.

Assembling multi-disciplinary teams with appropriate expertise is fundamental to delivering appropriate and effective risk assessment, communication, and management. Countries have varying approaches to prioritizing disease risks for contingency planning which reflect the economic, social, and cultural values of their communities. Two papers in this series explore risk prioritization and perception, through different disciplinary approaches. Bessell et al. use a semi-quantitative approach which uses a combination of the rate of disease spread, disease mitigation factors, impacts on animal welfare and production, the human health risks and the impacts on wider society to characterize exotic disease priorities for Scotland. In contrast, Waldman et al., explore the role of the social, economic, and cultural context in shaping the perceptions and practices of actors who play significant roles in risk management. This paper illustrates the importance of understanding "situated expertise" and particular forms of risk perception and practice which both enhance and compromise risk reduction in different ways" (Waldman et al.).

ANTICIPATE REGULATORY OR POLICY BARRIERS TO ENSURE EFFECTIVE IMPLEMENTATION OF SCIENTIFIC EVIDENCE

The foundations of evidence-based decision-making begin with robust data collection, access and sharing. Houe et al. acknowledge that although there may be a wealth of data generated, many datasets have emerged from different organizations and have been developed for other purposes, making it difficult to integrate them and use them to their full potential. Appropriate regulations and policies need to be in place for data access and sharing across organizational and legal boundaries. Sustaining the value of these datasets to researchers and decision-makers depends almost entirely on data accuracy and reliability; substantial changes in data architecture and structure, which inevitably occur over time, need to be taken into account to ensure that risk management decisions based on these data are justified and valid. Continued investment into the maintenance and "upkeep" of these data is therefore critical for these data to be useful to policy-makers.

INTEGRATE DIFFERENT DATA SOURCES TO IMPROVE DISEASE MONITORING AND SURVEILLANCE

Estimating the risk of incursion of disease depends on transparent data sharing, robust animal health recording systems and fit-for-purpose veterinary public health infrastructure which includes access to affordable diagnostic tests, laboratory facilities, and trained technicians, veterinary professional, paraprofessionals, and researchers to interpret and act on results. Georgaki et al. describe the advantages of the Bluetongue surveillance programme in Northern Ireland, which has evolved to include the use of risk assessments and simulation models to monitor the risk of incursion. Its design enables effective mitigation measures to be identified to minimize disease risk and provides additional assurances to protect NI's export markets in the European Union (EU) and third countries. The authors also highlight the benefits of including both active and targeted surveillance activities to enable early detection of disease. In Scotland, risk-based approaches are also used to identify high risk areas for vector-borne diseases, such as Louping ill virus (See Gilbert et al.). GIS-based data on environmental variables, when used in combination with sero-prevalence data, become a powerful tool to identify risk factors and improve opportunities for identification of alternative disease reservoirs. Both of these are important for informing disease management policies and identifying trade-offs between environmental and farming priorities and costs. These insights are echoed in the contributions by Carneiro et al. and Semango et al. which remind us of the value of traditional field-based epidemiology and recognize the importance of a systems-based approach. As highlighted by the example of COVID-2019, a broad and holistic understanding of the causal risk pathways is necessary to ensure that critical disease reservoirs are also appropriately incorporated into strategies for surveillance and risk mitigation.

INVEST IN PROACTIVE DEVELOPMENT OF RISK ASSESSMENT EXPERTISE AND GENERIC, FLEXIBLE TOOLS, AND FRAMEWORKS WHICH ARE READY-TO-USE IN DISEASE EMERGENCIES

The majority of the contributions in this Research Topic identified the usefulness of investing in proactive veterinary risk assessments which include risk pathways that can be flexibly adapted and re-used in times of emergency to ensure business continuity (see Auty et al.; de Vos et al.; Taylor et al.; Umber et al.; Walz, Middleton et al.; Walz, Evanson et al.). For example, estimates of the risk of onward transmission of disease associated with movements of carcasses from de-populated farms to other areas for disposal inform risk management decisions about movements of vehicles, animals and animal products out of disease control areas (Umber et al.; Walz, Evanson et al.). While there is a lot of guidance available for animal-related product movements and for a variety of carcass types, there may be country, disease or species-specific gaps which are necessary to fill in order to "assist regulatory authorities in using risk" to guide decision-making (for example to grant permitted movement or deny a request to move for live animals or carcasses) (see Umber et al.). Proactively working to elucidate these risks coupled with efforts to identify and address data and research gaps can help countries minimize the risk of disease spread while also minimizing the impact of the outbreak response on unaffected farms.

INCORPORATE SOCIAL SCIENCE AND HUMANITIES EXPERTISE TO IMPROVE AND DISCRIMINATE BETWEEN DIFFERENT RISK MANAGEMENT DECISIONS

Risk assessment is essential to target critical control points which are amenable to risk reduction. Although technical solutions—such as improved diagnostic testing regimens and disease control strategies—are available, their effectiveness depends on the compliance and uptake of interventions by key stakeholders. Two papers explored the likelihood of uptake of technological interventions, using distinct approaches. Mohr et al., used economic game theory as a framework to evaluate farmers' strategic decision-making in different contexts. The work explores the uptake of an effective diagnostic test for sheep-scab—a disease which costs more than £8 million per year to the UK industry. In theory, the benefits of control should outweigh the costs of the test. However, this paper illustrates that the likelihood of uptake depends very much on the farmer's perception of risk to the herd and whether they take a long- or short-term view of profitability. Liu et al. explore this problem in a different way. The authors construct different behavioral typologies of farmers which they refer to as: "non-adopters," "current adopters," or "future adopters" with respect to different technologies. Their paper suggests that in order to be successful, we need to better understand our stakeholder populations so that policies, regulatory incentives, and complementary training can be appropriately targeted to ensure effective uptake and positive behavioral change.

A FORWARD LOOK: CREATE NEW PATHWAYS TO IMPROVE DECISION-MAKING

New technologies and methodologies in human and veterinary medicine, epidemiology, agricultural production systems, and business tools and approaches have the capacity to deliver large volumes of high-quality data and complex analyses to improve animal and zoonotic disease surveillance and outbreak preparedness. However, scientific evidence is usually only a small part of the evidence base for decision-makers. Incorporating these advances into policy-making can be challenging, given the silos that exist between human and animal health institutions, differences between research, policy and industry timescales, and the need to consider multiple evidence bases and different stakeholder groups. Without established effective and explicit communication channels between scientists, policy, and industry audiences, researchers will struggle to respond to policy needs with relevant research to inform decision-making in a timely and robust manner. Models of science-policy delivery through innovative, multi-disciplinary partnerships between academia, industry, and government (such as the Scottish Government Centers of Expertise, described by Boden et al.), may offer a solution, particularly when combined with purposeful communication and innovation aimed at these five lessons.

AUTHOR CONTRIBUTIONS

LB was responsible for the concept and writing of this manuscript. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Opportunities for Improved Disease Surveillance and Control by Use of Integrated Data on Animal and Human Health

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The global challenges and threats from infectious diseases including antimicrobial drug resistance and emerging infections due to the rapidly changing climate require that we continuously revisit the fitness of our infrastructure. The databases used for surveillance represent an important infrastructure. Historically, many databases have evolved from different needs and from different organizations. Despite growing data storage and computing capacities, data are, however, rarely used to their full potential. The objective of this review was to outline different data sources available in Denmark. We applied a one-health perspective and included data sources on animal demographics and movements, medicine prescription, diagnostic test results as well as relevant data on human health. Another objective was to suggest approaches for fit-for-purpose integration of data as a resource for risk assessment and generation of evidence for policies to protect animal and human health. Danish databases were reviewed according to a systematic procedure including ownership, intended purposes of the database, target and study populations, metrics and information used, measuring methods (observers, diagnostic tests), recording procedures, data flow, database structure, and control procedures to ensure data quality. Thereby, structural metadata were gathered across available Danish databases including animal health, zoonotic infections, antimicrobial use, and relevant administrative data that can support the overall aim of supporting risk assessment and development of evidence. Then illustrative cases were used to assess how combinations and integration of databases could improve existing evidence to support decisions in animal health policies (e.g., combination of information on diseases in different herds or regions with information on isolation of pathogens from humans). Due to the complexity of databases, full integration at the individual level is often not possible. Still, integration of data at a higher level (e.g., municipality or region) can provide important information on risks and hence risk management. We conclude by discussing how databases by linkage can be improved in the future, and emphasize that legal issues are important to address in order to optimize the use of the available data.

Keywords: one health (OH), animal health, human health, databases, Denmark

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INTRODUCTION

The growing possibilities for collecting information on demographic factors on animals and humans, their environment and movements, disease and performance data as well as treatment or prescription data have resulted in availability of an enormous amount of stored information. All this information is gathered in different databases, each with their own history, owner and administrator, design and purpose of data collection, quality criteria etc. This technological transformation has rarely been a coordinated process, but rather represents different initiatives taken by the veterinary authorities, by reference laboratories, public health authorities, private stakeholders, academia, and more generally, by the different ministries in the government that has developed administrative databases. The technological transformation opens new possibilities and the potential of these possibilities is not yet clearly described or understood.

The complexity of many global challenges on animal health and related issues requires that all these data are integrated to a higher extent than is done today to improve effectiveness in surveillance and control of health issues, including risk assessment and development of guidance for best practice. Integration does not necessarily mean that data from different sources are directly merged, but merely that the information from different sources is used in a coordinated effort to address complex research questions or challenges from veterinary- and human public health, including the massive challenges related to climate change and antimicrobial drug resistance. An integration of data requires that the databases can fulfill a number of demands including documentation of data sources, data flow, database structure and control procedures to ensure data quality and security. As an example, the European Food Safety Authority (EFSA) regularly collects data from the member states of the European Union (EU), and these data need to be harmonized to increase data quality and reduce biases/uncertainties in risk assessments (1). Moreover, the general need for guiding principles for scientific data management and stewardship has been emphasized (2). There are multiple examples that integration of health information across species is beneficial in terms of identifying emerging health issues (3), understanding risk factors and transmission mechanisms (4, 5) and controlling health issues (6), but as mentioned above we argue that the use of data can and should be improved considerable in the future in order to address emerging threats in a much more timely and effective way.

The objective of this paper was to present the different One Health data types available in Denmark, including data on animal demographics and movements, animal, and human medicine prescription, diagnostic test results and other health related data sources including relevant data sources on human patients and demographics. Furthermore, we mention some administrative databases that have proven to be of value for research and risk assessment. Another objective was to suggest approaches for better integration and improved use of data to provide evidence for risk-based policies to protect animal and human health. This will be discussed in the light of data ownership and requirements due to the European General data Protection Regulation (GDPR). To be more specific, the paper focuses on major production animal species and zoonotic agents, which will be exemplified by three illustrative cases:

1) The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)
2) *Salmonella* Dublin
3) *Campylobacter* infections.

METHODS

Identification of Existing Databases and Their Documentation of Content

Databases with potential relevance for animal health were identified based on the research needs in the veterinary contingency work. In addition, the Danish legislation was scrutinized to identify data that must be recorded according to legislative orders. Furthermore, the authors have for many years been involved in research projects using databases and therefore have knowledge about many additional databases. Those research activities have often involved direct engagement of database owners and administrators who could provide additional details on the content of databases as well as the origin and flow of data.

In addition to databases directly related to animal health, databases in human health that can be related to occurrence of specific pathogens in livestock were included. As examples, we present research and surveillance on the occurrence of antimicrobial resistance, *Salmonella* Dublin and *Campylobacter* infections.

The databases were examined in relation to ownership, intended purposes of the database, target and study populations, metrics and information used, measuring methods (observers, diagnostic tests), recording procedures, data flow, database structure, and control procedures to ensure data quality.

Context—Setting and Population

Denmark is a Scandinavian country of 43,000 km^2, a population of 5.8 million (2018) and a life expectancy at birth of 80.9 years (7). The health system is tax-funded and visits to general practitioners and hospital admission are free of cost to all residents. Secondary health institutions are administered at regional level. A number of administrative registers are maintained all using a common key (the civil registry number, which is a unique code, provided to all individuals with residence in Denmark). Access may be given to linked, anonymized information from such registers for research purposes, and thereby the Danish population has been described as "one big cohort" (8).

The largest livestock sector is the pig industry. There are around 3,000 pig farms in Denmark with more than 12 million pigs on farm and producing more than 17 million pigs annually sent for slaughter in Denmark at a few large cooperative abattoirs, and around 14 million weaned pigs sold for export, mainly to Germany (9, 10). Around 90% of the produced pork is exported leading to a high demand for data used for breeding,

TABLE 1 | Databases on animal health embedded in Danish legislation with information publicly available.

Database name	Purpose	Variables
CHR Herd level	Demographic information on herd level; population composition	Owner; geographic location; species; herd size; notifiable diseases
CHR Animal level Cattle	Demographic information on animal level	Birth date; birth condition; sex; movement (both sender and receiver); date of slaughter; date of death
Movement database (pigs)	Veterinary preparedness	Animal type, no transported, mortality, date; Source and destination herds Trucks incl. nationality
VetStat	Recording of prescription medication at herd level	Medication name and active substance; species; age group; ordination group; Vet authorization and practice no; Drug store ID; prescription date etc.
Meat inspection recordings	Food safety; price deduction for farmer	Abattoir ID; animal category; clinical findings at ante-mortem inspection; pathological lesions observed post-mortem
Zoonosis register	Surveillance of Salmonella	Antibodies in meat juice and blood
Welfare control data	Recording of Danish Veterinary and Food Administration control data	Reason for control; visit date No of infringements of animal welfare legislation: Warning, enforcement notice or police report

TABLE 2 | Databases on animal health in Denmark at national laboratories.

Database name	Purpose	Variables
SSI LIMS	Diagnostics and surveillance	Notifiable infectious diseases, date species, pathogens etc.
Ester/DTU-VET Center for diagnostik	Diagnostics and surveillance	Endemic diseases, date, species, pathogens etc.

quality, food safety, animal welfare, and traceability purposes. Therefore, the industry hosts and manages several databases for documentation purposes. The second largest livestock industry is the cattle sector with 1.5 million cattle including around 560,000 dairy cows in ∼2,800 dairy farms producing milk and milk products for a few dairy companies that export to a large market. Denmark also has around 180 broiler chicken farms that produce around 114,000,000 broilers for slaughter every year (11). All livestock holdings are identified in a central registry, which will be discussed below. This enables data to be linkable. Furthermore, it is possible to integrate the human health and veterinary databases by e.g., geographic coordinates or postal codes.

DETAILS TO UNDERSTAND KEY PROGRAMMATIC ELEMENTS

A key element of infrastructures in both monitoring and surveillance programs are the existence of high quality databases. A full list of identified databases and their variables are outlined in **Tables 1–5**. In **Supplementary Material**, some key features from selected databases are presented as background information to understand the potentials in the cases used for exemplification.

In the following, further details on the data and their potentials are provided in three illustrative cases of monitoring health and disease in Denmark.

Illustrative Cases

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)

Background

DANMAP collects data from several different sources including food and hospital laboratories, slaughter plants, veterinary practices as well as general practices for people. DANMAP functions as a surveillance system of both the consumption of antimicrobial agents as well as the occurrence of resistant bacteria in the three sectors: livestock, food, and humans (12, 13).

Problem to be addressed

DANMAP was among the first examples of integrated surveillance for antimicrobial drug resistance, where integration was implemented in two dimensions: Human and animal, and drug use and resistance in both clinical infections and indicator bacteria. Thereby, DANMAP has served as a source of inspiration for many other countries (14). However, the concept of DANMAP has, by and large, remained constant over the years (15) with a published report available often in the fall of the coming year, thereby creating a time lag of 9 to 11 months before annual data become available. Hence, an important objective is to make the data available in real time, and also to continuously improve use of the data sources beyond descriptive analyses.

Data availability

DANMAP has from the beginning taken advantage of the databases on antimicrobial drug use held by the Danish Medicines Agency (**Table 1**), whereas data on antimicrobial sensitivity testing has been available only after long delays. This is partly due to a work intensive procedure, where data are collected from different microbiological laboratories that use different data formats. Hence, a lot of resources have been used to import, merge and clean the data before data analysis can begin. Furthermore, clinical data have been meager, which prevents

TABLE 3 | Databases in Denmark owned by the industry or privately owned.

Database name	Purpose	Examples of variables
Cattle database	Breeding, health advice, research	Milk yield, disease treatments, reproduction, Salmonella Dublin surveillance levels and diagnostic results from individual cattle and bulk-tank milk
SPF-database	Secure good biosecurity/health status; Document freedom	Disease status on several well defined contagious diseases
Efficiency control pigs	Production management	Number of weaned pigs, feed efficiency, growth
Poultry 'Kik' data	Quality control in chicken production	GIS-coordinates, distance to neighbors, buildings, hygiene, climate, mortality
Efficiency-control poultry	Production management	Growth, egg production, feed consumption, mortality

TABLE 4 | Selected databases in Denmark on human health that can be related to animal health or other animal related information.

Database name	Purpose	Variables
Register of enteric infections	First-positive (6 month period) patients of diagnosed gastrointestinal bacterial infections	Patient identifier (cpr number), date of sample, requesting doctor, laboratory, bacterial diagnosis (species level), foreign travel
Clinical disease notification database	Notified patients with a series of specified infectious diseases	Patient identifier, diagnosis, dates, relevant clinical information (underlying illness etc.), mode of transmission, place of infections, disease specific characteristics
Danish Microbiology Database (MiBa)	Information of clinical microbiological analyses performed since 2010	Patient identifier, diagnosis, dates, requesting doctor, laboratory—data are unstructured upon receival.
The National Patient Register	Hospitalized patients	Patient identifier, diagnoses codes (ICD8/10), in/out dates, examinations and treatment information, and more.
The Danish Cancer Register	All cancer patients	Patient identifier, relevant dates, type and location of cancer, treatment information, and more.
Euro-MoMo	Mortality data from Denmark and other European countries	Data of death per age group from Denmark and 20 other countries/states.

TABLE 5 | Selected administrative databases in Denmark with relevance for One Health surveillance or research.

Database name	Purpose	Variables
Danish Civil Registration System	Population register	Person identifier (cpr number), first-level family members, current and previous addresses, vital status, civic status, and more.
Register of Causes of Death	Medical post-mortem examination registrations	Person identifier and time, cause, place, and manner of death.
Central Register of Buildings	Buildings register	Address, purpose, size, installations, construction data, dates of construction, and amendments.
Meteorological data	Weather and climate data	Area and period, temperature, wind, rainfall, and more.

analysis of risk factors for drug resistance. Denmark is now working on an online access to human resistance testing (16), and the report for 2018 will be a prototype for this, and we hope that veterinary data also will be available soon.

Potentials

With online availability of data, the collation and analysis of data can be developed into an on-going activity that improves the timelines and enables rapid identification of emerging trends (15). Furthermore, richer data including risk factors and clinical outcomes will enable risk assessment and serve as a tool for research. The full potential of this transformation is not yet fully described, and will depend on legal issues as well as the resources that will be available for data analyses and data visualization.

A recent FAO report (17) states under lessons learned that "Change takes time. Most of the initiatives have been implemented gradually, giving farmers and veterinarians time to adjust and devise smart solutions," "The well-organized Danish agricultural industry has been an important factor in achieving this success," and "The proposed solutions may not be directly transferable to other countries as they may have different incentives to drive change at all levels of society."

Such statements underlines the need for activities at the community level to achieve the potentials.

Salmonella Dublin

Background

In Denmark, there is an on-going surveillance and control program for *Salmonella* Dublin in cattle. Although, *S.* Dublin relatively seldom occurs in humans, it is associated with a high case fatality rate and it is therefore considered as an important zoonosis (18, 19). In Denmark, *S.* Dublin is notifiable meaning that owners of animals with a suspicion of salmonellosis must call a veterinarian who should seek to confirm or reject the diagnosis (20), and laboratories that isolate salmonella bacteria have to report the results to the veterinary authorities.

Problem to be addressed

Hitherto, no direct association between human cases and *S.* Dublin in cattle has been demonstrated in the literature (19). However, work on comparison of whole-genome sequencing of strains from both populations is currently on-going. If the occurrence of *S.* Dublin in cattle and humans is correlated, the information on occurrence and location of infected premises and infected cattle can be used to assess the risk of transmission from cattle to humans through contact. Furthermore, it can inform policies on how to prevent transmission from live animals or transmission via contaminated meat.

Data availability

The legislation requires that all farms are categorized into one of three defined infection levels. Monitoring of *S.* Dublin is mainly based on bulk tank milk from dairy herds and blood samples from non-dairy herds (20). The bulk tank samples are obtained repeatedly with 3 months intervals, and blood samples are collected either at the slaughterhouse when the herd delivers animals to slaughter or on-farm on the initiative of the farmer. The samples are analyzed for antibodies directed against *S.* Dublin (21). Level 1 herds are considered most likely free of *S.* Dublin. Level 2 is given to herds if (a) the herd does not live up to the Level 1 antibody test-criteria, (b) the infection status is unknown (e.g., insufficiently tested), (c) *S.* Dublin bacteria are detected or (d) there has been contact to cattle from a Level 2 or 3 herd. Finally, Level 3 is given to herds with (a) *S.* Dublin bacteria detection in a persistently infected Level 2 herd during mandatory intensified fecal sampling, or (b) diagnosis of salmonellosis (i.e., clinical disease). Level 3 herds are placed under official veterinary supervision with special hygienic restrictions including hygienic slaughter procedures for food safety reasons. The infection status of each herd is publicly available of the internet page of The Danish Food and Veterinary Administration (https://chr.fvst.dk). The surveillance scheme provides a large amount of longitudinal and repeated cross sectional data from all cattle herds in Denmark starting in 2002, which has been used frequently over the years for research and program development purposes (21–23).

Potentials

Previously, the correlation between the residence of human *S.* Dublin cases and distance to cattle farms has been investigated (19) concluding that the infection risk was independent of living near to cattle farms. However, the infection statuses of the cattle farms were not taken into account in that study. Hence, it could strengthen the investigation, if the *S.* Dublin status of the cattle farms at the time of the identification of the human case had also been included in the analysis. This is potentially possible as all necessary data are available and if data from different sources can be and are allowed to be integrated.

The process of furthering knowledge and better implementing data has been done in the Danish livestock and public health sector separately. The Danish cattle advisory center, SEGES, has a website with weekly updated status of national and regional prevalences and locations of test-positive cattle herds. SSI has an interactive webpage of laboratory results in which it is possible to get summary statistics of human *S.* Dublin cases including some demographics of these (see https://statistik.ssi.dk//sygdomsdata#!/?sygdomskode=SALM&stype=9&xaxis=Aar&show=Graph&datatype=Laboratory). Data are not integrated across species in these websites, and it is not known whether it would improve the control efforts in the surveillance and eradication programme to illustrate all of the data more clearly in both places. However, these two sources are used frequently by the working groups supporting decision making in the S. Dublin programme.

Campylobacter Infections

Background

Human illnesses caused by foodborne and zoonotic infections constitute important public health problems in modern developed societies. A good understanding of the infection sources, risk factors, and the disease burden is necessary in order to be able to devise evidence-based ways of addressing these challenges. This effort demands a cross-sectorial approach and combining data sources collected from different sectors is valuable or even necessary. To illustrate this, we will here briefly mention research, where different Danish data sources have been combined in order to address One Health research questions, using *Campylobacter* infections as an example.

Problem to be addressed

Campylobacter is the leading cause of gastrointestinal infections in Denmark, as indeed in Europe as a whole (24). In Denmark, several successive national action plans have aimed at reducing the number of infections in poultry and humans (25). This has potentiated the need to address the possible transmission routes, which has been done via linkage of data from different sources.

Data availability

Data from the national monitoring of poultry flocks at slaughter were combined with the national surveillance data on human patients. Climate data (in particular historic temperature and rainfall series), geographical data including geo-coded address data, national data on buildings, data from the population register (to form cohort and control reference populations), and data from the National Patient Register (**Tables 4**, **5**) were extracted and linked. Population-based case-control studies have established consumption of fresh chicken meat (26) and a number of other factors including pets and leisure activities (27) as major risk factors for human infections. Locating human cases addresses, geocoding them and performing register-linkage to housing information showed risk of infection to be pronounced in rural areas in particular among children (28). Analyzing meteorological data showed both chicken flock infection levels and human infections to correlate with increasing temperature in Scandinavia (29) and, at a more detailed level, in Denmark (30). Linking human surveillance data with several social information registers, showed *Campylobacter* to primarily affect the affluent segments of society (31).

Potentials

Combining database information for the purpose of research into transmission routes of *Campylobacter* has shown to have a significant potential and such studies should be further pursued. On-going studies at the SSI aim to model the effect of heavy rain-events for local outbreaks, model the effect of different climate change scenarios in Scandinavia and describe the burden of infections by following post-infectious sequelae of patients and non-patients using the population registry and hospital diagnosis data.

DISCUSSION AND CONCLUSIONS

The globalization with increasing traveling and movements of animals and their products challenge an efficient food production providing global food security and food safety. Further, climate change triggers changes in spread of disease demanding increased preparedness in our disease surveillance and control. The developments in antimicrobial resistance are mentioned as one of the most important global health threats by WHO. All these developments require that both the veterinary and public health authorities are provided with the most precise and up to date evidence for disease occurrence and spread in order to take effective and innovative decisions on interventions. In order for this to happen, we must utilize our technical capacities to provide access to information and databases across veterinary fields, food products, human health, and administration. In this paper, we have demonstrated that we have reached important milestones in these efforts. For example, the Danish *Salmonella* Dublin eradication programme was initiated as a joint initiative between the veterinary authorities and the Danish cattle sector in 2002 based on research and documentation activities over the previous 5 years. The programme has been led by a cross-sectoral steering committee and supported by a technical working group with representatives from all essential stakeholders over the years including industry, laboratory, academic, and public health/food safety institutions. This approach builds on experiences from prior successful disease control programmes in the cattle sector (32), but still there is a much greater potential that is not yet utilized.

The campylobacter examples show how human and veterinary health data can be linked with databases not normally used for public health, such as the databases on climate or housing, leading to new insights in the epidemiology of these infections. Furthermore, they emphasize that use of national registers, including the population register, facilitates analyses using the entire Danish population as a cohort, thereby giving considerable statistical power.

We recommend that individual countries meet the mentioned requests by collaboration between sectors and authorities. In particular, data must be made available and there is a need to fund development projects with the purpose of facilitating data sharing and providing platforms for data analysis and visualization. The process of furthering knowledge and implement better use of data must include elaboration of systematic database protocols and transparent visualization of data including descriptive analysis of key variables (disease occurrence, medicine consumption etc.), which will enable the next step of integrating the data. Such a systematic approach will increase the generalizability of the findings of the three illustrative cases to include databases on climate, vectors, and other information related to animal and human health. The increased availability and transparency of databases and their specific data can to a much higher extent be used at university both in teaching specific courses, and when the students need to write bachelor or master theses. Further, the research based advisory activity for the authorities can use the data to improve monitoring of the current situation and hence set up better warning systems both at the national level, and also at herd level for use by the local advisors and veterinary practitioners. Finally, researchers can elaborate new and more innovative research questions involving several animal species and humans.

Special attention should be given to secure that rules of GDPR will not prevent an efficient use of data. Concerning GDPR, it is stated in the legislation that data must be collected explicitly for given purposes and that data collection shall not include more information than is needed for the given purposes. In addition, there are regulations to secure the anonymity of individual persons. Such requirements will sometimes make it difficult to integrate data on the levels of individual people or individual farms and it may be necessary to integrate data at a higher level, e.g., municipality or region. Increased use of professional data managers can in future be a very important step in helping researchers and other users of data to overcome obstacles concerning GDPR. Further limitations can consist of unwillingness to provide data on matters that may be sensitive for industry and authorities. Also lack of experience with use of data can be a problem. Professional data managers can in general also ensure that the quality criteria for use of databases being put forward in many guidelines (e.g., 1, 2) are met. For data integration to be feasible such professionals should work across different sectors to secure coherence in the ontology of the databases. If, for example, different databases use terms such as "diagnosis" or "disease" they need to be defined in the same way or at least it must be very transparent how the terms are defined (and scored/graded) in the different databases (33, 34). In addition, the use of definitions and coding may change within the same database over time and such changes must be fully transparent for the user.

Challenges have previously been identified to One Health surveillance (e.g., legal and data sharing issues, unclear responsibilities and structural barriers between ministries) (35). Such challenges continue to exist and it takes considerable effort from several parties to overcome these challenges. As illustrated by the three cases presented in this paper, it is very important continuously and actively to support the use and integration of data.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

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The Sero-epidemiology of *Neospora caninum* in Cattle in Northern Tanzania

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Neospora caninum is a protozoan intracellular parasite of animals with a global distribution. Dogs act as definitive hosts, with infection in cattle leading to reproductive losses. Neosporosis can be a major source of income loss for livestock keepers, but its impacts in sub-Saharan Africa are mostly unknown. This study aimed to estimate the seroprevalence and identify risk factors for *N. caninum* infection in cattle in northern Tanzania, and to link herd-level exposure to reproductive losses. Serum samples from 3,015 cattle were collected from 380 households in 20 villages between February and December 2016. Questionnaire data were collected from 360 of these households. Household coordinates were used to extract satellite derived environmental data from open-access sources. Sera were tested for the presence of *N. caninum* antibodies using an indirect ELISA. Risk factors for individual-level seropositivity were identified with logistic regression using Bayesian model averaging (BMA). The relationship between herd-level seroprevalence and abortion rates was assessed using negative binomial regression. The seroprevalence of *N. caninum* exposure after adjustment for diagnostic test performance was 21.5% [95% Credibility Interval (CrI) 17.9–25.4]. The most important predictors of seropositivity selected by BMA were age greater than 18 months [Odds ratio (OR) = 2.17, 95% CrI 1.45–3.26], the local cattle population density (OR = 0.69, 95% CrI 0.41–1.00), household use of restricted grazing (OR = 0.72, 95% CrI 0.25–1.16), and an increasing percentage cover of shrub or forest land in the environment surrounding a household (OR = 1.37, 1.00–2.14). There was a positive relationship between herd-level *N. caninum* seroprevalence and the reported within-herd abortion rate (Incidence Rate Ratio = 1.03, 95% CrI 1.00–1.06). Our findings suggest *N. caninum* is likely to be an important cause of abortion in cattle in Tanzania. Management practices, such as restricted grazing, are likely to reduce the risk of infection and suggest contamination of communal grazing areas may be important for transmission. Evidence for a relationship between livestock seropositivity and shrub and forest habitats raises questions about a potential role for wildlife in the epidemiology of *N. caninum* in Tanzania.

Keywords: Tanzania, *Neospora caninum*, livestock-husbandry, prevalence, risk factors, reproductive loss

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INTRODUCTION

Neosporosis, caused by an obligate intracellular protozoan parasite, *Neospora caninum,* is a livestock disease with worldwide distribution. The parasite causes disease in cattle and small ruminants, with cycles involving domestic dogs (*Canis lupus familiaris*), coyotes (*Canis latrans*), and the Australian dingo (*Canis lupus dingo*) as definitive hosts reported (1, 2). Cattle can become infected when they feed on pastures contaminated by wild or domestic canine feces containing sporulated *Neospora* oocysts (3). Transmission can also occur trans-placentally when a cow is infected during pregnancy or following the reactivation of a latent infection in a pregnant animal (4, 5). In cattle, the parasite causes abortions, stillbirths, neonatal deaths, early fetal loss, and embryo reabsorption (3, 6) with reproductive losses usually observed during the second trimester of pregnancy. The parasite can also cause disease early in gestation which may increase the calving interval or present as infertility (7). Congenital infection can also lead to the birth of weak, premature calves, or calves with neurological disease, or they may be born with no obvious clinical signs. Global economic losses due to neosporosis to the beef and dairy industries are estimated at up to one billion US dollars annually (3, 8). *Neospora caninum* is therefore regarded as a major, economically important pathogen of cattle (8). Recent reports suggest that *N. caninum* can also cause disease in small ruminants (9–12), however the potential economic impacts are yet to be assessed.

Despite the economic importance of neosporosis in cattle, there are no treatments or vaccines currently commercially available. Prevention and control therefore relies on reducing exposure of cattle to infectious *N. caninum* oocysts (13), culling out seropositive dams, or restricting breeding to sero-negative dams (3). Reported risk factors for *N. caninum* infection in cattle include the presence of dogs in cattle-keeping households, history of abortion, herd size, hygiene practices (14), handling of abortus (15), introduction of new cattle to the herd (16), grazing practices (17), and production system (3). The positive association with dog ownership has been found to be further increased when dogs have access to cattle placentas and fetuses (18, 19).

The reported seroprevalence of *N. caninum* exposure in cattle ranges between 7.6 and 41% in the Americas (15, 20), 10.7 and 19.6% in Africa (14), 4.1 and 43% in Asia (21, 22), 0.5 and 27.7% in Europe (23), and 10.2% in Oceania (24). These data may not be directly comparable due to differences in serological methods and cut-off values used, but they do provide evidence of the global distribution of the parasite (3). In East Africa, *N. caninum* seropositivity was recently found in 17.9% of farm dogs and 25.6% of cattle in the Nakuru District of Kenya, with exposure in farm dogs associated with free-roaming (25). In Kenya, serological evidence for *N. caninum* infections has also been reported in wild animals, including zebra (*Equus quagga*), eland (*Taurotragus oryx*), buffalo (*Syncerus caffer*), gazelle (*Gazella thomsonii*), impala (*Aepyceros melampus*), and warthog (*Phacochoerus africanus*), as well as spotted hyena (*Crocuta crocuta*) and cheetah (*Acinonyx jubatus*) (26).

Little is currently known about the epidemiology and impacts of *N. caninum* in Tanzania. This study aimed to establish the seroprevalence in cattle across northern Tanzania and to quantify the association between *N. caninum* seropositivity and a range of potential risk factors. To explore disease impacts, we also assessed the relationship between the rate of cattle abortions within a herd and the within-herd seroprevalence of *N. caninum* exposure.

METHODS

Study Design

Livestock samples and household questionnaire data were collected as part of the "Social, Economic and Environmental Drivers of Zoonotic disease" (SEEDZ) study (grant no. BB/L018926/1). The methods have been described elsewhere (27). Briefly, this was a cross-sectional survey conducted in six districts in Arusha Region (Arusha, Karatu, Longido, Meru, Monduli, and Ngorongoro Districts) and four districts in Manyara Region (Babati Rural, Babati Urban, Mbulu, and Simanjaro Districts), Tanzania, between February and December 2016. The study involved quantitative and qualitative data collection and was designed with a target sample of 400 households in order to address a range of questions relating to zoonotic disease transmission. A multistage sampling design was used, with village as the primary sampling unit. Twenty villages were selected from a spatially referenced list of all villages in the study area (from the Tanzanian National Bureau of Statistics) using generalized random tessellation stratified sampling (28). Livestock sampling was conducted at two to three sites within each village using a central point approach, with livestock owners invited to bring animals to a pre-selected point by notifying them of the event through traditional village-level communication routes (i.e., a network of village elders) at least 24 h before the event. Central point sampling events were run in collaboration with the Tanzanian Ministry of Livestock and Fisheries as part of village-level disease control activities, including the provision of anthelminthics. Up to 10 households were selected at random from all who attended each central point event using a random number generator. Ten cattle were randomly selected per household in order to detect infection with 90% confidence assuming a within-herd prevalence of 25% (29). Cattle <6 months of age were excluded from the sample.

Ten milliliters of blood were collected using jugular venipuncture into plain vacutainers. Samples were allowed to clot before serum extraction on the day of collection. Cattle were aged by dentition. Within 1 week, livestock keepers were visited in their homes and a questionnaire was conducted with the household head. Questions focused on household demographics, economics, livestock management and livestock health. Household co-ordinates were collected using a handheld GPS (Garmin eTrex, Garmin Ltd, Olathe, Kansas, USA). Pre-tested household surveys were conducted in Kiswahili or Maa using Open Data Kit data collection software (https://opendatakit.org/) on tablet computers.

Ethical Approval

All participants whose animals were sampled and who completed questionnaires provided written informed consent. The protocols, questionnaires and consent procedures were approved by the ethical review committees of the Kilimanjaro Christian Medical Centre (KCMC/832) and National Institute of Medical Research (NIMR/2028) in Tanzania, and in the UK by the ethics review committee of the College of Medical, Veterinary and Life Sciences, University of Glasgow. Approval for the animal elements of the study was provided by the Clinical Research Ethics Committee at the University of Glasgow School of Veterinary Medicine (39a/15). Permission to publish this manuscript was granted by the Director of Veterinary Services, Tanzania.

Serological Testing

Serum samples were heat treated at 56°C for 2 h prior to export for serological testing. Testing was performed at the Moredun Research Institute, UK, using an in-house ELISA.

Preparation of Recombinant *Neospora caninum* SRS2

Forward (5′ tcg gta ccg gtg tcg ggt gcg ccg ttc aag 3′) and reverse (5′ atc ccg ggt cag tac gca aag attg ccg ttgc 3′) primers were designed for the *N. caninum* SRS2 antigen gene. The primers were used to amplify a region of the gene SRS2 that encodes amino acids 20 to 354. The PCR amplicon was cloned directionally into the pQE31 expression vector (QIAGEN, UK) using restriction enzymes *Kpn*I and *Xma*I. After confirming the validity of the expression clone by sequence analysis, the construct was used to express and purify the recombinant His-tagged *N. caninum* SRS2 antigen in the *E. coli* strain M15, containing plasmid pREPp4, following the QIA*expressionist*^{TM} (QIAGEN) instructions.

Detection of *Neospora caninum* Antibodies in Cattle Sera

Microwells of 96-well medium binding plates (Greiner Bio-One, UK) were coated at 4°C overnight with recombinant *N. caninum* SRS2 antigen (amino acids 20-354) at a concentration of 0.5 μg/ml in 0.1 M sodium carbonate buffer. Following washing, wells were blocked for 1 h at 37°C with 4% Marvel dried milk powder diluted in phosphate buffered saline containing 0.05% Tween-20 (PBST). Plates were washed and control and test sera were added in duplicate at a dilution of 1:500 in 2% Marvel diluted in PBST and incubated for 2 h at 37°C. Following washing, Horse Radish Peroxidase-conjugated rabbit anti-bovine IgG (Sigma, UK) was added at a dilution of 1:2000 in PBST and incubated for 2 h at 37°C before washing and the addition of substrate (tetramethylbenzidine). Reactions were stopped by the addition of 2M H_2SO_4 and the optical density of each plate was measured at 450 nm using a microplate reader. Duplicate samples of positive and negative control sera were included on each plate. The positive control sample was pooled sera from three cows from a farm in Scotland which had each suffered an abortion, were positive for *Neospora* antibodies with a commercial ELISA, and in which histopathology indicated neosporosis. The negative control sample was pooled sera from three cows which had no history of *N. caninum* infection and which were negative with a commercial ELISA. Test thresholds for defining positive and negative results on the basis of ELISA sample to positive (S/P) ratios were determined using a bimodal latent class mixture model implemented within a Bayesian framework, as previously described (30, 31). The resulting S/P ratio cut-off that maximized diagnostic sensitivity and specificity was 18.3, with an estimated sensitivity of 74.3% (95% CrI 67.3–81.3) and specificity of 95.7% (95% CrI 93.6–97.5). Given limited information on the epidemiology of *N. caninum* in cattle in Tanzania, we also derived an S/P ratio threshold of 25 which maximized specificity [99.9% (95% CrI 99.8–1.0)] at the expense of sensitivity [58.7% (95% CrI 50.3–66.7)] (31). This higher threshold ensured a high level of confidence in positive results, particularly given the low to moderate expected seroprevalence in the region (32–34). We used this conservative threshold for inference, and include results derived using the more liberal threshold for reference.

Statistical Analyses

Prevalence Estimation

The "observed" prevalence estimates at both the conservative (24) and liberal (18.3) S/P thresholds were adjusted by diagnostic specificity and sensitivity in order to derive "true" prevalence estimates (35). Adjustment for diagnostic test performance was performed using the *prevalence* package (36) in the R statistical environment version 3.6.0 (37).

General Contextual Analysis

Given the hierarchical nature of the study design, in which sampled cattle were clustered by household and village, we first performed a general contextual analysis to examine the relative effects of these grouping-levels in explaining variation in the odds of *N. caninum* seropositivity (38). A null logistic regression model was run with random effects at the household- and village-level but without fixed effects. The median odds ratio (MOR) and intra-cluster correlation coefficient (ICC) were calculated using the estimated variance in household- and village-level intercepts. The MOR provides an estimate of the magnitude of heterogeneity in odds of infection at each level while the ICC provides an estimate of the correlation in infection probability at each level (39). The ICC was estimated using the latent variable approach (40). We also examined whether the residual log odds of infection at the village-level showed evidence of spatial autocorrelation using the Moran's I statistic.

Risk Factor Assessment

The null logistic model was extended to explore potential risk factors for *N. caninum* seropositivity. Risk factors were identified from questionnaire and open-source environmental and demographic data. These included: village-level livestock production system; household- and village-level dog ownership; feeding parturient materials from cattle to dogs; wildlife contact; environmental conditions expected to influence *N. caninum* oocyst survival; household management of grazing; herd size; household ownership of small ruminants and chickens; cattle introductions in the past 12 months; and local cattle population density. Village-level livestock production system was defined as "pastoral" (the majority of livelihoods based primarily on livestock production) and "mixed" (the majority of livelihoods based on a mixture of livestock and crop production) by local experts (district veterinary officers). The village-level dog ownership variable was the median number of dogs kept by households surveyed in each village. A number of potential proxies for wildlife contact were used. These were: farmer reports of observing any wild ungulate or carnivore (since wild canid observations were very rare) over the past 12 months; whether the household was within a wildlife area (conservation area, game controlled area, game reserve, national park, nature reserve, or wildlife management area) according to the world database on protected areas (UNEP-World Conservation Monitoring Centre, https://protectedplanet.net/); and the proportion of an 80 km area surrounding households (a circle with 5 km radius) that was classified as shrub or forest land (NASA Landsat Program, 2003, http://glcf.umd.edu/data/landsat/). Environmental variables that were hypothesized to influence oocyst survival were annual mean temperature and the average precipitation in the wettest quarter of the year (41), the clay, sand and organic carbon content of soil (42). Altitude was derived from shuttle radar topography mission data (43). Grazing management was split into two categories: restricted grazing in which cattle were tethered on pasture around the household or zero grazing in which fodder is brought to confined animals, and extensive grazing with a herdsperson. Local cattle population density was extracted at the household-level from the Food and Agriculture Organization's 2010 gridded livestock of the world data (44). All spatial data were manipulated in QGIS (version 2.14.3). Individual-level risk factors were cattle age ($<$18 months or $\geq$ 18 months on the basis of dentition), sex, and breed (indigenous or improved dairy cross).

The relationship between potential risk factors and individual level *N. caninum* seropositivity was first examined using univariable logistic regression. Given the large number of potential predictors and the fact that several of these predictors were included to represent similar features (e.g., wildlife contact, soil characteristics, etc.), we performed model selection. We used a Bayesian model averaging (BMA) approach for model selection (45). Model averaging was performed using an indicator variable with the Gibbs variable selection formulation (46). Briefly, this involves including a latent indicator variable (w) for each variable (m) in the model, w_m. In a Bayesian context, the value of w_m is 1 if the linear predictor includes m and 0 if it does not. Hence, the posterior estimate for w_m represents the probability of inclusion of a particular variable in the regression equation and therefore an indication of its importance in explaining observed variation in the outcome of interest (i.e., the proportion of times the variable contributes to the posterior estimate). The model averaged co-efficients for predictors represent a sample from all possible models that are defined by all possible combinations of w indicator variables (47). Where w_m is close to 0, the co-efficient for m will also be shrunken toward 0, where w_m is close to 1, its effect will be preserved.

Given the low expected sensitivity of the diagnostic assay used, the null, univariable and multivariable logistic regression models were adjusted for test performance using the following formula (35):

$$pa_i = p_i \times Se + \left(1 - p_i\right) \times (1 - Sp)$$

Where pa_i is probability of a positive test result in individual i (i.e. the "true" seroprevalence) given the predicted probability of being seropositive, p_i (the "observed" seroprevalence), and the sensitivity (Se) and specificity (Sp) of the diagnostic test. We used positives and negatives defined using the conservative S/P cut-off, and therefore an estimated Se of 0.587 and Sp of 0.999 for adjustment.

Null, univariable and multivariable logistic regression models were run in JAGS via the *R2jags* package (48). Random effects were included at the household and village-level in all models. Weakly informative normal priors were used for all fixed and random effects. Convergence after a minimum burn-in of 50,000 and at least 100,000 iterations with a thinning interval of 20 was assessed by visual examination of three MCMC chains. The log of the number of cattle owned by a household was used on the expectation of a non-linear relationship with *N. caninum* seropositivity. All continuous predictors were standardized to have a mean of zero and standard deviation of one. Pairs of continuous variables were examined for collinearity using a Spearman's rank correlation coefficient: one of a correlated pair ($\rho > 0.65$) was excluded based on relative biological importance. Assessment of goodness of fit for the final multivariable model selected by BMA was made using a posterior predictive check (the "Bayesian *p*-value") (49). This involves a comparison of the sum of the observed squared Pearson's residuals with the sum of squared Pearson's residuals expected from a distribution matching that specified by the model under assessment. Values close to 0.5 (and away from 0 and 1) suggest reasonable model fit (47). The Moran's I statistic for the null logistic regression model was calculated from village-level residuals using the *ape* package (50) in R.

Assessment of Disease Impacts

A mixed effects negative binomial regression was used to examine the relationship between the reported number of cattle abortions over the past 12 months and the within-herd prevalence of exposure to *N. caninum*. The log of the number of female cattle owned by the household at the time of the survey was included as an offset so that the abortion rate was modeled. Village was included as a random effect. Village-level production system was included to control for potential confounding. Negative binomial models were run in JAGS using the settings described above. Adjustment for test misclassification was not performed, instead we compare results derived using the conservative (24) and liberal (18.3) S/P cut-offs. Goodness of fit for models using each cut-off was assessed using the Bayesian *p*-value, as described above.

RESULTS

We tested 3,015 cattle serum samples, out of which 379 [12.6%, 95% Confidence Interval (CI) 11.4–13.8] were seropositive for *N. caninum* antibodies. Adjustment for test performance resulted in a true seroprevalence of 21.5% (95% CrI 17.9–25.4). On the basis of the liberal cut-off, the observed prevalence was 22.0% (95% CI 20.5–23.5), and the true prevalence was 25.3% (95% CrI 21.1–29.7). Of the 380 households sampled, 186 (49.0%, 95% CI 43.8–54.1) had at least one seropositive animal. This was 67.9% (95% CI 62.9–72.5) on the basis of the liberal cut-off. There was substantial variation in the true prevalence of infection between villages [3.2% (95% CI 0.3–9.2) to 60.3% (95% CI 43.6–79.1)] (**Figure 1**). Observed and true village-level prevalence estimates are provided in the **Supplementary Materials**.

The MOR and the ICC at the household level were 4.2 (95% CrI 3.0–6.7) and 39.9% (95% CrI 28.3–54.8), respectively; the MOR and ICC at the village level was 2.8 (95% CrI 1.9–4.8) and 19.7% (95% CrI 8.9–38.2), respectively. To put the household MOR into context, we would expect that, all else being equal, when comparing cattle in two different households anywhere in the study area, the odds of *N. caninum* seropositivity would be, in median, over four times higher for an animal in the household with higher within-herd prevalence than for an animal in the household with lower within-herd prevalence. In terms of ICC, we can say that around 40% of the differences in individual animal *N. caninum* exposure risk are at the household-level. Both of these measures suggest high levels of clustering of infection risk at the household level. Village was less important in structuring variation in infection risk. There was no evidence in autocorrelation (and therefore spatial clustering) in village-level residual odds of seropositivity (Moran's $I = -0.08$, $p = 0.57$).

The number and proportion of *N. caninum* seropositive samples and associated univariable odds ratios (OR) in relation to each categorical variable is shown in **Table 1**. A description of the continuous variables and the association with *N. caninum* seropositivity is shown in **Table 2**. We were able to conduct questionnaires in 360 households, representing 2,838 individual animals. Annual mean temperature was very strongly inversely correlated with altitude ($\rho = -0.99$). Altitude can be expected to be linked to a range of environmental effects, including temperature, and we therefore use altitude as the predictor of interest. Sand content of soil was inversely correlated with silt ($\rho = -0.80$) and clay ($\rho = -0.95$) content. While all soil properties can be expected to influence moisture content, which in turn can be expected to influence oocyst survival, we use sand content of soil in our multivariable analysis to reflect relatively high levels of water filtration and relatively low levels of water saturation (i.e., drier soils).

Risk Factors for *N. caninum* Seropositivity

The outputs from the BMA procedure are summarized in **Table 3**. Variables with a probability of inclusion >0.5 were

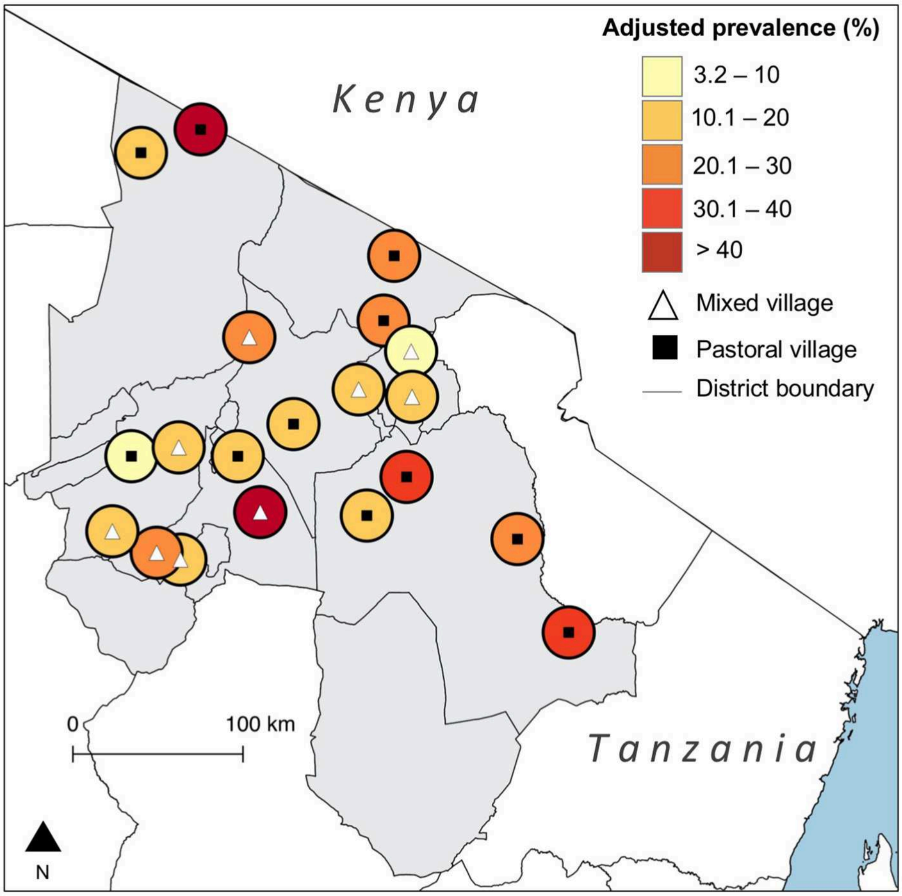

FIGURE 1 | Map showing the village-level prevalence of *Neospora caninum* seropositivity in northern Tanzania with adjustment for diagnostic test performance. (Created using QGIS version 2.14.3, shapefiles from https://gadm.org/).

TABLE 1 | Individual and household-level characteristics of categorical variables and their relationship with the seroprevalence of *Neospora caninum* in cattle in northern Tanzania.

Risk factor		Total *N* (%)	*Neospora* seropositive *n* (%)	Univariable regression
				OR (95% CI)
Individual-level				
Age	<18 months	835 (29.4)	70 (8.4)	Ref
	≥18 months	2,003 (70.6)	285 (14.2)	2.49 (1.73–3.69)
Breed	Indigenous	2,567 (90.5)	334 (13.0)	Ref
	Cross	271 (9.5)	21 (7.7)	0.61 (0.24–1.55)
Sex	Female	1,894 (66.7)	248 (13.1)	Ref
	Male	944 (33.3)	107 (11.3)	0.79 (0.56–1.10)
Household-level				
Keep chickens	No	412 (14.6)	41 (10.0)	Ref
	Yes	2,404 (85.4)	312 (13.0)	1.15 (0.63–2.15)
Keep small ruminants	No	207 (7.3)	28 (13.5)	Ref
	Yes	2,631 (92.7)	327 (12.4)	0.85 (0.40–1.81)
Keep dogs	No	801 (28.2)	98 (12.2)	Ref
	Yes	2,037 (71.8)	257 (12.6)	1.03 (0.62–1.70)
Feed placenta to dogs	No	463 (16.3)	66 (14.3)	Ref
	Yes	2,375 (83.7)	289 (12.2)	0.88 (0.49–1.59)
Cattle introduction	No	1,974 (69.6)	246 (12.5)	Ref
	Yes	864 (30.4)	109 (12.6)	1.09 (0.70–1.71)
Restricted grazing	No	2,637 (93.0)	349 (13.2)	Ref
	Yes	198 (7.0)	6 (3.0)	0.22 (0.07–0.65)
Production system	Mixed	1,223 (43.1)	148 (12.1)	Ref
	Pastoral	1,615 (56.9)	207(12.8)	1.15 (0.40–3.41)
Wildlife area	No	1,477 (52.5)	163 (11.0)	Ref
	Yes	1,339 (47.5)	190 (14.2)	1.50 (0.67–3.49)
See wildlife	No	1,091 (38.4)	130 (11.9)	Ref
	Yes	1,747 (61.6)	225 (12.9)	1.36 (0.79–2.36)

age >18 months; the local cattle population density; the percentage cover of shrub or forest land in the environment surrounding a household; and household use of restricted grazing. Older animals had more than two times the odds of being *N. caninum* seropositive compared to younger animals [Odds ratio (OR) = 2.17, 95% CrI 1.45–3.26]. While there was no evidence for a relationship with household herd size, local cattle population density was negatively associated with *N. caninum* seropositivity (OR = 0.69, 95% CrI 0.41–1.00). Cattle in households that reported using restricted grazing had reduced odds of seropositivity (OR = 0.72, 95% CrI 0.25–1.16). The credibility intervals for this variable broadly overlap one, so while it can be considered a moderately important predictor in explaining variation in *N. caninum* seropositivity (with a 0.63 probability of being in the model), the evidence for the size and direction of the effect should be considered weak. There was no evidence of a relationship between farmer reports of observing wildlife in the past 12 months or household location within a wildlife area and *N. caninum* positivity, but cattle kept in households in areas with a high percentage of shrub or forest cover were more likely to be *N. caninum* seropositive (OR 1.37, 95% CrI 1.00–2.14). There was no evidence for a difference in *N. caninum* seropositivity between production systems.

Assessment of Disease Impacts

The reported number of abortions in the past 12 months in study households ranged from 0 to 162. The seroprevalence of *N. caninum* in herds with at least one positive animal ranged from 8 to 100%, with an average of 24.6% (28.6% using the more liberal cut-off). There were five households in which the number of reported abortions over the past 12 months exceeded the number of adult female animals present at the time of the survey. We treated these as having 100% abortion rates (i.e., reduced the number of abortions to match the number of females). The multivariable negative binomial regression resulted in an incidence rate ratio (IRR) of 1.03 (95% CrI 1.00–1.06). Hence, for every 10% increase in within-herd *N. caninum* seroprevalence, the rate of abortion could be expected to increase by around 1.3 times. Production system was strongly associated with abortion rate, with this being considerably higher in households in pastoral villages than in mixed villages (IRR = 16.7, 95% CrI 3.6–133.5). The positive relationship between abortion rate and within-herd *N. caninum* prevalence was observed when the five households with 100% abortion rates were excluded from the dataset (IRR = 1.02, 95% CrI 1.00–1.05). There was not an important difference in results derived using the conservative and liberal cut-offs (data not shown). The Bayesian p-value for negative

TABLE 2 | Household-level characteristics of continuous variables and their relationship with the seroprevalence of *Neospora caninum* in northern Tanzania.

Risk factor	Median, mean (range)	Univariable regression
		OR (95% CrI)
Number of dogs in village	2.00, 1.65 (0.00–3.00)	1.11 (0.78–1.58)
Cattle number	20, 63.96 (1.00–1,200)	1.15 (0.66–1.98)
Local cattle population density	0.8, 40.30 (0.2–5,820)	0.55 (0.34–0.87)
Sand content of soil (%)	48, 49 (31–66)	0.95 (0.60–1.44)
Organic content of soil (%)	14, 15 (1–55)	1.42 (1.07–1.89)
Clay content of soil (%)	33, 32.63 (18.00–47.00)	0.99 (0.65–1.57)
Silt content of soil (%)	18, 18.89 (11.00–28.00)	1.03 (0.71–1.51)
Precipitation of wettest quarter (mm)	406, 420 (251–719)	1,02 (0.64–1.71)
Mean annual temperature (°C)	19.5, 19.3 (14.5–24.1)	0.97 (0.58–1.62)
Altitude (m)	1,410, 1,470 (610–2,420)	1.06 (0.62–1.82)
Shrub or forest land (%)	0.12, 0.19 (0.00–0.99)	1.59 (1.08–2.38)

TABLE 3 | Risk factors to *Neospora caninum* in cattle in northern Tanzania selected using Bayesian model averaging.

	Indicator variable	OR	95% CrI
Age	1.00	2.17	1.45–3.26
Local cattle population density	0.81	0.69	0.41–1.00
Shrub or forest land	0.78	1.37	1.00–2.14
Restricted grazing	0.62	0.72	0.25–1.16
Production system (pastoral)	0.48	0.89	0.36–1.51
Breed (cross)	0.39	0.95	0.51–1.50
Feed placenta to dogs	0.39	0.95	0.60–1.28
Keep small ruminants	0.38	0.99	0.64–1.52
Wildlife area	0.36	1.03	0.67–1.78
Keep chickens	0.36	1.05	0.79–1.67
Number of dogs in village	0.36	1.06	0.84–1.66
See wildlife	0.33	1.02	0.74–1.49
Keep dogs	0.31	1.00	0.73–1.36
Sex (male)	0.28	0.98	0.75–1.17
Cattle introduction	0.27	1.01	0.78–1.33
Organic carbon	0.19	1.01	1.00–1.05
Sand content of soil	0.05	1.00	1.00–1.00
Altitude	0.02	1.00	1.00–1.00
Precipitation of wettest quarter	0.01	1.00	1.00–1.00
Cattle number	0.00	1.00	1.00–1.00

binomial models using different ELISA cut-offs ranged between 0.4 and 0.47.

DISCUSSION

In this study, we report an overall prevalence of *N. caninum* seropositivity of 21.5% among cattle in northern Tanzania. While the seroprevalence of *N. caninum* exposure varies between study villages and appears to be linked to environmental and demographic conditions, we find no evidence for a difference in prevalence between pastoral and mixed production systems. The moderately high seroprevalence we observe suggests neosporosis is likely to be an important cause of reproductive losses in cattle in northern Tanzania. Indeed, we find evidence for a positive association between within-herd *N. caninum* seroprevalence and abortion rates. A recently published study in neighboring Kenya provides further support for the importance of *N. caninum* as a cause of abortion in the region, with seropositivity of the pathogen reported to be associated with a greater proportion of fetal loss than either *Brucella* spp. or bovine viral diarrhea virus (32).

This is not the first study to report evidence for *N. caninum* infection in Tanzania. Barber et al. reported a seroprevalence of 22% in dogs in 1997 (51). A previous study in cattle in northern and north-eastern areas of Tanzania reported a seroprevalence of 8.1% in 2003 (33). However, the sample size was low and limited in its geographic coverage and it is therefore unclear whether the higher true prevalence reported in this study represents an increase in seroprevalence in northern Tanzania. A larger study conducted in the southern highlands (around 700 kilometers from our study area) in 2017 reported a seroprevalence of 4.5% (34). We found no evidence for an association between individual cattle *N. caninum* seropositivity and household- or village-level dog ownership, or with households reporting feeding placenta to dogs. The absence of a relationship with dog ownership was also reported from the southern highlands of Tanzania (34). Infection can be maintained in cattle populations by transplacental transmission (52), but there is no reason to suspect that dogs do not act as reservoirs of *N. caninum* for cattle in Tanzania, and a high seroprevalence of infection has been found in dogs in both Kenya and Tanzania (25, 32, 33, 51). The lack of an observable effect for household-level dog ownership may point to the importance of contamination of grazing areas by free roaming dogs. Dogs in Tanzania are owned by specific households, but often roam far during the day (53). While we did not find a relationship with village-level dog ownership, it could be expected that free-ranging dogs infected with *N. caninum* could contaminate grazing areas across a wide area, thereby potentially exposing cattle from multiple households to oocysts shed by a single dog. This mechanism is thought to be important for the transmission of other dog-mediated pathogens to livestock in northern Tanzania (54).

Our data provide evidence for a negative relationship between cattle population density and *N. caninum* seropositivity in northern Tanzania. The biological explanation for this relationship is unclear, particularly since cattle population density is strongly correlated with human population density (55) which, in turn, tends to be correlated with dog population density (56). Dog population density has been found to predict *N. caninum* seropositivity in other settings (57). The observed negative effect with cattle population density in this study may represent a lack of confounding control by production system. In our study area, small holder production systems (i.e., mixed crop and livestock, with small cattle herd sizes) are found primarily in peri-urban areas with high human and cattle population density. These are also the areas in which restricted grazing predominates (none of the pastoral households in our study reported restricted grazing). It could therefore be expected that cattle reared in small holder households are at lower risk of *N. caninum* exposure than cattle reared in pastoral households, which are found in low cattle population density areas and practice extensive grazing. The lack of an observable effect by production system in our study (and the potential lack of control for the effect of cattle population density) may be due to the non-specific nature of the definitions used. Our mixed farming category includes both small-holder and agro-pastoral households. Agro-pastoral households practice mixed crop and livestock production but tend to have larger herd sizes and are found in more rural, low cattle population density locations than small holder households in our study area. Livestock reared in agro-pastoral households could therefore be expected to have a different *N. caninum* risk than those reared in small holder households. Further work to explore the effect of production system on *N. caninum* risk in Tanzania, including better control for the range of livestock production systems that exist in the region, would be valuable.

While we did not find evidence for a relationship between either cattle being reared in a wildlife area or farmer reports of seeing wildlife in the past 12 months and *N. caninum* seropositivity, we did find evidence for a strong association with levels of forest and shrub cover in the area surrounding households. It could be hypothesized that such areas would support the largest wildlife populations, and particularly small and medium sized members of the *Carnivora* order. We are not aware of any studies that have directly evaluated the role of wildlife as reservoirs for *N. caninum* in cattle in Tanzania, but serological studies have demonstrated positivity in cheetah and spotted hyena in Kenya (26). These wild carnivores, among others, are found in northern Tanzania, particularly in pastoral settings. Sylvatic cycles have been demonstrated in other settings, including in the Australian dingo (1, 2), water buffalo (58) as well as those involving rodents (59–61). Further work to explore the role of wildlife in the epidemiology of *N. caninum* in Tanzania is recommended. We included the forest and shrub cover variable to represent wildlife habitat suitability, however alternative explanations for its effect on *N. caninum* exposure risk should also be considered. These include the reduced availability of grassland in forest and shrub areas, resulting in greater concentration of cattle grazing in smaller areas. Alternatively, while we did not find a relationship with precipitation, altitude or soil type, the microclimatic conditions that are particular to forest and shrub areas may favor *N. caninum* oocyst maturation and survival. Unsporulated *N. caninum* oocysts are said to be highly resistant in the environment (62) and are thought to survive for several years (3). However, limited work has been conducted on the impact of macro or micro-climatic conditions on oocyst survival or rates of maturation (3), particularly in the African context.

We observed that animals >18 months were more likely be *N. caninum* seropositive than juvenile animals. A similar relationship with age has been reported widely (32, 63, 64). Cattle are infected with *N. caninum* for life, and this effect is likely to represent the cumulative exposure risk to sporulated oocysts in the environment as animals age (3).

There are several limitations to our study that should be considered. While we find weak evidence for a relationship between within-herd seroprevalence and abortion rate within a household, it should be noted that these seroprevalence estimates are based on a maximum sample of 10 animals per household. Estimates of within-household seroprevalence are therefore based on small sample sizes and associated with very low precision. Additionally, these data are likely to be strongly influenced by recall bias. This is likely to be a particular issue for abortions associated with *N. caninum,* which tend to occur in the second trimester and may therefore be missed or not recollected by livestock keepers. Cattle breeding in the study area is often unplanned and pregnancy diagnosis rare, hence it is likely that only a proportion of abortions will be noticed and reported by participating farmers. Data collection followed a central point procedure in which farmers were invited to attend the sampling event and which may therefore have introduced selection bias: any farmer who did not attend was not included in the sample. We sought to reduce this as much as possible by running several sampling events at different points within the same village and by linking sampling with village-level disease control to incentivize attendance. Finally, while the focus of this study was on cattle, there is growing evidence that sheep and goats can be affected by neosporosis (5, 9–12). Since the majority of cattle-keeping households in rural Tanzania also keep small ruminants, and the majority of these are freely grazed on communal grazing lands, there is a great need for future studies in the country to incorporate sheep and goats into assessments of the epidemiology and impacts of *N. caninum*.

Our study results have a number of implications for disease control in Tanzania. Despite the moderately high prevalence of infection detected in this study, we are not aware of the availability of routine testing for neosporosis in either government or commercial laboratories in Tanzania. Provision of such testing would assist farmers and veterinarians with herd health planning and may be particularly valuable for the growing dairy industry in Tanzania. We find some evidence of a relationship between within-herd seroprevalence and herd-level abortion rates, suggesting that the control of *N. caninum* could contribute to reduced reproductive losses among cattle in the region. Recent research from northern Tanzania demonstrates that cattle abortions are negatively associated with schooling expenditure and positively associated with food expenditure (65). *Neospora caninum* infection and associated abortions can be expected to contribute to this negative impact on household welfare. Our results indicate several potential control points. We find some evidence that restricted grazing is associated with reduced risk of *N. caninum* infection and may therefore be a strategy cattle-keepers can use to reduce their abortion risk. It is important to note, however, that restricted grazing requires greater resources in terms of labor and the purchase or collection of fodder. This management system is therefore likely to be impractical for many households, and particularly those in pastoral systems, with large herds relying on extensive grazing in often marginal environments. Reducing contamination of the environment with dog feces could also be expected to contribute to reduced infection risk. Such an approach may be possible in areas where dogs are well-controlled, but in the presence of free ranging dogs, preventing contamination of communal grazing areas is likely to be challenging. Village dogs in these settings may also play an important role in reducing contamination of the grazing environment by deterring the wild canids from the grazing areas close to community settlements. Overall, further work is required in Tanzania, and East Africa more broadly, to explore approaches that can be used, and their applicability to different production systems, in order to control this economically important parasite.

CONCLUSION

N. caninum seropositivity is moderately common in cattle in northern Tanzania and is likely to be a cause of abortion. We find some evidence that management practices, such as restricted grazing, reduce the risk of infection, suggesting contamination of communal grazing areas may be an important source of infection. Evidence of relationships between livestock seropositivity and shrub and forest habitats may also suggest a role for wildlife in the epidemiology of *N. caninum* in Tanzania that would be a valuable area for future study. To date, limited research has been conducted on the epidemiology and control of *N. caninum* in East Africa, but this parasite is likely to be an important cause of abortions and thus an economically important parasite to monitor and control.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

GS and WG performed data analysis and manuscript drafting. TK, ES, and WG performed data collection. CH, KT, KA, EI, and FK performed laboratory analysis. SC acquired funding. KK, FL, JB, JC, WG, and SC provided supervision. All authors reviewed and provided input into the manuscript.

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The Risk of Foot and Mouth Disease Transmission Posed by Public Access to the Countryside During an Outbreak

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During the 2001 UK FMD outbreak, local authorities restricted rural access to try to prevent further disease spread by people and animals, which had major socio-economic consequences for rural communities. This study describes the results of qualitative veterinary risk assessments to assess the likelihood of different recreational activities causing new outbreaks of foot and mouth disease, as part of contingency planning for future outbreaks. For most activities, the likelihood of causing new outbreaks of foot and mouth disease is considered to vary from very low to medium depending on the control zone (which is based on distance to the nearest infected premises), assuming compliance with specified mitigation strategies. The likelihood of new outbreaks associated with hunting, shooting, stalking, and equestrian activities is considered to be greater. There are areas of significant uncertainty associated with data paucity, particularly regarding the likelihood of transmission via fomites. This study provides scientific evidence to underpin refinement of rural access management plans and inform decision-making in future disease outbreaks.

Keywords: foot and mouth disease, risk assessment, policy, rural access, transmission, fomites

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INTRODUCTION

Highly contagious diseases of livestock have the potential for significant impact, not only on the agricultural industry but also the wider economy and on society. Foot and mouth disease virus (FMDV) is both easily transmissible and able to persist in the environment (1, 2), meaning that control strategies must aim to prevent transmission via fomites as well as direct contact. Therefore, foot and mouth disease (FMD) has the potential for substantial societal impact; control strategies rely not only on mandatory slaughter of infected and in-contact animals and restrictions on movement and trade of susceptible livestock species (3, 4), but may also require restrictions on the activities of non-susceptible animals and people, who may transmit the virus mechanically.

During the 2001 UK foot and mouth disease outbreak, UK local authorities took a precautionary approach to disease control and used blanket bans to close all footpaths, even in uninfected areas, to try to prevent further disease spread by people and animals. These measures had major socio-economic consequences for rural communities (5). The tourism sector suffered the greatest financial impact and is estimated to have lost around £3bn due to the outbreak, due in large part to the perception that "the countryside was closed" (6, 7). Post-outbreak reports highlighted the need for more research on the likely efficacy of biosecurity measures such as footpath closures, and more transparent risk-based decision making, particularly regarding rural access (5, 7).

Although the exceptional scale of the 2001 outbreak in UK undoubtedly exacerbated the issues of rural access (8, 9), the role of people accessing to the countryside in contributing to onward transmission of FMD remains an important question that has not been addressed in Scotland or in other countries that are FMD-free. In light of this, a suite of veterinary risk assessments (VRAs) were developed to consider the risk of disease spread associated with recreational access to the countryside. Here, we describe the risk assessments and conclusions as well as highlighting key assumptions and knowledge gaps.

MATERIALS AND METHODS

Risk questions were developed for each of 12 countryside activities: walking, cycling, canoeing, fishing, horse riding, staging equestrian events, staging a horse racing meet, staging other events on agricultural land, staging sporting events such as running competitions or triathlons, drag hunting, stalking deer, and shooting birds. For each activity, the risk question took the form "What are the risks of causing new outbreaks of foot and mouth disease (FMD) by walking, and other similar activities such as dog walking, and climbing?"

The risk assessments followed a standard approach, considering (i) hazard identification; (ii) risk pathway; (iii) legislation, definitions and assumptions; (iv) release and exposure assessment; (v) consequence assessment; and (vi) overall likelihood levels and risk management options. A qualitative approach was chosen over a quantitative approach after careful consideration of the paucity of data on which to base a quantitative assessment. Definitions of qualitative likelihood levels used were derived from those published by the World Organization for Animal Health (OIE) and adopted by the UK Department for Environment, Food and Rural Affairs (DEFRA) (10, 11) and are presented in **Table 1**.

A risk pathway was developed for each activity that identified the steps involved in release of and exposure to FMDV. A review of the available literature was used to identify all relevant factors which are likely to influence these steps. A search of the scientific literature published in peer-reviewed journals was done using the following search terms: "foot and mouth disease" and: "wildlife"; "transmission"; "fomites"; "environment"; "survival." Important references were also identified in key review papers (12–15). In addition, previous risk assessments including those produced during the 2001 FMD outbreak in UK (9), were used to inform the exposure and release assessments. On collation of risk factors, key knowledge gaps or areas of uncertainty were identified for each step in the pathway. Likelihood estimates for each step were developed based on the information available. Likelihood estimates assumed compliance with standard statutory measures in place during an FMD outbreak but did not take into account any additional mitigation measures specific to the activities in question. In reality it is unlikely that these activities would be permitted in the absence of additional mitigation measures aimed to reduce the risk of onward disease transmission. Relevant specific mitigation measures were identified in consultation with the Animal and Plant Health Agency (responsible for implementing disease control) and additional likelihood estimates were provided for each step assuming these mitigation measures were in place. Compliance was assumed, although areas of particular concern for non-compliance were highlighted in the risk assessment. The consequences of a new outbreak as a result of the risk pathway were considered, and final risk levels based on a combination of the likelihood of exposure and release and the severity of the consequences (11). The VRAs were reviewed by the Scottish Government and the UK National Experts Group on Foot and Mouth Disease.

TABLE 1 | Definitions of qualitative likelihood estimate levels.

Likelihood level	Description
Negligible	So rare that it does not merit consideration
Very low	Very rare but cannot be excluded
Low	Rare but could occur
Medium	Occurs regularly
High	Occurs very often
Very High	Events occur almost certainly

RESULTS

Individual VRAs for each activity can be seen at https://www.gov.scot/publications/foot-and-mouth-disease-veterinary-risk-assessments-vras/.

Hazard Identification

The hazard is FMD virus. There are seven serotypes of FMD virus: O, A, C, SAT1, SAT2, SAT3, and Asia 1. Different serotypes (and different strains within each serotype) have different characteristics, including variation in host species susceptibility, length of incubation period, ease of detecting clinical signs and transmission (16–19). Much research is based on the UK 2001 outbreak, which was caused by serotype O, strain PanAsia (20). However, future outbreaks may involve other serotypes/strains and therefore present different epidemiological situations.

The specific risk is that attending, conducting or staging leisure activities in the countryside during an FMD outbreak may involve people or associated fomites that have been, or come into, contact with FMDV and with susceptible livestock, leading to FMD spread via people or other fomites to cause further disease outbreaks.

Risk Pathway

Risk pathways were developed for each activity comprising release and exposure assessments. A summary risk pathway is shown in **Figure 1**. Release included persons, animals, vehicles or other equipment (i) already contaminated on leaving the home premises; (ii) becoming contaminated on the way to or from the activity, contaminating roads or the environment; (iii) coming into contact with susceptible livestock whilst on the way to or from the activity; (iv) becoming contaminated

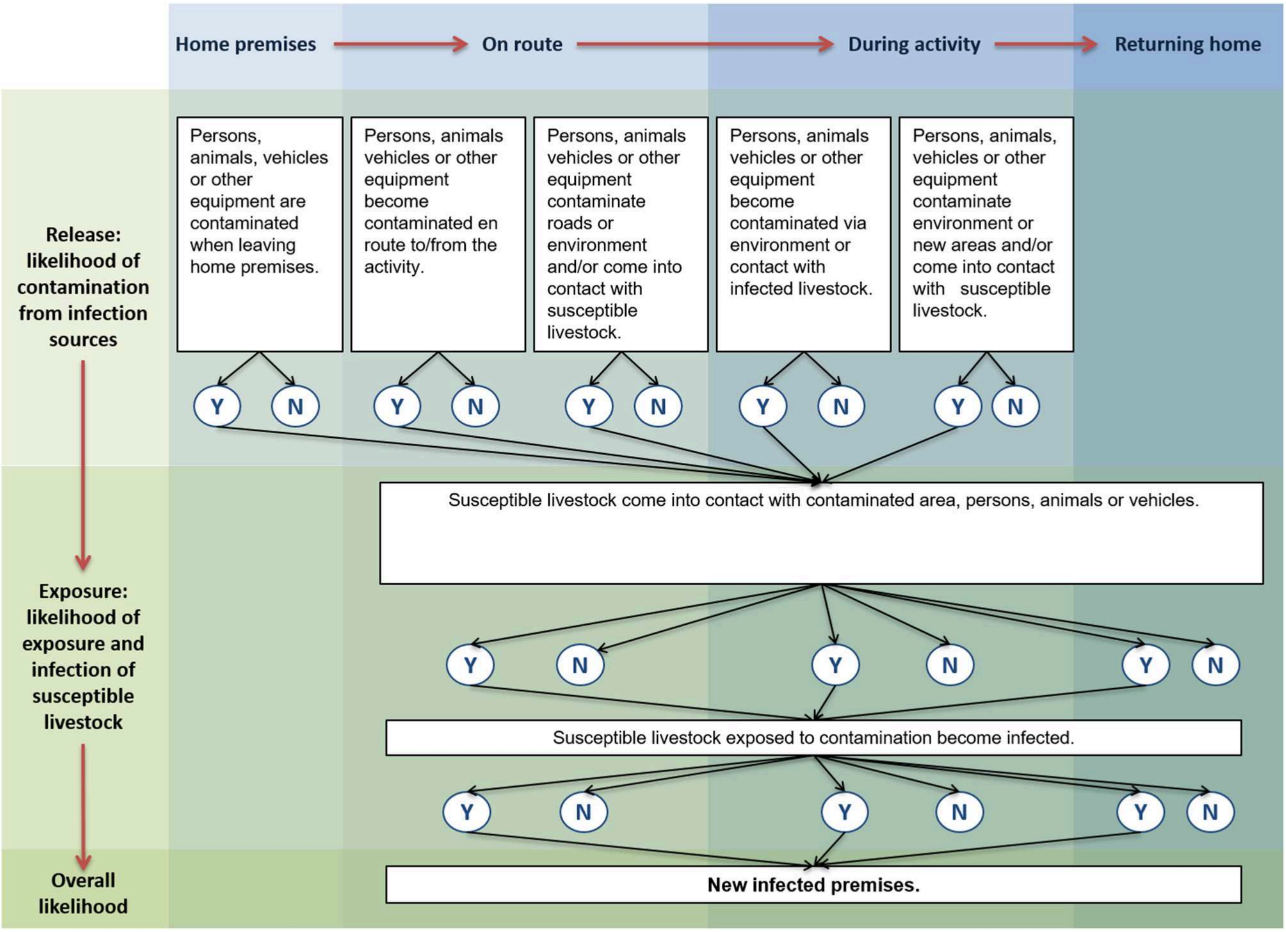

FIGURE 1 | Summary risk pathway. Individual risk pathways were developed for each of 12 activities that require access to the countryside. This summary pathway illustrates the common steps in the risk pathway from release of FMDV to exposure of susceptible livestock.

via the environment or through contact with infected livestock during the activity; and (v) contaminating the environment, moving contamination to new areas, or coming into contact with susceptible livestock during the activity. Exposure included susceptible livestock being exposed and ultimately infected, through coming into contact with contaminated areas, persons, animals or vehicles, and could occur on return to the home premises, whilst traveling to or from the activity, or whilst doing the activity.

Legislation, Definitions, and Assumptions

For the purposes of these VRAs, "access to the countryside" was defined as recreational activity involving people, vehicles, equipment, and in some cases, animals. Statutory disease control requirements limit access and activities on premises where FMD is suspected or confirmed (3). Control zones are put in place on suspicion and confirmation of disease to prevent spread of disease (**Figure 2**). When suspicion of disease cannot be ruled out, and diagnostic samples are taken from suspected cases, a Temporary Control Zone is put in place surrounding the suspect premises. On disease confirmation, a protection zone (PZ) is set up around an infected premises, with a minimum radius of 3 km, or more if necessary to control disease. A surveillance zone (SZ), with a minimum radius of 10 km from the infected premises, is set up around the protection zone. A national movement ban is enforced by introducing a Restricted Zone (RZ). These zones place restrictions on movements and activities around infected premises to prevent spread of disease. Later in the outbreak, restrictions may be relaxed either through reducing the size of the RZ or through allowing some resumption of normal activities under license within the RZ, SZ, or PZ. In this VRA, RZ is used to refer to areas which are within the RZ, but do not also fall within the PZ or SZ. Some rural activities are specifically prohibited within particular control zones, for example deer stalking and drag hunting are not permitted within a PZ. Land access rights within Scotland are liberal (21) although Scottish Ministers and local authorities have ability to restrict access for disease control purposes.

Release and Exposure Assessment

Each step in the risk pathway is discussed below. A summary of key factors, uncertainties and likelihood levels for each step in

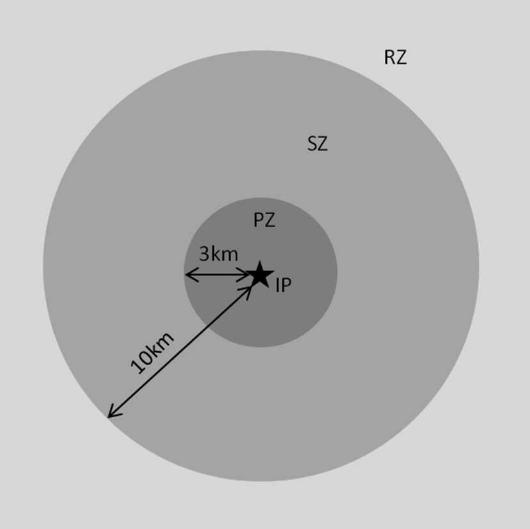

FIGURE 2 | Zoning during an outbreak: Protection, surveillance and restricted zones. During an outbreak of FMD, movement control zones are put in place to help control spread of disease. A protection zone (PZ) is set up around an infected premises (IP), with a minimum radius of 3 km, or more if necessary to control disease. A surveillance zone (SZ), with a minimum radius of 10 km from the infected premises, is set up around the protection zone. A restricted zone (RZ) is set up outside these areas and extends as far as necessary to prevent disease spread; it may extend to the whole of Scotland. The number and extent of these zones changes as the outbreak progresses with new zones being created around newly identified infected premises. Zones are lifted as disease is eradicated from premises once disinfection and verification of disease freedom is met.

the pathway is presented in **Table 2**. Mitigation measures specific to each activity are provided in the individual VRA documents (https://www.gov.scot/publications/foot-and-mouth-disease-veterinary-risk-assessments-vras/) and key mitigation measures are summarized in **Table 2**.

Release Assessment

Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment are contaminated when leaving home premises

People, fomites or non-susceptible animals present a risk of FMD transmission if they become contaminated with FMDV. The likelihood of contamination is greatest on or close to premises with FMD. Premises with FMD may be detected ("infected premises") or as yet undetected. On detected infected premises, control measures are in place to reduce the likelihood of FMDV contamination of people, fomites or the environment. However, contamination remains a possibility. In a PZ there are known infected premises, in a SZ known infected premises are located >3 km away and in a RZ known infected premises are located >10 km away (3). Once a national movement ban is in place, most transmission occurs by local spread (<3 km from a premises with FMD) (8, 22, 23), so zone is also a reasonable indicator of the likelihood of proximity to undetected infected premises. Early in the outbreak, there is increased risk of undetected infection in all zones. The risk of undetected premises with FMD arising from spread over longer distances can be better quantified by analysis of movement data to identify movements of animals from areas where FMD has been detected that have occurred before the implementation of movement restrictions. The likelihood of detection and transmission is also influenced by FMD virus strain.

FMD may be present on premises but remain undetected because (i) animals show no or mild clinical signs; (ii) animals are incubating infection; (iii) animals show clinical signs but these are not observed; or (iv) clinical signs are not reported. Although the peak of transmission occurs shortly after the appearance of clinical signs (24), infected livestock may excrete FMDV for several days before the appearance of clinical signs or in the absence of clinical signs, potentially leading to transmission or contamination prior to disease detection, particularly in cattle and pigs (25). Transmission via contaminated surfaces has been documented before the onset of clinical signs (26). FMD in sheep can be difficult to detect clinically as not all animals show clinical signs, and clinical signs are usually mild and short lived (27). There is therefore a greater risk of undetected infection on sheep-only premises.

Contamination of people People can carry FMDV on their clothes, footwear and bodies and pass it to susceptible animals. Veterinarians and other people were incriminated in spread leading to 10 of 51 outbreaks during the 1967–1968 outbreak in UK (28). When people handled pigs infected with FMDV then immediately handled susceptible sheep and pigs, all animals became infected (29). Including hand washing and changing outer wear reduced the risk on onward infection, whilst showering and changing outer wear prevented it (29, 30). It should be noted that these infections occurred when contact with susceptible animals immediately followed handling of pigs with clear signs of FMD, in laboratory conditions. The likelihood of similar transmission from handling animals that are incubating an infection, or that only show mild clinical signs, such as sheep, is much lower.

There is also evidence that people can carry FMDV in their nasal cavities, but the likelihood of this leading to infection in susceptible animals without close and prolonged contact is negligible. One incident is described where infection was passed from sick pigs, via people, to a susceptible cow, despite the people involved fully disinfecting, showering and changing clothes. The infection was assumed to have passed via the nasal cavity. However, this required prolonged contact with infected pigs and deliberate coughing, blowing and sneezing on the muzzles of the susceptible cattle (31). No FMD virus was detected in nasal swab samples collected from four investigators 12–84 h after they had been exposed to the virus, but virus was detected in the nasal swab from one of four investigators immediately after examining sick pigs at post-mortem (29). Screening of nasal swabs over several experiments following handling of various combinations of infected cattle, sheep, and pigs showed swabs to frequently test positive for virus by PCR but only occasionally on virus inoculation, and only one person tested positive the next day (PCR only), suggesting the likelihood of virus survival in the

TABLE 2 | Key factors, uncertainties and likelihood levels for each step of the risk pathway.

Evidence for each step of risk pathway	Key knowledge gaps and uncertainties	Likelihood level without mitigation, key risk factors	Likelihood levels with mitigation, key mitigation measures
1. Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment are contaminated when leaving homepremises			

- Proximity to detected infected premises
- Proximity to undetected infectedpremises
  - Outbreak stage
  - Virus strain
  - Livestock speciespresent
- Degree of contact with livestock
- Cleansing anddisinfection
	Likelihood of virus survival on different materials and under different conditions
	Quantitative data on the likelihood of transmission via people, animals, vehicles, and equipment under differentconditions
		PZ—low/medium
		SZ—low
		RZ and rest of country—very low
		Key factors influencingrisk:
		- Contact with susceptible livestock increases risk
		- Stage of outbreak—early in outbreak uncertainty regarding undetected infection increasesrisk
			PZ—low
			SZ—very low
			RZ and rest of country—very low
			Key mitigationmeasures:
			- Cleansing and disinfection on leaving home premises
			- People/vehicles/equipment that have had contact with IP not to visit areas with susceptiblelivestock

2. Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment become contaminated on route to/from theactivity			
- Proximity of route to premises with detected or undetected FMD - Length and duration of journey - Number and nature of stops - Cleansing anddisinfection	Quantitative data on the likelihood of transmission via people, animals, vehicles, and equipment under different conditions	PZ—low/medium SZ—low RZ and rest of country—very low Keyfactors: - Stage of outbreak—early in outbreak risk is higher - Stops at premises with or close to susceptible livestock, multiplestops	PZ—low SZ—very low RZ and rest of country—very low Key mitigationmeasures: - Cleansing and disinfection of vehicle on arriving at activity - Avoiding multiple stops, especially on equinepremises
3. Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment contaminate roads or environment and/or come into contact with susceptible livestock on route to/from theactivity			
- Proximity of route to premises with susceptible livestock - Length and duration of journey - Number and nature ofstops	Quantitative data on the likelihood of transmission via people, animals, vehicles, and equipment under different conditions	Low Keyfactors: - Stops at premises with or close to susceptiblelivestock	Low Key mitigationmeasures: - Cleansing and disinfection on leaving home premises, and at any other stops - Avoiding multiple stops, especially on equinepremises
4. Risk of contamination from infection sources: Persons, animals vehicles, or other equipment become contaminated via environment or contact with infected livestock duringactivity			
- Proximity to premises with detected or undetected FMD - Presence and density of susceptible livestock at the location where the activity takes place - Presence of free ranging dogs - Level of use of land where activity takes place - Wildlife in locality - Meteorologicalconditions	Virus survival in different meteorological and ecological conditions	PZ—low to medium/high SZ—low to medium RZ and rest of country—very low tolow/medium Keyfactors: - Stage of outbreak—early in outbreak risk levels higher - Presence (current or recent) of susceptible livestock in area activity is taking place - Proximity, density, and likelihood of contact with susceptible species - Disturbance of wildlife - Number of peopleattending	PZ—low to medium SZ—low to low/medium RZ and rest of country—very low to low Key mitigationmeasures: - Preventing public coming into contact with livestock - Not parking vehicles where they can come into contact with livestock or feces - Keeping dogs onleads

(Continued)

TABLE 2 | Continued

Evidence for each step of risk pathway	Key knowledge gaps and uncertainties	Likelihood level without mitigation, key risk factors	Likelihood levels with mitigation, key mitigation measures
5. Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment contaminate environment or new areas and/or come into contact with susceptible livestock duringactivity			
- Presence and density of susceptible livestock at the location where the activity takes place - Number of people, animals, vehicles doingactivity	Quantitative data on the likelihood of transmission via people, animals, vehicles, and equipment under different conditions	Low to medium/high Keyfactors: - Presence (current or future) of susceptible livestock in area activity is taking place - Proximity, density, and likelihood of contact with susceptible species - Disturbance of wildlife - Number of peopleattending	Low Key mitigationmeasures: - Preventing public coming into contact with livestock, e.g., encourage public to stick to footpaths - Not parking vehicles where they can come into contact with livestock - Keeping dogs onleads
6. Exposure and infection: Susceptible livestock come into contact with contaminated area, persons, animals, orvehicles			
- Presence and density of susceptible livestock at the location where the activity takes place, or on contaminated routes - Meteorologicalconditions	Virus survival in different meteorological and ecological conditions	Very low to medium Keyfactors: - Proximity, density, and likelihood of contact of susceptible livestock - Presence of susceptible livestock at homepremises	Very low to medium Key mitigationsmeasures: - Keep susceptible livestock away from potentially contaminated areas (e.g., during and after events held on agricultural land) - Cleansing and disinfection on return to homepremises
7. Exposure and infection: Susceptible livestock exposed to contamination becomeinfected			
- Degree of contamination (viral dose) - Livestockspecies	No specific uncertainties	Very low to medium - Virus load present in contamination - Species	Very low to medium

Ranges of likelihood levels are provided in column 3 and 4 to illustrate the likelihood levels for different activities The key factors that drive these likelihood levels (often factors that are specific to individual activities) are indicated.

nasal cavities of personnel 16–22 h after exposure to infected animals is very small (32). Again, although theoretically possible, the likelihood of transmission via virus survival in a person's nasal cavity due to contact with animals on an undetected premises, or from animals that are not showing obvious clinical signs, is very small.

The risk of contamination is greatest if people have had contact with infected animals, and next greatest if they have had indirect contact, for example if they have been to premises where FMD is present (either detected or undetected) but not handled livestock. The risk is therefore present for anyone who keeps susceptible livestock or has visited premises with susceptible livestock (including occupational exposure such as veterinarians) due to the risk of undetected infection. The likelihood and amount of contamination varies with species infected, stage of infection, degree of contact, and any biosecurity measures in place (29). Although it is known that contaminated people have played a role in causing new outbreaks (8, 33, 34), there is not sufficient information to quantify the risk with any certainty.

Contamination of vehicles and equipment. Vehicles and equipment can act as fomites. Virus can survive in slurry for up to 9 days at 20°C, to 14 weeks at 5°C (35). Virus is also still viable when dried onto surfaces (36, 37), although the length of time virus can survive for is less well-quantified. Contaminated vehicles and equipment have been implicated in spread in previous outbreaks (8, 28, 33). In UK in 2007, vehicles contaminated with virus from a laboratory effluent system were suspected to have moved virus to susceptible cattle farms (38). As with contamination of people, the greatest risks of contamination are associated with vehicles that have visited premises where FMD is present, which is most likely to occur if they are located close to areas where FMD is known to be present (i.e., the PZ or SZ). Keeping susceptible livestock or visiting premises with susceptible livestock also present an increased risk due to the possibility of undetected infection. Equipment may be contaminated from use in other areas, for example boats, bicycles, riding equipment, fishing tackle, guns. However, there is not sufficient quantitative information to assess the risk with any certainty.

Contamination of non-susceptible animals such as dogs and horses. Animals such as dogs and horses are not susceptible to FMD but may become contaminated and carry the virus mechanically (12). The likelihood of dogs being contaminated, and the factors that influence it, are similar as for people and will be greatest if dogs have had access to infected livestock or livestock products (34). Equine premises are often close to or associated with premises where susceptible livestock are kept and may source products such as straw from livestock-keeping premises, which can act as fomites. FMDV can survive on bedding and food stuffs such as hay, straw and bran for over 100 days at 16°C [reviewed by (1)] or longer in winter [reviewed by (2)]. Imported straw was identified as the most likely incursion route for an outbreak in Japan in 2000 (39). The proximity of the equine premises to areas where FMD is known to be present, movement history of horses, presence of susceptible livestock on the same or adjacent premises, and sources of feed and bedding will influence the risk that horses are contaminated. Events that bring together large numbers of horses from multiple areas, such as events, point to points, shows, competitions, drag hunts, and race meets present an increased risk of contaminated horses being present.

Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment become contaminated on the route to/from the activity

People, vehicles or other equipment could become contaminated whilst traveling to the location of the activity. The likelihood depends on the proximity of the route to known infected premises, the presence of undetected infected premises (which is influenced by the stage of the outbreak and zone as discussed above), the length of the journey and the number of stops or destinations. Any stops made at premises where susceptible livestock are kept, or are close by, increase the likelihood of contamination. For example, horseboxes traveling to events where they stop at multiple yards to collect horses would have a higher likelihood of becoming contaminated on the route, as well as increasing the risk of moving FMDV between premises. The amount of farm traffic and animal movements, and biosecurity arrangements of local premises will influence the likelihood that roads are contaminated.

Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment contaminate roads or environment and/or come into contact with susceptible livestock on route to/from the activity

Contaminated people, vehicles or other equipment may contaminate the roads or surrounding areas whilst traveling to the location of the activity. As for step 2, this risk is influenced by the length of the journey and the number of stops made, particularly on premises where susceptible livestock are kept, or are close by. The likelihood of coming into contact with susceptible livestock is influenced by the density and proximity of livestock in the area.

Whilst a contaminated person, animal or vehicle could lead to further contamination, the virus load by this stage would be very low.

Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment become contaminated via environment or contact with infected livestock during activity

People, vehicles, equipment, or non-susceptible species such as dogs or horses may come into contact with contaminated areas or infected livestock during the activity. Areas may become contaminated from current or previous presence of infected livestock or livestock products, from infected wildlife, or through movement of contamination on fomites. FMDV-infected livestock may be detected (in which case by the premises is bound by statutory regulations and entry is not permitted) or undetected. Contamination of areas used for recreational activities by infected livestock, or risk of contact with infected livestock, is therefore likely to be due to undetected infection. This is most likely to happen close to infected premises, or at the start of an outbreak when the risk of widely dispersed undetected premises is higher due to animal movements (see step 1 for detailed consideration of premises with undetected infection). The likelihood that the presence of infected animals on the premises leads to contamination of areas where activities might take place, depends on how recently the infected animals were present, number of infected animals, species, virus excretion, environment conditions (which influence FMDV survival), and management and grazing patterns (which vary by season). Contamination could also be introduced via muck spreading with contaminated feces or other by-products.

In other parts of the world, wildlife can play an important role in FMD transmission (40). All British deer species are susceptible to infection and can transmit virus to domestic livestock experimentally (41). Wild boar are susceptible and can transmit infection to domestic pigs, although boar show only mild clinical signs (42). Sero-surveys and diagnostic testing of deer and wild boar did not reveal any positive animals in UK, Netherlands or Germany following the outbreaks in 2001 in livestock (43, 44). However, seropositive roe deer and wild boar were found following livestock outbreaks in Thrace (45, 46). In Europe, models usually conclude that deer and boar populations cannot maintain infection in the absence of outbreaks in livestock (45, 47). Although there is no evidence that deer or boar have played a role in FMD transmission in UK, their involvement in facilitating local disease spread does remain a risk.

Other species such as hedgehogs and rodents can be infected with FMDV, but are unlikely to be very important in transmission (48, 49). Wildlife can also move FMDV mechanically if they become contaminated, for example scavengers such as seagulls, crows and foxes (33, 34, 50). Overall, the risks of further spread of FMDV associated with wildlife are very low but any activity which causes disturbance to wildlife does increase this risk, especially close to premises where FMD is present.

Risk of contamination from infection sources: Persons, animals, vehicles, or other equipment contaminate environment or new areas and/or come into contact with susceptible livestock during activity

Contaminated people, vehicles or equipment, or non-susceptible species such as horses or dogs, may introduce contamination to the area. The potential area that could be contaminated is related to the type of activity. The likelihood also varies with the number of people, vehicles, equipment, and non-susceptible species involved, the number that are contaminated and the degree of contamination. Dogs or horses may spread contamination over larger areas than, for example, walkers alone. The proximity, density, and the management type of any susceptible livestock influences the likelihood of contact, for example for penned dairy cows would be feasible to prevent contact with people and dogs but this could be difficult for extensive sheep production.

If people, vehicles, equipment, or non-susceptible species such as dogs or horses become contaminated during the activity they may move contamination into new areas. This is particularly important for activities that involve more than one premises, for example drag hunting that may cover land associated with multiple premises. The risks are influenced by the distance traveled or area covered, number of premises involved, and the number of people, vehicles, equipment, and non-susceptible species involved.

Any potential contact between contaminated people, vehicles or other equipment, or non-susceptible species such as horses or dogs, and susceptible livestock presents a risk of transmission. The greatest risks are associated with the presence of susceptible livestock in the area where the activity is taking place. The likelihood of contaminated people, vehicles or other equipment coming into contact with susceptible livestock during the activity also depends on the type of activity being conducted, the area or distance covered during the activity, and the type of land used for the activity. If the activity is taking place in areas which are not agricultural land and are never used for grazing susceptible livestock or growing feed or bedding for susceptible livestock, the risks are negligible. Activities that involve greater numbers of people increase the risk that some will be contaminated. If the number of contaminated personnel and vehicles is greater, the total probable amount of FMDV that would be released would increase.

Dogs, if present for example for walking, or for deer stalking or shooting birds, may cover larger distances and be more likely to come into contact with susceptible livestock. In addition, the presence of dogs can encourage cattle to approach and may increase the risk of transmission, if dogs or people are contaminated. It is possible that contaminated people, vehicles, equipment, or dogs could come into contact with susceptible wildlife. Whilst any contact between people and deer is only likely to occur with deer that have been shot, and are therefore being removed, susceptible species such as deer could come into contact with contaminated vehicles. Dogs (particularly if not restrained) or horses may also disturb wildlife, increasing the risk of virus dissemination by infected wildlife, as is also the case for any events that could lead to movement of wildlife such as deer stalking.

Exposure Assessment

Exposure and infection: Susceptible livestock come into contact with contaminated area, persons, animals, or vehicles

Susceptible livestock could come into contact with contamination left on the route, during the activity or if contaminated people return to their home premises where livestock are kept. There are also risks for livestock which are later moved onto to an area where contamination has been introduced due to survival of FMDV in the environment. FMDV can survive on soil for 2–5 days at temperatures above 16°C, up to 5 weeks at 3–7.5°C, and over 20 weeks under snow or at temperatures below 5°C [reviewed by (1, 2)]. Survival duration increases with decreasing temperatures, increasing relative humidity and presence of organic material and varies with virus strain [reviewed by (1)]. There are therefore risks to livestock that come into contact with an area where contamination has been introduced, even after some time as passed, in the right conditions. The likelihood of this happening is influenced by the presence, proximity and density of susceptible livestock in the contaminated area, and degree of contamination.

If roads are contaminated, susceptible livestock could come into contact with FMDV, if (i) livestock are moved on public roads; (ii) livestock adjacent to public roads are exposed; or (iii) contamination is moved, for example on other vehicles, into premises where susceptible livestock are kept. In the PZ, SZ, and RZ, movements of livestock on public roads are not permitted except under license for specific activities, for example movement of dairy animals for milking.

Exposure and infection: Susceptible livestock exposed to contamination become infected

If susceptible livestock are exposed to FMDV they may become infected. The likelihood that exposure of susceptible livestock to FMDV in the environment results in infection is not well-characterized (51), but is likely to vary by species, the virus dose exposed to and transmission route. When considering the infection of susceptible livestock via contaminated environment, the transmission route could be aerosol or oral. Cattle and sheep are relatively susceptible to aerosol infection, whilst pigs are not (52–54). Pigs are more susceptible than ruminants by the oral route, although higher doses are generally require for oral infection than aerosol infection [reviewed by (13)]. In general transmissibility is moderate when animals are kept in close contact; not all exposed animals become infected, and some only sub-clinically (13, 55). The variability observed through experimental infections suggests transmission would be much less efficient when animals are outdoors and in less close contact (56, 57).

The likelihood of infection is proportional to the virus dose (53). Indirect transmission is likely to involve lower virus doses than direct transmission and therefore is less likely to result in infection. The likelihood of infection occurring following fomite to fomite transmission can therefore be assumed to be very low.

Consequence Assessment

The end point of the risk pathway for all activities was the presence of infected livestock on a previously uninfected premises. The consequences of this include the health and economic impacts both for the individual farm infected, and for the wider livestock industry and economy, of prolonging an FMD outbreak. Since the consequences for each risk pathway were the same, only the likelihood levels are presented here.

Final likelihood levels for each activity in the PZ, SZ and RZ are presented in **Table 3**.

DISCUSSION

The movement of people (and other non-susceptible animals) to, from and during activities in the countryside during an FMD outbreak carries a risk of indirect spread of FMDV to uninfected farms. Indirect transmission of FMDV via fomites is an important potential source of infection, and any vehicles, people, non-susceptible animals or equipment that come into contact with FMDV present a risk of passing disease to any livestock with which they subsequently come into contact. This study assessed the risks associated with access to the countryside during an FMD outbreak to allow increased transparency in future decision-making.

For most activities, the likelihood of causing new outbreaks of FMD was assessed to be very low in the RZ, assuming compliance with specified mitigation strategies. Risk increases in the SZ and is greatest in the PZ, closest to identified infected premises. This is predominantly due to the risks associated with local spread leading to contamination or the roads and environment close to known infected premises, and the increased risk of undetected infected premises. In the early stages of an outbreak, the likelihood of undetected infected premises is greatest and the geographical extent of the outbreak is most uncertain, hence a more conservative assessment of risk is appropriate during this period. Across all zones, activities which increase the risk level are those that involve large groups of people, vehicles, movement of non-susceptible animals such as dogs and horses, and activities involving susceptible wildlife species. Although horses are not susceptible to FMD, a sizeable proportion of horse stables are closely associated with other livestock enterprises in various ways (e.g., sheep grazing on nearby premises). Therefore, horses (and associated people, vehicles, and equipment) are considered a more likely vehicle for FMDV in the face of an outbreak than other non-susceptible animals or people from the general public. An additional factor in Scotland is that countryside access is not limited to paths or specific areas (21), and there are likely to be more opportunities for people to come into contact with livestock, wildlife and contaminated areas.

TABLE 3 | Likelihood levels of the activities assessed in the protection zone, surveillance zone, and restricted zone.

Activity	Protection zone	Surveillance zone	Restricted zone
Walking	Medium[a]	Medium	Low
	Medium	*Low*	*Very low*
Cycling	Medium	Medium	Low
	Medium	*Low*	*Very low*
Canoeing	Medium	Medium	Low
	Medium	*Low*	*Very low*
Fishing	Medium	Medium	Low
	Medium	*Low*	*Very low*
Horse riding	Medium	Medium	Low
	Medium	*Low/medium*	*Very low*
Staging an equestrian event on agricultural land	Medium/high	Medium	Low/medium
	Medium	*Low/medium*	*Low*
Staging a race meet	Medium/high	Medium	Low
	Medium	*Low/medium*	*Low*
Staging other events on agricultural land	Medium	Medium	Low
	Medium	*Low*	*Very low*
Organized sporting events	Medium	Medium	Low
	Medium	*Low/medium*	*Low*
Drag hunting	Not permitted	Medium	Low
	Not permitted	*Medium*	*Very low*
Stalking/shooting deer	Not permitted	Medium	Low/medium
	Not permitted	*Medium*	*Low*
Shooting birds	Medium	Medium	Low
	Medium	*Low*	*Very low*

[a] *Likelihood levels are shown without any mitigation strategies in place (not italics), and assuming mitigation strategies are in place and complied with (italics).*

The conclusion of the VRAs was that for most activities, the likelihood of causing new outbreaks of FMD is considered to be medium (occurs regularly) in the PZ, low (rare but could occur) in the SZ, and very low (very rare but cannot be excluded) in the RZ, assuming compliance with specified mitigation strategies (**Table 2**). However, the likelihood of new outbreaks associated with hunting, shooting, stalking, and equestrian activities is considered to be greater.

The most important source of uncertainty within the VRAs is attributable to a paucity of data on the likelihood of transmission via fomites. The lack of data is perhaps surprising given the priority given to FMD research since 2001. However, meaningful field data on fomite transmission would be virtually impossible to collect during an outbreak and experimental studies are expensive to conduct and could only ever partially address this question.

There are three main options for management of the risks associated with countryside access: (i) do not permit access to the countryside; (ii) do not permit activities when or where the risk of FMDV being present is greatest (i.e., in a PZ or SZ, in early stages of an outbreak, or over agricultural land where susceptible livestock are present); (iii) permit activities from the early stages of an outbreak but under certain conditions. This study highlights that there is no justification for automatically preventing access to the countryside at a Scottish level. Real risks remain, particularly close to premises with FMD, but for most activities, the risk is very low at greater distances from premises with FMD, particularly once the early stage of an outbreak have passed and the likelihood of undetected infection has reduced. Therefore, options (ii) or (iii) are appropriate, depending on the activity. Specific mitigation measures are listed in the individual VRA documents.

Much of the information available to inform this analysis is based on FMDV serotype O. This serotype has been responsible for most of the large outbreaks that have occurred in countries that are usually FMD-free in the last few decades, and many of the reported experimental studies on transmission and survival of FMDV use serotype O [for example (24, 25, 29, 35)]. However, incursions of other serotypes could occur. Species susceptibility, length of incubation period, ease of detecting clinical signs and transmission are known to vary between serotypes and strains. For example, pigs infected with serotype C produced more aerosol virus that those infected with serotype O (17), while pigs infected with serotype A shed more virus than pigs infected with O or Asia (18). Whilst there is no clear evidence that virus survival in the environment, likelihood of infection via fomites, or susceptibility of wildlife species differ between serotypes, these aspects have not been widely studied and there is not sufficient information available to have confidence that differences do not exist. Any differences to these parameters could affect the risk levels described.

Although this risk assessment focused on Scotland, the risk pathways described here are likely to be appropriate for other countries that are usually FMD free without vaccination. However, the factors that influence the risk level at each step of the pathway may vary between countries, depending on factors such as the likelihood of undetected infected premises, the likelihood of coming into contact with livestock on the way to/from or whilst conducting the activity (which could depend on the specific nature of outdoor activities and the ways that susceptible livestock are kept) and the likelihood that susceptible wildlife are present. These risk factors and the subsequent likelihood levels should be reviewed if the risk assessments are to be used elsewhere.

A risk assessment approach to this issue was appropriate because it allowed the available evidence to be compiled and assessed, whilst still provided documents that can be used by policy-makers for decision making. A qualitative approach was taken in this study because there were insufficient data to support a quantitative approach. A risk matrix approach, widely used including in veterinary science (58) was considered. However, risk matrices can give a false impression of scientific robustness, whilst actually relying on subjective risk level estimates which may be influenced by a range of other considerations such as personal knowledge and beliefs (59, 60). Examples of uses within the field of veterinary medicine have also highlighted the issues of the inability to account for marked variation in estimates within categories, and loss of information with successive levels of coding, particularly when the model does not take a modular step-wise form (61). Therefore, we used a qualitative descriptive approach that would allow us to conclude an overall risk level and highlight areas of particular uncertainty and variability. It is acknowledged that formally soliciting expert opinion (62) may have reduced uncertainty in some parameters. However, the policy imperative did not allow time for this and the subsequent rounds of peer-review process reassured us that our original risk estimates would not be substantially altered.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

HA, LB, DM, and GG conceived and designed the study. HA and LB performed the analysis. HA, LB, and DM wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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PERSPECTIVE
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Perspectives From the Science-Policy Interface in Animal Health and Welfare

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The aim of this paper is to present scientific perspectives from the science-policy interface in animal health and welfare, with an emphasis on factors critical to scientific effectiveness. While there is broad acceptance of the value of scientific information to inform policy-making, interactions at the science-policy interface are not without difficulties. The literature highlights the need for scientists to build policy relevance to the research focus from the outset, to engage with policy-makers and other stakeholders throughout, to use platforms to facilitate science-policy dialogue, and to disseminate research findings appropriately. In the author's experience, there are a range of factors linked with effectiveness at the science-policy interface in animal health and welfare including a passion for public interest research, scientific independence, a commitment to scientific quality and openness, the opportunities afforded from partnership and collaboration, and an interest in strategic thinking and systems change. In an increasingly complex and rapidly changing world, an objective evidence base for policy decision-making is more important than ever. There is a need for particular attention to the value of collaboration between the natural and social sciences, a recognition among scientists and policy-makers that science is not value-free, the importance of effective communications, and the need to assess and communicate uncertainty. Further, there are particular challenges with science conducted in support of policy development for industry. It is hoped that this paper will stimulate and contribute to discussion and debate, both among scientists and between scientists and policy-makers, to increase scientific effectiveness at the science-policy interface in animal health and welfare.

Keywords: animal health, animal welfare, science-policy interface, decision-making, policy, science

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INTRODUCTION

Animal health and welfare policies are plans of action; essentially the framework and details that underpins programs in surveillance, control, and eradication, among others. Policy-makers consider a range of factors during decision-making, including available scientific evidence but also social, economic, and political concerns (1, 2). As highlighted by Hueston (2), the policy-making process is influenced by organizational culture and existing rules and regulations, and constrained by legal authorities, political correctness and resource availability.

Many scientists work at the interface between science and policy in animal health and welfare, generating scientific information to inform policy decision-making. At this interface, scientists are seeking both to uphold the integrity of their work and to maximize its value to policy-makers and other stakeholders. Scientists are seeking 'science-informed policy', where animal health policy is informed by science that is excellent, balanced, and clear.

The aim of this paper is to present scientific perspectives from the science-policy interface, with an emphasis on factors critical to scientific effectiveness, drawing on the literature, and the author's own experiences. The author has worked at the science-policy interface over a number of years, both at a national level in Ireland, as Director of the Centre for Veterinary Epidemiology and Risk Analysis (CVERA) at University College Dublin (UCD) (3) and at the European level, as member and chair of both the Animal Health and Welfare (AHAW) Panel and Scientific Committee of the European Food Safety Authority (EFSA) (4).

THE SCIENCE-POLICY INTERFACE: AN EXAMPLE

The science-policy interface, essentially the interplay between science and policy, is well-illustrated using the example of climate change, as this concerns players and issues that are recognizable by many in the general population. The 'science' is primarily represented by the Intergovernmental Panel on Climate Change (IPCC) (5), a United Nations (UN) body established in 1988 and currently with 195 member countries, and the 'policy' by the so-called Conference of the Parties (COP) to the UN Framework Convention on Climate Change (UNFCCC) (6), who meet formally at the annual UN Climate Change conference. Currently there are 197 Parties to the UNFCCC, including 196 countries as well as the European Union (EU). The role of the IPCC is to provide policymakers with comprehensive scientific assessments (currently in its 6th assessment cycle) on the current state of scientific, technical, and socio-economic knowledge about climate change, its impacts and future risks, and options for reducing the rate at which climate change is taking place. Further, the IPCC periodically releases special reports, most recently on the impact of climate change on the oceans and cryosphere (the frozen parts of the planet) (7). Thousands of experts from relevant scientific disciplines worldwide contribute to the development and multiple reviews of the reports, with the aim to provide the highest standards of scientific excellence, balance, and clarity. Calibrated uncertainty language is used throughout each assessment, to communicate confidence (a qualitative assessment of the validity of each study finding based on the type, amount, quality and consistency of evidence, and the degree of agreement) and likelihood (a quantified measure of uncertainty expressed probabilistically) for each study finding (8). The annual UN Climate Change conference is the global forum for multilateral discussion on matters relating to climate change. In pursuit of this objective, the UNFCCC, also known as the Convention, establishes a framework for decision-making and action-taking, with the objective "to stabilize greenhouse gas concentrations in the atmosphere at a level that would prevent dangerous anthropogenic interference with the climate system" (9). The annual UN Climate Change conference provides the forum for negotiation and compromise toward collective decision-making on the Convention and other legal agreements that were subsequently negotiated, including the Kyoto Protocol in 1997 (establishing legally binding obligations for developed countries to reduce their greenhouse gas emissions) and the Paris Agreement in 2016 (which considered the mitigation of greenhouse gas emissions, adaptation, and finance). Effective interaction between science and policy is critical to international climate negotiations. The international climate regime is built upon a clear understanding of the causes of climate change, and the threats posed by it. Scientific information is also critical to the periodic review of long-term global goals. Science is reliant on the UNFCCC parties to promote and cooperate in research and systematic observation of the climate system (10).

This IPCC-UNFCCC example provides some clarity of the differing roles played by science and policy at the science-policy interface. In the area of animal health and welfare, although the models of engagement may differ, the roles of science and policy at the science-policy interface are surprisingly similar.

DIFFERING MODELS OF ENGAGEMENT AT THE SCIENCE-POLICY INTERFACE IN ANIMAL HEALTH

Models of engagement between scientists and policy-makers in animal health and welfare are likely to vary substantially, depending on a range of factors including the organizational structure, tradition, and the mechanisms used to fund scientific research. The following are examples of science-policy engagement models with which the author is familiar:

- *EFSA in support of the European Commission (EC).* EFSA is an independent EU agency that conducts scientific assessments in response to requests from the European Commission, the European Parliament and EU Member States. The EFSA's AHAW Panel has produced a series of scientific opinions to support policy decision-making in the EC for African swine fever (ASF) preparedness and response in Europe [for example (11, 12)]. Similarly, the AHAW Panel has developed scientific opinions on animal welfare topics, including the welfare of farmed animals at slaughter (13–16). Although EFSA opinions are developed within a formal, legislated structure (17), there is close contact between the requestor and EFSA from interpretation of the mandate through to the conclusions of the assessment. The opinions conform to relevant in-house guidance documents, including those relating to uncertainty (18).
- *CVERA in support of the Irish Department of Agriculture, Food and the Marine (DAFM).* Over several decades, CVERA has led research in support of the national bovine tuberculosis (bTB) eradication program in Ireland, seeking to clarify and address constraints to eradication. The national bTB eradication program is managed by DAFM, and the interaction between science and policy has been substantial and ongoing, in identifying research needs, assisting with study design, interpreting study findings, and translating results into policy changes. Research has regularly contributed to policy adjustments, relevant to cattle [including (19, 20)], wildlife (21, 22), and the broader program (23, 24). In the

field of animal welfare, CVERA has recently developed, and is currently evaluating, a framework to allow critical evaluation of private animal health and welfare standards in quality assurance programs (25).

- *CVERA in support of Animal Health Ireland (AHI).* AHI is a public-private partnership, established in 2009 with the aim to contribute to a profitable and sustainable farming and agri-food sector in Ireland through improved animal health (26). Prior to AHI establishment, the initial scientific work (27–30) was undertaken independent of policy, seeking to create an evidence base to underpin discussion with, and consideration by, government and industry policy colleagues. Following AHI establishment, however, there has been a highly interactive partnership between science and policy across a highly applied portfolio of scientific research relating to the eradication of bovine viral diarrhea (BVD) [including (31–33)], the control of Johne's disease (JD) (34–36), and milk quality and intramammary antimicrobial usage (37–40). Policy colleagues contribute substantially to the scientific research, particularly at the start (context setting and question formulation) and at the end of a project (study interpretation and application).

There are other models of engagement at the science-policy interface in animal health and welfare, each influenced by a range of factors including resource availability, and cultural context. Engagement at this interface differs between national and international settings, and in countries at different stages of development. Nonetheless, there is a need to work effectively at the science-policy interface to ensure, as far as possible, that animal health and welfare policy is science-informed.

WORKING EFFECTIVELY AT THE SCIENCE-POLICY INTERFACE

Perspectives From the Literature

There is broad acceptance of the value of scientific information to inform policy-making. This process is facilitated within the EU, where science and policy in animal health are legislatively distinct (17), and each of EFSA's scientific opinions is publicly available. As reasonably suggested by Bogenschneider and Corbett, 'the pursuit of public good cannot be left solely to the interplay between power and self-interest' (41). Nonetheless, interaction at the science-policy interface is not without difficulties, as has been highlighted in the literature. From the perspective of policy-makers, science can be considered fragmented and uncoordinated, leading to the development of outputs that lack relevance, and usefulness (42). Further, the 'real world' can be perceived to move more quickly than science can accommodate, with a potential disconnection between what policy-makers want to know, and the answers that science can realistically provide (41). Conversely, and reflecting the different traditions between science and policy, it has been suggested, possibly with some hyperbole, that scientists can view policy as 'driven by political ideology, conventional wisdom, folklore, and wishful thinking … [representing] the triumph of hope over wisdom, sentiment over demonstrated effectiveness, [and] intuition over evidence' (43).

Broadly, four approaches have been suggested to create an environment for sustained interaction between researchers and policy-makers (42), including:

- *Creating opportunities for interaction*, including through dialogue, mediation, and co-construction of knowledge. It has been suggested that this is achieved more effectively through small groups rather than larger conferences (42).
- *Assembling and synthesizing knowledge and gleaning their policy implications.* This is perhaps most clearly illustrated by the work of the Cochrane Library (44) which seeks to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews, and other synthesized research evidence. In veterinary medicine, similar approaches have been used, for example with bovine tuberculosis (45).
- *Improving the way that research is presented, disseminated, and communicated.* Boden et al. (46) outline the different perspectives of scientists and policy-makers, and the importance of 'knowledge brokers' in the transfer and translation of information between them.
- *Within the scientific community, an improved understanding and appreciation of the nature of political decision-making.* Policy-making operates within an institutional culture that sets powerful constraints on what can and cannot be done (47). It is rational but highly complex, as policy-makers faced many opposing (and often irreconcilable) forces. It is also fluid and unpredictable, influenced by the political process, and error-free decisions are expected to be made with haste. Policy-making favors the status quo (41).

In summary, strategies to advance an evidence-based policy agenda will center on the role of relationships (41). As suggested by Stringer and Dougill (48), it is important for scientists to build policy relevance to the research focus from the outset, to engage with policy-makers and other stakeholders throughout, to use platforms to facilitate science-policy dialogue, and to disseminate research findings appropriately.

The Author's Perspectives

In the author's experience, there are a range of factors linked with effectiveness at the science-policy interface in animal health and welfare, including a passion for public interest research, scientific independence, a commitment to scientific quality and openness, the opportunities afforded from partnership and collaboration, and an interest in strategic thinking and systems change.

- *Research in the public interest.* At this interface, scientists will be aware of their role in constructively influencing (inter)national policy development in animal health. For this reason, a passion for and commitment to public interest research is an important prerequisite to working effectively in this role.
- *Scientific independence.* Scientific independence must be a key value underpinning scientific contribution at the science-policy interface. Policy-makers have multiple interests to consider during policy development (relating, for example, to governance, social issues, and factors affecting

implementation), in addition to science (2). For this reason, it is critical that the scientific evidence provides a robust and factual account of current understanding, unfiltered by those issues that will subsequently be considered in the policy mix. Realistically, therefore, the scientist is seeking to ensure that policy decision-making is science-informed rather than science-led (2). As reflected in the founding regulation of EFSA (17), a key tenet of food safety in the EU is the separation of the processes of risk assessment (science) and risk management (policy decision-making), which was formalized primarily in response to the loss in public confidence in food safety in Europe consequent to the bovine spongiform encephalopathy (BSE) crisis. Similarly, the separation of science (that is, the IPCC) and policy (the UNFCCC) is reflected in the above-mentioned climate change example. Nonetheless, scientific independence has the potential to be one of the most significant challenges for those working at the science-policy interface, in large part as a consequence of the proximity to the politics with which the science is being conducted. Funding also has the potential to impact scientific independence. In the CVERA context, this challenge is being tackled through an enduring commitment to public interest research, to scientific quality and openness through publication, and through partnership and collaborations with other scientific institutions. An independent management board, with policy representation, was recently established to provide independent oversight (49).

- *Scientific quality and openness.* Scientific publication is an essential output of the scientific process providing a benchmark for scientific excellence, a means to promote openness and transparency, and a permanent record for perpetuity. For those working at the science-policy interface, scientific publication also provides scientists with an opportunity to explore and disseminate ideas, including those at odds with the status quo. By definition, scientific knowledge undergoes critique and review and is subject to change (2).
- *Partnership and collaboration* are critical at this interface, both with policy-makers and with other scientists. Scientists must be willing to engage with policy colleagues, to ensure scientific outputs are 'fit for purpose', which EFSA has described as scientific outputs that are contextual, socially sound and accountable, while remaining scientifically robust (50). Collaborative links between CVERA and other scientific colleagues has offered opportunities for innovation. This is particularly true in the context of methodological advances, for example with modeling [for example (33, 36)] and the social sciences (38, 51).
- *Strategic thinking and systems change.* The scientific process is underpinned by curiosity, comparison and long-term thinking. Given this context, scientists have the potential to contribute valuable strategic perspectives at the science-policy interface. Further to an earlier example, the animal health landscape in Ireland was transformed with the establishment of AHI, which is tackling non-regulatory animal health issues through a process of national dialogue and consensus. In the years prior to AHI establishment, scientists contributed greatly, including through the aforementioned publications (27–30), in support of fundamental change in national approaches to animal health policy.

FURTHER REFLECTIONS

We are facing an increasingly complex and rapidly changing world. Global connectedness has grown rapidly, which has facilitated complex transnational supply chains (52) and increased transboundary movement of people and products (53). Further, human impacts are linked to broader environmental concerns, including climate change (54, 55), species decline (56, 57), and plastics pollution (58, 59). In a recent exploration of possible futures, the Joint Research Center of the European Commission (the EU Science Hub) presented four feasible future global scenarios, each assuming a changing climate (2°C by 2050), progressive natural resource depletion, and an increasing human population (9 billion by 2050) (60). Concurrently, we are in a challenging era when scientific facts are often dismissed or ignored, or where values are increasingly more influential than facts in shaping public opinion (50).

These global changes are entirely relevant to and have important implications for animal health and welfare policies, both internationally and nationally. Critical animal health challenges, such as ASF (61) and antimicrobial resistance (62), are influenced by the same drivers of connectedness and human impacts, among others. These drivers are clearly apparent in the global expansion in ASF, for example, from Georgia in 2007 (63) and subsequently across Eurasia. Animal health and welfare policies also have the potential to positively impact global challenges. For example, disease control/prevention can improve on-farm production efficiencies and can also contribute to the mitigation of greenhouse gases (64).

Given the complexity of these challenges, an objective evidence base for policy decision-making is more important than ever (65), including in animal health and welfare. While there are substantial and ongoing challenges, there is reason to be optimistic. As suggested by Bogenschneider and Corbett (41), 'empirical evidence and rigorous analysis can play a larger role if we take the time and care to do things right. … the need is there, the interest is there, the science is there'. Nonetheless, there are several areas where particular attention should be paid.

- Policy-makers need knowledge of both the context and the detail with respect to the scientific question, to ensure that they have as complete a picture as possible of the issue at hand. To facilitate this, there is a need for collaboration between the natural and social sciences, to provide policy-makers with an understanding of the 'why' as well as the 'what'. Milk quality improvements in Ireland were facilitated by an understanding of both key technical issues (37, 39) and of factors that constrained collective action by stakeholder organizations (38).

- There is a need to recognize that the work of scientists is not value-free (50, 66). Values underpin the decisions that we make, both as people and scientists (1), with the potential to influence at many points during the scientific process, particularly at the start (when choosing the topic of study, when determining the questions to ask, when designing the study to answer these questions) and end (when interpreting the study results, during the framing and communicating of the study findings) (66).
- The importance of effective communication cannot be overstated and has been critical in shifting the views of the Irish farming community with respect to the biosecurity implications of livestock movement (67) and of control measures sufficient to reduce time-to-eradication in both the national BVD (33) and bTB (24) eradication programs.
- There is the need to assess and communicate uncertainty to ensure that scientific conclusions provide reliable information for decision-making. In this context, uncertainty has been defined as all types of limitations in available knowledge that affect the range and probability of possible answers to a particular policy-relevant scientific question (18).

To this point, the discussion has focused on generic challenges at the science-policy interface in animal health and welfare, noting that these are relevant to most situations. When conducting scientific research in support of policy development for or in collaboration with industry (as opposed to government), however, there are several particular (indeed, often additional) challenges that scientists may face. There is a need for a shift in paradigm from ‘certainty’ to ‘managed risk’ for example, when determining herd JD risk in the national JD control program in Ireland (34, 36). Some consideration will be required on the amount of evidence deemed sufficient for decision-making and subsequent action by industry, somewhat akin to the differing levels of evidence that are sufficient for proof in a civil (‘the balance of probabilities’) vs. criminal (‘beyond reasonable doubt’) trial (68). Further, non-scientific (often financial) questions frequently predominate, and there is potential for conflict between science and commercial reality.

CONCLUSIONS

This paper focuses on scientific effectiveness at the science-policy interface in animal health and welfare. This issue is increasingly important, given a rapidly changing world and multiple global and local challenges. In this paper, the author draws from the literature and personal experiences, but also from the well-recognized example of climate change. A number of factors are linked to scientific effectiveness at the science-policy interface, including a passion for public interest research, scientific independence, a commitment to scientific quality and openness, the opportunities afforded from partnerships and collaboration, and an interest in strategic thinking and systems change. Despite its importance, there has been little published discussion on this issue in the area of animal health and welfare. It is hoped that this paper will stimulate and contribute to the discussion and debate, both among scientists and between scientists and policy-makers, to increase scientific effectiveness at this interface.

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SM conceived and wrote the manuscript.

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Farmers' Uptake of Animal Health and Welfare Technological Innovations. Implications for Animal Health Policies

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The paper analyses the uptake of animal health and welfare technologies by livestock farmers focusing on the identification of different behavioral patterns occurring in subpopulations of farmers and the assessment of the effect socio-economic and attitudinal factors have on these patterns. The technologies of interest include new genomic technologies, animal electronic identification (EID) for farm management, cattle surveillance, welfare qualitative behavioral assessment, anaerobic digestion, pedometers or activity monitors to detect oestrus and increase fertility/conception, and webcams/smart phones/tablets for animal husbandry. We use latent class analysis modeling and cross-section survey data to construct typologies of farmers based on technological uptake and heterogeneous characteristics. Our results suggest that, while three fifths of the farmers are "non-adopters," a third is classified as "current adopters" of animal EID for farm management, and a twelfth as "future adopters" of either or more types of animal health and welfare technologies. Age, agricultural income, perceived difficulty to invest in new technologies, agri-environmental scheme membership, and frequency of access to information on animal EID for farm management and cattle surveillance through British Cattle Movement Service, are significant predictors of typology membership. The findings are policy relevant as they give quantitative evidence on the factors influencing technological uptake and, as such, help identify the most likely adopters and optimize the cost of targeting them. As information access was found to be among the factors influencing multiple technology adoption, policy instruments should include the provision of training as regards the implementation of technologies and their combined impact on farm. Farmers' adoption of interrelated innovations suggests the need to coordinate individual policies aimed at encouraging uptake of different technologies. As shown here, this would concern not only synchronizing animal health and welfare policies, but also their interaction with others such as agri-environmental ones. Moreover, the results show that animal health policies requiring regulatory compliance may lead to voluntary uptake of additional or complementary technologies which relate to not just meeting but exceeding standards of animal welfare and health practices.

Keywords: latent class analysis, technology uptake, model selection, farmer typology, animal health

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INTRODUCTION

Farming populations within most countries tend to exhibit a range of goals and farming objectives, reflecting production-orientation and embedding of social values (1–4). This heterogeneity found within farming populations presents particularly intractable problems for policy makers seeking to promote multiple goals for their agricultural systems. Over the last three decades agricultural systems in high income countries have shifted from the aim of solely producing food to one in which environmental and social considerations need to be met. In Europe, these changing policy signals are embodied in the reform documents of the Common Agricultural Policy and related regulations and support focused on socially desirable consequences such as protection and enhancement of animal health, welfare and the environment (4). In response, farmers have tended to exhibit a range of motivations toward these changing goals (2, 5, 6). Based on the psychological concept of social distance, Kagan and Scholz (7) and Braithwaite (8) developed what they term "motivational postures" which range across a variety of levels of engagement with social and regulatory standards. Within the literature on farming populations similar mixtures of motivations have been found with respect to water quality prevention (9, 10); climate change awareness and mitigation (11–14) and the reform of the Common Agricultural Policy (2, 15). The argument used by these authors for exploring and classifying the degree of heterogeneity within a farming population are 2-fold, firstly to understand responses to a possible policy response (2) and secondly to offer direction for apportioning the level of advisory engagement or framing messages pertinent to particular issues within policy (11).

An underexplored area within the literature on farmer typology relates to the uptake of animal health and welfare technologies. This represents a mixture of regulatory compliance (e.g., electronic identification (EID) scheme for sheep), and voluntary standards established by interest groups [e.g., Linking Environment and Farming (LEAF)] or established by processors or retailers to ensure a higher premium for enhanced standards. Hence, the motivation for this study is to explore, using a classification approach and survey data, farmers' motivations for uptake of technologies which relate to meeting and exceeding standards of animal welfare and health practices, their classification in typologies based on technology adoption behavior, and implications for animal health policy.

DATA AND METHOD

Survey Design and Data Collection

The data used in this study are drawn from a representative telephone survey of Scottish agricultural holdings, which took place in 2013. While the central aim of the survey was to identify the impact the Common Agricultural Policy (CAP) reforms on farm structural changes, a specific section was focused on animal health and welfare technological uptake on Scottish farms. The sampling frame (∼10,000 farms) was derived from the June Agricultural Census (JAS) and stratified by region, activity, size and farming enterprise. A potential limitation of the study is related to the JAS under-representation of "very very small" farms (business holdings with <0.5 standard labor requirements). However, based on findings from the literature (16) confirmed by this study, larger farms are more likely to uptake technologies and thus we consider this potential bias to be inconsequential to the results of the analysis. This study analyzed data for 1,746 livestock farms from a total of 2,416 fully completed questionnaires from livestock, crop and mixed farms. After discarding missing values, the total number of valid observations was 1,502.

The section of the questionnaire used in this analysis and consistent with the use of Latent Class Analysis included close-ended questions on the following: socio-economic characteristics (gender, age, education, tenure status, duration of involvement in the business, number of employees, agricultural income, recipient of Single Farm Payment (SFP), succession prospects, organic certification, and participation in agri-environmental schemes); perceived effects on business management from changes in technology, succession planning, access to advice/information, changes in animal welfare regulations and policies; perceived difficulty to invest in new technologies; frequency of access to novel technological information on EID for farm management and cattle surveillance; perceived effects of the use of new knowledge or technology on the welfare of animals on own farm during the past 10 years; technology adoption behavior during the past 10 years (new genomic technologies, animal EID for farm management, cattle surveillance, qualitative behavioral assessment (QBA), anaerobic digestion, pedometers or activity monitors to detect oestrus and increase fertility/conception, webcams/ smartphones/tablets for animal husbandry); and intentions to adopt technologies during the next 10 years (new genomic technologies, animal EID for farm management, cattle surveillance, qualitative behavioral assessment (QBA), anaerobic digestion, pedometers or activity monitors to detect oestrus and increase fertility/conception, webcams/smartphones/tablets for animal husbandry).

The aforementioned statements were used to form explanatory variables (whose descriptive statistics are presented in **Table A1**) influencing behaviors and intentions to uptake technologies, and independent variables representing behaviors and intentions (whose descriptive statistics are presented in **Table 1**).

The statistics presented in **Table 1** show low rates of adoption and intentions to adopt except for animal EID for farm management (almost a third of the sample) and cattle surveillance (about an eighth). Intentions to uptake showed higher percentages than the current behaviors associated to most technologies, more strongly so for anaerobic digestion (more than twice), genomic technologies (higher by a third) and webcams/smart phones/tablets for animal husbandry (higher by more than a quarter).

Latent Class Analysis

Latent class analysis (LCA) (17, 18) is a statistical technique for the analysis of multivariate categorical data, also known as a type of finite mixture model. Applied in social sciences, LCA is often used to identify behavioral typologies. Typically, the

TABLE 1 | Descriptive statistics of technology adoption behaviors and intentions.

	Since 2005 have you applied/started to apply on your business/holding any (technological) innovations: (%) said YES	In the next 10 years are you planning to apply on your business/holding any (technological) innovations: (%) said YES
New genomic technologies	87 (5.8%)	138 (9.2%)
Animal EID for farm management	447 (29.8%)	354 (23.6%)
Cattle surveillance	199 (13.2%)	230 (15.3%)
QBA	73 (4.9%)	93 (6.2%)
Anaerobic Digestion	37 (2.5%)	86 (5.7%)
Pedometers or activity monitors to detect oestrus and increase fertility/conception	85 (5.7%)	116 (7.7%)
Webcams/smart phones/tablets for animal husbandry	139 (9.3%)	192 (12.8%)

observed data take the form of a series of categorical responses referred to as manifest variables or items e.g., in this study these are questions about technological uptake and intentions (dichotomous variables). LCA classifies individuals into classes, which are latent when the classification criterion is based on a latent variable (i.e., a construct that is not directly measureable used to estimate the distribution for each subgroup of the population across the items of interest). The latent class (LC) classification model assigns each observation into a latent class with an estimated probability—the latent class membership—which in turn produces expectations about how that observation will respond on each item. Furthermore, the LC classification model is extended using an LC regression model which allows the inclusion of class-specific explanatory variables/covariates to predict latent class membership. This makes LCA the appropriate tool for answering the purpose of this study of identifying typologies of Scottish farmers based on health and welfare technological adoption, and estimating the effect of variables such as socio-economic characteristics to predict the latent class membership.

As regards testing and estimating LC models, the traditional likelihood ratio test (LRT) cannot be used to test nested LC models due to its assumption of a chi-square difference distribution which is not applicable in LCA (19, 20). Therefore, the test of statistical significance of nested models is not easily met and thus a *p*-value is not a straightforward means to comparing nested models. The literature offers alternative likelihood-based techniques, for example Lo et al.'s (21) approximation of the LRT distribution [albeit disputed by (22) who claimed that there was a flaw in their mathematical proof of the test for normally distributed outcomes] or the bootstrap likelihood ratio test (BLRT) by McLachlan and Peel (20). The principle behind BLRT is to use bootstrap samples to estimate the distribution of the log likelihood difference test statistic. Theoretically, the BLRT can therefore provide a *p*-value between a paired comparison of the LC classification models with k-1 and k class solutions. However, implementation of the BLRT has not commonly occurred due to the fact that the paired comparison between two nested models is time consuming, especially when the classification model contains a large number of parameters to estimate. More practical alternatives to the traditional LRT technique include the Akaike's Information Criterion (AIC) (23) and the Bayesian Information Criterion (BIC) (24), which are statistical information criteria (IC) commonly used for the indication of goodness-of-fit and comparison between nested models. Nylund et al. (25) compared the performance of the traditional ICs used to determine the number of classes in mixture type models. They concluded that BIC is superior to all other ICs, especially for larger datasets, and this confirms findings of other authors (18, 26, 27). In contrast, AIC has been shown to overestimate the correct number of components in finite mixture models (28, 29).

Thus, in this study, we used BIC to determine the number of latent classes in each of the LC classification models estimated and as a criterion for model selection among the nested LC regression models (with class-specific covariates). We used backward elimination technique for model selection of the nested LC regression models, where the full model was initially set up to include all covariates of interest and then step by step variables whose absence improves model fit (iteratively testing for the smallest BIC value) were removed until no further improvement was possible.

The LC models were fitted using the package poLCA in the statistical software R (30, 31). poLCA is an R package used to estimate LC classification models for manifest variables with any number of possible outcomes, and LC regression models with class-specific covariates.

RESULTS

The aforementioned methodological steps were applied to the study of the current adoption and intentions to adopt seven types of animal health and welfare innovations (presented in **Table 1**). The analysis followed two stages: firstly, it identified the possible number of latent classes from various LC classification models based on technological innovation adoption and intentions to adopt. Namely it identified different characteristics from individuals' patterns of response as regards both current and intended uptake, which led to the formation of subgroups (latent classes) in the population. In the second stage it examined the effects of the explanatory variables of interest on the latent class membership. This is an essential step which explains which factors can predict individuals' latent class membership.

Three-Class LC Classification Model

Item Elimination

Farmers were asked two questions, one about their current technological uptake behavior and another about their intentions, both applied for each of the seven technologies. The 14 questions (items) were used to identify the latent classes in the LC classification model. However, responses on current

TABLE 2 | BIC and AIC for LC classification models with two-class to five-class solutions.

LCA model	BIC	AIC
2-class LCA	8695.37	8572.25
3-class LCA	8476.23	8288.87
4-class LCA	8451.47	8199.87
5-class LCA	8455.72	8139.89

adoption of five out of seven technologies in all LC classification models had very low (close to zero) estimated probabilities across all latent classes, except for the uptake of animal EID for farm management and cattle surveillance. Thus the final LC classification model included nine items: two items of current adoption (animal EID and cattle surveillance) and all seven items based on intentions to uptake. The statistical results presented in the remaining of this paper consider only nine items.

Determining the Number of Latent Classes

Latent class classification models from two-class to five-class solution were estimated. **Table 2** shows BIC and AIC values for LC models with two-class, three-class, four-class and five-class solutions.

BIC suggested the selection of the LC model with four-class solution, as this model reached the minimum value (8451.47). As expected, AIC tends to over-fit the data, which means that AIC values decreased while the number of latent classes increased.

Next we checked graphically the characteristics of each latent class from the LC classification model with four-class solution (**Figure A1**) and some issues were identified. Namely there was an equal probability of answering "yes" or "no" to certain items in certain latent classes. This was the case for EID uptake in latent classes three and four, and cattle surveillance uptake in latent class four. This issue is referred to as unidentified item in the study of LCA. It is important in an LC classification model that all class-memberships in each latent class are identified, i.e., the probability of being in one response category should be significantly >0.5. Thus we discarded the four-class solution model and the preferred model was the LC model with a three-class solution.

The characteristics of each identified subgroup of farmers from the LCA three-class solution model are shown in **Figure 1**. The majority of farmers (70%) were classified in the first class. This class represented a subgroup of farmers who are technological "non-adopters," with small probabilities (<0.2) of saying "yes" to both uptake and intentions to uptake animal health and welfare technologies. The second class contained one quarter of the sample of farmers who had a higher probability (about 0.6) of saying "yes" to both uptake and intentions to uptake animal EID for farm management. Therefore, the second latent class was labeled as the "EID adopters." Finally, the third latent class contained only about 5% of the farmers who have greater probabilities (values between 0.65 and 1.00) of saying "yes" to intentions to uptake animal health and welfare technological innovations. The third class therefore represented the future technology adopters, which was labeled as the "future adopters."

Three-Class LC Classification Model With Explanatory Variables

We tested the effect of explanatory variables of interest (see **Table A1**) on latent class membership. Model selection between LC classification models with a large number of explanatory variables is computationally demanding and disentangling dependency among explanatory variables is not always straightforward. Therefore, we applied backward selection (32) based on BIC to estimate an LC multiple regression model. For nested models, a model with a smaller BIC value is an indication of improved goodness-of-fit.

The final model is presented in **Table 3**, which shows that six variables (age; intention to remain in agri-environmental schemes until 2020; perceived difficulty of investing in new technologies; frequency of access to information on EID for farm management; frequency of access to information on cattle surveillance) out of the 21 variables were significant. Together they predicted individuals' latent class membership.

We recoded age (initially a variable with five categories, see **Table 1**) based on the assumption that the effect of age on the individuals' latent class membership was linear. We set values of 30, 40, 50, 60, and 70 to represent the average age for each age group, respectively, and examined the effect of age in increments of 10 years on individual's class membership.

We also recoded the variable "proportion of agricultural income in total income from this business/holding" (initially with five categories) into a variable with three categories (**Table 3**) due to the fact that more than half of the farmers stated that more than 75% of their income was from agriculture. The three recoded categories represented the group with low proportion of agriculture income (<25%, this being the reference group to which the other two categories were compared), the group with mixed type of income (25–75%) and the group with mostly agricultural income (more than 75%).

Additionally we recoded the variable "perceived difficulty of investing in new technologies" (initially a variable with five categories) into a numerical variable based on the assumption that the equal distance between each paired categories was not fundamental to the focus of this study.

Following results presented in **Table 3**, further clarification of two issues was needed for a better understanding of the results. The proportions of estimated class membership shifted to some extent compared to the initial three-class LC classification model. The characteristics of the three latent classes told a similar story but with a slight diversion (see **Figure 2**).

Figure 2 presents the characteristics of the three latent classes identified in the LC classification model, which show a variation after the inclusion of the explanatory variables. The first class contained 60% (previously 70%) of the farmers, but still with very low probabilities for both uptake and intentions to uptake technologies. Therefore, the first class still represented the

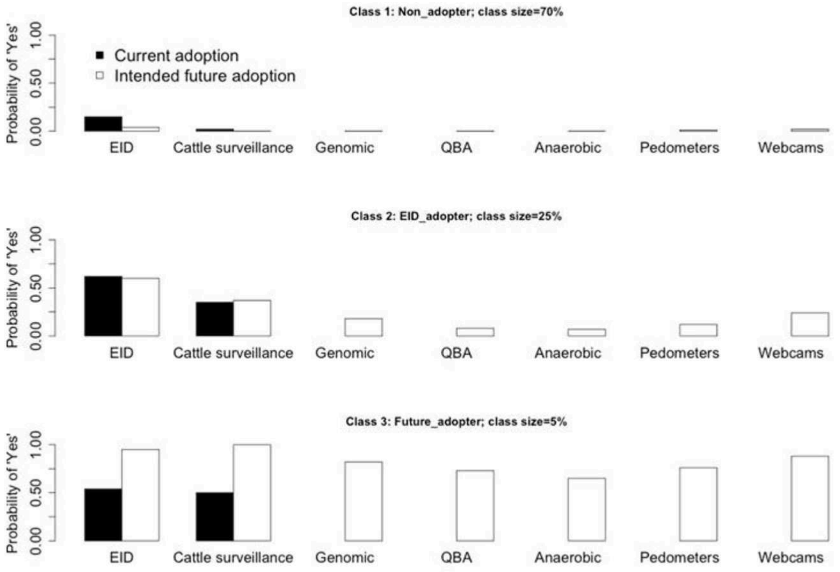

FIGURE 1 | The characteristics of the LC classification model with three-class solution.

"non-adopters." The second class contained about one third (previously 25%) of the farmers, but the probability of the intentions to uptake EID dropped below 0.5 (0.44). Since the probability of current adoption of EID was still >0.5 (0.61), the results suggested the second class became the group of "EID current adopters."

The third class contained 8% (previously 5%) of the population, and it was still referred to as the "future adopters."

The estimated coefficients presented in **Table 3** are logarithms of odds ratios as the latent class analysis presents the probability of preferring "yes" over "no" (odds ratio) then takes a natural logarithm of the odds ratio. Additionally, the estimated coefficients are presented as paired comparisons between two latent classes to the effect of the logarithm of odds ratio. This leads to a less than straightforward interpretation of the coefficients. The rule of thumb is that for a categorical variable a positive coefficient implies that the comparator latent class has greater logarithm of odds value than the base latent class while moving from the reference category to the comparator category of this categorical variable. Thus the practical interpretation is that a positive coefficient implies an increasing likelihood of belonging to the comparator latent class group (if "yes" rather than "no" was stated) when the comparator category rather than the reference category of this categorical variable was chosen. On the other hand, a negative coefficient implies an increasing likelihood of belonging to the base latent class group (if "yes" rather than "no" was stated) when the comparator category rather than the reference category of this categorical variable was chosen. For a continuous covariate, a positive coefficient implies an increasing likelihood of belonging to the comparator latent class group while increasing the value of the variable, and the opposite holds, namely a negative coefficient implies an increasing likelihood of belonging to the base latent class group while increasing the value of the variable.

Still it would be more straightforward to visualize how each of the six covariates can predict the probability of latent class memberships while changing each of their outcomes. Therefore we used **Figures 3**, **4** to graphically represent the estimated effects of the six covariates presented in **Table 3**. The estimated probability of latent class membership was computed without the intercepts (to remove the effect due to different latent class group size), which enabled us to see the pure effect of each covariate.

To begin with, the effect of age is presented in **Figure 3A**. It shows that with increasing age there is an increasing probability of becoming a "non-adopter." This is in contrast with the other two classes, where the probabilities decline with increasing age, indicating that younger farmers have higher probabilities to become either "EID current adopters" (class two) or "future adopters" (class three) than older farmers.

The proportion of agricultural income in the total income had also a significant effect on the latent class membership (**Figure 3B**). Farmers are more likely to become "EID current adopters" if a large proportion (higher than 75%) of their income was from agriculture on farm when compared with farmers with lower agricultural income (<25%). In other words, famers who stated that their farms have <25% agricultural income are more likely to become the "non-adopters." There is no statistical evidence for a significant association between the proportion of agricultural income and the membership of the "future adopters" class, although graphically the dotted line (future adopters) catches up with the dashed line when the proportion of agricultural income is >75%.

Figure 3C presents the effect of the variable "perceived difficulty of investing in new technologies" on latent class

TABLE 3 | The final three-class LC regression model (coefficients are estimated of logarithm of odds ratio using backward model selection technique).

Model		**Class 2 vs. Class 1**			**Class 3 vs. Class 1**			**Class 3 vs. Class 2**		
		Coe.	**SE**	***P*-value**	**Coe.**	**SE**	***P*-value**	**Coe.**	**SE**	***P*-value**
Intercept		−1.43	0.534	0.008	−2.77	0.807	0.001	−1.34	0.869	0.123
Age		−0.02	0.007	0.005	−0.04	0.010	0.001	−0.02	0.011	0.154
Remain in agri-environmental scheme until 2020: no (vs. yes)		−0.80	0.158	<0.001	−0.76	0.244	0.002	0.04	0.253	0.875
Percentage of agricultural income in total income: (vs. <25%)	25–75%	0.23	0.249	0.363	−0.25	0.379	0.510	−0.48	0.407	0.243
	>75%	0.76	0.222	0.001	0.37	0.332	0.260	−0.39	0.362	0.284
How difficult do you find investing in new technologies?	0.27	0.070	<0.001	0.45	0.111	<0.001	0.18	0.117	0.116	
How often do you look for information on EID for farm management? (vs. never)	weekly	1.75	0.259	<0.001	0.60	0.342	0.079	−1.15	0.367	0.002
	monthly	1.02	0.229	<0.001	0.16	0.325	0.612	−0.85	0.357	0.017
	yearly	1.34	0.279	<0.001	0.55	0.416	0.182	−0.79	0.436	0.071
How often do you look for information on cattle surveillance through British Cattle Movement Service? (vs. never)	weekly	0.28	0.234	0.228	2.18	0.464	<0.001	1.89	0.481	<0.001
	monthly	0.63	0.217	0.004	2.12	0.445	<0.001	1.49	0.465	0.001
	yearly	−0.14	0.325	0.676	1.07	0.584	0.066	1.21	0.625	0.053

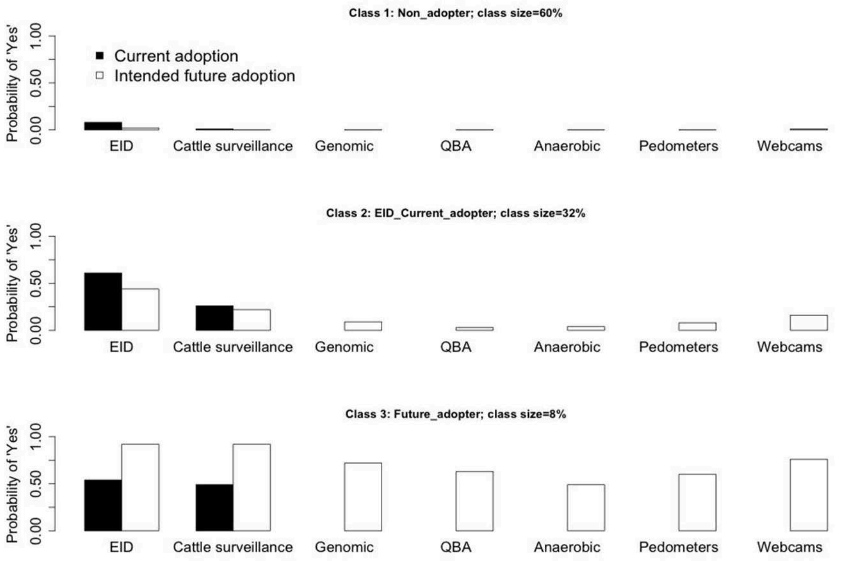

FIGURE 2 | The characteristics of the LC three-class regression model (with six explanatory variables).

membership. Both the "EID adopters" and the "future adopters" groups had greater probabilities than the "non-adopters" group, which confirms the positive logarithms of odds ratios in **Table 3** (0.27, 0.45). Moreover, farmers with stronger perceptions as regards the difficulty of investing in new technologies showed a higher probability of belonging to the "future adopters" group. Although there was a mild declining trend in the "EID current adopters" group, the odds over the "non-adopters" group were still greater than one.

The "non-adopters" group showed a strong declining pattern positively associated with stronger perceptions as regards the difficulty of investing in new technologies. In other words, farmers who found it more difficult to invest in new technologies were more likely to become either "EID current adopters" or "future adopters."

Figure 3D shows the effect of the agri-environmental scheme membership on the probability of belonging to one of the three latent classes. The pattern suggests that current members of agri-environmental schemes who were more likely to cease membership by 2020 were also more likely to belong to the "non-adopters" group compared with farmers with an agri-environmental scheme membership who were more likely to belong to either the "EID adopters" or the "future adopters" groups.

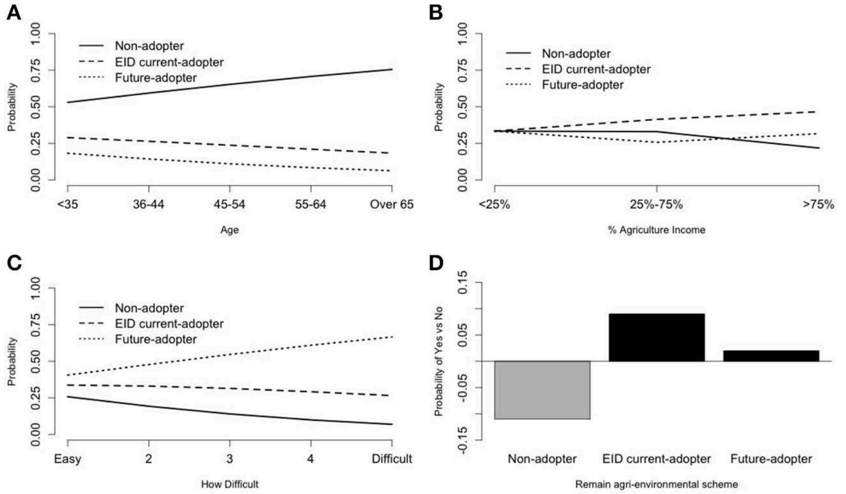

FIGURE 3 | (A) Age as predictor of class membership based on technological uptake and intentions. **(B)** Agricultural income as predictor of class membership based on technological uptake and intentions. **(C)** Difficulty to invest in new technologies as predictor of class membership based on technological uptake and intentions. **(D)** Agri-environmental scheme membership as predictor of class membership based on technological uptake and intentions.

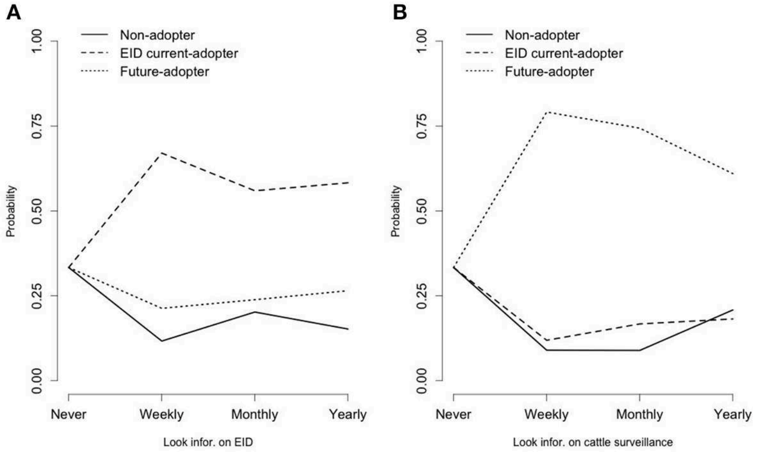

FIGURE 4 | (A) Frequency of access to information on EID for farm management as predictor of class membership based on technological uptake and intentions. **(B)** Frequency of access to information on cattle surveillance as predictor of class membership based on technological uptake and intentions.

The last two of the explanatory variables, frequency of access to information on EID for farm management and cattle surveillance, are presented in **Figures 4A,B**. **Figure 4A** shows a pattern which suggests that more informed farmers (who checked information about EID more frequently) had a higher probability of belonging to the "EID current adopters" group than those who never looked for such information. However there is no significant association between the frequency of looking for information and the likelihood of becoming "future adopters."

The pattern in **Figure 4B** about farmers' frequency of access to cattle surveillance information shows that farmers who looked for cattle surveillance information (especially on a weekly or monthly basis) had a much higher probability to become "future-adopters" than those who never looked for such information.

DISCUSSION AND CONCLUSIONS

This study identified three groups of farmers in a typology analysis based on farmers' uptake and intentions to uptake animal health and welfare technologies. The characteristics of the three groups were estimated with and without controlling for socio-economic and attitudinal covariates.

When no explanatory variables were considered, the majority of farmers (more than two thirds) were classified as "non-adopters," i.e., farmers less likely to uptake or to intend to uptake either or more of the seven types of animal health and welfare technologies analyzed. The second largest group (a quarter of farmers) contained the "EID adopters," i.e., the farmers already using animal EID for farm management and those willing to uptake animal EID for farm management in the following 10 years. The third and smallest group (a twentieth of farmers) contained the "future-adopters," i.e., the farmers willing to uptake either or more of the animal health and welfare technologies.

After controlling for socio-economic and attitudinal covariates, the characteristics of the three groups based on technological uptake remained similar for both the "non-adopters" and the "future-adopters," albeit with a change in size, i.e., the "non-adopters" group decreased to three fifths of farmers, while the "future adopters" group increased to include about a twelfth of farmers. However a more significant change occurred in the second group labeled "EID adopters" in the model without covariates (which contained farmers already uptaking or willing to uptake animal EID for farm management in the next 10 years), which after controlling for covariates became the "EID current adopters" group (which contained farmers showing current uptake).

The effects of the six class-specific explanatory variables included in the three-class latent class regression model showed expected patterns that confirmed findings from the literature.

Age can be a significant influence on technological uptake in many technology adoption studies (33, 34). Our results show that the younger the farmers, the more likely they were to belong to either the group of "EID current adopters" or to the "future-adopters" group. On the other hand, the older the farmers, the more likely they were to be part of the "non-adopters" group.

Farmers' financial status (income, investment, profitability) has been found to influence technological adoption (34–37). Deriving relatively more income from agricultural activities and thus demonstrating a stronger focus on agricultural rather than non-farm activities is more strongly linked to adoption of technologies directly connected with agricultural production (38). Our results support the latter and suggest that farmers with a larger proportion (>75%) of their total income originating from agriculture were more likely to belong to the group of "EID current adopters." On the other hand, farmers with <25% agricultural income were more likely to belong to the "non-adopters" group.

Farmers' perceptions of the difficulty to invest in new technologies influenced their membership in a specific technological uptake group, namely those with stronger perceptions about investment difficulties were more likely to belong to the "EID current adopters" group or to be willing to become the "future adopters." This finding might be explained by the fact that farmers who have adopted technologies or intended to adopt were more aware of the investment needs related to technological uptake and might have experienced investment difficulties while uptaking or attempting to uptake new technologies. Another potential reasoning could be linked to the size of investment required for the specific case of EID technology uptake, which is less significant than that required for uptake of some of the other technologies mentioned.

The literature has shown that innovative behaviors tend to go hand in hand, i.e., individuals who adopted specific innovations are also more likely to uptake or intend to uptake other innovations more or less related to the ones adopted in the past (38–40). Our results showed a positive relationship between membership in agri-environmental schemes and uptake of animal health and welfare technological innovations. Farmers who were members of agri-environmental schemes and who intended to maintain their membership during the next 10 years were more likely to belong to either the "EID current adopters" or the "future adopters" groups.

And finally, one of the main influences on technological uptake, access to information about the specific technologies has been consistently referred to in the technology adoption literature (41–47). Our results suggest that the higher the frequency of access to information on animal EID for farm management, the higher the probability of farmers belonging to the "EID current adopters" group. Similarly, farmers who looked for information on cattle surveillance through British Cattle Movement Service on a weekly or monthly basis were more likely to become the "future adopters" than those who never looked for information.

The findings are policy relevant as they give quantitative evidence on the factors influencing technological uptake and, as such, help identify the most likely adopters and optimize the cost of targeting them. As information access was found to be among the factors influencing multiple technology adoption, policy instruments should include the provision of training as regards the implementation of technologies and their combined impact on farm. Farmers' adoption of interconnected technological innovations suggests the need to coordinate individual policies aimed at encouraging uptake of different technologies. As shown here, this would concern not only synchronizing animal health and welfare policies, but also their interaction with others such as agri-environmental ones. Moreover, the results show that animal health policies requiring regulatory compliance may lead to voluntary uptake of additional or complementary technologies which relate to not just meeting but exceeding standards of animal welfare and health practices.

DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because confidentiality agreements restrict access to this dataset. Requests to access the datasets should be directed to LT, luiza.toma@sruc.ac.uk.

AUTHOR CONTRIBUTIONS

JL led the analysis and contributed to the writing. LT led the writing and contributed to the analysis (variable and model selection). AB and AS contributed to the writing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00410/full#supplementary-material

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A Risk-Based Permitting Process for the Managed Movement of Animals and Products of Animal Origin as a Tool for Disease Management

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During a foreign animal disease (FAD) outbreak, in addition to detecting, controlling, containing, and eradicating the FAD, one of the goals of response in the United States (US), and many other countries, is to allow the managed movement of non-infected animals and non-contaminated animal products from within FAD control areas to facilitate continuity of business (COB). Permits issued by government authorities are the mechanism by which such managed movements are allowed in the US, resulting in permitted movements. The overall purpose of issuing permits during an outbreak is to minimize the risk of disease spread while still allowing movement of products or animals; thus, the risk associated with each permitted movement must be considered. Currently, there are federal guidelines for the various permit types and purposes. These guidelines state that permits should be "based on science and risk-based information." However, federal guidelines with specific procedures to determine risk are not readily available nor do they explicitly enumerate measures to assist regulatory authorities in using risk to guide decisions to grant permitted movement or deny a request to move. Although some pro-active risk assessments (RAs) have been conducted to determine risk of moving certain animals and their products, there will always be animal and product movements for which no pro-active RAs exist. We present here a process description of steps to conduct risk-based permitting with appropriate resource allocation to permitting by industry and regulatory authorities during an FAD outbreak.

Keywords: permitting, permitted movement, risk assessment, managed movement, foreign animal disease, disease outbreaks, continuity of business

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INTRODUCTION

During a foreign animal disease (FAD) outbreak in the United States (US), the goals of response include not only detecting, controlling, and eradicating the FAD but also continuity of business (COB) for companies and farms with non-infected animals and non-contaminated animal products (1). Key among the many critical activities required to achieve these goals simultaneously, are quarantine and movement controls for animals and premises at highest risk of disease infection and/or spread. Written permits issued by responsible regulatory authorities are a mechanism by which movement controls can be implemented, resulting in permitted movements. The process by which permits are managed (i.e., submitted, reviewed, issued or denied, recorded, and tracked) is called "permitting" in the US. Other countries appear to have comparable approaches—requiring written, or otherwise designated, competent authority approval—to managed or controlled movements during animal disease outbreaks, though specific "permitting" terminology is lacking [for example, see European Commission Council Directives and Commission Decisions for control of various diseases and the Zoning and Compartmentalization Chapter of the World Organization for Animal Health (OIE) Terrestrial Animal Health Code] (2, 3). A key objective of permitting is to allow for movements that are unlikely to spread disease, based on scientific evidence, and that prevent unintended consequences of movement controls (e.g., overcrowding; depopulation and disposal of animals that are not infected)—in other words, permitting should decrease risk. In this context, permitting approaches risk as a combination of the epidemiological probability of an event (i.e., movement results in disease spread) and the consequences of the event (i.e., consequences of disease spread).

The US Department of Agriculture (USDA) FAD Preparedness and Response (FAD PReP) Manual for Permitted Movement explicitly states that "permits and associated requirements should be based on science and risk-based information" (4). However, federal guidelines with specific procedures to determine risk are not readily available nor do they explicitly enumerate measures to assist regulatory authorities in using risk to guide decisions to grant or deny a permitted movement. Similarly, specific published procedural guidelines could not be found for other countries known to utilize movement controls during disease outbreaks. Although some pro-active risk assessments (RAs) have been conducted that evaluate the risk of moving certain animals and their products in specific outbreak scenarios, there will always be animals and product movements that need to occur but no pro-active RAs exist. Additionally, the guidance on how to apply the process of permitting and what the roles and responsibilities are for industry and regulatory officials is not intuitive. We present here two processes to facilitate COB: (1) using a risk-based approach to guide permitting decisions for animal and animal product movements, and (2) appropriate resource allocation by industry and regulatory authorities to permitting during an FAD outbreak. These concepts can be translated further by regulatory authorities into individualized state permitting plans or perhaps for incorporation into national emergency response plans in countries beyond the US.

EXISTING GUIDELINES FOR PERMITTED MOVEMENT IN THE US

The USDA Animal and Plant Health Inspection Service Veterinary Services (APHIS VS) has broad authority over interstate movements and the ability to intervene during FAD incidents in the US[1]. However, states have primary authority over intrastate movements as well as requirements for entry into their respective state. As a result, each state may have a unique system and criteria for allowing permitted movement in an outbreak situation. Regional approaches that help coordinate permitting across borders may therefore have great value for areas with interconnected agricultural systems.

The FAD PReP Manual for Permitted Movement provides broad guidance on permit types and premises descriptions related to managed movement, as well as a process for using the Emergency Management Response System 2.0 (EMRS2) for the requesting, review, and approval of permits and also data management for traceability (4). The specific permit guidance and mitigation criteria that address the risk of specific animal and product movements are not available for all situations. Nor does a pre-defined process exist that delineates how roles and responsibilities for permitting are to be carried out by industry and regulatory officials.

In general, it is the responsibility of the producer to ensure that the criteria for permitted movements (e.g., specific biosecurity, diagnostics, etc.) are met and documented before the movement occurs. The originating and destination states have the discretion to then validate or check that these criteria satisfy the state's particular needs (4). Specific to COB movements, several detailed permit guidances based on pro-active RAs are available as part of existing Secure Food Supply (SFS) plans (6).

EXPERIENCE FROM PREVIOUS OUTBREAKS

Movement controls have had a role in effective outbreak control in multiple outbreaks (7–10). Valuable experience has been gained from previous large outbreaks in particular that have necessitated high-throughput operations for activities such as permitting, managed movements, and laboratory testing (8, 11). During the 2014/2015 highly pathogenic avian influenza (HPAI) outbreak, over 7,500 permits were issued for approximately 20,000 movements and these managed movements were accomplished without spreading disease (8, 12). However, this high-throughput significantly strained industry and government resources and likely would not have been sustainable had the

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Abbreviations: COB, continuity of business; EMRS2, emergency management response system 2.0; FAD, foreign animal disease; FAD PReP, FAD preparedness and response; HPAI, highly pathogenic avian influenza; PAG, permitting advisory group; PMIP, pre-movement isolation period; RA, risk assessment(s); SFS, secure food supply; USDA APHIS VS, United States Department of Agriculture, Animal and Plant Health Inspection Service, Veterinary Services.

[1] If an USDA Extraordinary Emergency Declaration or similar national emergency declaration is made, the USDA (or federal government) then has authority over both intrastate and interstate movement. If no such declaration is made, then the USDA provides the oversight [in coordination with State Animal Health Officials (SAHOs) and the unified Incident Command] for interstate permitted movements and any movement that relates to international trade. For more information on State and Federal authorities, see the NAHEMS Guidelines: Quarantine and Movement Control (5).

outbreak continued (8, 13). Comparatively, avian influenza outbreaks in 2016 and 2017 were more limited in size and scope and did not necessitate such high-throughput permitting operations (9, 10).

High-throughput needs during any large FAD outbreak can consume staff resources unless a process for delegating responsibilities to both industry and regulatory representatives is used. Previous outbreaks have shown how the want and need to stop the spread of disease are equal for impacted commercial agriculture industries and regulatory officials. Yet, despite this common desire, it is the agricultural industry that has more immediate knowledge of activities occurring on farms that may expand or reduce an outbreak. Importantly, industry partners also have the ability to implement risk mitigation measures and do so for other pathogens daily. Our proposed risk-based permitting process builds on these experiences and is founded in the public-private partnerships that grew from the 2014–2015 HPAI outbreak.

PROPOSED RISK-BASED PERMITTING PROCESS

The risk-based permitting process can serve as a method for agricultural industries needing business continuity to use during an FAD outbreak, helping build on their knowledge and increase their ability to work with state and federal authorities to inform and perform permitted movements. A functional risk-based permitting process should ensure that, for all permits, risk is considered before a permit to move is approved or denied. This requires an objective understanding of the risk of the movement, including any mitigations that will be used to decrease risk, knowledge that mitigations can and will be applied properly, and an understanding of the context of the move. When these things are known, then the process of risk-based permitting can occur.

A step-wise risk-based permitting process is described below, including roles of responsible parties during each step (see **Table 1**). While the exact responsible party, down to the specific person, will need to be determined by individual states or responsible regulatory officials, the delegation and communication of roles is a key factor in preparedness. This becomes most clear when considering the management of risks associated with a movement. In order for successful risk mitigation, sufficient resources need to be allocated to the mitigation process. From a permitting perspective, this means that appropriate and sufficient numbers of people need to be available to conduct each step. This necessitates a realistic estimate of availability and capability of both regulatory officials and industry personnel.

1. **Define desired movement:** Defining the movement for which a permit is desired means that all of the information required for a permit request are identified. Specifically, what item will be moved; why the item will be moved; where are the origin and destination premises of the item movement; and when will the move occur (4). Typically, a movement will be defined via a question or actual movement request from industry or from within a unified incident command.[2] Once the movement is defined, the risk of that movement needs to be evaluated to determine if a permit should be granted and if any specific mitigations and other criteria are needed to address any risk to an acceptable level.

TABLE 1 | Proposed steps for risk-based permitting [responsible party/ies included in brackets].

1. **Define desired movement:** what item is to be moved; why is the item to be moved (e.g., moving direct to farm, to landfill, or into commerce); where are the origin and destination premises; and when will the move take place (over what dates).
   [Industry or unified Incident Command]
2. **Conduct situational assessment:** Responsible regulatory officials determine if the current outbreak situation and premises circumstances can allow for a potential permitted movement.
   a) If not, process stops here.
   b) If movement may be possible, proceed to step 3.
   [Unified Incident Command]
3. **Determine if applicable risk assessment exists:** review existing risk assessments and available guidance.
   a) If a risk assessment does not exist or is not applicable, move to next step and conduct an *ad hoc* risk assessment.
   [Permitting Advisory Group]
4. **Determine risk and feasible risk mitigations:** either from an existing applicable risk assessment or during an *ad hoc* risk assessment process, identify feasible risk mitigations (i.e., permit guidance/criteria) for the movement and determine the final risk rating for the movement.
   [Permitting Advisory Group]
5. **Determine acceptability of movement given final risk:** responsible regulatory officials consider situation/outbreak circumstances to determine if a movement with the given risk level (identified during the previous step 4) is acceptable.
   [Permitting Authority]
6. **Allocate resources:** delegate responsibilities for oversight and communication of movement requirements to appropriate personnel based on risk.
   [Industry and Unified Incident Command]

2. **Situational assessment:** Before the resource-demanding process of risk-based permitting moves further, responsible regulatory officials should determine if the circumstances of the current outbreak situation and premises can allow for a potential permitted movement. In some cases, all movements will simply be stopped and the risk-based permitting process ends here. If movements may be possible, depending on the risk posed by the movement, then the risk-based permitting process proceeds to the next steps and the unified incident command refers the movement request or question to a Permitting Advisory Group (see Step 3 text).
3. **Determine if an applicable risk assessment exists:** The process to determine risk takes multiple steps and multiple people. These steps and who will accomplish them are

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[2] Incident Command refers to the organizational element responsible for overall management of the outbreak incident. In the US, this terminology comes from using the Incident Command System (a standardized approach to the command, control, and coordination of on-scene incident management, providing a common hierarchy within which personnel from multiple organizations can be effective) (14). A unified Incident Command is used when more than one agency has incident jurisdiction or when incidents cross political jurisdictions as is common with animal disease outbreaks.

often not included in emergency preparedness plans. Having specific roles for people and positions delineated in state or national plans can speed a permitting process during an outbreak. For example, if an RA for a particular movement already exists then much work can be avoided by simply referencing the RA. However, the permitting authority not only has to ascertain if such an RA exists but also, determine if the existing RA is applicable to the requested movement.

Creation of a Permitting Advisory Group (PAG) will assist in both determining if an applicable RA exists and also determining a final risk rating (the next step in the process, Step 4) for a requested movement. The PAG ideally comprises individuals with expertise regarding the disease, the specific commodity, the industry, RA, outbreak circumstances, and regulatory requirements. The PAG may include additional participants depending on the specific movement or outbreak in question. The subject matter experts of the PAG will be able to assist in locating and reviewing any existing RA and any associated guidance. Close communication and collaboration among individuals of the PAG—with an outlet for rapid, up-to-date communication with the unified Incident Command—is needed to evaluate existing RAs for their applicability to the outbreak.

While having an RA ready for use at the outset of an outbreak can greatly assist a risk-based permitting process, pro-active RAs are based on many assumptions. If not all assumptions are met for a particular premises or situation, then the overall risk conclusion of a pre-existing RA may not be applicable to the desired move, even if the disease and commodity are the same. A specific example where applicability may be a concern is with assumed mitigation measures. For instance, the Pre-Movement Isolation Period (PMIP) is a mitigation measure intended to reduce the risk of disease exposure on a premises in the days leading up to animal movement in order to increase the likelihood of disease detection pre-movement. For some existing poultry RAs (e.g., birds to market or pullets off a farm), it is assumed that a PMIP is in place for a certain number of days pre-movement (15, 16). However, in some situations, like at the outset of an outbreak or immediately after a new Control Area is established, a full PMIP may not have been implemented for a premises requesting a permit. In that case, the risk rating will not be accurate and in fact, the risk may be much higher. In such a situation, the permitting authority would need to weigh the immediacy of the need for the move, the feasibility of waiting the full PMIP, and the potential to expand the outbreak by approving the move as is. Again, review of existing RAs and their applicability necessitates knowledge of the outbreak situation and industry circumstances specific to the premises in question.

4. **Determine risk and mitigation measures:** In addition to providing insight into the likely risk of particular movements, pro-active RAs also have the benefit of elucidating feasible measures that can mitigate risk. In the process of reviewing an existing RA, these mitigation measures can be compiled into permitting guidances or permitting criteria that must be implemented to achieve the risk level indicated in the RA (6). Risk assessments may even include supplemental information that could be considered on a case-by-case basis to lower risk levels (16).

If an existing RA is not applicable or if none exist, then, to move forward with risk-based permitting, risk will need to be evaluated for the particular movement and circumstances. This could be accomplished via an *ad hoc* risk assessment or similar science- and risk-based evaluation (4). The need for *ad hoc* RA will arise in every outbreak since there is always a level of uncertainty about the nature of the next outbreak, what pathogens will be involved, and what commodities will be affected. Further, agricultural industries are constantly changing and the processes used to create and move products are in constant flux. Because changes impact how activities, like biosecurity, happen, they also impact the risk of those activities. Full RAs take significant time (months to years) to complete and usually include both quantitative and qualitative analyses. Quite often, the proactive full RA estimations report likelihood ratings based on a six-level scale, specifically negligible, very low, low, moderate, high, and extremely high. An abbreviated *ad hoc* process, on the other hand, can be completed in a much shorter timeframe than a full RA. It is important to note, however, that the *ad hoc* process is based on the best available information, not necessarily all information. Furthermore, since the process is shortened, there will be a higher degree of unknown risk. Thus, the levels of uncertainty surrounding risk as a result of the *ad hoc* process must be included in the final consideration. While the detailed methods for an *ad hoc* RA are beyond the scope of this paper, we propose that the same PAG identify and consider risk pathways, detection methods, and mitigation strategies to evaluate overall movement risk and to reduce the unknown factor by defining permit specific conditions and criteria needed.

5. **Determine acceptability of movement once the final risk rating is given:** Once a risk rating and mitigation measures are determined, we recommend assigning the defined movement to these categories: (1) negligible/low risk; (2) moderate/high risk; or (3) unknown risk. The negligible/low-risk category can be assigned to those movements that received a likelihood estimation of negligible, low, or very low. Similarly, movements that received a likelihood estimation of moderate or high would be placed in the moderate/high-risk category. This organization by category is intended not to undermine the goals of current policies and procedures for managing all risk that is non-negligible. Rather, the proposed categories here are intended to facilitate resource allocation between industry and regulatory officials with regard to the remaining aspects of the permitting process, in particular, the allocation of resources for direct oversight.

At this stage, once a risk rating for the movement is provided by the PAG, the permitting authority will need to determine whether or not it is acceptable to allow the movement to occur given the risk category. For a movement with a risk that is very high and/or deemed unacceptable for current circumstances, the

TABLE 2 | An example of risk-based permitting resource allocation.

Negligible to low risk movements

- Utilize multiday permits (blanket permits) for movements from one premises to one destination that occur over a period of days.
- Permit requestor (industry) manages the criteria and needed surveillance/diagnostic reporting under the permit for the approved time period
    - Maintain a Monitored Premises status
    - Report any changes in situation
- Movement reporting is done at regular intervals to meet traceability needs
- Incident Command communicates any change in outbreak situation that may affect premises status
- Regulatory officials audit permit criteria requirements at level commensurate with risk
    - Negligible risk movements-—1 out of 20 permits
    - Low risk movements-—1 of 10 permits

Moderate to high risk movements

- Utilize single movement permits for a single movement from one origin premises to one destination premises
- Regulatory officials audit permit criteria requirements at level commensurate with risk
    - Moderate risk movements—one out of five permits
    - High risk movements—one out of one permits

movement should be denied. For a movement with a risk deemed acceptable for current circumstances, then adequate resources are allocated for oversight of the permitted movement, and the resources allocated should be commensurate with the risk of that movement.

6. **Allocate resources for oversight and communication:** Risk-based permitting requires understanding and allocation of responsibilities by both industry stakeholders and regulatory officials. Transparent communication about the risk-based decisions made, responsibilities, and resource limitations can help increase confidence in and compliance with the process by all stakeholders, leading to success. During highly contagious disease outbreaks, regulatory personnel will be stretched from a resource availability perspective. With the multitude of disease response activities involved with such outbreaks, there is a need to reduce straining resources. Utilizing a risk-based permitting structure that allocates resources based on the likelihood and consequences of disease spread can be a more efficient use of resources, focusing on movements that pose the most risk (**Table 2**). Specifically, the resources needed for auditing permitting criteria can be allocated according to the risk. Descriptions and communication of resource needs will assist all stakeholders' understanding of how many and what resources will be needed.

CONCLUSIONS

When risk is incorporated into the permitting process, there remains the very real possibility that sometimes the risk, regardless of the level, will be considered too great to allow the requested movement to occur. For example, although an existing RA indicates a low likelihood that a large number of HPAI infected pullets would be moved when all Secure Poultry Plan mitigation practices are strictly implemented on a premises (16), if the destination premises for the movement is a large layer complex, then the risk may still be considered unacceptably high due to the high consequence to the layer industry if that pullet movement were allowed and the layers became infected. Conversely, if live animals are to be moved to a single-age premises with no other animals on-site (e.g., pullets to single-age layer premises, growing pigs to an empty finisher, calves to an empty pasture or feedlot) the risk may be acceptable to industry even if there is a chance of moving infected but undetected animals. Thus, even for a requested movement with a non-negligible risk, the permit request may be approved following the risk-based process and communication described above. Additionally, whether a certain level of risk is acceptable also may change as an outbreak progresses. For example, during initial phases of an outbreak, any amount of risk may be considered too high as movements are stopped and quarantines put in place in an effort to rapidly stamp out the disease. However, in later phases of an outbreak, there may be more severe animal welfare impacts to weigh against disease spread risk posed by various movements.

Utilizing a transparent approach that includes regulators and industry in the process of risk-based permitting has definite utility in high-consequence animal disease outbreaks. In order for responsible regulatory officials and industry to accept movements during an outbreak, all stakeholders need to be confident in the entire process. This includes the process of risk evaluation, the mitigation procedures and processes that are followed to address known risks, and the process of managing the movements from within a control area during an outbreak, including communication. Previous large outbreaks have demonstrated how response resources rapidly can be consumed and how resource-intensive the permitting process can be. Utilizing the process prosed here could help decrease demands on limited regulatory resources commensurate with risk. The process proposed here allows regulatory officials to focus more of their efforts on moderate to high-risk movements but it does not remove them entirely from the process for low or negligible risk movements. The goal is to efficiently and effectively balance resource allocation between industry and regulators. Importantly, this process includes specific steps for both industry and regulatory officials to have input into evaluating risk of defined movements and determining whether outbreak-specific circumstances dictate such risk as acceptable or unacceptable to allow permitted movement.

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Epidemiological Study of *Mycobacterium bovis* Infection in Buffalo and Cattle in Amazonas, Brazil

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Bovine Tuberculosis (BTB) is an endemic disease in about one hundred countries, affecting the economy causing a decrease in productivity, condemnation of meat, and damaging the credibility on international trade. Additionally, *Mycobacterium bovis* the major causative agent for BTB can also infect humans causing a variety of clinical presentations. The aim of this study was to determine BTB prevalence and the main risk factors for the *Mycobacterium bovis* prevalence in cattle and buffalos in Amazonas State, Brazil. Tissue samples from 151 animals (45 buffalo and 106 cattle from five herds with buffalo only, 22 herds with cattle only, and 12 herds with buffalo and cattle) were obtained from slaughterhouses under State Veterinary Inspection. *M. bovis* were isolated on Stonebrink medium. The positive cultures were confirmed by polymerase chain reaction (PCR) testing. The apparent herd and animal prevalence rates were 56.4 and 5.40%, respectively. Regarding animal species, the apparent prevalence rates were 3% in cattle and 11.8% in buffalo. Generalized Linear Mixed Models (GLMM) with random effect were used to assess the association with risk factors on the prevalence. Species (buffalo), herds size (>100 animals) and the presence of both species (buffalo and cattle) in the herd were the major risk factors for the infection by *Mycobacterium bovis* in the region. The findings reveal an urgent need for evidence-based effective intervention to reduce BTB prevalence in cattle and buffalo and prevent its spread to the human population. Studies are needed to understand why buffalo are more likely to be infected by *M. bovis* than cattle in Amazon. Recommendations for zoning, use of data from the inspection services to generate information regarding BTB focus, adoption of epidemiological tools, and discouragement of practices that promote the mixing of cattle and buffalo, were made.

Keywords: bovine tuberculosis, *Mycobacterium bovis*, zoonosis, cattle, buffalo, epidemiology

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INTRODUCTION

Bovine tuberculosis (BTB) remains one of the world's major health problems in livestock. BTB affects the national economy of countries where disease is endemic by causing a decrease in productivity, condemnation of meat in slaughterhouses, and decreasing the ability for international trade (1). During 2015 to 2016, 179 countries reported the presence of the disease in livestock and/or wildlife, demonstrating its wide geographical distribution (2).

Mycobacterium bovis (M. bovis) is the causative agent of BTB and is also responsible for the zoonotic tuberculosis (TB) which is a major impediment for the success of the global efforts to end TB by the year 2030 (3). Although estimates of the global burden of zoonotic TB are imprecise, in 2016 WHO estimated that there were 147,000 new cases of zoonotic TB in humans and 12,500 deaths due to the disease (4). The human burden of disease cannot be reduced without controlling BTB in the animal reservoirs (4).

In many industrialized countries, the implementation of national BTB programs, based on regular tuberculin testing and removal of infected animals, had led to the successful eradication or a major reduction in the incidence of BTB in cattle herds (5). However, these control measures have been only partially effective in countries or regions with a wildlife reservoir of infected animals, such as the United Kingdom (UK), New Zealand and the United States of America (USA) (6–8). Furthermore, these measures are not affordable in most countries of the world, particularly in countries which have a high prevalence of BTB in their domesticated livestock population (9).

In Brazil, the National Program for the Control and Eradication of Brucellosis and Bovine Tuberculosis (PNCEBT) was establish in 2004 and is based on the sacrificing of all animals displaying positive reaction to tuberculosis tests (10). In recent years epidemiological studies were conducted to determine the BTB status in several Brazilian states (11–24), however no studies were conducted in Amazonas State. Moreover, a detailed understanding of the risk factors involved in the *M. bovis* transmission is an identified gap in BTB studies. Understanding the epidemiology of the disease is fundamental for the development of efficient disease control strategies (9, 25).

Statistical modeling studies are important to elucidate the transmission dynamics of BTB within and between herds (26–29). Additionally, mathematical modeling studies have been carried out to analyze disease transmission and provide insight into useful control measures (30–33).

This study aims to ascertain the prevalence of BTB and, through statistical modeling, unveil the main risk factors of the disease in cattle and water buffalos in Amazonas State, Brazil. Ultimately our goal is to propose evidence-based measures to improve the regional programs for the eradication of TB caused by *M. bovis* in livestock and humans.

MATERIALS AND METHODS

Study Population

In Amazonas State, cattle and buffalo, are predominantly managed in extensive and semi-confined systems, there are no herds raised in a total confined system. In an extensive system, animals remain in the pasture most of the time and the feeding system is based strictly on grazing with mineral salt being offered in feeders on the pasture. Herd health is based on palliative care of animals that present wounds or signs of illness, and the preventive care is restricted to semi-annual vaccination of Foot and Mouth Disease. Cattle are predominantly mixed *Bos indicus* or mixed *Bos taurus indicus*; buffalo are predominantly mixed breeds Murrah, Carabao, and Mediterranean. In semi-confined models, animals are gathered daily in pens where food supplementation and mineral salt are provided in separate feeders. Within the Semi-confined systems, herd health is more appropriate, animals are observed daily for injuries or signs of illness, the preventive care usually is composed of control of parasites, vaccination against Foot and Mouth Disease and Brucellosis. Cattle are predominantly of the Nelore and Girolando breeds, for beef and dairy, respectively. Buffalo are predominantly Murrah (dairy and beef) and Mediterranean (dairy).

In common, the husbandry systems of the two species are influenced by flooding during the raining season. During the rainy season (November to June) herds remain at the mainland areas. During the dry season (July to mid-November) weaned calves, steers, heifers, and dry cows are transported to shared floodplain grassland for beef or recovery purpose. Apui is the only municipality in this study not influenced by flooding.

Buffalo and cattle are raised adopting the same management farming system, but due to having more resistance to flooding in regard hoof problems, buffalos are moved from the mainland to the floodplains earlier, and moved back later, than cattle. On average, buffalos spend an additional 3 months in floodplains compared to cattle.

Herds ($n = 39$) from three intermediary regions and 13 municipalities were included on this study. Twenty-two herds (56.4%) were composed only by cattle, 12 herds were composed of buffalo and cattle (30.8%), and five (12.8%) herds were composed only by buffalo. The total number of animals inspected during the sampling were 832 (229 buffalo and 603 cattle), and from those 151 samples tissues (45 buffalo and 106 cattle) were obtained (**Table 1**). The median age group of inspected animals in both species were from 25 to 36 months old, and the mean herd size was 142 for cattle and 84 for buffalos.

Of all the animals in the study, 48.3% were from small size herds, 28.4% from medium herds, and 23.1% from large herds. Additionally, 82.7% of the animals were from farms with herds of only one specie (cattle or buffalo). With regard to the purpose, 49.6% of the animals were from herds with mixed purpose, beef and dairy animals represented 31.1 and 19.2% of the sampling, respectively (**Table 2**).

TABLE 1 | Distribution of the sampling by origin, number of animals inspected, sample by species, and percent of the sampling, Amazonas State, Brazil.

Region	Municipality	Animals inspected	Buffalo	Cattle	%
Labrea	Apui	122	0	26	17.22
	Manicore	19	0	1	0.66
	Novo Aripuana	83	0	14	9.27
Manaus	Autazes	108	24	2	17.22
	Careiro	24	1	1	1.32
	Careiro da Varzea	121	0	14	9.27
	Iranduba	7	0	4	2.65
	Manacapuru	98	0	4	2.65
	Manaquiri	6	0	6	3.97
	Pres. Figueiredo	80	0	26	17.22
Parintins	Itacoatiara	56	2	8	6.62
	Parintins	50	9	0	5.96
	Urucara	58	9	0	5.96
TOTAL		832	45	106	100.00

Criteria for Inclusion

The study was based on a convenience sampling of adult animals sent for commercial slaughter at three major slaughterhouses in Amazonas State.

From herds with a report of the official tuberculin skin test (TST) performed and reactive buffalo or cattle, samples of all animals sent to the slaughterhouses, with or without Lesion Suggestive of Tuberculosis (LST), were collected. The Caudal Fold Test (CFT), the Simple Cervical Test (SCT), and the Comparative Cervical Test (CCT) are the official tests of detection. The CFT and SCT were adopted as screening tests for beef and dairy cattle, respectively, while the CCT was adopted as a confirmatory test for animals positive at the screening test (5). From herds with unknown TST status, samples were collected from all animals with visible tubercles and from animals with suspicious granulomatous lesions.

The inspection of the animals was performed by State Veterinary Inspection Service (SIE) trained officials, LST were defined as granulomas a mass or nodule of chronically inflamed tissue, yellow or tan, and either caseous, caseo-calcareous or calcified. The same criteria for detection of lesions were used for cattle and buffalo.

Study Design

This study is a cross-sectional study performed from July of 2016 to February of 2018. Two samples per animal were collected, one from the suspicious tissue and other from the respiratory system lymph nodes found with increase of volume or LST or from the medial retro-pharyngeal lymph nodes in case of no alterations found in lymph nodes. The option for the medial retro pharyngeal lymph nodes is based on our experience in Michigan (34). The unit of analysis was the animal. The individual animal was considered BTB positive if the culture growing was confirmed by the polymerase chain reaction (PCR) as *M. bovis*, in either tissue samples. For the herd-level analysis, the herd was considered infected when it presented at least one animal confirmed positive by the PCR analysis. The animals were slaughtered for commercial purposes, there were no animals sacrificed due to this study.

TABLE 2 | Description and descriptive statistics for animal-level risk factors evaluated for 151 animals (106 cattle and 45 buffalo) in 39 herds in Amazonas State.

Risk factor[a]	Description	*N*	%
Specie	Cattle	106	70.20
	Buffalo	45	29.8
Herd size	Small	73	48.34
	Medium	43	28.48
	Large	35	23.18
Herd age	≤12 months	0	0
	13–24 months age	42	27.81
	24–36 months age	54	35.76
	≥36 months	55	36.42
Cattle and buffalo	No	125	82.78
	Yes	26	17.22
Farming system	Confined	0	0
	Semi-confined	79	52.32
	Extensive	72	47.68
Purpose	Beef	47	31.13
	Dairy	29	19.21
	Mix	75	49.67
Habitat	Floodplains	71	47.02
	Mainland	80	52.98
History	No	129	85.43
	Yes	22	14.57
Herd health	No	46	30.46
	Yes	105	69.54

[a] *Admitted to the starting multivariable model because it passed screening ($p < 0.50$).*

Preparation and Culture of Samples

Lesions from suspected animals (10–25 mg) were processed and inoculated in duplicate into Stonebrink medium (35). The Stonebrink medium has the same composition as Löwenstein–Jensen, except that glycerol is replaced by 0.5% sodium pyruvate, further incubated at 37°C and evaluated weekly for 90 days to verify bacterial growth. One medium per sample were used and the colonies with characteristics suggestive of *M. bovis* were submitted fur DNA extraction.

DNA Extraction

The bacterial colonies were washed with 500 µL of Tris-EDTA (TE) buffer in micro-tubes and inactivated in a dry bath for 1 h at 87°C, with subsequent centrifugation at 14,000 rpm for 2 min. The pellet that formed was discarded and the supernatant containing the mycobacterial DNA was transferred to new micro-tubes and stored at −20°C for subsequent analysis.

Microorganism Identification by PCR

The mycobacterial DNA samples were submitted to standard PCR according to Sales et al. (36), using primers Mb.400.F (5′AACGCGACGACCTCATATTC3′) and Mb.400.R

(5′AAGGCGAACAGATTCAGCAT3′), which amplify a 400 base pair (bp) DNA fragment flanking the region of differentiation 4 (RD4), specific to *M. bovis* (37). The PCR products were stained with Gel Red and submitted to 1% agarose gel electrophoresis in 1X TAE buffer and visualized in a PhotoDocumentor under ultraviolet light.

Sample Size

The sample size should be determined based on expected prevalence in samples from slaughterhouses, however, we are unable to find a previous study with this sample source in the region. In Amazonas state, only one study about prevalence of BTB in buffalos (*Bubalus bubalis*) was found, based on comparative cervical test (CCT) showing a prevalence of 20.4% (38). Recent studies about BTB prevalence in the region, also based on CCT, showed results ranging from 0.12 (cattle) to 7.2% (buffalos) in Rondonia and Para State, respectively (24, 39). Thus, as this study is based on a convenience sampling of cattle and buffalo, an expected prevalence of 10% was used for sample size calculations. With a test sensitivity of 97%, Type I error of 0.5%, and power of 80%, the minimum sample size needed was 139 animals.

Risk Factors

The risk analysis was based on data obtained directly from the Animal Transportation Guide (GTA) and secondary data provided by the Amazonas State Animal Health Agency (ADAF). From each carcass sampled, epidemiological information, such as: origin, specie (cattle or buffalo), herd size, herd age, presence in the farm of both species, farming system, purpose, habitat, herd history of TB, and presence or absence of regular herd health practices, was collected.

Origin was defined by the municipality described on the GTA mandatory for the movement of animals from the farm to slaughterhouses. The species involved were cattle and water buffalo (*Bubalus bubalis*), the last raised in the region as livestock for the same purposes as cattle. Herd size was divided into three categories: (1) Small, herds $\leq$ 99 animals, (2) Medium, herds from 100 to 199 animals, and (3) Large herds with more than 200 animals. The same criteria were used for cattle and buffalo. Herd age was divided in 4 categories: (1) Animals $\leq$ than 12 months, (2) Animals, 13–24 months age, (3) Animals, 24–36 months age, and (4) Animals older than 36 months. The median age rank of the herd was used for the analysis. The study looked at the species composition of the herd, classifying if the herd is composed only of cattle, only of buffalo or a mix of cattle and buffalo.

Farming systems were divided in three categories: (1) Extensive, characterized by farms with mixed breed herds, low technological level and productivity, (2) Semi-confinement, characterized by farms with a predominant breed, adequate technological level and productivity, and (3) Confinement, characterized by farms with well-defined breeds, specialized for beef or dairy, excellent technical level and productivity.

The purpose of the farm was classified as adopted by ADAF as, Dairy—farms with the main activity to produce milk; Beef—farms of beef cattle; and Mix—farms without mainly objective defined, either can be dedicated to beef, in full or partial cycle (breading, rearing, and fattening) and to produce milk. In mixed farms, beef and dairy animals share environments and facilities.

Regarding the habitat, farms were classified according to the grazing area of the animal. In the Amazon region, herds can be moved between two ecosystems according the river flooding: The floodplains areas flooded during a 6-month period characterized by natural pastures of high nutritional value and the mainland areas not under influence of the rivers and characterized by artificial pasture planted after the removal of the native vegetation. Cattle and buffalo herds were classified according to the exposure to Floodplain grazing.

Based on secondary data from ADAF, animals were classified according to the historic presence or absence of BTB in their herds of origin. As the Brucellosis State Program requires vaccination of heifers which can only be done under veterinary supervision, herds with a register of vaccination were classified as having regular veterinary assistance, otherwise they were classified as not having regular herd health.

Statistical Analysis of Expected Data

The prevalence was calculated by counting the data (animals *M. bovis* positive) per the reference population during the period of the outcome, according to method described by Dohoo et al. (40).

Given the nature of the outcome and number of risk factors, a multi-variable logistic regression model and a Generalized Linear Mixed Model (GLMM) with random effect was used to assess the influence of the risk factors on the prevalence, using 95% confidence intervals ($P \leq 0.05$).

A summary of statistics was computed for each of the risk factors of interest (SAS® 9.4, SAS Institute Inc., Cary, NC, USA). Univariable logistic regression for distinguishable data was conducted for each of the risk factors to assess their degree of association with the outcome variable (41).

The risk of *M. bovis* infection was evaluated using logistic regression for distinguishable data. The dependent variable (*M. bovis* status) was defined as positive if the animal had at least one sample culture positive confirmed by PCR and negative if hadn't reach the inclusion criteria. Due to sampling conducted at the farms, a random-effects term was included during modeling to account for extra-binominal variation attributable to lack of independence between individual animals within farms (41).

The likelihood ratio statistic was used for model development. Therefore, inclusion or exclusion of risk factors were done to test the model. Only those animals, having a complete data set were used for multivariable analysis. Rather than using a fully-saturated model containing all risk factors assessed, a starting model containing a selected subset of risk factors was utilized (41). The starting model included farm and individual-animal-level risk factors having risk ratios (RR) with a $p \leq 0.5$ on univariable logistic-binomial regression. A forward method of variable evaluation using the likelihood ratio statistic was conducted to assess risk factor inclusion or exclusion from the final model. After a variable was added only the ones with a $p \leq 0.35$ were kept on the model. The goodness-of-fit of the final model was evaluated by calculating the likelihood ratio statistic between the starting and final models and comparing it to the chi-square distribution. Ultimately, the most parsimonious model, was chosen to represent the data collected.

Model development (**Table 2**) provides summaries of herd and individual-animal-level risk factor data compiled for the 151 animals (106 cattle and 45 buffalo) involved in the study. The Generalized Linear Mixed Models (GLMM) with random effect at the individual-animal level were presented at **Table 3**.

The project obtained all necessary approvals from MSU-IRB and IACUC and from IFAM's CEPSH and CEUA.

RESULTS

M. bovis Infection

The overall animal rate prevalence was 5.4%. At individual-animal level, a total of 151 animals (45 buffalo and 106 cattle) were considered suspect of BTB and had tissues collected for laboratory analysis, and from those a total of 45 animals (27 buffalo and 18 cattle) were confirmed by culture and PCR as positive for *M. bovis* infection. Prevalence within species was 3.0% in cattle and 11.8% in buffalo (**Table 4**).

The overall herd prevalence was 56.4%, 22 out of 39 herds had at least one animal confirmed as infected by *M. bovis*. The apparent prevalence in herds composed only by cattle, by buffalo and cattle, and only by buffalo was respectively, 45.4, 66.7, and 80% (**Table 5**). As reported before there were no significant differences between LST samples and no LST (42).

Results from the univariate logistical analysis revealed animals from dairy herds ($p = 0.004$), frequent veterinary assistance ($p = 0.0004$), and history of BTB ($p = 0.004$) were more likely to be infected with *M. bovis*. Additionally, animals that attend the floodplains ($p = 0.001$), from extensive farming systems ($p = 0.006$), and from herds with more than 100 animals ($p = 0.05$) were also more likely to be infected. Moreover, animals equal or older than 25 months were 2.7 times more likely to be infected, and buffalo and cattle living together are 2.63 times more likely to have *M. bovis* infection (**Table 6**).

DISCUSSION

The observed herd prevalence 56.4% and animal rate prevalence 5.40% were the highest reported in Brazil to date (10–23). Considering only cattle, the 3.0% animal prevalence this study is the highest found in the country, where before the range was 0.04–1.3% (13, 16). It should be noted that the number of animals and herds were less than to previous studies, which may represent a limitation in this study. On the other hand, our results were based on microbiological and molecular diagnosis, while the other Brazilian studies were based only on TST screening, meaning that our results represent specificity superior to the previous studies in Brazil. In view of that if the true prevalence is the same than the observed on TST screenings, we would expect a lower prevalence than in the previous studies. Considering the

TABLE 5 | *M. bovis* prevalence by herd in Amazonas State, Brazil.

Herd	Prevalence (%)*
Buffalo	4/5 (80%)
Cattle	10/22 (45.4%)
Buffalo and cattle	8/12 (66.7%)
TOTAL	22/39 (56.4%)

**The herd was considered infected when it presented at least one animal confirmed positive by the PCR analysis.*

TABLE 3 | Generalized Linear Mixed Model with random effects of farm and individual-animal-level risk factors associated with the infection by *M. bovis* in 832 animals (106 cattle and 45 buffalo) in 41 farms in Amazonas State.

Risk factor	Description	b	SE(b)	*P*-value	OR	95% CI
Specie	Buffalo	2.5768	1.5379	0.0968	13.15	0.623-277.28
	Cattle	0				
Herd size	Large	1.6474	1.3817	0.2358	5.19	0.336–80.399
	Medium	1.7940	1.6770	0.2872	6.01	0.216–167.20
	Small	0				
Cattle and buffalo herds	No	−1.8588	1.4870	0.2140	0.15	0.008–2.973
	Yes	0				
Random effects		4.071	2.0659			

TABLE 4 | *M. bovis* prevalence by species in Amazonas State, Brazil.

Species	N. animals inspected	N. of animals from which the samples were collected	N. of animals with Legion Suggestive of Tuberculosis (LST)	Positive (culture + PCR)	Study prevalence (%)
Cattle	603	106	13	18	3.0
Buffalo	229	45	33	27	11.8
Total	832	151	46	45	5.40

TABLE 6 | Univariate Logistic Regression of farm and individual-animal-level risk factors associated with the infection by *M. bovis* in 832 animals (106 cattle and 45 buffalo) in 39 herds in Amazonas State.

Risk factor	Description	b	SE(b)	*P*-value	OR	95% CI
Buffalo and cattle	Yes	0.96	0.45	0.03	2.63	1.07–6.45
	No	0				
Farming	Extensive	1.01	0.37	0.006	2.76	1.33–5.71
	Semi-confined	0				
Habitat	Floodplains	1.20	0.37	0.001	3.35	1.59–7.03
	Mainland	0				
Herd age	≥25 months	0.99	0.50	0.04	2.71	1.007–7.31
	<25 months	0				
Herd health	Yes	1.98	0.56	0.0004	7.24	2.40–21.80
	No	0				
Herd size	Large	0.84	0.44	0.05	2.33	0.98–5.54
	Medium	0.44	0.43	0.96	1.55	0.65–3.68
	Small	0				
History	Yes	1.41	0.49	0.004	4.13	1.554–11.013
	No					
Purpose	Dairy	1.51	0.53	0.004	4.54	1.59–12.96
	Mix	0.66	0.45	0.14	1.93	0.79–4.68
	Beef	0				
Specie	Buffalo	1.06	0.20	0.001	8.40	3.73–18.89
	Cattle	0				

sensitivity of 28.2% and specificity of 57.1% found in a controlled field study (43), the practice of TST as a screening test for BTB in Amazonas can result in a worrisome number of false-negative animals remaining in herds.

The absence of compensatory measures on the PNCEBT, is a factor to be considered as a hamper for the producers' adherence to the program, successful countries on BTB eradication adopted the screening and elimination police as well as compensatory measures to incentivize animal owners within the programs (5). Moreover, the only study found in Brazil assessing the use of TST as screening for buffaloes, found 10.81% of false positive and 33.33% of false negative on caudal fold test (CFT) and 0% of false-positive and 66.66% of false-negative on the CCT (44). These testing limitations for buffalo can represent a major challenge to elimination of BTB in Amazonas. Regardless, the observed herd and animal prevalence rates show the need for effective intervention to reduce the rates of disease in livestock populations. Additionally, it should be pointed out that there a number of slaughterhouses without inspection services in inner cities and there is a local preference for regional cheese made from raw milk. Both these practices substantially increase human exposure to *M. bovis* in Amazonas State.

This is the first BTB epidemiological study in Brazil which includes both cattle and buffalo, to our knowledge. The significantly higher prevalence in buffalo ($p > 0.0001$) agrees with previous studies (38, 39, 45). Factors that might contribute to these results can be inherent to the species, such as behavior. Buffalo are very social and commonly under pasture have a tendency to aggregation. Buffalo are also better adapted to protect themselves from the heat than cattle, in order to reduce the thermic stress, they spend lot of time wallowing in the mud, which can be a potential source of spreading *M. bovis* within the herd. This is consistent with other studies stating respiratory transmission via the inhalation of contaminated aerosols or fomites is the most efficient form of transmission, requiring few numbers of organisms as an effective dose (9, 46).

Another factor might be the differences in herd management between cattle and buffalo. Local farmers understand buffalo are more resistant to harsh environmental conditions than cattle, consequently buffalo farmers may provide less feed and routine herd health management to buffalo compared to cattle.

A third major factor to consider is genetic differences between Buffalo and cattle or related to the *M. bovis*. Are buffalo more susceptible to *M. bovis* infection than cattle? In cattle, *Bos indicus* seems to be more resistant than *Bos taurus* (11, 17, 25, 27, 47), does the same occur in buffalo? Or it may not be a host factor. Does *M. bovis* more able to infect buffalo than cattle? Studies to clarify these questions are needed. Regarding control polices, actions adequate to the reality must be in place, such as: inspection services must be more alert during inspection of buffalo carcasses in abattoir and milk in milk plants, as well as information from SIE should be used to identify infected herds.

Cattle and buffalo from large size herds were more likely to have BTB than animals from small size herds consistent with other studies conducted in Brazil (11, 12, 15, 17, 18, 22, 23) and around the world (47–53). Herd size is a major risk factor, since the number of animals in the herd increase the possibility of the transmission of the *M. bovis* increases. Moreover, in Amazonas, large herds are more commercial than small size herds, meaning that they have frequent introduction of animals from other herds and movement of animals increases BTB transmission risk within the herd. Similar results were found in the neighboring State of Rondonia (24). Modern modeling studies in England reveal that movement of infected animals was responsible for 84% of newly infected farms (31). Due to the large territory a good measure to control and eradicate the BTB should the use of the current Foot and Mouth disease zoning for implementation of a BTB zoning and implementation of control measures specifics by the zone, such as: classification of the zones according BTB prevalence, tuberculosis test requirements by zone, and movement control between the zones.

The presence of cattle and buffalo herds on the same farm increases the risk of *M. bovis* infection regardless of the specie. The presence of different livestock species increases the potential for interactions and inter-dependency among cattle and buffalo management; greater exposure leads to greater incidence. Modeling studies suggest that the environment is seriously contaminated when the practices that promote the mixing of cattle and buffalo occur, which also suggests that the cross-infection route promotes the persistence of BTB infection in cattle and buffalo populations (32). Experience in Australia showed that the complete eradication of BTB from cattle herds was possible only after the elimination of buffalo (*Bubalus bubalis*) population (5). This measure is not feasible for Brazilian circumstances, but the practices that promote the mixing of cattle and buffalo must be discouraged.

In this study, animals managed in semi-intensive and extensive systems were 52.32 and 47.68% of the sampling, respectively. Cattle and buffalo from extensive systems were 2.76 more likely to have been infected by *M. bovis* than animals raised in semi-intensive systems. This can be explained by the fact that animals in extensive systems are more likely to frequent the floodplains where multiple herds share the same pasture thereby increasing their exposure. In addition, in extensive systems, the TST and slaughter of reactors are less frequent than in semi-intensive systems. In order to determine if farming systems are influenced by other risk factors, the multivariable logistic regression demonstrated that once other factors are controlled, extensive systems are in fact protective. Although the risk factor didn't meet the eligibility criteria ($p = 0.50$) to remain in the final model, the result is coherent since semi-intensive herds are more commercial with frequent introduction of new animals from different herds and these findings agree with other studies in Brazil (12, 13, 18, 21, 23).

Based on previous studies of BTB risk factors, the purpose (milk, beef, and mix) is an important risk factor for *M. bovis* prevalence (11–13, 18, 19, 21, 23), however in this study when other risk factors are controlled the purpose of the farm wasn't significant ($p > 0.81$). The regional characterization of the farms in three categories might be an explanation for our results. The "Mix" category adopted to farms with no defined objective (milk or beef) represented almost half of the sampling and can be responsible for confounding within the model. The appropriate characterization of the farming system should be evaluated, considering other factors like breeds predominant in the herd, infrastructure, and the characteristic of neighboring herds. This may provide more accurate representation of the data for models aiming to figure better strategies to break the chain of infection of *M. bovis.*

CONCLUSIONS

- The findings reveal an urgent need for evidence-based effective intervention aiming to reduce BTB prevalence in cattle and buffalo herds and to prevent the spread of *M. bovis* to the human population.
- Species, herd size, and production system need to be considered when developing disease surveillance and control program in Amazon.
- State zoning according the bTB prevalence and adoption of measures specific for zones is highly recommended.
- Information from Inspection Services should be used to identify infected herds.
- Practices that promote the mixing of cattle and buffalo must be discouraged.
- Studies are needed to understand why buffalo are more likely to be infected by *M. bovis* than cattle in Amazon.
- Epidemiological tools, such as modeling should be adopted for BTB control and eradication in Amazon.

This study can stimulate a discussion about the many factors potentially impacting BTB eradication schemes in Brazil and possibly stimulate new research in the areas identified.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by MSU-IRB and IACUC and from IFAM's CEPSH and CEUA.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Veterinary Science

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Bluetongue Disease Control in Northern Ireland During 2017 and 2018

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Since the emergence of bluetongue virus in central and northern Europe in 2006, Northern Ireland's (NI) surveillance programme has evolved to include the use of risk assessments and simulation models to monitor the risk of bluetongue incursion. Livestock production is of high economic importance to NI as it exports approximately 75% of its agricultural produce. Its surveillance programme is designed to enable effective mitigation measures to be identified to minimize disease risk, and to provide additional assurances to protect NI's export markets in the European Union (EU) and third countries. Active surveillance employs an atmospheric dispersion model to assess the likelihood of wind-borne midge transfer from Great Britain (GB) to NI and to identify high risk areas. In these areas, the number of cattle tested for bluetongue is proportionally increased. Targeted surveillance is directed to ruminants imported from restricted countries and regions at risk of bluetongue. Targeted surveillance on high risk imports assists in early detection of disease as, despite all controls and preventive measures, legally imported animals may still carry the virus. In November 2018, a bluetongue-positive heifer was imported into NI. A case specific risk assessment was commissioned to estimate the likelihood of spread of bluetongue as a result of this incursion. November is the tail end of the midges' active period and therefore there was considerable uncertainty pertaining to the survival of midges inside a cattle shed and the potential for incubation of the virus in the vectors. An evidenced-based approach was adopted where temperature and midge abundance was monitored in order to minimize uncertainty and give an accurate estimate of the likelihood of virus spread to other animals following the arrival of the positive heifer. The heifer was destroyed and the evidence indicated that the risk of successful completion of the extrinsic cycle within the local midge population was negligible. This paper describes NI's surveillance programme between January 2017 and December 2018 and the case of a positive imported animal into the country. The importance of effective surveillance in early detection of threats and the usefulness of risk assessments is highlighted through the case study.

Keywords: risk assessment, surveillance, bluetongue, Northern Ireland, wind-borne, midges, *Culicoides*

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INTRODUCTION

Bluetongue (BT) is an economically important, vector-borne, viral disease of ruminants, which can lead to high levels of mortality and abortions (particularly in sheep). Incursion of any of the 27 serotypes can lead to international restrictions on live animal trade, as outlined by the European Community and World Organization for Animal Health (also known as OIE) regulations. NI agriculture is mainly based on beef and dairy production systems (approximately 1.6 million cattle) (1) with 75% of its agricultural produce being exported, and hence very vulnerable to any restriction on such trade.

Bluetongue virus (BTV) is predominantly spread by certain species of biting *Culicoides* midges which vary according to geographical distribution. Midges become infected by feeding on the blood of viraemic ruminants and transmit BTV through subsequent feeding, which is required for the successful production of their eggs. Virus development in midges and transmission of BTV to ruminants are unable to occur in ambient temperatures below approximately 12°C (2) Incursion into regions free from BTV can occur through movement of viraemic animals into the area or by carriage of infected midges by wind plumes, both of which can occur over relatively long distances (3).

Historically, BTV had been mainly confined to the tropical and subtropical areas of the world. Within the last decade, there have been several outbreaks of BT, mainly of serotype 8, in central and northern Europe. After the 2008 BT virus serotype 8 (BTV8) epidemic which spread from France to Hungary and Sweden, there was a period without any cases being reported in central or northern Europe (2010–2014 inclusive). In August 2015 BTV8 re-emerged in France where it still remains present (as of April 2019). In 2018 BTV8 was detected in Switzerland and Germany and in March 2019 the virus was also found to be circulating in Belgium. At the end of March 2019, the whole of France, Switzerland and Belgium and a significant region of Western Germany were declared BT restricted zones according to Commission Regulation 1266/2007, meaning that formal regulations and restrictions on the movement of ruminants from such areas were applied.

The European Union introduced BT specific legislation in 2000 with Council Directive 2000/75, laying down provisions for the control and eradication of the disease. Subsequently Commission Regulation 1266/2007 was introduced, which outlined clear definitions of what constitutes a BT case and a BT outbreak. It establishes the minimum harmonized requirements for monitoring and surveillance of the disease in the European Community. This regulation clarifies that a case of BT is only confirmed if clinical signs or positive laboratory test results are the consequence of virus circulation in the holding in which the animal is kept. Member states are required to indicate circulation of the virus based on a set of epidemiological data.

This definition is not in complete accordance with the OIE terrestrial animal health code. The OIE code defines infection with BT as either the isolation of the virus from an animal or its products, or the detection of BTV antigen, RNA, or antibodies from an animal that shows clinical signs or is epidemiologically linked to a suspected or confirmed case.

EU Commission Regulation 1266/2007 was amended by Commission Implementing Regulation 456/2012 which changed the minimum requirements for monitoring and surveillance of BT. The current criteria for member states to demonstrate freedom from BT entails passive clinical surveillance and annual active surveillance including serological or virological testing of a representative sample of the bovine population, which is sufficient to detect disease prevalence of 20% with 95% confidence, within each 45 km by 45 km region. The legislation gives freedom to member states to formulate their own surveillance strategy within these criteria.

NI has remained free of BTV with the only detection of BT being in February 2008 when pregnant heifers imported from the Netherlands gave birth to calves that were seropositive and viraemic for BTV8. This was the first evidence of transplacental transmission of BTV8 from imported pregnant cows in NI. Surveillance on cattle and midges did not reveal any spread of the virus and only a single nulliparous *Culicoides* midge was caught on-farm during a nationwide survey in February 2008 (4).

The necessity to respond to legislative requirements and to address the risk of BT incursion into NI have been the drivers for developing a surveillance programme based on evidence and risk assessments.

Surveillance

Since the BT epidemic in Europe in 2006 the risk of BT to NI has been monitored continuously. For 2017 and 2018 the threat of BT for NI came from wind-borne arrival of infected midges, or importation of infected ruminants. The closest infected country in 2017 and 2018 was France, for which wind-borne transfer of midges to NI was highly unlikely, but possible for GB. Risk assessments conducted by the Department for the Environment, Food and Rural Affairs (DEFRA, UK) in 2016 and 2017 estimated that the risk of introduction of BT to GB was low to medium, or, between 5% and 80% depending on the season of year (5).

Monitoring and surveillance programmes in NI are designed to mitigate these risks and consist of active surveillance of susceptible animals, targeted surveillance of imported animals and passive surveillance of reported suspect cases.

National vector surveillance was conducted in NI over 5 years (2008–2013), concluding after the end of the vector-free period in May 2013. A proportion of this dataset has been published (6).As the island of Ireland has always been BT free, and GB was declared BT free in 2011, an internal cost-benefit analysis concluded that sufficient information on vector species, distribution and seasonal profiles had been collected over the preceding 5 years to meet the requirements of Commission Regulation (EC) 1266/2007 with respect to vector monitoring outside of a restricted zone. Vector monitoring has thereafter been conducted on farm premises following a suspected BT case, in order to obtain specific localized information on vector presence and prevalence.

Active Surveillance

April to November is the risk period during which temperature may be suitable for midge activity and virus replication according to studies conducted in NI (6). Model output showing the wind-borne spread of midges are provided by the Met Office daily from 1st April to 30th November using the Numerical Atmospheric dispersion Modeling Environment (NAME). NAME is a Lagrangian particle-trajectory model used to model the atmospheric transport and dispersion of a range of gases and particulates (7). In NAME, emissions into the atmosphere are simulated by creating a large number of computational particles where each computational particle represents, in this case, a certain number of midges. These particles are then advected along by the ambient three-dimensional wind field provided by the Met Office's Numerical Weather Prediction model with turbulent dispersion processes being simulated using random-walk methods. The computational particles can also evolve with time to account for various atmospheric processes that might affect midges in the atmosphere, including wash-out by precipitation.

NAME is run twice a day with model particles being released into the atmosphere over a 2 h period at sunrise and a 3 h period at sunset to represent the diel periodicity of midge activity (8) The particles are released from 10 m above ground level, a height assumed to be above the normal flight boundary layer of midges (8) The modeling takes into account the effects of temperature, wind speed and precipitation on midge activity at take-off, and the effect of precipitation on route on an hourly basis (9) In parallel to NAME runs for midges, NAME is run for the same source locations and time periods for tracer particles to indicate the movement of the air, not accounting for midge physiology and behavior. Three fixed locations in France, two fixed locations in GB, as well as locations in Belgium, Netherlands and Denmark, are used as source release sites for NAME. These locations are arbitrary and are used to illustrate the potential risk of incursion across the seas if BT was found near one of these coastal locations.

Active surveillance consists of a serological survey of a sample of susceptible cattle. Vaccination against BT is not permitted in NI except under license, therefore all homebred cattle are expected to be seronegative. As all high risk imported animals are tested, the most probable route of BTV infection for the endemic cattle population is through wind-borne incursion. Wind plumes carrying BTV infected midges could only arise from GB and hence the risk posed by spread from GB was monitored daily from two locations (Liverpool, England and Ayr, Scotland). This provided quantification of the risk posed if BTV became established in GB and also enabled annual monitoring for any undisclosed BTV incursion. The Normandy (France) dispersion point was monitored to evaluate possible spread to the Republic of Ireland as establishment there would pose a high risk of eventual spread to NI (results not presented). Monitoring this point also confirmed that wind-borne transfer of midges from Normandy to NI is highly unlikely.

The Department of Agriculture Environment and Rural Affairs (DAERA) recorded high risk days for wind borne transfer of midges from GB. The risk of midges' arrival was considered high when the NAME model trajectory indicates possible transfer of midges from GB and/or France to the island of Ireland, and low when it indicates that tracer particles could arrive. When the model trajectory indicates possible transfer of midges over a NI county, in the morning, the evening, or both, this day is recorded as a high risk day for this county (**Figure 1**).

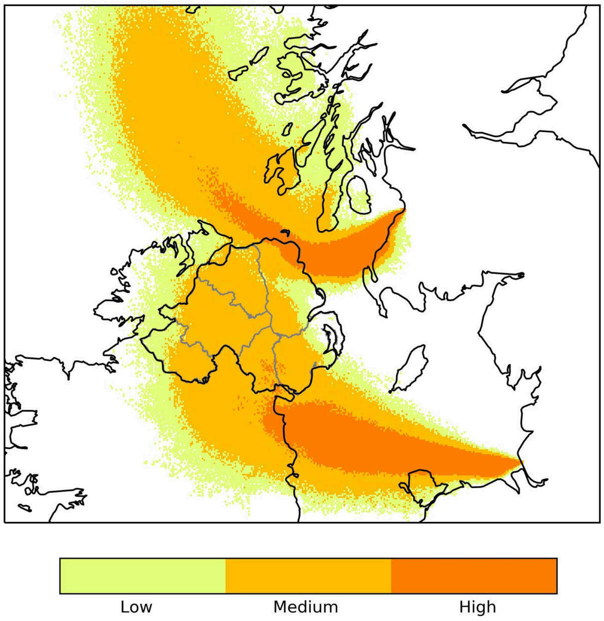

FIGURE 1 | Output from the Numerical Atmospheric-dispersion Modeling Environment (NAME) showing relative concentration of midge particles released around sunset 29/06/2018 from hypothetical source locations in Ayr and Liverpool.

TABLE 1 | Number of days where wind borne transfer of midges from GB to Northern Ireland was highly likely in 2017 and 2018.

	Liverpool (England)		Ayr (Scotland)	
Year	**High risk days**	**Low risk days**	**High risk days**	**Low risk days**
2017	4	5	11	9
2018	8	7	14	5

There were 22 high risk days for midge transfer from GB to NI in 2018 and 15 in 2017 (**Table 1**). The counties most at risk for midge transfer from the Liverpool monitoring point were Down and Antrim, while the counties most at risk for midges from Ayr were Antrim, Londonderry and Down. The model trajectory indicated possible dispersal of midges throughout all counties of NI on 4 occasions in 2018 and 3 in 2017. However, midges will attempt to land once over coastal areas and thus the NAME model output is only representative for wind-blown midge transport over water bodies. Overall, County Antrim is at higher risk from wind borne midges from GB followed by County Down and County Londonderry.

Sampling design was determined by the risk in each county, the cattle population, legislative requirements and historic surveillance recommendations. European Commission Regulation 1266/2007, which details the minimum BT surveillance requirements, states that the sample size must be able to detect a minimum prevalence of 20% with 95% confidence, within each 45 by 45 km region. NI's area is 14,129 km^2 containing approximately 7 regions of 45 by 45 km within it (10) Historically, the OIE recommended detection of a minimum prevalence of 0.5% with 95% confidence, in the bovine population. NI's survey sample is based on this minimum prevalence within the total area of the country. The bovine population is structured in herds and this was selected as the most appropriate epidemiological unit for the survey of BT, a vector borne infectious disease. The sample size to detect 0.5% prevalence with 95% confidence, using an imperfect test with hypothetical sensitivity and specificity 95% and 100% respectively, was calculated to be 629 cattle herds (FREECALC2 from http://www.ausvet.com.au/). This sample size is able to detect a minimum prevalence of 3.5% with 95% confidence, within each 45 by 45 km region of NI. Modeling outputs suggested that testing four adult animals per herd would be optimal for detecting BT presence (11) To enable regional sampling to be systematic, a sample size proportionate to the total number of cattle present was drawn for each of the six counties, with an arbitrary 10% increase in sampling for the counties considered to be at higher risk from wind borne incursion (**Table 2**).

Sampling took place in the vector-free period, mostly from January to March. This period was selected to coincide with the time of Brucellosis sampling on farms to improve cost efficiency of disease surveillance programmes and to satisfy the condition of detection of seroconversion. Cattle were tested for BT antibodies in serum by competitive Enzyme Linked Immunosorbent Assay (cELISA).

For this survey, 719 herds (2,876 animals) were tested for BT antibodies with cELISA in 2017 and 617 herds (2,468 animals) in 2018. Geographical distribution of the sample taken on years 2017 and 2018 is shown in **Figure 2**. One animal had a positive cELISA result in 2017 and one had a positive cELISA result in 2018. Both animals were tested again, in 13 and 28 days respectively, with cELISA, for presence of antibodies and, additionally, with reverse transcription polymerase chain reaction (RT-PCR) for presence of virus. At the re-tests the cELISA results were positive but the PCR results were negative for both animals. These results indicate the presence of antibodies against BT but absence of the virus. The 2017 animal was a cow born in GB in 2008 and imported to NI in 2013. As this was not an indigenous animal and its vaccination and exposure status outside NI could not be verified, it was excluded from the survey results. The 2018 animal was indigenous and had no apparent links to GB or other countries. This result triggered immediate movement restrictions on all the animals of the herd (25 cattle), compulsory housing, whole herd re-test and clinical and epidemiological investigations. When all actions were completed, there was no indication of either the presence or circulation of the virus. The animal showed no clinical signs and there was no evidence of a link with any other suspected or confirmed cases of BT in another country. Circulation of BTV was ruled out.

Targeted Surveillance

Current DAERA policy is to test all ruminants imported from BT restricted countries and regions and countries at risk of BT in mainland Europe. In 2017 and 2018, cattle and sheep were imported from Austria, Belgium, Denmark, France, Germany, the Netherlands and Sweden. France reported BT cases in 2017 and 2018 and Germany in 2018. Imports from these countries were considered high risk.

Targeted surveillance consists of serological and virological testing of all susceptible species from at risk countries in mainland Europe within 5 to 7 days from arrival in NI. Animals arriving from BT restricted zones are tested immediately, either at the port of entry or at the farm of destination, and tested again 5 to 7 days later. Imported animals remain in isolation facilities until the results of the post-import tests are available. The tests conducted are RT-PCR on whole blood to detect viraemia and cELISA on serum to detect antibodies. The presence of antibodies in vaccinated animals provides reassurance of vaccine efficacy, while antibodies in unvaccinated animals may indicate natural infection.

TABLE 2 | NI's sample frame for BT serological surveillance.

County	Divisional Veterinary Office (DVO)	Number of cattle herds	Number of cattle	Percentage of cattle	Adjusted percentage	Adjusted herd quota
Armagh and Down	Armagh	2,427	157,175	10%	10%	60
Antrim	Ballymena	1,443	108,647	7%	8%	46
Antrim and Londonderry	Coleraine	2,673	204,227	13%	14%	86
Tyrone	Dungannon	2,910	175,314	11%	11%	67
Fermanagh	Enniskillen	3,082	153,824	10%	10%	59
Antrim	Mallusk	1,707	134,709	9%	9%	57
Londonderry	Londonderry	956	61,076	4%	4%	26
Down and Armagh	Newry	3,972	209,147	13%	15%	88
Down	Newtownards	2,023	165,250	11%	12%	70
Tyrone	Omagh	3,089	191,526	12%	12%	73
	Total	24,282	1,560,895	100%	106%	631

DAERA has divided NI in 10 areas for administrative purposes. Administration of each division is provided by the Divisional Veterinary Office (DVO). The table shows the number of cattle herds by DVO, cattle population by DVO, percentage of total cattle population, percentage of cattle increased by 10% in high risk areas (adjusted percentage) and adjusted number of herds to be sampled for BT by DVO.

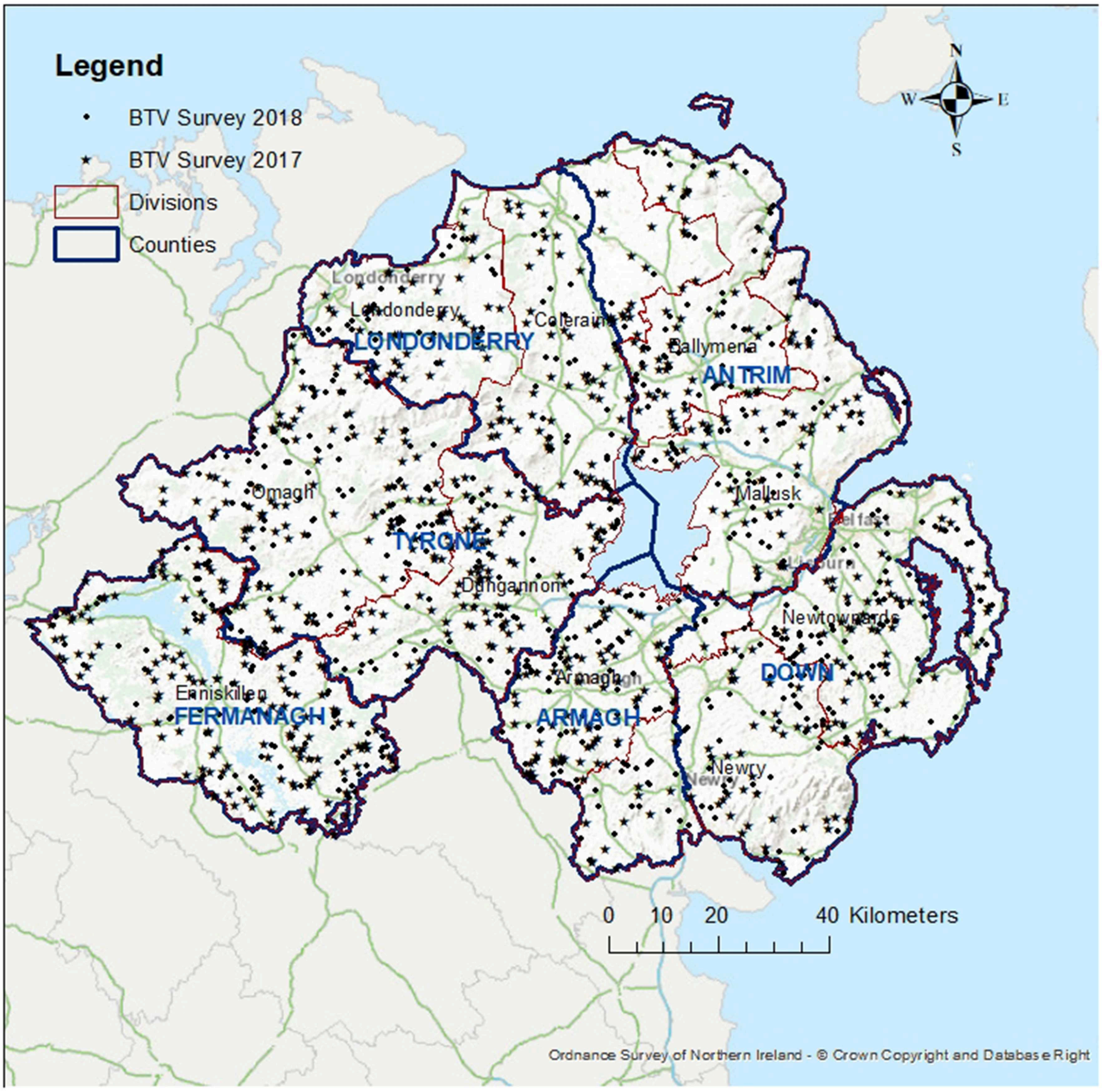

FIGURE 2 | Map of Northern Ireland showing the location of the cattle farms sampled in 2017 (star) and in 2018 (dot), the six counties (blue boundaries) and the 10 administrative divisions of DAERA (red boundaries).

In total, 236 consignments were identified for testing between January 2017 and December 2018. This resulted in 3,476 tests in consignments of cattle and sheep imported from mainland Europe and 41 tests in progeny of cows that were pregnant at the time of import. All except one (99.9%) of the RT-PCR tests were negative for BTV. The positive animal was a heifer imported from France in November 2018, and the case is outlined below. As expected, seroconversion was observed with cELISA in vaccinated animals from restricted zones where vaccination is a requirement for export. Antibodies were also detected in 10 other cattle at the post-import test while in isolation. Nine of them were imported from Austria between October 2017 and February 2018, and one from Denmark in August 2018. Austria had reported BTV4 outbreaks throughout 2016 and those animals were, most likely, previously immunized. These results were not surprising as BT antibodies can be detected at least 5 to 6 years after vaccination or natural infection (12, 13) In addition, out of 3,476 cELISA tests, two were initially positive but they were negative on re-test, which is explained by an estimated specificity of the cELISA test of 99.0% (95% CI 97.2–99.6%) (14).

Case Study

In November 2018, following routine post import surveillance, a single heifer in a batch of 9 imported cattle from France tested positive for BTV using the OIE recommended RT-PCR Hofmann assay (15).

The animals were imported from France on 29th November, at a time when the whole country was a restricted zone and vaccination for BTV4 and BTV8 was compulsory for all exports. The export health certificates accompanying the animals indicated that they were vaccinated. The positive maiden heifer was in a batch of 5 heifers with the same destination herd. A breeding bull and 3 other cattle were also part of this load and went to separate holdings. In line with NI's surveillance programme, the imported cattle were blood sampled at the farm of destination on arrival and they were kept in an isolation facility on the farm. The batch of 5 heifers was tested with the confirmatory RT-PCR Shaw and Toussaint assay 6 days later, and the results confirmed that one heifer was positive for BTV8 (16, 17). Following this result in line with agreed disease control strategies the animal was humanely destroyed. The remaining heifers were negative for BTV. All imported cattle were also tested for antibodies by cELISA and found seropositive which was expected given their vaccination history. A confirmatory third post-import test on the 4 remaining imported heifers was completed in another 6 days, with the same results. The affected heifer was brought into a beef breeding herd of 126 animals which were kept separate, put under movement restriction, and tested twice, at 5 and 11 weeks after the import.

A case-specific veterinary risk assessment was authorized by the Chief Veterinary Officer (CVO) immediately after detection of the positive import, to examine the risk of BTV infection spreading from the positive heifer to the rest of the cohort. Only one possible transmission pathway was identified, which was midges inside the isolation shed feeding on the infected animal and transmitting the virus to the rest of the isolated heifers. Although it was reported that the isolation shed was treated with cypermethrin insecticide before the arrival of the imports, there was uncertainty around the presence and abundance of midges inside the shed. The maximum environmental temperature recorded by the Met Office station for the area ranged from 4.5°C to 10.2°C between 29th of November and 4th December. There was also uncertainty regarding the temperature range inside the isolation shed.

Entomological surveillance conducted in NI between 2008 and 2013, in accordance with regulation 1266/2007, identified that the vector-free period was between December and April (6). Nonetheless, variations exist from year to year and there were instances where midges had been found to still be active mid-December (6). Replication of the virus in the midge is likely to cease at temperatures below 12°C.

Although environmental temperature was below this limit, the temperature inside the shed could be higher, therefore survival of infected midges and transmission capacity inside the cattle shed could not be excluded. If the temperature inside the shed was, and remained above 15°C, the extrinsic incubation period for virus replication was estimated at 20 days (2).

It was therefore recommended to monitor the shed's temperature and midges' activity. Local surveillance of cattle and sheep on neighboring farms was not recommended on this occasion, as the likelihood of virus replication in midges outside the shed was considered negligible due to the incident occurring at the very end of the normal NI vector active period.

Two mains-powered (240 v) Onderstepoort UV light traps were set up on the farm. The first trap was placed inside the shed above the quarantined animals at a height of 2.7 m and the second trap was mounted on the outside wall of the shed at a height of 1.3 m. Four Tinytag TGP-4500 (Gemini Data Loggers, Chichester, UK) temperature loggers were similarly placed inside ($n = 2$) and outside ($n = 2$) of the shed close to the traps until the beginning of March. Temperature was logged each hour. *Culicoides* trapping commenced on 10 December 2018, with two 24 h samples taken each week until 28 February 2019, when the restrictions on the farm were lifted. Any *Culicoides* captured were identified to group level (*Obsoletus, Pulicaris, Impunctatus,* "other") using wing patterning following the key of Boorman (18). The parity of the females (nulliparous or parous) was assessed using abdomen pigmentation following Dyce (19).

A total of 32 midges were caught in 43 trap collections. The majority of *Culicoides* collected ($n = 30$) were female Obsoletus group. Only a single male (Obsoletus group) and a single female "other" were collected. Most ($n = 27$) midges were trapped in the outside trap with only five Obsoletus females caught inside. A maximum of 14 Obsoletus group females were caught on 10 January 2019, with 11 in the outside trap and three on the inside one. A total of seven parous females were caught over the sampling period (all Obsoletus group) with a maximum of three caught in one 24-h period (**Figure 3**).

During the recording period the average temperature inside the shed was 7.2°C and outside was 6.3°C. Inside the shed the temperature ranged from −1.3°C to 12.0°C whilst outside this was −5.5°C to 13.6°C. The temperature was recorded above 12°C on the outside temperature loggers only, occurring on 6 days between mid-February and the beginning of March. For this particular shed, the effect of housing was not to increase upper temperatures but rather the body-heat of the livestock had the effect of moderating lower night-time temperatures (**Figure 3**).

Following negative results of all cattle tested on the farm both 5 and 11 weeks after the disposal of the positive heifer and the absence of a significant *Culicoides* midge population (i.e., reflecting Regulation 1266/2007: fewer than five parous females caught overnight in any one light trap collection during the surveillance period) the probability of BTV circulation was estimated to be negligible with a high degree of confidence.

DISCUSSION

Continuous and robust surveillance at, or above, legislative requirements and international standards is central to maintaining the BT free status of NI. Nevertheless, surveillance programmes need to be both efficient and cost effective. While the logistical approach utilized during BT surveillance in NI was very cost effective, the sample size utilized was higher than the minimum EU requirement. The additional sampling through use of the herd rather than the individual animal as the sampling unit was based partly on epidemiological rationale (as infection may be clustered within different herd management groups) and partly to provide additional assurance to non-EU countries thus protecting such export markets. This system builds on previous preliminary work in NI (20) and on experiences on risk based surveillance and midge based wind dispersion models documented elsewhere (21–23).

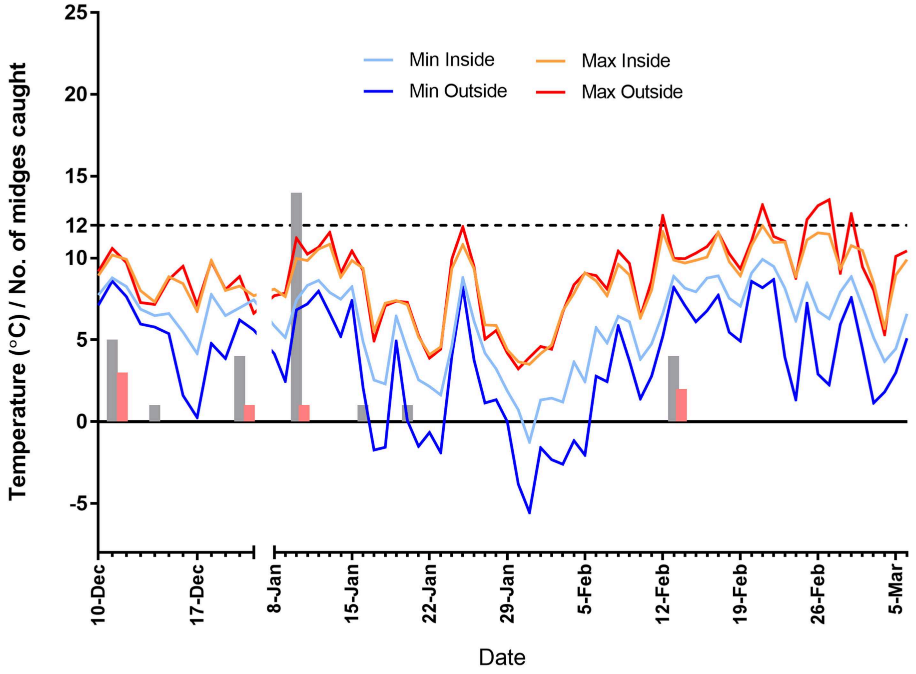

FIGURE 3 | Average maximum and minimum hourly temperature recordings inside and outside the shed containing the quarantined animals, for the period of 10 December 2018 to 6 March January 2019 (no recordings were taken over the Christmas period). Light trap counts of female *Culicoides* are denoted by grey bars, with parous female counts denoted by red bars. The temperature limit to virus replication in midges is 12°C, which is denoted by a dashed line.

Improved efficiency can be achieved with a risk-based approach. In the case of serological survey for active surveillance, use of the NAME model has greatly improved the capacity to identify areas at higher risk of midges arriving from GB, and to increase BT surveillance toward these areas without increasing the sample size, therefore keeping the cost at the same level. NAME also models wind-borne transfer of midges from Normandy in the north of France, the country closest to NI with BT restriction zones in 2017 and 2018. It is highly unlikely that midges are transferred by the wind directly from France to Northern Ireland. This was confirmed by the model as there were no risk days for wind-borne dispersal of midges from France to NI.

During design of the surveillance system consideration must be given to practicalities that may hinder its implementation. The sampling frame as presented in **Table 2** indicates that the target number of herds to be tested in a year is 631. However, during implementation, the actual number of herds tested deviated slightly from this target (719 and 617 herds tested in 2017 and 2018, respectively). Factors such as farming activities, co-ordination and timely release of resources forced alterations to the survey at the phase of implementation. This is not unexpected and a safety margin, to mitigate the risk of insufficient surveillance to maintain freedom, is necessary. In the current NI surveillance, the target number for the survey is well above the legislative requirements which provides flexibility during implementation. The sampling frame presented by the on-farm blood sampling for brucellosis surveillance provided an ideal and cost-effective platform with which BTV serological surveillance could be combined, which was not available to many of the other EU countries. However, this is an area of concern for the future as NI completes 5 years of brucellosis free status in 2020, with the requirements for brucellosis serological sampling being reduced therefore other surveillance protocols will have to be devised.

The Republic of Ireland (ROI) has examined the possibility of using blood samples from cull cows collected at abattoirs for country wide surveillance in order to demonstrate freedom from BTV and potentially other bovine viral infections (24). The study has indicated that blood samples from cull cows which were collected under the ROI brucellosis surveillance programme can also be used for BT surveillance. There were sufficient cull cows tested to allow a sample that was geographically stratified to cover the whole country. It was representative of the cattle population and its density, and the size of the sample was sufficiently large to satisfy EU requirements for disease freedom. This approach makes surveillance programmes less costly as more than one disease is tested from each sample. Sampling at abattoirs instead of farms has the additional advantages of saving time and resources and reducing the stress of a farm visit to cattle and farmers.

Another advantage of the NI situation is being part of an island, which mitigates against vector borne spread of BT to some degree as well as having physical limited access points for entry of livestock to the island as a whole. This enables much easier quantification of these incursion routes compared to mainland European countries, particularly in relation to use of assessing the risk from wind plumes. Application of some of the measures used in NI may be limited in such countries.

In the case of a positive import, the veterinary risk assessment identified transmission pathways, narrowed down the population of cattle at risk of infection and pinpointed areas of uncertainty. Unnecessary restrictions and testing of neighboring farms were avoided. Close collaboration between risk assessors and risk managers was essential to formulate the next steps of the disease control strategy. In this case, more information was needed to give an estimate of the probability of virus circulation in midges inside the cattle shed. The case happened at the end of the vector-active period and the presence of parous midges and virus circulation could not be excluded based on environmental temperature alone.

Resources were focused on gathering epidemiological data on the shed temperature and the capacity of midges to replicate and transmit BTV. Elucidation of this area of uncertainty increased confidence in the risk estimate.

Another situation where epidemiological data for BT surveillance is valuable is in the event of BT cases being identified within 150 km of NI, which could be in GB, the Isle of Man or the ROI. In such circumstances, parts of NI would be found inside the surveillance zone. This would have an impact on movement of animals and national and international trade. European Council Directive 2000/75 makes provision for changes to the boundaries of the zone when a duly substantiated request is made by a Member State (25). Having a well-documented, long standing surveillance programme would be fundamental, if NI wanted to request alteration of such zones on geographical, meteorological and epidemiological grounds.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All samples from animals were obtained within an official context relating to disease control and surveillance. All sampling procedures complied with national and European regulations.

AUTHOR CONTRIBUTIONS

AG wrote the first draft of the manuscript and organized the wind-borne transfer of midges database and performed sample size calculations. FM and AG contributed in conception of the manuscript. AM wrote a section of the manuscript and provided entomological data and analysis. DM took accountability of field operations of the case study. SM and WT contributed to the manuscript, provided NAME data, and took accountability for NAME model outputs. KB, VH, and BC took accountability for laboratory testing. FM, IM, DM, AM, and VH critically revised the manuscript. All authors read and approved the submitted version.

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The Risk of Infection by African Swine Fever Virus in European Swine Through Boar Movement and Legal Trade of Pigs and Pig Meat

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African swine fever (ASF) is currently spreading westwards throughout Europe and eastwards into China, with cases occurring in both wild boar and domestic pigs. A generic risk assessment framework is used to determine the probability of first infection with ASF virus (ASFV) at a fine spatial scale across European Union Member States. The framework aims to assist risk managers across Europe with their ASF surveillance and intervention activities. Performing the risk assessment at a fine spatial scale allows for hot-spot surveillance, which can aid risk managers by directing surveillance or intervention resources at those areas or pathways deemed most at risk, and hence enables prioritization of limited resources. We use 2018 cases of ASF to estimate prevalence of the disease in both wild boar and pig populations and compute the risk of initial infection for 2019 at a 100 km^2 cell resolution via three potential pathways: legal trade in live pigs, natural movement of wild boar, and legal trade in pig meat products. We consider the number of pigs, boar and amount of pig meat entering our area of interest, the prevalence of the disease in the origin country, the probability of exposure of susceptible pigs or boar in the area of interest to introduced infected pigs, boar, or meat from an infected pig, and the probability of transmission to susceptible animals. We provide maps across Europe indicating regions at highest risk of initial infection. Results indicate that the risk of ASF in 2019 was predominantly focused on those regions which already had numerous cases in 2018 (Poland, Lithuania, Hungary, Romania, and Latvia). The riskiest pathway for ASFV transmission to pigs was the movement of wild boar for Eastern European countries and legal trade of pigs for Western European countries. New infections are more likely to occur in wild boar rather than pigs, for both the pig meat and wild boar movement pathways. Our results provide an opportunity to focus surveillance activities and thus increase our ability to detect ASF introductions earlier, a necessary requirement if we are to successfully control the spread of this devastating disease for the pig industry.

Keywords: risk assessment, disease transmission, pork product, swine disease, wild boars, European Union (EU), disease hotspot, riskiest pathway

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INTRODUCTION

African Swine Fever (ASF) is an infectious disease of several members of the *suidae* family that is caused by African swine fever virus (ASFV) belonging to the Asfarviridae family (1). Animals can become infected with ASFV via nasal, oral, subcutaneous, or ocular penetration, and once infected they will shed the virus into the environment (2), and even after death their carcasses can continue to contribute to virus dissemination since the virus can persist in blood and tissues for prolonged periods. It has been demonstrated that the virus can remain viable in feces and urine up to 8 and 15 days, respectively, (3) and for weeks in pork meat and processed products (4–8). There is also the possibility that ASFV can spread via soft ticks, which is the predominant method of spread between warthogs, bush pigs, and wild pigs in the disease origin area in sub-Sahara Africa, although they are not a requirement for disease spread (1). Thus, ASFV has a high capacity for transmission by both direct and indirect contact with infected animals, or via the environment, vectors, and animal products.

ASF is recognized as one of the most important and dreaded diseases of pigs for several reasons. Firstly, it can spread to pigs in disease-naïve areas through numerous different entry routes such as trade in live animals and animal products, wild animal migrations, fomites, vehicles, and vector movements (9, 10). This makes it particularly challenging to implement effective preventive measures in order to minimize the risk of incursion of the disease. Secondly, until now, no vaccine has been available for ASF (10). Thirdly, if introduction of ASF does occur in a region, the disease can have a devastating impact on the swine sector as it can result in huge losses (10). Some viral strains demonstrate a high virulence potential and can effect a lethality rate near 100% (11). Once the introduction of the disease in a region is confirmed, culling of sick animals and restrictions for live animal and animal product trade follow in order to limit the spread of the disease to neighboring areas or other countries; these mitigation measures lead to further economic damage for farmers and food producers. Finally, management and eradication of the disease in areas with new incursions or endemic areas is difficult, resource-intensive, and costly due to the infectivity durability of the virus in the environment, the many transmission pathways and the potential establishment of a wild animal reservoir population, which could be supported by competent vectors (if present) (1). Therefore, effective methods to help decision makers decide where to focus limited surveillance resources are very useful and can help to reduce the economic impact of an ASF outbreak.

The epidemiological situation of ASF has changed rapidly over the last few decades. Historically, the disease was mainly present in the African swine population but, after entering Portugal in 1957 likely due to swill feeding with contaminated food waste, it became endemic in the Iberian peninsula and several linked outbreaks were observed in Italy, France, Malta, Belgium, and the Netherlands during the following years (12). Apart from Sardinia, where the disease continues to persist until now, ASF was considered completely eradicated from Europe in 1995. However, in 2007, outbreaks were reported in domestic and wild boars in Georgia, the first time outside of sub-Saharan Africa in many years (1). The virus introduction was probably caused by the import of contaminated meat from Madagascar or Mozambique (12). Despite the effort to contain and eradicate the disease, ASF spread progressively to other countries in the Caucasian region such as Armenia, Azerbaijan, and the Russian Federation in 2007–2008 (12, 13). Migration of infected wild boars, trade of infected animals and derived meat products, poor biosecurity measures and delayed notification by small farmers seem to be the most important factors that hampered the disease eradication and lead to a constant spread toward the European Union (EU) during the following years (14, 15). New outbreaks concerning domesticated and wild pigs were reported in Ukraine (2012), Belarus (2013), Poland and Baltic countries (2014) (16). EU Member States (MS) responded to this rapid escalation of the disease situation by intensifying biosafety mitigation measures and setting up specific surveillance programmes and information campaigns for veterinarians, farmers, and travelers (9). However, until now (May 2019), ASF is still present in the mentioned countries and outbreaks in pigs or wild boars have also been notified by the Czech Republic, Hungary, Bulgaria, and Romania (12, 16). Several ASFV infected wild boars were also found in Belgium confirming that ASF is able to make large geographic jumps (15). In addition, since 2017 the disease began to progress rapidly in an easterly direction, with the Russian Federation registering new cases in East Siberia followed by China in 2018 and Mongolia, Vietnam, and Cambodia in 2019 (17).

Direct contact between sick and healthy animals is one of the most evident ways of virus transmission considering that saliva, urine and feces are heavily contaminated (18). Although animal health legislation of all European countries bans live animal trade from high-risk areas, the absence of clinical signs during the latent period makes the early identification (and notification) of new outbreaks in ASF-free regions difficult as well as the detection of infected pigs by the border authorities of the destination country. As such, there can be a fairly large time window at the start of an ASF outbreak in a region where no one is aware the disease is circulating in the pig population and thus infected pigs may be traded. Another prominent cause of incursion of ASFV in European ASF-free areas is by import of pork products derived from infected animals (2). If the disease is not detected by Local Authorities at farm or abattoir level, infected pigs can be slaughtered and their contaminated carcasses used for fresh or processed pork products. Swill feeding is illegal in most countries around the world, including the EU, but despite this, some pigs raised in backyard or free-ranging small farms are fed with untreated food leftovers or catering waste (18). The prolonged survival of the virus in edible tissues and the low infectious dose required to infect animals make this transmission pathway particularly relevant, as proven by several outbreaks in recent years (19). Even if waste pork products are properly disposed of, wild boar are still potentially able to get access to landfills or waste bins, become infected after contacting/ingesting the contaminated food, and transmit the virus to the local animal population. Wild boar can play an important epidemiological role not only in this transmission pathway but they can also be responsible for transboundary spread of the disease due to their natural dispersal ecology in search of new territory (20).

Indeed, although wild boars normally remain close to their natal home range, studies reported that they are capable of covering long distances (up to 250 km) (21). A new outbreak can occur when infected wild boar are able to gain access to farms and contact susceptible domestic pigs, such as those on farms with poor biosecurity measures. As an example, the initial infection of the Lithuanian pig population with ASF is believed to be due to movements of infected wild boars from Belarus (19, 22).

Due to the importance of ASF and the recent incursion into Europe, several risk assessments have been performed in order to estimate the likelihood of introduction of ASF into Europe or specific European countries, using qualitative, semi-quantitative and quantitative models. In 2010, the European Food Safety Authority (EFSA) evaluated the risk of endemicity of ASF in the Caucasus region and the consequent risk of release into Europe through several potential routes (13). A few years later, the same qualitative model, which was based on expert elicitation, was used to update the results given new epidemiological and experimental evidence (23). Recently, two similar semi-quantitative methodologies, which rely on expert knowledge, were developed to assess the ASF risk, via multiple pathways, to Belgium (24) and Finland (25). Furthermore, semi-quantitative frameworks, which score the risk of ASFV release in the EU, have been published for a single route of disease entry such as wild boar movements (26, 27), illegal importation of pork and pork products (28) and transport-associated routes (29). Regarding the quantitative risk models, only a few have been developed until now. Mur et al. (30) estimated the probability of ASFV entry for each country of the EU through the import of live pigs and, a few years later, the same group presented a risk assessment considering multiple ASFV entry pathways of high relevance for transmission, although some of them were still modeled adopting a semi-quantitative approach (31). Recently, Lange et al. (32) developed a mechanistic model to simulate the spread of the disease in wild boar populations in Europe and subsequently to assess the impact of control measures, presence of natural, or artificial barriers and management strategies of wild animal populations implemented by affected EU MSs. Lastly, Simons et al. (33) assessed the risk of entry of ASF into EU MSs using a quantitative model for a number of pathways, although did not consider whether this could lead to infection in susceptible pigs or wild boar in those countries.

Apart from Lange et al. (32), all of the models listed above, whether qualitative or quantitative, assessed the risk for a single or multiple EU countries at a country level. Furthermore, some of the models assessed the risk of entry only and did not consider the transmission to susceptible pig or wild boar populations. Only one of the models (33) was able to quantitatively assess the incursion risk by multiple pathways, however, due to only assessing risk of entry, it was not possible to compare pathways in that model to indicate which pathway was of greatest risk. In this study, we adapt a generic risk assessment framework (34) to assess quantitatively the risk of infection with ASFV in domestic pigs or wild boar across Europe at a fine spatial scale (100 km^2 cells) via multiple pathways, namely trade in live pigs, trade in pig meat products, and movement of wild boar. We create risk maps for 2019 of the probability of infection in pigs and boar for each pathway and for all pathways combined, in order to identify hotspots of ASFV incursions in the EU, and the pathways of most importance in each area.

MATERIALS AND METHODS

We assess the probability of at least one infection in boar or pigs through three pathways of transmission within Europe, namely: legal trade of pigs, legal trade of pig meat, and movement of wild boar. We acknowledge that other pathways may be important for transmission of ASFV, such as legal movement of meat within the EU via travelers, but could not find data of sufficient detail or quality to parametrize these with enough certainty (2, 9). The wild boar pathway is assessed for the whole of Europe, whereas the other two pathways are restricted to EU MSs only due to lack of data in other European countries. The approach is stochastic and applies the framework outlined in Taylor et al. (34). The risk assessment framework is outlined in brief below and we highlight how it is followed for each of the pathways. The risk of ASF is assessed through these three pathways separately and combined into one overall risk at a spatial scale of 100 km^2 raster cells. The risk assessment uses reported cases in 2018 in order to predict the risk of ASF infection in 2019.

The Generic Risk Assessment Framework

The generic framework for performing quantitative spatial assessments of risk of infection is designed to be suitable for many disease entry pathways (**Figure 1**), with the aim of answering the risk question "What is the risk of infection of a pathogen in Area B due to the presence of that pathogen in Area A?"

Adopting this framework, we calculate the risk of initial infection with ASFV via a single pathway by estimating how many infectious animals/products (depending on the entry pathway) will enter a new Area B given the disease is present in Area A, whether detection of those animals/products would occur, the probability of survival of the animal and pathogen, and the rate of contact and transmission to susceptible animals in Area B. In this risk assessment for ASF, Area B is defined to be EU MSs and Area A is the whole world. We compute the risk assessment at a 100 km^2 cell level in Europe by first calculating the number of infected units entering cell c of Area B, $I_k(c)$, as:

$$I_k(c) \sim Bin\left(N_k(c), p_k\right), \tag{1}$$

where k is a region of Area A (defined for each pathway), $N_k(c)$ is the number of units (pigs/boar/pig meat) moving from region k to cell c and p_k is the prevalence in the relevant species in region k. We thus define $I(c) = \sum_k I_k(c)$ as the total number of infected units entering cell c from all of Area A. For the trade pathways, we define the regions of Area A to be countries around the world. For the wild boar movement pathway, we define the regions of Area A to be 100 km^2 cells in which we estimate prevalence to be non-zero, based on reported cases in Europe.

For the detection step, in this ASF case study, we assume there is no detection of infected animals or products in the trade or movement pathways. The only relevant EU decree regarding movement of pigs or pig meat involves a restriction on trade from

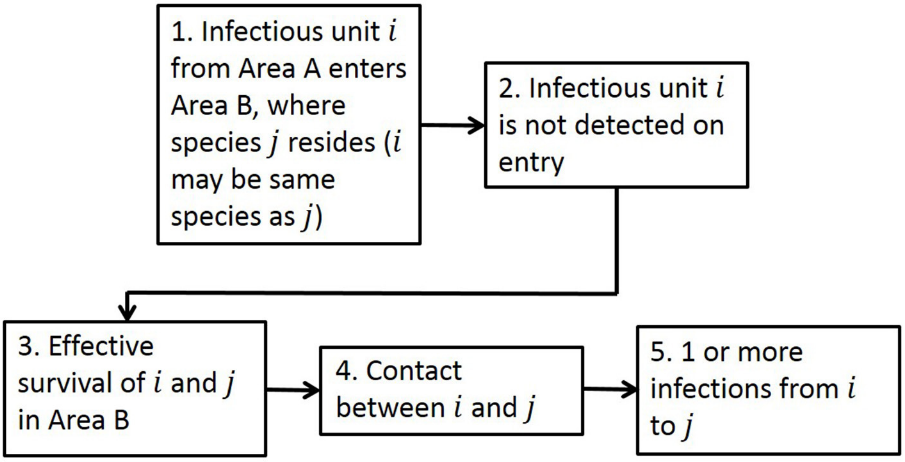

FIGURE 1 | The generic framework for calculating risk of infection spatially, as seen in Taylor et al. (34). There are five steps in the framework: Entry, Detection, Survival, Contact, and Transmission to address the risk question "What is the risk of infection of a pathogen in Area B due to the presence of that pathogen in Area A?" The term "unit" in Step 1 addresses the fact that it could be infected animals or products or contaminated items entering.

ASFV infection zones once cases are detected, and we account for this in the prevalence estimates. Otherwise, any testing of pigs or pig meat is voluntary and the exact procedures may vary widely by country. We therefore assume no inspection or testing of traded pigs and pig meat occurs, and treat this as a worst-case scenario. However, we do perform a scenario analysis with detection included, with method and results provided in the **Supplementary Info S3**.

We use the disease metric R_0 to describe the survival of the pathogen/animal, as well as contact and transmission between the infectious units and susceptible pigs and wild boar. R_0 is a measure of the expected number of new infections that would occur if one infectious unit were to enter a susceptible population. Our equation for $R_0(c)$ includes information on the susceptible populations at risk in cell c, the pathway of entry, the transmission between infected and susceptible animals and the duration of infection. Each parameter from $R_0(c)$ is drawn from a distribution of likely values. The number of initial infections, $N_I(c)$, in cell c is then calculated by $I(c)$ draws from a Poisson distribution with mean given by $R_0\,(c)$:

$$N_I\,(c) = \sum_{1}^{I(c)} \xi$$
$$\xi \sim \ Pois\,(R_0\,(c))\,.$$

Each infected animal entering cell c will in turn infect an average of $R_0\,(c)$ susceptible animals. We represent this by a Poisson distribution with mean $R_0\,(c)$, as this distribution simulates the number of events that can occur given the expected number, and ensures a non-negative integer value is returned. There are $I(c)$ infected units entering cell c, each with the same Poisson distribution, which produces the summation, to give $N_I(c)$ new infections overall. The probability $R_{I,X,p}(c)$ or $R_{I,X,b}(c)$ that at least one susceptible animal would become infected in cell c due to entry via a single pathway X is then given by the proportion of the simulations where infection occurs in a susceptible pig or boar, respectively. We outline in greater detail below how we compute each step of the risk assessment for each of the pathways below. Within the model, we use the Poisson distribution, as outlined above, or the Binomial distribution to simulate the expected number of successful events that occur if each event has the same probability of success.

Legal Trade of Live Pigs

The legal trade of live pigs is the easiest to implement under the framework outlined above as there is good data availability for parameters for each step in the pathway. For the entry of infectious animals, we use trade data from TRACES (35) to determine the total number of animals ($N_k\,(c)$) moving from each region k of Area A to each cell c of Area B and input this into Equation (1). The TRACES data includes a post-code for the destination of the trade, the country of origin and total number of animals moving in 1 year from that country to that post-code destination. We convert the destination post-codes to latitude and longitude values to find the 100 km^2 cell of entry. We calculate prevalence at a country level to coincide with the TRACES data on origin of trade. For prevalence data in each country of the world, we use output from the model outlined in Simons et al. (36), which uses OIE data on recent reported cases of ASF (excluding cases in Sardinia due to successful containment on the island) to calculate prevalence in each country of the world. This model for prevalence incorporates under-reporting, trade restrictions within infected zones and the length of latent period of the disease to compute an accurate prevalence estimate. We assume that all animals are destined for farms. Therefore, we assess the survival, contact and transmission rates assuming contact with susceptible pigs on a farm. To calculate the survival, contact and transmission between imported pigs and susceptible pigs on a farm, we use the following equation for R_0:

$$R_0 = \frac{\gamma\beta S(c)}{r}.$$

In this equation, γ is the contact rate between pigs, β is the probability of transmission given contact between pigs, $S(c)$ is the number of susceptible pigs that the animal could have contact with and r is the rate of an infected pig dying from or recovering and no longer shedding ASFV. We assume no contact with wild boar in this pathway. For further details of how this pathway is computed, see **Supplementary Info S1** and Taylor et al. (34) in which a case study for the live animal trade pathway was performed for Lumpy skin disease.

Movement of Wild Boar

As there are no datasets on wild boar movement between countries, never mind between 100 km^2 cells, we instead use a model of boar movement at the cell level. This is based on boar ecology, such as which age groups and gender tend to undergo dispersal events compared to home range movement and the reason for movement. The model for movement of boar is adapted from Simons et al. (33) and is explained fully in Taylor et al. (37); we outline the key steps here. The model uses data on boar abundance and the habitat suitability of Europe at a cell level for boar (38). We include two types of boar movement—within a home range and long-range dispersal. When performing home range movement, the boar traverses the whole of its home range area. For long-range dispersal, we fix a total number of steps that each dispersing boar will perform, based on maximum distances of boar dispersal and our cell size. In order to determine the direction of boar movement from each cell we use the habitat suitability score for each cell as a proxy for deciding where boar would want to move to. We calculate the ratio between the habitat suitability in each neighboring cell and the overall habitat suitability of all the neighboring cells and use that to determine the probability of the boar moving to each cell. We assume one dispersal event each year and assume that a dispersing boar spends the rest of the year performing home-range movement.

We calculate $N_k(c)$, the number of boar moving from all cells (k) in Area A which have non-zero prevalence to cells (c) in Area B, by combining the probability of moving to each cell and the total number of boar in the origin cell, using an abundance map of boar across Europe (38). Then to determine how many infected boar enter each cell c in Area B using Equation (1), we estimate prevalence in wild boar for each origin region k, which in this case are also 100 km^2 cells, using the locations of reported ASFV cases in wild boar, an under-reporting factor to account for infected boar carcasses not being found or reported, and the abundance of boar in each cell.

We calculate the potential transmission of ASFV from these infected boar to susceptible boar and pigs in the destination cell using two separate equations for R_0 for transmission to boar and pigs. For wild boar contact with pigs, we use a similar formula to the R_0 for live pig trade, in which we include the number of susceptible pigs in the area at risk, the length of the infectious period in live boar, the contact rate between boar and pigs and the probability of transmission given contact. We adapt the equation for R_0 for boar by including two additional factors—group dynamics and contact with carcasses. As wild boar primarily live in matrilineal groups (39), we use different contact rates for within and between group contact. ASFV is both highly virulent with almost 100% mortality and highly persistent, such that carcasses can remain contaminated for a long time. Thus, we include the possibility that a susceptible boar could become infected from an infected boar carcass, by considering data on contact rates between live boar and boar carcasses, the probability of transmission via such contact and the length of time the boar carcass is available for contact. The equations for R_0 are included in **Supplementary Info S1** and further explanation is provided in Taylor et al. (37).

Legal Trade of Pig Meat Products

There are datasets available on the amount of legally traded pig meat products, such as from Comext (40) which gives information on the amount (in tons) of pig meat products that are imported into each EU MS from both within and outside of the EU. Similar to the legal trade of pigs pathway, we use output from the model reported in Simons et al. (36) to estimate the prevalence of ASFV in pig meat products at time of slaughter in each country of the world. When calculating the entry of pig meat products from infected pigs, we use the same Binomial formula as outlined above but now use volume of product instead of number of animals—our unit in **Figure 1** is now grams of pig meat products. We also have to take into account the many different product types that fall under the category of pig meat. The Comext data are split into different product types by a product code, representing the different products that are traded and the different processes each of the products may undergo. We simplify this data into 12 categories for product type, based on similarities of product composition, and five processes that the product may undergo, which leads to 21 product types overall (since not all product types will undergo all types of processes). See **Supplementary Info S1** for a final list of all product types and processes. We keep these separate at this stage and estimate the amount of product from infected pigs for each of the 21 product types entering each EU MS.

As the legal trade in pig meat products is primarily for human consumption, this pathway focuses on estimating the probability that this meat for human consumption could end up inadvertently being contacted or consumed by domestic pigs or wild boar. We assume that wild boar can be in contact with food waste through landfill and other locations (e.g., waste bins outside households or in parks, nature reserves etc.) which may contain pig meat waste products. For domestic pigs we assume that biosecurity levels on commercial farms across Europe are high and so the probability of potential contact with imported pig meat is negligible and therefore it was decided it was not necessary to consider this further. However, for backyard pig farms we consider the possibility of contact due to illegal swill feeding. Due to the need to consider how pig meat products could end up in waste or being swill-fed to a backyard pig, there are a few additional considerations in the contact, survival, and transmission steps of the pathway. We include a more detailed version of the generic risk pathway for the food pathway (**Figure 2**) and describe these additional steps below.

Entry

The Binomial Equation (1) is used to compute the entry of product from infected animals by combining the total amount in grams of each product traded from the country of origin to the destination country and the prevalence in the country of origin. Similar to the live pig trade pathway, the prevalence at a country level is estimated using the method outlined in Simons et al. (33). We assume each gram of pig meat product from each country has the same probability of being derived from an infected pig. As above, we sum over all source regions to produce the total amount of infected product in grams entering each destination country C, for each product type z, which we denote by $I(C,\ z)$.

Viral Load

For ease of computation regarding contact, survival and transmission, we switch at this point to perform our computations using the total viral load entering each country rather than the amount of infected product. We calculate $v(T_S,\ C,\ z)$, the initial viral load in product z for all grams of product z destined for country C at time of slaughter (T_S). The viral load at time T_S will be higher than the viral load at time of entry to country C, but we include this decay over time in the survival step instead. As we do not include detection on entry, the amount of infected product on entry is the same at time of slaughter and time of entry. The initial viral load at time T_S is based upon the average composition of each product type from different animal tissues (namely meat, fat, offal, skin, and bone) and the viral load concentration in infected tissues. See **Supplementary Info S1** for the proportions for each product type z split into the component tissues. We use estimates of an average viral load concentration in each tissue, from experimental data, assuming that the pig was slaughtered before clinical signs appeared (it was assumed that any pig showing clinical signs would be immediately removed from the food chain) and the virus concentration follows an exponential relationship from the day of infection until the viremia peak and decreases similarly until the day the virus is not detectable. Thus, the initial viral load is calculated as

$$v\left(T_S,\ C,\ z\right) = \sum_{z_p} p_{z_p} I(C,\ z) 10^{v_I(z_p)},$$

where z_p represents the different tissues in product z, p_{z_p} is the proportion of product z that is composed of tissue z_p and $v_I(z_p)$ is the initial viral load concentration in tissue z_p.

Survival

We consider three steps when estimating the survival of the virus in each product type: the survival of virus during animal slaughter and meat processing, during transport time and during cooking. Processing occurs in the origin country, transport is between countries, and the cooking process for any raw meat imported occurs in the destination country C. Thus, this survival step estimates how the viral load will change from time of slaughter, T_S, to the time of consumption of the product, irrespective of whether this product will end up being in contact with pigs or boar.

Different processes that may be applied to pig meat products include salting, drying, smoking, and being chilled or frozen. For virus survival during processing, we determine the remaining viral load in each product matrix after processing by assuming an exponential decay of viral load, using data on the decay rate in each tissue, the process that is undergone for that product type and the length of time that process will take. The viral decay rate, $r_v(z)$ depends on the product type z, as it is calculated based upon the maximum virus survival time in products that have undergone different processes. For estimating the decay due to processes, we did not include the fact that the processes themselves may reduce the viral load further, we only included the time taken for a process to occur. For some products, it is possible that multiple processes are applied, however, these processes may or may not be undergone simultaneously. Therefore, for these, we assume the process that takes the least amount of time as this is a worst-case assumption for amount of remaining viral load. Therefore, the viral load after time of processing (T_p) of product type z destined for country C, $v(T_p,\ C,\ z)$, is

$$v\left(T_p,\ C,\ z\right) = v\left(T_S,\ C,\ z\right)\left(1 - r_v\left(z\right)\right)^{t_p},$$

where t_p is the assumed time taken to undergo the process.

To estimate the viral load after transport (T_T), we estimated the average time taken for transport between different countries. This was based on the distance between the country of origin of the trade and the destination country, the speed of two transport methods—fast (e.g., flight) or slow (e.g., ship/rail/lorry) transport between the countries, and the proportion of trade that would occur via fast or slow transport. For further details of how the average time, $t_T(C)$, for transport to country C was estimated, see **Supplementary Info S1**. Therefore, the viral load after transport $v(T_T,\ C,\ z)$, is calculated as:

$$v\left(T_T,\ C,\ z\right) = v\left(T_p,\ C,\ z\right)\left(1 - r_v\left(z\right)\right)^{t_T(C)}.$$

Lastly, we included virus survival during cooking in the destination country C. We assumed that products which had been salted, smoked, or dried would not undergo a cooking process but all other product types would. ASF virus is killed if food is cooked to 60°C for at least 10 min (41), and hence to determine the viral load remaining after cooking (T_C), we apply the Binomial equation to the viral load after transport (for relevant products z) and the probability that the food is not cooked to at least 60°C, $p_{C<60}$.

$$v\left(T_C,\ C,\ z\right) \sim Bin(v\left(T_T,\ C,\ z\right), p_{C<60}).$$

Therefore, $v\left(T_C,\ C,\ z\right)$ is the final viral load in product z at time of consumption, based upon the decay of viral load from time of slaughter due to processing, transport time, and cooking. The total viral load in country C at time of consumption is then calculated by summing over all product types:

$$v\left(C\right) = \sum_{z} v\left(T_C,\ C,\ z\right).$$

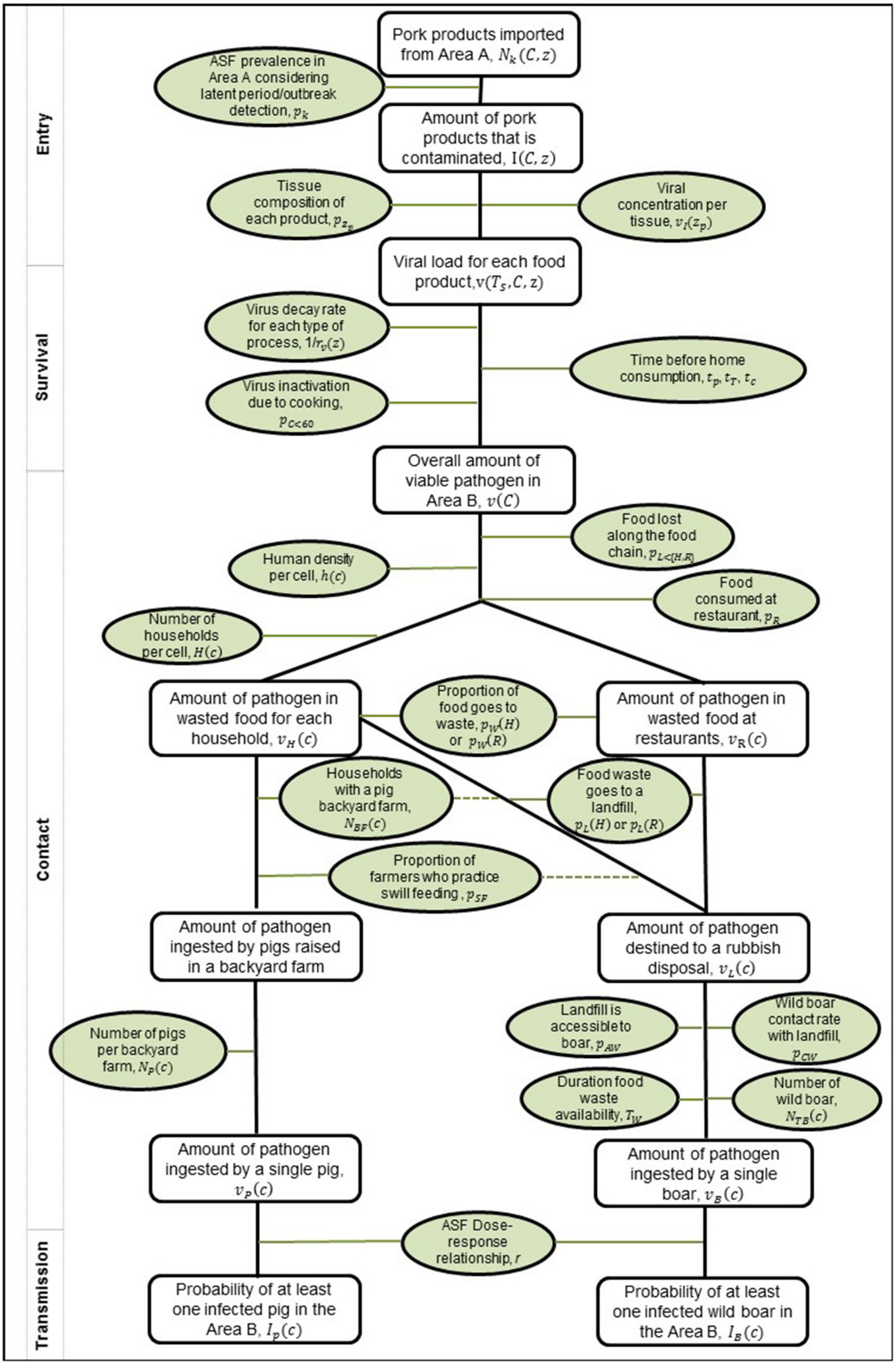

FIGURE 2 | Risk pathway for the risk of ASFV infection in pigs and wild boar via the legal trade of meat products pathway. Probabilities or inputs considered for each step are outlined in green ovals, and the outputs along the pathway as rectangles. On the left, the boxes indicate how this framework fits within the more generic framework in **Figure 1**. The dashed lines indicate that the converse to the statement can also lead to meat products at a rubbish disposal.

Contact

There are multiple steps to consider when asking how meat from an infected animal entering each EU MS would potentially have contact with susceptible pigs or wild boar. The Comext dataset on trade only indicates the destination country of the trade and does not give any finer spatial resolution. As the pig meat is intended for human consumption, we distribute the infected pig meat around the country based on human density in each EU MS at a 100 km^2 cell level. Therefore, if in one cell in a country there lives 1% of the population of that country, then 1% of the infected pig meat entering the country will go to that cell. Therefore, the viral load entering each cell c, $v(c)$, in country C is

$$v(c) = v(C)\frac{h(c)}{h(C)},$$

where $h(c)$ is the abundance of humans in cell c and $h(C)$ is the abundance of humans in country C.

We assume that pig meat will have one of two destinations—a non-household setting (e.g., in restaurants or by food producers; hereafter referred to as restaurants) or a household. A small proportion of food is lost along the food chain, for example during distribution, prior to reaching a restaurant or household ($p_{L<\{H,R\}}$), and then we split the total amount of infected meat by whether it will go to a restaurant (R) or a household (H). As pigs and boar are unintended recipients of the pig meat, we estimate how much meat they could be in contact with by estimating how much of the pig meat is wasted. Therefore, the total viral load in each cell that is wasted at a restaurant is estimated as

$$v_R(c) = p_W(R)p_R(1 - p_{L<\{H,R\}})v(c),$$

where p_R is the proportion of pig meat that goes to a restaurant and $p_W(R)$ is the proportion of food wasted at a restaurant. We perform a similar calculation for the amount of viral load remaining if food goes to a household. As each backyard farm will be connected to a single household, we estimate the amount of viral load at a household, $v_H(c)$, that is subsequently wasted, as

$$v_H(c) = p_W(H)\frac{p_H(1 - p_{L<\{H,R\}})v(c)}{H(c)},$$

where p_H is the proportion of food that goes to a household, $H(c)$ is the number of households in cell c and $p_W(H)$ is the proportion of food wasted at a household. We estimate the number of households in each cell c, $H(c)$, using a Poisson distribution:

$$H(c) \sim Pois(\overline{H}(c)),$$

where $\overline{H}(c)$ is the expected number of households in cell c, determined by the number of people in cell c, $h(c)$, divided by the average number of people per household in that country.

We now need to consider whether a backyard pig or boar could actually be in contact with this viral load. First we consider the situation for domestic pigs, by considering the viral load per household, $v_H(c)$, and the likelihood that a backyard pig would be in contact with it. To do this, we estimate the number of backyard pig farms ($N_{BF}(c)$) in each cell c, using a Poisson distribution,

$$N_{BF}(c) \sim Pois\left(\overline{N}_{BF}(c)\right).$$

$\overline{N}_{BF}(c)$ is the expected number of backyard farms in cell c, which we outline how to compute in the **Supplementary Info S1**. The number of these backyard pig farms that swill feed their pigs is then estimated as

$$N_{SF}(c) \sim Bin\left(N_{BF}(c), p_{SF}\right),$$

where p_{SF} is the probability that a household with a backyard pig farm would illegally swill-feed their swine. This probability (see **Supplementary Info S1**) is not country-specific as sufficient data to be able to refine the parameter to country level are missing. $N_P(c)$ is the total number of backyard pigs in cell c which would swill feed, calculated as

$$N_P(c) = \sum_{1}^{N_{SF}(c)} Pois(\overline{N}_{PF}(C)),$$

where $\overline{N}_{PF}(C)$ is the average number of pigs on a backyard farm which differs by country C.

Therefore, if a pig is swill fed, which is determined by the number of swill-feeding backyard farms $N_{SF}(c)$ and the number of pigs on those farms, $N_P(c)$, the amount of viral load that a single pig would have contact with is

$$v_P(c) = v_H(c)\frac{N_{SF}(c)}{N_P(C)}.$$

For wild boar contact with wasted pig meat products, there are two potential sources of wasted products that could end up in landfill or other sources of refuse—from a household that does not swill feed (whether it has a backyard pig farm or not) and from restaurants. We use the term landfill to denote any refuse site, including waste bins at household or in public locations. We define $v_L(c)$ as the viral load going to a landfill in cell c and compute it as

$$v_L(c) = T_W(p_L(R)v_R(c) + p_L(H)(H(c) - N_{SF}(c))v_H(c)).$$

As $v_H(c)$ is the amount of viral load in product at a single household, we multiply it in the equation above by $H(c) - N_{SF}(c)$, the number of households in cell c that do not swill feed, to recreate the total amount wasted in cell c from those households. We also consider the proportion of waste that will be disposed of in a landfill or other rubbish disposal that wild boar can have contact with (compared to e.g., waste that goes toward biofuels), with separate proportions for restaurant waste $p_L(R)$ and household waste, $p_L(H)$. We also reduce the amount of viral load in a landfill site by the duration of time that the waste will be available for boar, T_W, (as landfills are added to regularly, older waste will be difficult to access due to newer waste being placed on top; for other refuse sites, the waste will be taken away frequently). Due to lack of data on landfill locations, we assume that all waste is disposed of in the same cell as the waste was produced.

We now need to consider the likelihood that wild boar could have contact with this viral load at a landfill to estimate the amount of viral load each wild boar could be in contact with. To estimate this, we consider two probabilities—boar approaching and trying to contact landfill sites, p_{CW} and boar being able to gain access to the landfill sites, p_{AW}. The number of boar trying to contact the waste site, $N_{BW}(c)$, is given by

$$N_{BW}(c) \sim Bin\left(N_{TB}(c), p_{CW}\right),$$

where $N_{TB}(c)$ is the total number of boar in cell c. The probability that contact will be successful depends on the access to the site, which is given by a Bernoulli distribution, leading to

$$N_B(c) = N_{BW}(c)\, Bern\left(p_{AW}\right)$$

as the number of boar accessing the site, $N_B(c)$, and eating food waste at a landfill. The accessibility to the waste will clearly be different depending on whether it is a landfill or a public bin near a forest, but we assume an average parameter across all types of refuse sites.

Lastly, we need to calculate the amount of viral load that a single wild boar could be in contact with in cell c, $v_B(c)$. We do this based on the approximation that an average boar will eat a household's weekly amount of waste (see **Supplementary Info S1**) and distribute the infected meat equally among households. This leads to

$$v_B(c) = \frac{v_L(c)}{H(c)}.$$

Transmission

For the viral transmission to pigs or wild boar, given contact with the contaminated meat, we assume an exponential dose-response relationship as this is both a common assumption in microbial risk assessment (42) and has been used to assess response to ASFV exposure (43). Given the viral load that a pig or boar could contact or ingest, we assume that a pig or boar will become infected given by the formula

$$I_p(c) = 1 - e^{-r v_P(c)}$$

shown here using the pig viral load, $v_P(c)$ as illustration, where r is the dose-response parameter from experimental studies.

Risk of Infection via Pig Meat Products

The equation above assesses if a single pig or boar will become infected due to the consumption of expected viral load that a pig or boar could be in contact with. We now combine this with the number of backyard pigs or boar at risk to calculate the probability of at least one infection in boar or pigs per year. Similar to the equation for $N_I(c)$ in the generic framework, we calculate $N_{I,P}(c)$, the number of infections in backyard pigs in each cell c, and $N_{I,B}(c)$, the number of infections in boar in each cell c, as

$$N_{I,P}(c) = Bin\left(N_P(c), I_p(c)\right),$$
$$N_{I,B}(c) = Bin\left(N_B(c),\ I_B(c)\right).$$

As indicated in the generic risk framework, the probability of at least one infection in boar, $R_{I,F,b}(c)$, or pigs, $R_{I,F,p}(c)$, in cell c via this pathway is estimated by the proportion of simulations in which $N_{I,B}(c) > 0$ or $N_{I,P}(c) > 0$, respectively.

Overall Risk of Infection

The methods outlined above detail how the probability of at least one infection in boar or pigs is estimated per pathway. We combine these results, which are independently calculated, to produce the probability of at least one infection in boar or pigs in cell c via any of the three pathways considered. We define $R_{I,P,s}(c)$ as the probability of at least one infection in cell c via the trade in live pigs pathway in species s (either pigs or boar), $R_{I,M,s}(c)$ as the probability of at least one infection in cell c via the movement of wild boar pathway in species s, $R_{I,F,s}(c)$ as the probability of at least one infection in cell c via the trade in pig meat pathway in species s, and lastly $R_{I,T,s}(c)$ as the probability of at least one infection in cell c via any of the three pathways in species s. Then we calculate $R_{I,T,s}(c)$ as.

$$R_{I,T,s}(c) = 1 - \left(1 - R_{I,P,s}(c)\right)\left(1 - R_{I,M,s}(c)\right)\left(1 - R_{I,F,s}(c)\right).$$

Data

We include details of datasets used in the three pathways in **Table 1**. This accounts for the data that differed by country or by cell, whereas data that was represented by a single number or a distribution, primarily disease-related parameters, are provided in the **Supplementary Info S1**.

Sensitivity Analysis

We perform a sensitivity analysis of key parameters with the most uncertainty in the food pathway. In particular we analyze the effect of uncertainty on the following parameters: probability that food is cooked sufficiently to kill the virus ($p_{C<60}$), the proportion of food that is wasted in a household or restaurant ($p_W(H)$, $p_W(R)$), the probability of illegal swill-feeding (p_{SF}), the accessibility of landfills for boar (p_{AW}) and the duration of waste availability (T_W). We measure the sensitivity of the food pathway to these parameters by focusing on those cells which are hotspots of disease risk, which we define to be any cell which has a probability of infection in boar of 0.02 or higher, or a probability of infection in pigs of 0.0001 or higher. For full details of the sensitivity analysis, see **Supplementary Info S3**.

RESULTS

The risk of infection with ASFV for pigs and wild boar is calculated for all EU MSs at a 100 km^2 level for each pathway and also combined to produce an overall risk for each species.

TABLE 1 | The datasets used for three pathways, with a detailed description of the data used, the date the data is from and a reference for the data source.

Model input	Data used	Date range	References
Number of legal live pigs traded	TRACES data which states origin country, post-code location of end location, and number of pigs traded in a year.	2017	(35)
Prevalence of ASF in pigs	Country-level results from Simons et al. (33) which estimates prevalence using reported cases of the disease (from the OIE), under-reporting, the likelihood of an outbreak, the latent period of disease and stopping trade after disease is detected	Reported cases up to and including all of 2018	(33, 36, 44)
Prevalence of ASF in wild boar	Estimated prevalence at a 100 km^2 cell level using reported cases of the disease and an under-reporting factor.	All wild boar cases in 2018	(44)
Wild boar abundance	A map of wild boar abundance and habitat suitability across Europe at a 1 km^2 cell	2015	(38)
Amount of pig meat traded	Comext data from Eurostat which outlines country of origin, country of destination and amount in tons for many different product types related to pig meat.	2017	Comext data from Eurostat (40)
Number of pigs	Eurostat data on the number of pigs in each NUTS2 region	2017	agr_r_animal data from Eurostat (40)
Number of pig farms	Eurostat data on the number of pig farms in each NUTS2 region	2016	ef_lsk_main data from Eurostat (40)
Number of Backyard Pigs	Eurostat data on the average number of pigs on a backyard farm	2010	Pig farming sector—statistical portrait 2014 (40)
Number of Backyard Pig Farms	Eurostat data on the number of backyard pig farms in each EU MS	2010	Pig farming sector—statistical portrait 2014 (40)
World Map	Accurate world map indicating boundaries of countries	2017	Made with Natural Earth
NUTS map	Map of NUTS1 and NUTS2 regions in Europe	2018	(45)
Human density	A world map of the human population at a 1 km^2 cell level	2015	(46)
Pig density	A world map of the pig density at a 5 km^2 cell level	2014	(47, 48)
Number of households	Number of households in each EU MSs	2017	lfst_hhnhtych data from Eurostat (40)
Population	Population size in each EU MSs	2017	demo_pjan data from Eurostat (40)

All the data is freely available apart from the TRACES dataset, in which access is via competent authorities within the TRACES network.

Overall Risk

We plot the overall probability of at least one infection in wild boar and pigs for all three pathways combined (**Figure 3**).

Predominantly, for both wild boar and pigs, the risk is focused in Eastern Europe with Latvia, Lithuania and parts of Poland in particular having many cells of high risk. There are also high risk areas in the east of Hungary and parts of Romania. Most countries have some areas of risk for wild boar transmission while transmission to pigs is much less frequent. This does not necessarily mean there is no risk for pigs in those countries, but the risk is too low to see on the scale forced by the high risk in other countries, combined with the fine spatial scale meaning it may be difficult to see the cells with very faint color. Considering the risk per pathway, below, allows us to investigate this in more detail. However, a detailed outline of how many cells fall within the different probability categories for the combined risk and for each pathway is provided in **Supplementary Info S2**. We also considered the risk when aggregated up to a country level, to compare the highest risk pathway for each country for infection in both wild boar and pigs (**Supplementary Info S2**).

Legal Trade of Live Animals

The probability of at least one infection in pigs at a 100 km^2 cell level for EU MSs is plotted in **Figure 4**. The original data for trade in live pigs was provided at a post-code level, and since there are only a few locations with a non-zero probability, in comparison to the size of Europe, we show these results using points to represent the post-codes, rather than plotting at the cell level.

According to the model, many farms across the EU are not expected to import any pigs at all. Of those that do import, the probability of importing an infected pig was low on most farms, based on prevalence data. There were only 310 farms that had a probability of 1×10^{-4} (i.e., one case expected in 10,000 years) or higher of importing an infected pig. We assume negligible risk in **Figure 4** for any farm with probability $<1 \times 10^{-4}$ of importing an infected pig. Of those farms that do import, the probability of subsequent infection of a susceptible pig on most farms was low or very low; farms which have over a 10% chance of having at least one infection in a susceptible pig are in Poland, Latvia or Lithuania. The farm with the highest probability, at 65%, of at least one infection in a susceptible pig is in Lithuania and the pigs originated in Estonia.

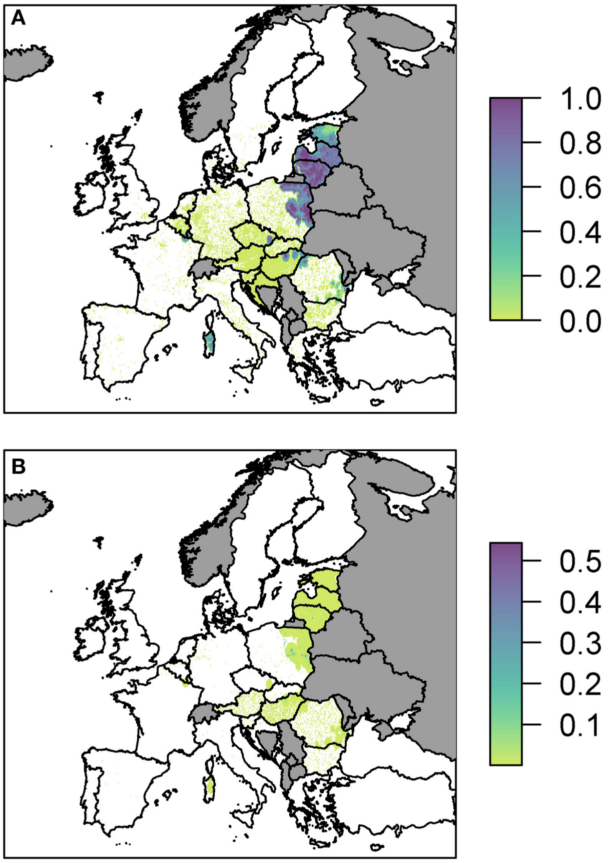

FIGURE 3 | The probability of at least one infection with ASFV in **(A)** wild boar or **(B)** pigs in 2019, plotted at a 100 km^2 cell level across Europe. Countries in gray have insufficient data to compute the risk.

As can be seen from **Figure 4B**, there are a large number of farms in the Netherlands, Germany, and France which have a small risk of infection occurring. In comparison (**Figure 4C**) fewer farms are at risk of importing infected animals in Poland, Latvia and Lithuania, but on those farms that do, the probability that this leads to infection is higher. This is primarily due to where the animals are imported from. Infected pigs imported by France, Germany and the Netherlands have primarily come from Belgium, which has a low estimated prevalence of infection in pigs for 2019 due to the wild boar cases in 2018. However, infected pigs entering Poland, Latvia and Lithuania are primarily coming from Latvia, Lithuania, and Estonia which have higher prevalence estimates.

When we combine all farms in a country together to compute a probability of at least one infection per country (**Supplementary Info S2**), we find that Poland has the highest risk with a 99.4% chance that at least one infection will occur on any farm in Poland from live pig trade. Lithuania also has a very high probability of 97.6%. There is then a drop to a 25% probability for Latvia, followed by Hungary, Germany, and the Netherlands, which has a 5% chance overall.

Movement of Wild Boar

The probability of at least one infection in wild boar or pigs via entry through the movement of wild boar is shown in **Figure 5**.

The risk to boar or pigs is very similar in terms of location, as all the risk is focused on the areas of reported cases in 2018. Wild boar movement is relatively local, with dispersal over long distances unlikely (49), and hence the disease is not expected to spread far due to boar dispersal (37). In order to see this more clearly, we zoom in to three regions to gain a better perspective of the risk to various regions in Europe due to wild boar movement (**Figure 6**). The distinct outbreak in Belgium demonstrates most clearly this risk region around previous cases, with a hotspot of high risk where the Belgium cases in 2018 were located, surrounded by an area of higher risk. However, this risk region is not symmetric as the boar movement is determined by habitat suitability, and infection of other boar depends on where boar are in the area—**Figure 6A** indicates that there is a higher risk to the south of the original cases toward France than north of the original cases.

Due to the high prevalence of cases in Poland, Latvia, and Lithuania in 2018, there is a large risk region throughout these countries (**Figure 6B**). As there were so many cases, the risk regions around each local outbreak are no longer distinct and hence there is a broader pattern of where infection could occur. We also highlight the area on the border of Hungary and Romania (**Figure 6C**) where there were cases in wild boar in 2018. There were many cases of ASF in Romania in 2018, but they were predominantly in pig farms, and hence our estimate for wild boar prevalence is relatively low, indicating not many cases of ASF in wild boar in Romania in 2019 due to wild boar movement.

The risk to domestic pigs due to wild boar movement is lower than the risk to wild boar (**Figure 5**). This is because the probability that wild boar will have contact with domestic pigs is very low as is the likelihood that this contact will lead to viral transmission—transmission via direct contact is most efficient via blood contact e.g., due to animals fighting, which is less likely to occur between boar and pigs compared to within boar groups. However, some Eastern European countries still end up with a very high probability of at least one infected domestic pig through this route; Poland has the highest risk with a predicted 100% chance of infection in pigs, followed by Lithuania (95%), Romania (80%), Hungary (77%), and Latvia (46%).

Legal Trade of Pig Meat Products

We present the probability of at least one infection in wild boar and pigs via the legal trade in pig meat products pathway (**Figure 7**).

The probability of at least one infection in pigs via the trade in legal pig meat products is very low overall, with the highest risk in any cell being 6×10^{-4}, noticeably lower than the highest risk via the two other pathways in a single cell. This risk is also focused mainly on a few countries; Hungary, Romania, Lithuania, Austria, and Latvia. For Lithuania, Austria and Latvia, this is primarily due to the amount of meat from infected pigs entering the country; for Hungary it is a combination of amount of trade and a high average number of pigs on each backyard farm; for Romania it is due to the considerably larger

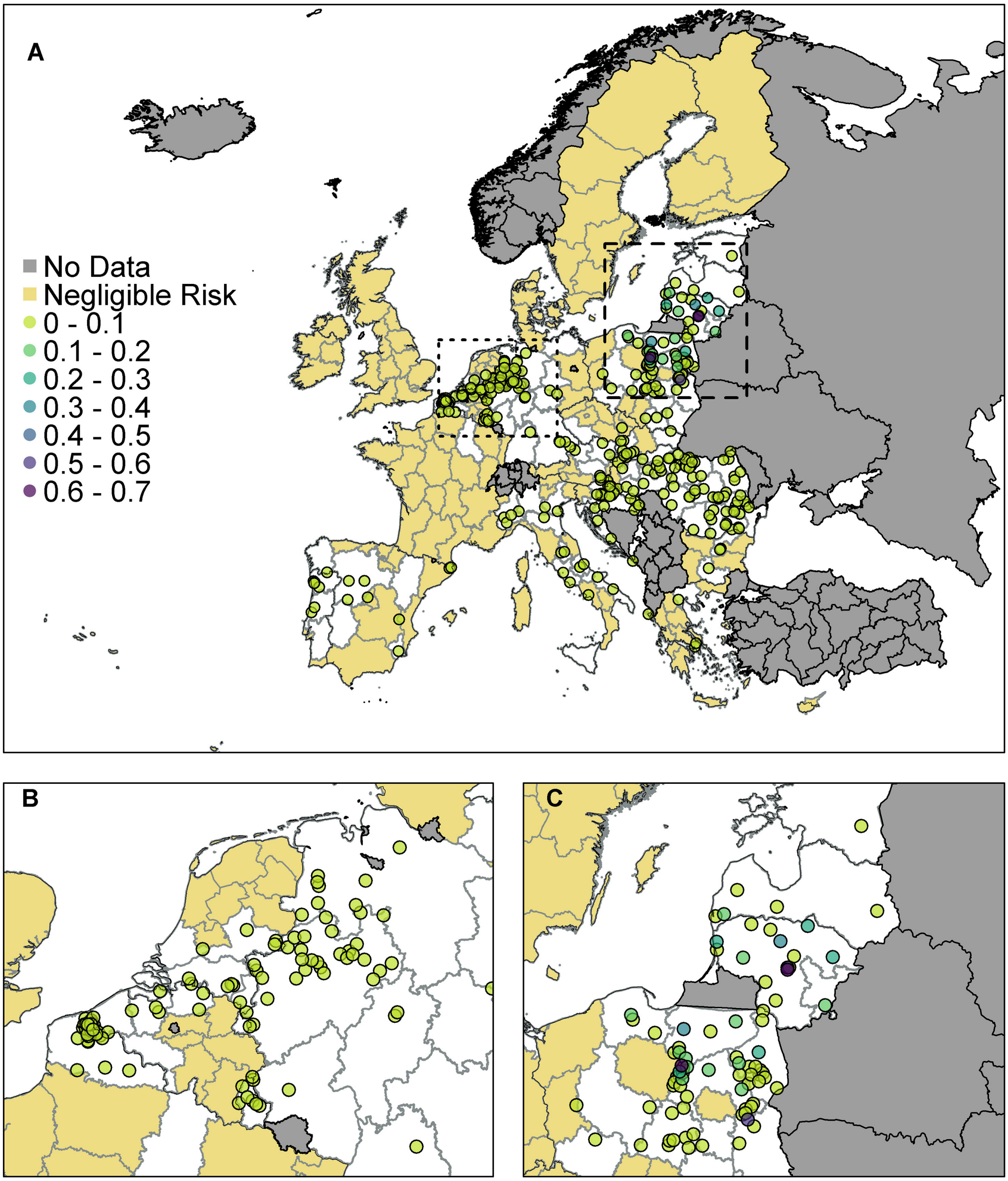

FIGURE 4 | The probability of at least one infection of ASFV in pigs in 2019 from trade of live pigs at a farm level. In **(A)** all of Europe is plotted while in **(B)** the map is zoomed in to the dotted rectangle in **(A)** and in **(C)** the map is zoomed in to the dashed rectangle in **(A)**. All farms indicated by a circle imported at least one infected animal in at least one simulation and the color indicates the probability that one or more susceptible pigs became infected. Countries in gray have insufficient data to complete the risk assessment. All farms in the regions with negligible risk either did not import any pigs or did not import any infected pigs. ©EuroGeographics for the administrative boundaries.

number of backyard farms in the country (more than 10 times any other country in Europe). At the country level, Hungary has the highest risk with a probability of 14.5% of at least one infection in pigs (**Supplementary Info S2**). The risk of ASF in boar via this pathway, in comparison, is much higher, and many countries across the whole of Europe have hotspots of higher risk (**Figure 7B**). This is because imported meat is more likely to end up at a landfill than being swill fed to backyard pigs. Although Hungary, Lithuania, Austria, Croatia, and Latvia have the most cells within their country at risk, giving the impression from the

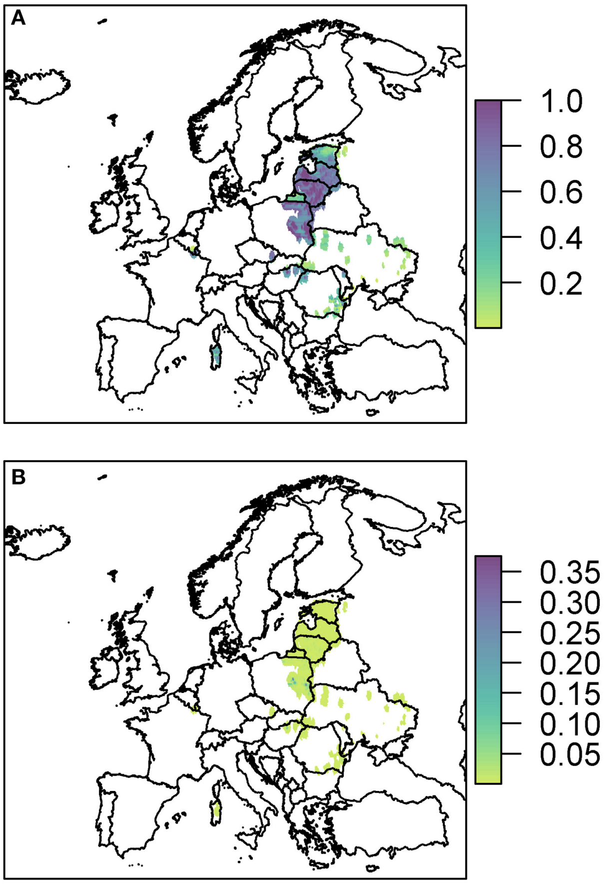

FIGURE 5 | The probability of at least one infection of ASFV in 2019 in boar **(A)** and pigs **(B)** due to wild boar movement is plotted at a 100 km^2 cell level across Europe. Prevalence in wild boar is estimated from reported cases in 2018.

map that they may have the highest risk, the country with the highest risk for boar for this pathway is actually Italy. It has a probability of 99.7% of at least one infection in boar due to a small number of high risk cells, including in Sardinia.

Pathway of Highest Risk

For each 100 km^2 cell we plot which pathway is the highest risk for that cell, for both wild boar and pigs (**Figure 8**), indicating at a finer scale where resources for different pathways should be focused. For most cells where wild boar movement can lead to infection in wild boar or pigs, this will be the pathway of highest risk. The legal trade of pig products pathway dominates as the highest risk pathway for infection in wild boar or pigs for many countries across Europe, with a focus on central Europe (e.g., Hungary, Austria, Germany, and Croatia). Dispersed throughout Europe are cells in which the legal trade of pigs is the highest pathway, highlighting the fact that this pathway is not widespread across Europe, due to the small number of farms importing infected pigs but, when it does occur, it is usually the riskiest pathway in that cell.

Sensitivity Analysis

We measure the sensitivity of the food pathway to changes in 5 uncertain parameters in **Figure 9** by considering changes to the hotspots of disease risk in the baseline results. For the wild boar, we find that the duration of waste availability (sensitivity WA) and boar accessibility to landfills (BA) are the two most influential parameters. BA increases the maximum of the probability of infection in boar, up to 0.2 in some cells, although the median is still similar to the baseline results. WA leads to a larger number of cells across Europe considered a hotspot, i.e., probability of infection > 0.02 (**Figure 9A**). However, although these new cells are hotspots, in general the probability of infection in these cells are in the lower range (i.e., most of these cells have a probability of infection around 0.05). As such, the median of the overall distribution of the probability of infection in the hotspot cells is lower (**Figure 9C**), although the highest risk cells (i.e., cells with probability >0.09) still exist. This is clearer to see in the map across Europe of the probability of infection in boar and pigs for the sensitivity analysis, provided in **Supplementary Info S3**.

For infection in pigs, the probability of illegal swill-feeding (SF) and the proportion of meat that goes to waste (WP) are the two most influential parameters as they both increase the number of cells considered hotspots i.e., probability of infection >0.0001 (**Figure 9B**) and increase the average and maximum probabilities of infection in those hotspots (**Figure 9D**). For both boar and pigs, the model is not sensitive to the probability that food is cooked sufficiently to kill the virus (FC).

DISCUSSION

ASF is a porcine disease of significant concern worldwide that is currently devastating the pig industry with reports that pig meat production has dropped by 30% in 2019 in China alone (50). The reduction in trade and subsequent costs are amplified by the cost of control, such as culling, cleansing, and disinfecting, implementation of fencing and increased hunting, and the costs of prevention, such as increased surveillance, dissemination of disease information and suggested/required prevention measures for farmers and the larger public (10). Therefore, prioritization of these measures is wise in order to utilize the available resources as optimally as possible. Risk assessments can be useful tools to provide a means for determining where the risk of disease is highest and which pathways are of most concern. They can indicate where the best places are to perform surveillance to prevent disease entry, or ensure quick and timely discovery of disease to allow the possibility of eradication before the disease infects the pig population at large in a country or becomes endemic in the wild boar population. In this study, we have performed a risk assessment for ASF in EU MSs that assesses the risk for 2019 at a fine spatial scale for three pathways in order that surveillance can be targeted to disease risk hotspots that are dependent on the pathway of entry. Overall, we found that the highest risk of infection in 2019 by ASFV via the three pathways of legal trade of pigs, movement of wild boar, and legal trade of pig meat products, is in Eastern European countries where the cases have so far been concentrated. This is driven by the

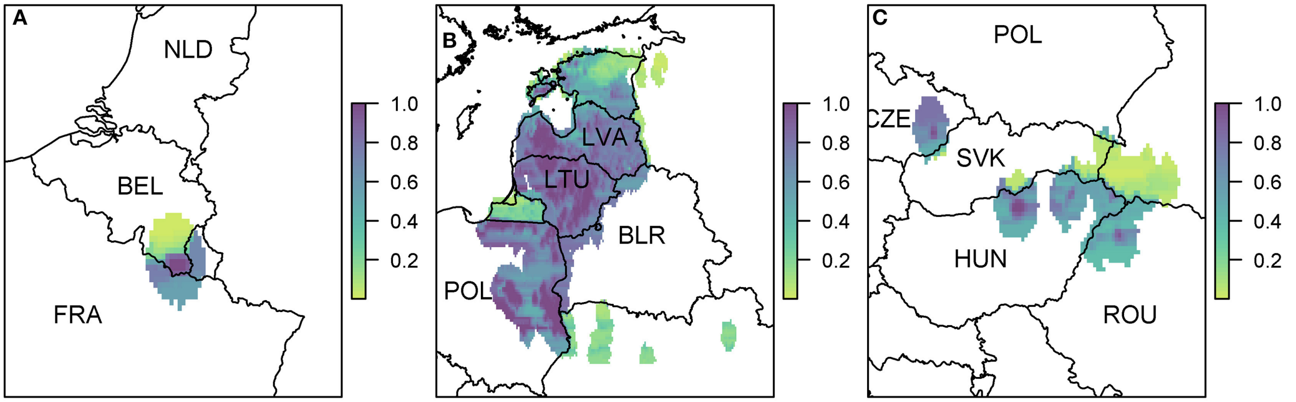

FIGURE 6 | The probability of at least one infection of ASFV in boar in 2019 due to wild boar movement at a 100 km^2 cell level. We zoom in to three regions where there were cases in 2018 **(A)** Belgium; **(B)** Poland, Lithuania, and Latvia; and **(C)** Hungary, Czech Republic, and Romania. Countries are indicated by their ISO3 code.

wild boar movement pathway and the legal trade of live pigs. For the wild boar movement pathway, this is focused on Eastern Europe primarily due to the fact that boar movement is relatively local. For the legal trade of pigs pathway, analysis of the pig trade input data suggests that many European countries trade more with their neighbors, so Eastern European countries which border ASFV infected countries are more likely to trade with them and hence have a higher risk than countries geographically further away.

The risk of ASF in boar or pigs differed by spatial location and in magnitude. The risk of ASF in boar was higher than for pigs across the two pathways of relevance (trade in pig meat products and movement of wild boar) and as an overall risk, and was more broadly spread across the whole of Europe. While EU MSs main concern regarding ASF may be to protect their pig industry from incursion of ASF, given the ability of ASFV to transmit from wild boar to pigs once it enters a country, our results suggest that EU MSs should also focus on surveillance and prevention in wild boar populations as the disease is more likely to enter via this source. This is in line with observed disease incursions within Europe, as ASFV has been found in most EU countries in the wild boar population first [e.g., Poland, Hungary, Czech Republic, and Belgium (16)]. For countries without ASF in wild boar populations already, model results suggest the risk in boars is driven by the legal trade of pig meat products and hotspots occur where there is high boar density or high human density. However, there is high uncertainty associated with these absolute values due to uncertainty in the underlying data. The underlying wild boar abundance map (38) made good use of limited data but is known to have some issues, for example predicting no wild boar on the border of Finland and Russia and overestimating the abundance in close proximity to large cities in countries like the UK which are known to only have a few very specific localized boar populations. This is due to the need to extrapolate wild boar abundance across the whole of Europe with data collected only from some locations.

The results for the legal trade of pigs pathway indicate that 310 farms have a 1/10,000 risk of an infected pig entering the farm or higher. If this many farms were actually importing infected pigs each year, we would expect many more ASF cases on pig farms via import than has been seen over the past few years. The

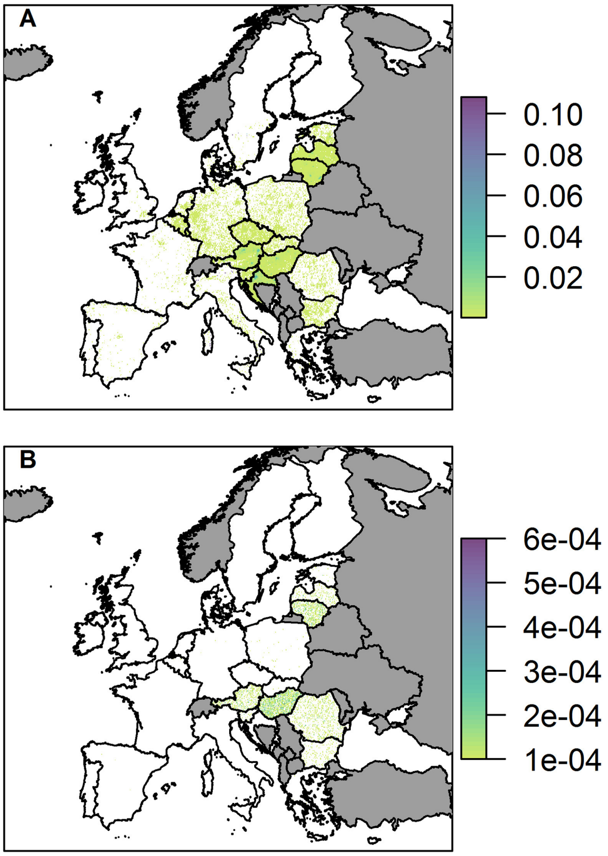

FIGURE 7 | The probability of at least one infection of ASFV in 2019 in **(A)** wild boar and **(B)** pigs, via trade in legal pig meat products, plotted at a 100 km^2 cell level across Europe. Countries in gray have insufficient data to complete the risk assessment.

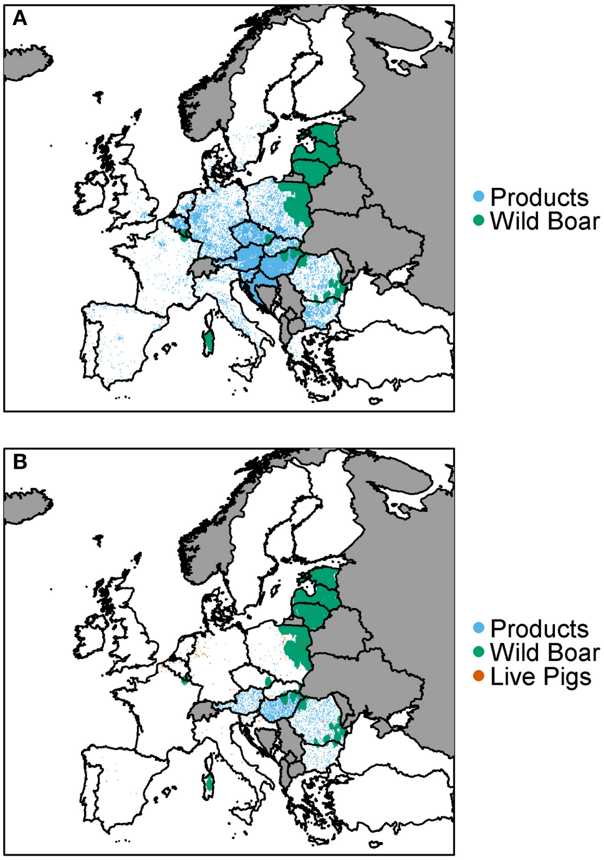

FIGURE 8 | The pathway which has the highest risk of infection of ASFV for **(A)** wild boar and **(B)** pigs is plotted at a 100 km^2 cell level across Europe. Countries in gray have insufficient data to complete the risk assessment.

model may be overestimating this risk as we are not including an inspection, testing or quarantine step in the pathway, which would reduce the risk if it does occur. Secondly, rather than using the raw OIE data for the ASF prevalence in pigs in each country we use an algorithm designed to account for data gaps and underreporting (33). This algorithm predicts the prevalence of ASF in 2019 based on historical cases up to and including those in 2018, and may overestimate in some situations. These results indicate that Poland and Lithuania have lower numbers of farms importing infected pigs, but each farm imports more infected pigs and therefore have higher chances of infection on farm, compared to the Netherlands, France, and Germany, which have many farms importing but each farm has a low probability of importing an infected pig and it subsequently leading to transmission (**Figure 4**). Thus, this could lead to different risk-based prevention in trade for each area. Poland and Lithuania would reduce their risk by trading with countries with lower prevalence of disease, while Germany, the Netherlands, and France would reduce their risk by having fewer farms importing fewer pigs.

Results indicate that the spread of ASF via movement of wild boar is limited to short distances (37), although ASF is able to cross borders easily due to the lack of detection of infected wild animals. The risk via this pathway is much patchier, with many countries not affected at all in their pig or boar populations. The risk to wild boar is much higher than for pigs, due to the lack of contact between boar and pig populations. However, transmission to pigs can occur which can be reduced by ensuring good biosecurity practices are in place on pig farms to prevent the contact between wild boar and domestic pigs (2, 22). One aspect of this pathway which has not been included is any control measures that may have been implemented around reported cases of ASF in wild boar. For example, in **Figure 6A**, the risk of ASF in boar in France due to wild boar movement from the Belgian 2018 cases is relatively high. However, we did not include the fact that Belgium erected a fence around their reported cases to stop wild boar movement and implemented increased hunting in the area (16). Therefore, in reality, the risk to France would be much lower, depending on the width and permeability of the fence (37).

The legal trade of pig meat products pathway indicates highest risk for pigs in Eastern European countries which have high numbers of both backyard pig farms and average number of pigs on a backyard farm (40). However, these countries still have a low overall risk in comparison to other pathways. The low risk for this pathway is due to low probability of swill-feeding, as it is illegal, and the low chances that meat from infected pigs will enter a household with a backyard farm.

As there are so many component parts in the legal trade of pig meat products pathway, this pathway is subject to the most uncertainty. This uncertainty can be delineated into three major sources—using data from outside the EU, making assumptions regarding the spatial distribution of data, and simplifying the complicated food and waste industries. Firstly, the use of data from outside the EU. It was not possible to always find relevant data for EU countries and so it was necessary to use data that had been gathered from other countries as a proxy. In particular, we used an estimate for Australia for the probability that swill feeding would occur (51). Given that swill feeding in Australia is illegal, as it is in the EU, we felt this to be a reasonable approximation. Regarding the proportion of products consumed in a restaurant, the proportion of waste lost in the distribution chain and the proportion of waste that goes to landfills, we used a study from the USA as again we could find no data for EU countries (52). We also used a different US study regarding the probability that food is cooked to 60°C to kill the virus (53). It is possible that there are significant differences between the USA and EU countries regarding cooking and waste practices. We made a number of assumptions regarding the spatial distribution of data within the EU. This included assuming an (almost) homogeneous distribution of backyard pigs in all EU MSs, based on analysis of the spatial distribution in Great Britain (see **Supplementary Info S1**). In reality, this may not be the case for some countries in Europe, for example Romania, have a huge backyard pig sector with most households having a backyard pig farm or being part of a community farm, whereas in Great Britain there are relatively few backyard farms. Therefore, it is possible that an increase in number of farms would change the spatial distribution. Similarly, we

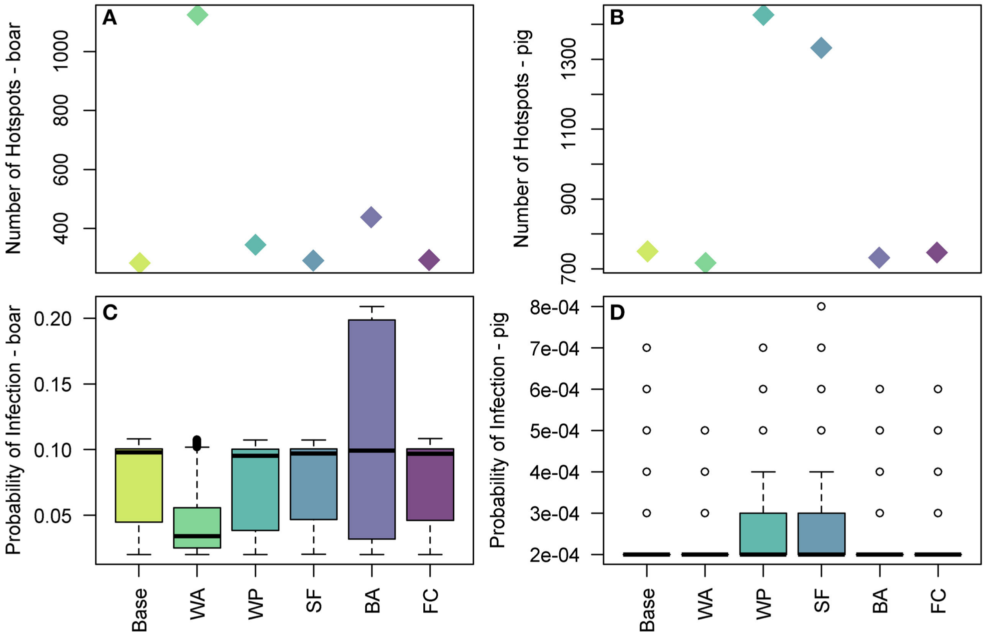

FIGURE 9 | The effect of uncertain parameters in the legal trade of pig meat products pathway on hotspots of disease risk across Europe. In **(A,B)** the number of 100 km^2 cells which are hotspots for wild boar infection and domestic pig infection are plotted, respectively, for the baseline and sensitivity parameters. In **(C,D)** the distribution of the probability of infection across 100 km^2 cells which are hotspots in Europe for wild boar and pig infection, respectively, for the baseline and sensitivity parameters. The baseline results, as shown in **Figure 7**, are denoted by Base. The sensitivity parameters are: WA, duration of waste availability for boar; WP, proportion of food that goes to waste; SF, the probability of illegal swill-feeding; BA, the probability that boar are able to access waste; and FC, the proportion of food that is cooked sufficiently to kill the virus.

assumed that the waste is kept in the same cell as it was produced. On the one hand, wild boar can access waste from intermediate waste sites (such as household or park rubbish bins) and so this assumption is suitable. However, potentially the waste is then conveyed to a small number of large collecting points. However, as we did not have data on the location of landfill sites, it was determined better to assume it stayed in the same cell. There was also a need to assume that all EU MSs acted in the same way, when in reality there could be many heterogeneities at a country level and even a finer scale. For example, the waste procedures may be different across each country, or even within each country, and the accessibility of landfills or other waste sites by boar may differ across Europe. Similarly the probability of swill-feeding is likely to be different across countries within the EU but due to a lack of data we assumed the same probability for all EU countries. Lastly, in order to parametrize this pathway given little data, we made simplifications regarding the food and waste industries. For example, we assumed that raw food would undergo a cooking process only in the destination country, when it is possible that salting, drying, or smoking processes were subsequently undergone after entry to the destination country. If meat underwent different processes after entry, this would likely change the viral load in the products upon consumption. There is also a lack of data regarding the effect of processes, such as salting, on the viral load in products, other than the decay due to the length of time for the process. Similarly, we did not separately consider the role of commercial bodies, such as food producers, when distributing the meat in each country. We assumed that the "restaurant" setting would cover all waste of meat that is not from a household setting. Although this restaurant option would be closer to food production than households in terms of amount of food wasted and the proportion of wasted food that goes to landfill, there may still be differences. For example, food producers may be more likely than restaurants to send their waste food to the biofuel industry or to other alternative places to landfills (52).

Given the numerous uncertainties with the legal trade of pig meat products pathway, we performed a sensitivity analysis on the most uncertain parameters within this pathway. This revealed that the model was most sensitive for estimation of infection in wild boar to parameters related to the waste procedures—the availability and accessibility of refuse waste to boar. Publication of waste procedures across multiple countries may reduce this uncertainty. For estimation of infection in pigs, the probability of illegal swill-feeding and proportion of pig meat products going to waste were the most sensitive parameters. It is very hard to reduce the uncertainty in the former parameter, due to its illegal nature, but data could be collated on the amount of food wastage across different food industry sectors to reduce the uncertainty in the latter parameter.

There are also uncertainty issues raised with the other pathways, for example, the map of wild boar abundance is based heavily on hunting bag records which are difficult to produce abundance estimates from accurately (54). Other uncertainties exist regarding boar ecology and movement dispersal. Data on wild animals and on abundance of species is difficult to collect and to ensure its accuracy, and therefore uncertainties will always remain when modeling a disease involving a wild species. Risk assessment is a prediction process and therefore, when asking what potentially could happen, there will always be both model and data uncertainty, lack of data or up-to-date data, and inaccurate data for wild and livestock species. For a model with such a broad scope, it is expected that there will be reasonable concerns about the specific absolute values. However, we believe we have found the best data possible for this risk assessment of ASF in Europe in 2019 and that our relative results regarding general trends, spatial hotspots, pathways of greatest risk, and comparisons between boar and pigs are robust.

Our risk assessment considered what we thought to be the most important routes for entry or spread of ASF in EU MSs. However, there are other potential routes that could lead to infection with ASF in boar or pigs, such as intra-country trade of pigs, illegal trade of pigs, or pig meat, non-commercial movement of pig meat (for example, travelers legally bringing meat across borders in Europe), and the transport of fomites (2, 9). Whilst our spatial framework is applicable to these pathways, they are difficult to parametrize in a quantitative setting across Europe due to lack of within-country data, free movement across Europe (leading to a lack of data regarding movement between countries), the extensive road and rail network, and the illegal nature of some of the activities. Simons et al. (33) considered an illegal pig products pathway, as well as the three considered here, for the entry of ASFV into EU MSs and found that the amount of meat from infected pigs entering each EU MSs was usually lower via illegal routes than legal routes, although there was more uncertainty associated with the illegal route. A few models have considered some of these routes in a semi-quantitative or qualitative manner indicating that these pathways could potentially be of greater risk than the three considered here. In a recent study that considers the risk of infection with ASFV in the Netherlands and Finland using multiple models (55), a semi-quantitative Finnish model (NORA) found that human transportation was the pathway of the greatest risk for Finland, and the qualitative Swedish model (SVARRA) found that the indirect pathway (including transport, human travel, feed, and bedding) was equal or higher risk than the three pathways in this risk assessment. Less recently, Mur et al. (31) considered the risk of introduction to European countries for multiple pathways using a semi-quantitative approach and found that the illegal trade and transport/fomites pathways were the riskiest for some countries (for illegal trade: France, Germany, Italy, and the UK; for transport: Belgium, Estonia, Lithuania, and Poland). However, this is based on a very different disease situation, as there were far fewer cases in wild boar in 2013 and hence the risk via the wild boar movement is expected to have increased since then given the current disease situation, and may therefore change the riskiest pathway per country if recalculated today. All risk assessments struggle to estimate the risk by pathways which are very stochastic in nature, usually due to human behavior. These behavioral aspects, such as whether farmers will implement good biosecurity, whether travelers will listen to warnings about not transporting meat products, or whether a driver will use a certain rest stop to eat their ham sandwich, are rare and unpredictable, making a risk assessment, especially on a fine spatial scale, unreliable. Perhaps connections with social science are required to understand these behavioral decisions and hence disease pathways more fully. However, it is generally considered that human-mediated transmission, for example, by non-commercial movement of meat products or fomites on transport, is one of the most important pathways for ASFV transmission (2). Therefore, risk assessments need to find a way to assess these pathways as accurately as possible.

Within this risk assessment we have taken a high-level approach, for example by modeling wild boar dispersal as a single event rather than considering the intricate population dynamics of wild boar. When considering exact management or control strategies to implement, a bespoke model including these intricate details may be required. Our high-level approach was taken in order to keep the risk assessment generic. Therefore, the movement of wild boar pathway can also be used for other wild animals that may transmit a different pathogen via either dispersal or home range movements, by only changing a few parameters. Similarly, the trade of live pigs and pig meat can be adapted for other species and diseases and, therefore, multiple diseases can be assessed using this overall framework. This can speed up risk assessment, especially for emerging diseases with little information to model intricately, and is useful for directing risk prioritization of diseases, pathways or locations. Furthermore, our risk assessment is easily updated with new data and able to be re-run quickly, allowing for changes in the risk profile across Europe to be monitored.

Our risk assessment for ASF indicates hotspots of high risk for disease incursion and infection, such as the border between Hungary and Romania for both the wild boar movement and legal trade of pig meat products pathways, or the area surrounding Belgium for the legal trade of pigs and pig meat. It also indicates which pathways should be the focus in different areas. These results can aid decision makers and risk managers to determine what type and intensity of surveillance, prevention and control measures are necessary for different regions for ASF. This risk assessment will assist EU MSs in their efforts for the prevention and detection of ASF, and our risk assessment framework is applicable for other locations, such as China, Vietnam and Cambodia, provided the equivalent data are available. As ASF continues to spread throughout Europe and across Asia, risk assessments such as this can determine how to best tackle the disease.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

RT, PG, LK, and ES developed the generic framework. RT developed the trade of live animals pathway. RT and RS developed the wild boar movement pathway. RT and RC developed the trade of products pathway. RT and RC wrote the manuscript with input from all co-authors.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00486/full#supplementary-material

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Planning "Plan B": The Case of Moving Cattle From an Infected Feedlot Premises During a Hypothetical Widespread FMD Outbreak in the United States

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In the event of a foot-and-mouth disease (FMD) outbreak in the United States, "stamping out" FMD infected premises has been proposed as the method of choice for the control of outbreaks. However, if a widespread, catastrophic FMD outbreak in the U.S. were to occur, alternative solutions to stamping out may be required, particularly for large feedlots with over 10,000 cattle. Such strategies include moving cattle from infected or not known to be infected operations to slaughter facilities either with or without prior implementation of vaccination. To understand the risk of these strategies, it is important to estimate levels of herd viremia. Multiple factors must be considered when determining risk and feasibility of moving cattle from a feedlot to a slaughter facility during an FMD outbreak. In addition to modeling within-herd disease spread to estimate prevalence of viremic animals, we explore potential pathways for viral spread associated with the movement of asymptomatic beef cattle (either pre-clinical or recovered) from an infected feedlot premises to offsite harvest facilities. This analysis was proactive in nature, however evaluation of the likelihood of disease spread relative to disease (infection) phase, time of movement, and vaccination status are all factors which should be considered in managing and containing a large-scale FMD outbreak in the United States.

Keywords: foot and mouth disease, FMDV, carcass, cattle, feedlot

INTRODUCTION

Foot and mouth disease (FMD) is a highly contagious viral disease affecting primarily cloven-hoofed animals. The disease is characterized by the development of vesicles in and around the mouth and on the feet. Although natural FMD infection rarely causes death of mature animals, the disease results in decreases in livestock productivity and causes serious economic impacts on international trade of animals and animal products (1). FMD was last reported in the United States (U.S.) in 1929 and in North America in 1952 (Canada) and 1954 (Mexico).

In the event of an FMD incursion in the US, the US Department of Agriculture Foreign Animal Disease Preparedness and Response Plan (FAD PReP) Red Book likely will be followed (2). This response plan details activities for outbreaks at various scales and geographies. Historically, "stamping out" has been the preferred tool, however if the FMD outbreak is at an endemic scale (Type 4: Widespread or National FMD Outbreak or Type 5: Catastrophic FMD Outbreak), other strategies proposed by the FAD PReP Strategy Document such as vaccinate-to-live and vaccinate-to-slaughter likely will be considered (3). At present, identification of FMD within a herd is reliant upon observation of clinical signs to trigger diagnostic testing of suspect individuals. This lack of population-level disease surveillance testing methods results in delayed detection until infection has spread at the farm level.

The US has a number of large-scale livestock production facilities. If one of these operations were infected, depopulation on-site likely is not practical. Instead, options for the management of these animals are needed if they are not depopulated, including use of vaccination before moving animals, allowing disease to progress through a herd before movement, and moving vaccinated animals from not-known to be infected premises to decrease local susceptible population. We use FMDV infection at a large scale cattle feedlot (over 10,000 head) to highlight some of the potential risks and considerations that decision-makers may factor into their response plans in the event of an FMD outbreak.

PREDICTING DISEASE SPREAD THROUGHOUT THE HERD

The shedding phase of FMD is the time interval between the time an animal begins shedding virus to the time an animal is no longer shedding virus and it generally includes pre-clinical and clinical infectious phases. A carrier phase is also possible; this includes animals that have recovered from clinical disease and have at least one positive esophageal-pharyngeal sample 28 days or more post infection (4). While hypothetically plausible, transmission of FMDV from carrier cattle to susceptible individuals has never been conclusively documented (5).

Five different hypothetical FMD management scenarios were explored. In order to estimate the number of cattle in each of the disease phases, a within herd disease spread model was developed and applied to the scenarios. This model used a 10,000 head beef cattle herd to determine the number of cattle in susceptible (S), latent (L), pre-clinically infectious (I_P), clinically infectious (I_C), carrier (C), and fully recovered (R) disease phases at different times over a time period of 65 days (**Figure 1**). This time period of 65 days was chosen based on the recovery time (i.e., no more infectious individuals) predicted by the model for a 10,000 head cattle herd. The main output of the model was the proportion of cattle in different phases of infection at different time points. The periods of time that would present the highest likelihood of virus transmission when shipping cattle to slaughter were then identified.

The model updates the number of cattle in each disease state every 24 h, which provides insight into the disease progression through the herd. The model considers the uncertainties in input parameters as well as the inherent variability associated with the course of infection in each animal and the spread within the group. Parameter distributions for the disease spread model were obtained from previous work (6–8). Additional information on model structure, parameters and inputs can be found in **Supplementary Material**.

The scenarios evaluated were:

- *Scenario 1: The disease is allowed to progress through an infected herd and at least 42 days have passed since the day clinical signs were initially detected prior to movement of asymptomatic cattle at or near target market weights to harvest.*
- *Scenario 2: The feedlot is actively infected (animals with clinical signs are present) and cattle not showing clinical signs of FMD (non-infected, latent, viremic non-clinical, recovered) that are at or near target market weights are moved to harvest without a waiting period.*
- *Scenario 3: Upon detection, all cattle in the infected feedlot are vaccinated, at least 42 days have passed since the day clinical*

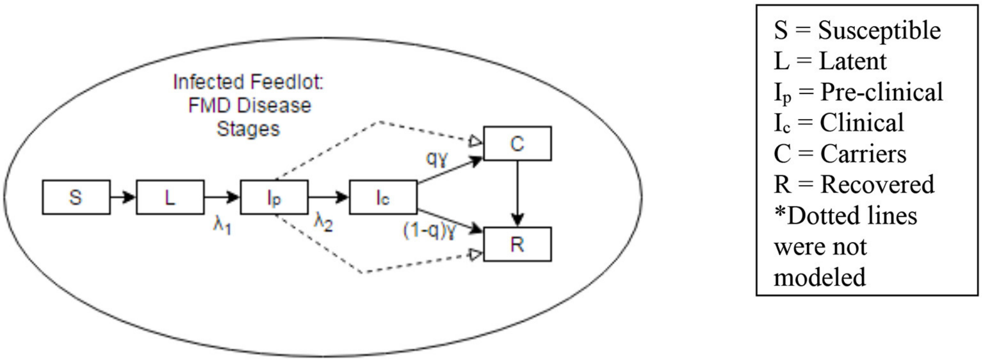

FIGURE 1 | Representation of disease states considered in a within-herd disease spread model. Dotted lines were not considered in the model.

signs were initially detected in the herd and asymptomatic cattle at or near target market weights are subsequently moved to harvest.

- *Scenario 4: Upon detection, all cattle in the infected feedlot are vaccinated, at least 14 days have passed as the waiting period post-vaccination and cattle not showing clinical signs of FMD (non-infected, latent, viremic non-clinical, recovered) that at or near target market weights are moved to harvest.*
- *Scenario 5: The feedlot is not known to be infected (infected but undetected or negative) and is located within a Control Area. All animals have been vaccinated and cattle at or near target market weights are moved to harvest after a 14-day waiting period.*

THE ROLE AND IMPACT OF VACCINATION

In situations where emergency vaccination is authorized, animals that get vaccinated are those not showing clinical signs of infection. Various vaccination strategies to control outbreaks and restore disease-free status have been employed in outbreaks in the Netherlands (9) and in South America (10). In experimental studies, if animals are sufficiently and adequately immunized by vaccination before virus challenge, both within-herd transmission and the likelihood of between-herd transmission will decrease (11–13). Emergency vaccination with high-potency vaccines against FMDV has been shown to be highly effective in preventing clinical signs in animals when the correct type and strain are used in the vaccines and when the vaccine was administered no fewer than 4 days prior to challenge with FMDV (14–17).

While vaccinated animals appear to be protected from clinical infection, sub-clinical infection may occur. Viral RNA titers are, on average, 100–1,000 times lower (two to three log reduction) in the positive samples of vaccinated animals compared with those of the unvaccinated animals, suggesting vaccination can help reduce the amount of viral shedding into the environment shortly after direct virus exposure (15). Other findings suggest that vaccination helps to significantly reduce clinical signs in cattle and prevent viremia (18, 19). On a herd-level, as the time between vaccination and virus challenge increases, it is likely that the proportion of animals showing clinical signs in a herd will decrease (18).

Some proportion of cattle may become persistently infected regardless of their vaccination status (20). Cox et al. (15) showed that 45% of vaccinated cattle became persistently infected where much of the virus persists within the oropharynx and/or pharyngeal fluid (21). Viral persistence may also be influenced by the amount of virus an animal was exposed to, as well as the type of vaccine itself (16).

It is assumed that unvaccinated cattle produce significantly higher quantities of virus and continue to excrete virus for longer periods of time relative to vaccinated cattle (22). This may impact the amount of virus found in the environment at the infected or recovered premises. The environmental viral load also may depend on how many animals were able to develop adequate immunity prior to virus exposure.

To date, most experimental studies focus on cattle that have been vaccinated at least 3 days prior to challenge with FMDV (23). This is in contrast to the proposed use of emergency vaccination in a herd in which FMD has already been detected. It can be assumed that during vaccination of infected herds, there may be animals in all stages of disease (e.g., naïve, latent, sub-clinical, clinical, recovered). For response purposes, it is also prudent to emphasize the importance of vaccinating nearby susceptible premises prior to moving animals off of infected premises. Identifying the effects of vaccines on viral shedding in animals that are exposed to the virus prior to inoculation is an area for further research.

TRANSPORTATION TIMELINES AND MOVING ANIMALS FROM AN INFECTED FEEDLOT

The decision to move asymptomatic (e.g., uninfected, latent, viremic non-clinical, and recovered) cattle from an FMD infected or recovered premises may be influenced by logistics, finances, risk tolerance, and other factors. While other destinations may be used in the event of an outbreak, the movement of cattle was modeled from feedlot premises to harvest only; movements to other types of facilities were not considered.

In a large cattle herd, it is assumed that ∼10% (1,000 cattle in a 10,000 head herd) of the herd will show clinical signs before the disease is detected. This could represent a worst-case scenario as the disease detection will be delayed due to inability for personnel to identify animals showing clinical signs until large numbers of lame animals are noted (24). It is predicted that the time until FMDV first detection would be ∼17.5 days (95% CI = 17.4–17.7) after disease introduction to the premises.

In the absence of vaccination, delaying movement until most of the herd has reached the recovered stage is one strategy to decrease virus spread. Scenario 1 estimates time until recovery for an individual animal at 42 days, however, when considering movement of a large herd, waiting an additional 6 days would result in a lower likelihood of disease transmission from infected animals. 96% (9,628/10,000) of a beef cattle herd of 10,000 head will have entered the recovered phase at 65.7 days after disease introduction to the premises (95% CI = 65.3–65.9) resulting in a viremic population of 0.009% (0.942/10,000) given a 48 day waiting period from time of detection. Of note, some proportion of animals in the recovered stage may have healing or scarred lesions remaining. While these animals do not represent a virus transmission risk, they may not be eligible for shipment until all lesions have resolved.

If unvaccinated, asymptomatic cattle are moved more quickly after disease detection (Scenario 2), there is a risk that asymptomatic cattle moved may include individuals in a viremic pre-clinical disease state. Additionally, a larger proportion of viremic (pre-clinical and clinical) cattle still remain in the herd, adding to virus contamination in the feedlot environment. After a waiting period of 25 days post-detection, most cattle have moved into clinical or recovered states; ∼0.012% (1.2/10,000) of pre-clinical cattle are predicted to be present in the herd.

Moving all cattle at once likely is not feasible, due to limited capacity of transportation resources and slaughter plant capacity. In this work, we provide a point-in-time proportion of cattle in each disease state in the overall herd. The model did not account for decreasing overall herd size as transports to market are ongoing, however as the waiting time progresses past 25 days, the likelihood of transporting pre-clinical animals decreases. This number, however, does not include the number of sub-clinical cattle that may be present in the herd and shedding a similar amount of FMDV as clinical cattle. Literature estimates that ∼11% of infected cattle may remain sub-clinical (25) as cited in Sutmoller and Olascoaga (26). The model did not account for sub-clinical cattle and this is a limitation of this methodology.

Vaccination status may have an effect on the likelihood of disease spread. Emergency vaccination of cattle has been shown to be effective in preventing or reducing clinical disease, reducing intra-herd transmission, and decreasing FMDV shedding. However, unlike the majority of experimental studies where animals had been vaccinated 3 or more days prior to disease exposure or challenge, the scenarios presented in this analysis involve the vaccination of cattle that may have already been exposed to the virus on an infected premises. Cattle that were vaccinated prior to exposure have been shown to remain carriers for a shorter period of time and harbor significantly less virus than cattle that were not vaccinated (22). It is unknown whether this applies to animals that are vaccinated after exposure to the virus. Vaccination after exposure may result in more viral shedding and more carriers being present than if the animals had been vaccinated prior to exposure.

If all cattle were vaccinated upon detection and movement was delayed until nearly the entire herd reaches the "recovered" state (Scenario 3), the primary concern for virus shedding is cattle in the "carrier" state. Similar to Scenario 1, 48 days post-detection represents the time at which 96% of a 10,000 head beef cattle herd was predicted to be in the recovered phase. The proportion of cattle in a carrier state when vaccination occurred very close to or after virus exposure is not known.

Cattle that have been vaccinated have been shown to have less severe or no clinical signs, and decreased viral shedding. There may also be some evidence to indicate fewer of these animals become sub-clinically infected (18). If FMDV was detected on day 17 and cattle were immediately vaccinated (Scenario 4), movement of these animals could occur no sooner than 31 days after initial infection (i.e., after the 14 day vaccine withdrawal period for slaughter). On day 31, ∼0.34% (34/10,000) of the herd will be in the latent phase, and ∼1.59% (159/10,000) of the herd will be in the pre-clinically infectious phase. Should a decision be made to move the eligible cattle on day 31 post-infection, there would be a larger likelihood of moving pre-clinical cattle relative to the longer waiting periods used in Scenarios 1 and 3.

If the feedlot is not known to be infected, it may truly be uninfected, or the level of clinical disease may be below the rate of detection (Scenario 5). Infection may occur any time before or after vaccination. The model predicts that it will take 17 days post-infection to reach 10% of the given population showing clinical signs of infection; thus FMDV will most likely not be detected in this herd prior to transport at the end of a 14-day vaccine withdrawal period for slaughter, resulting in the movement of infectious animals. A decision to move animals 14 days after vaccination (i.e., maximum 14 days after the herd was infected), represents a worst case scenario. Movement at this time could result in a large number of viremic pre-clinical animals being included in the transport. At Day 14, ∼3% (343/10,000) of the herd would fall in this category.

RISKS TO NEIGHBORING PREMISES AND EPIDEMIOLOGICAL CONTACTS

During an FMD outbreak, if a large feedlot operation is marketed early via transportation of animals to slaughter, the benefits of decreasing the local susceptible population must be weighed against the potential risks. Potential risks to surrounding premises and contacts include mechanical or aerosol transmission from movement of viremic animals or from the use of contaminated transport vehicles.

Pre-clinical and clinical cattle can shed virus in a variety of excretions and secretions, including high viral titers in nasal discharge, upper respiratory tract samples, skin lesions, probang (oropharyngeal) samples, and aerosolized virus, and to a lesser extent in urine and feces (27, 28). In contrast, carrier state cattle shed intermittently only from the esophageal-pharyngeal region (22). To date, there is no evidence that carrier cattle are capable of transmitting FMDV to susceptible animals, thus we assume transmission from these animals is not likely (5). The possibility of virus traveling via fomites on cattle hides, vehicle conveyance, or aerosolized in transit is possible, but further research in this area is needed to quantify the associated risk.

The absolute impact of vaccination after virus exposure on decreasing carrier state frequency or duration is unknown. Vaccination can, perhaps, be assumed to result in the possibility of lower levels of virus in the environment due to an assumed decrease in viral shedding from vaccinated animals.

Loading and transporting cattle from a feedlot that is currently infected means increased likelihood of contact with more virus in the environment when compared to a recovered feedlot, due to the presence of viremic animals that are actively shedding virus. While we assume that all transport vehicles will be cleaned and disinfected before and after each load of cattle, the risk for contamination of the vehicle may still remain. Additional logistical concerns may arise and include lack of washing facilities, waste water management concerns, and temperature and weather challenges. While these are outside the scope of this assessment, decision-makers should consider their potential impacts on viral spread.

LIMITATIONS

While scenarios and models such as those used in this analysis are useful for proactive disease outbreak response planning, they may not correlate exactly with the parameters that arise during a real outbreak. Data from previous outbreaks detailing within-herd spread is limited (29); in absence of outbreak data, this model was based on characteristics described in experimental work, where only limited numbers of animals and few virus strains have been studied. Differences in virus characteristics during an outbreak, therefore may vary. It was also assumed that all animals with adequate virus exposure would progress to clinical disease. Lack of consideration for potential animals in the sub-clinical state is a limitation of this design. Before applying the findings of any prospective work to an actual outbreak, parameters and assumptions of a model must be assessed and contextualized if work such as this is considered for use in decision-making.

The model also assumed that all animals at a feedlot had the potential for contact with one another, which is likely not true in a majority of the commercial feedlot industry in the US Cattle in the feedlot are grouped by lots and pens, and while some mixing may occur at entry and sort dates, this contact is neither homogenous or random. The decision to use a simplified homogenous random-contact model was based on the lack of within-herd spread data available from past outbreaks (29) and findings from a similar study in swine where simplification to a homogenous mixing model did not significantly change key outcomes (30). In that study modeling FMD spread on a swine operation compared within-farm transmission assuming homogeneous mixing of a closed population and compared it to transmission when features of farm structure, demography and movement were incorporated into the model. They found that the assumption of homogeneous mixing in a closed population may be sufficient when considering the mean time to detection of a herd based on the presence of clinical signs in post-weaning pigs (30).

Future work is needed to evaluate if this holds true for a beef feedlot setting. The model employed in this work did not account for variations in management structures, husbandry practices, feedlot set-ups or sizes which may all impact contact rates and lameness detection capabilities. Decreased contact rates between sub-populations in a large herd may significantly increase the amount of time needed for FMD to spread (and for animals to recover) on a premises-level, making this work somewhat of a “best-case” scenario with rapid spread. The role for aerosol spread between pens has also not yet been thoroughly investigated in a field setting. Conversely a larger proportion of lame animals in a given pen may occur sooner than that same proportion of lameness is noted premises-wide. In the event that the infected pen is one under intensive scrutiny (e.g., at/near market weight or other intensive husbandry processing procedure) this may speed detection by clinical signs, while if the pen remains relatively unobserved detection may be delayed. Finally, while the use of vaccination was considered, we did not account for potential delays due to the time required to manufacture, ship, and administer vaccines in an identified positive herd.

CONCLUSION

Incident managers tasked with managing large cattle operations during an FMD outbreak likely will consider many factors in deciding when and how to move potentially infected animals from an infected premises, including mechanism of spread, disease phase, time of movement, and vaccination status. It is likely that a single control strategy such as stamping out will be inadequate in the event that large feedlots become infected. When considering alternatives, the role of vaccination, especially when it is administered very close to or after viral exposure, remains unclear. Within-herd spread models such as the one used here are limited in the ability to represent all aspects of a potential outbreak. They may, however, be used as a step toward understanding the potential disease spread characteristics during an FMD outbreak, including the potential benefits of delaying movement on a known infected premises until clinical disease has resolved in the herd. Future work may incorporate new data as it arises, such as within-herd sub-populations, and changing more complex herd dynamics. During an outbreak, it is unlikely that just-in-time calculations will be available based on outbreak disease parameters. Proactive models may assist incident managers in gauging the likelihood that a load of cattle contains viremic and shedding animals (pre-clinical or carrier disease states), which pose greatest risk to other livestock premises. All proactive work must be reviewed for validity and applicability to a specific disease scenario at the time when it arises, and it is of great importance that proactive work such as this be interpreted in the context of available data and science as well as the assumptions and limitations. Overall, risks and benefits of moving asymptomatic cattle from an infected premises must be carefully assessed, as our results indicate there is no zero-risk period for moving cattle during disease progression through a herd.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

TG and FS led project development and provided oversight for this work. FS and KV formulated and developed the modeling components for this study. JE participated in drafting initial reports and literature review. EW updated previous work and wrote the manuscript. All authors reviewed and provided critical feedback on the manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00484/full#supplementary-material

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Modeling the Transmission of Foot and Mouth Disease to Inform Transportation of Infected Carcasses to a Disposal Site During an Outbreak Event

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In the event of a Food and Mouth Disease (FMD) outbreak in the United States, an infected livestock premises is likely to result in a high number of carcasses (swine and/or cattle) as a result of depopulation. If relocating infected carcasses to an off-site disposal site is allowed, the virus may have increased opportunity to spread to uninfected premises and result in exposure of susceptible livestock. A stochastic within-herd disease spread model was used to predict the time to detect the disease by observation of clinical signs within the herd, and the number of animals in different disease stages over time. Expert opinion was elicited to estimate depopulation parameters in various scenarios. Disease detection was assumed when 5% of the population showed clinical signs by direct observation. Time to detection (5 and 95th percentile values) was estimated for all swine farm sizes (500–10,000 head) ranged from 102 to 282 h, from 42 to 216 h for all dairy cattle premises sizes (100–2,000 head) and from 66 to 240 h for all beef cattle premises sizes (5,000–50,000 head). Total time from infection to beginning depopulation (including disease detection and confirmation) for the first FMD infected case was estimated between 8.5–14.3 days for swine, 6–12.8 days for dairy or beef cattle premises. Total time estimated for subsequent FMD cases was between 6.8–12.3 days for swine, 4.3–10.8 days for dairy and 4.5–10.5 days for beef cattle premises. On an average sized operation, a sizable proportion of animals in the herd (34–56% of swine, 48–60% of dairy cattle, and 47–60% of beef cattle for the first case and 49–60% of swine, 55–60% of dairy cattle, 56–59% of beef cattle for subsequent cases) would be viremic at the time of beginning depopulation. A very small fraction of body fluids from the carcasses (i.e., 1 mL) would contain virus that greatly exceeds the minimum infectious dose by oral (4–7x) or inhalation (7–13x) route for pigs and cattle.

Keywords: foot and mouth disease, FMDv, carcass, cattle, swine

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INTRODUCTION

Foot and mouth disease (FMD) is a highly contagious viral disease affecting primarily cloven-hoofed animal including key livestock production species such as cattle and swine. In the event that a case of FMD were detected in the United States (US), there would likely be serious economic impact on international trade of animals and animal products (1). The US has a preparedness and response plan for disease control and eradication in the event of a foreign animal disease event. This plan encompasses management of multiple animal species, and may include movement control, quarantine, vaccination, and depopulation measures (2).

Identification of FMD within a herd relies upon observation of clinical signs to trigger diagnostic testing of suspect individuals. Testing methods for population-level disease surveillance are lacking; this likely results in delayed detection until infection has spread at the farm level. Experimental and modeling studies of transmission in cattle (3) and swine (4) suggest that the infectious period in these species as close as under 24 h before the onset of clinical signs (fever or lesions). This underscores the important role of prompt detection by clinical signs to limit spread throughout the herd. Similarly, early detection decreased the length of epidemics in a multi-species model based on a cattle and feedlot-dense region of Texas, USA (5).

Depopulating an infected premises is performed to prevent further spread of Foot and Mouth Disease virus (FMDv) to susceptible animals and to limit additional FMDv shedding in latently or clinically infected individuals. If an outbreak were concentrated in a geographic area in which FMD can be readily contained without further spread, the response strategy of "stamping out" will likely be elected. "Stamping out," or immediate depopulation, is the preferred control method for clinically infected and in-contact susceptible animals as a means to reduce the potential of disease spread. It is assumed that the depopulation procedures would follow the United States Department of Agriculture, Foreign Animal Disease Preparedness and Response Plan (FAD PReP) Guidance (2).

FMD was eradicated from the United States in 1929 (6); historical data specific to the modern large-scale agricultural operations most common in the US are lacking. Especially in areas where empirical data is lacking, expert opinion has been a mainstay in informing proactive planning for FMD incursions, and aspects such as disease characteristics in a naïve population and depopulation techniques have been described (7, 8). Models have been used as another means of understanding potential disease scenarios and as a way to inform planning decisions. Most models focus on between-herd spread, and incorporate aspects such as vaccination strategies, movement characteristics, and geographic proximity in areas with multiple species, such as cattle, goats, and swine (5, 9–12). In all these studies depopulation is one option to limit disease spread; however, management strategies for carcasses after depopulation was not considered.

Swine and cattle (beef and dairy) are the two most prevalent livestock species in the US (13, 14). If a swine or cattle premises were infected and depopulated, the option to dispose of carcasses off-site may be needed due to environmental and other limitations of disposing a large biomass on-site. It is required for trucks to be leak-proof while hauling animal carcasses according to US Code of Federal Regulations (15), however, in the event of an FMD outbreak, other means of hauling carcasses may be employed. FMDv presents a containment challenge due to its persistence in the environment, especially when it is within organic material and protected from desiccation, heat and adverse pH conditions (16). Movement of FMDv-infected carcasses represents one of the main disease spread pathways during an outbreak. Proactively evaulating the potential risk of transmission and available mitigation meaures can allow risk managers to be better prepared for these scenarios in the event of an outbreak (**Figure 1**).

The aim of this study was to evaluate the likelihood that carcasses in a truckload from a depopulated infected premises would contain an infective FMDv dose at the time of transportation to disposal. This information is an important consideration for emergency preparedness and management officials in the event of a FMD outbreak, as off-site transportation of carcasses to disposal is a potential pathway to spread virus during an outbreak.

MATERIALS AND METHODS

A stochastic disease spread model was developed to simulate the transmission of FMDv within a swine, dairy or beef cattle herd and predict the proportion of viremic animals at the time of depopulation. The model was run for each of the livestock types, and it estimated the number of animals in various disease stages at each time step. Disease stages included: susceptible (S), latent (L), pre-clinical (PI), clinical (CI), and recovered (R) (17). Both pre-clinical and clinical animals were considered viremic and infectious to other susceptible animals within the herd (18, 19). The model updated the number of animals in each disease state every 6 h. The uncertainties in input variables, as well as the inherent variability associated with the course of infection in individual swine, dairy and beef cattle populations and the spread within the group were considered in the model in the form of distributions for the different parameters (transmission coefficient, duration of the latent, pre-clinical and clinical periods). Parameter distributions were obtained from previous FMD modeling studies and meta-analyses (18–20). The farm size scenarios used in the model were based on a compilation of statistics published by the National Agricultural Statistics Service (NASS) of the United States Department of Agriculture for 2014 (21). Average farm sizes were calculated for all production types within livestock category (swine, beef cattle, or dairy cattle). The model assumed that disease transmission was the same regardless of animal age. **Table 1** shows the inputs used in the disease spread model.

The model assumed random mixing among the entire population. The number of susceptible animals that become infected in each time step in the model was dependent on the adequate contact rate and the proportion of infectious animals in the herd at that time step. The same contact rate was used for both

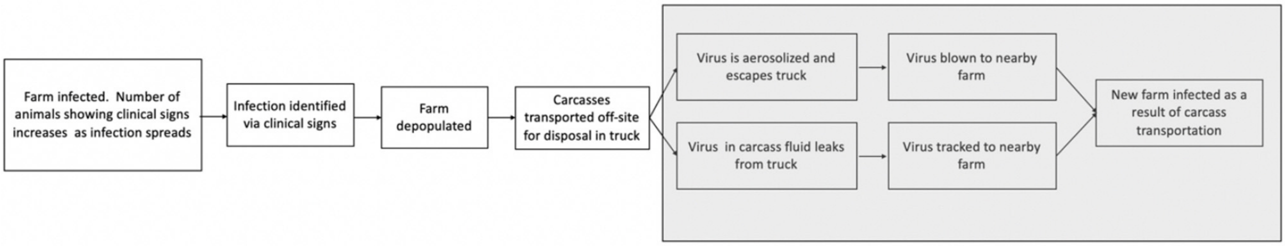

FIGURE 1 | Disease spread pathway by which FMDv may spread during the transportation of carcasses from an infected livestock premises to an off-site disposal location. Steps in gray represent the potential transmisson risks during transportation.

TABLE 1 | Input parameters used in the FMD spread model in swine, dairy and beef cattle premises.

Variable[a]	Input distribution/value	References
Latent period	Normal (2.31, 1.40) (swine)	(19)
	Weibull (1.78, 3.97) (cattle)	(18)
Pre-clinical period	Normal (1.485, 1.099) (swine)	(19)
	Gamma (α = 1.222, θ = 1.672) (cattle)	(18)
Clinical period	Poisson (λ = 5.195)-Normal (1.485, 1.099) (swine)	(19)
	Gamma (α = 4.752, θ = 0.736) (cattle)	(20)
Group size (head)	500, 1,000, 5,000, and 10,000 (swine) 100, 500, 1,000, and 2,000 (dairy) 5,000, 15,000, 30,000, and 50,000 (beef)	(21)
Adequate contact rate (contacts/day)	beta PERT (3.17, 6.84, 14) (swine)	(22)
	beta PERT (13, 54, 216) (cattle)	(17)
Detection threshold	5% of group	

[a] *Distributions refer to swine groups of more than 200 head.*

index and subsequent case scenarios. The adequate contact rate (k) is defined as the mean number of other animals each infected animal comes into contact with per unit time such that the contact is adequate to transmit infection. Thus, the probability (P_t) that an animal becomes infected and the number of newly infected, latent individuals (L_{t+1}^{new}) in a given time step can be expressed as:

$$P_t = 1 - e^{-\left(\frac{k\, I_t}{N-1}\right)} \tag{1}$$

$$L_{t+1}^{new} \sim Binomial(S_t, P_t) \tag{2}$$

where N is the total population size of the farm, I_t is the number of infectious animals (pre-clinical or clinical) and S_t is the number of susceptible individuals at time t. Transitions between other disease stages (from L to PI, PI to CI and CI to R disease stages) were simulated based on the duration of each period, which was determined individually for each animal.

The disease spread model also estimated the time to detect FMD infection in the herd based on the active observation of clinical signs, which is one of the surveillance measures that may be applied in an outbreak at the herd level (23). The threshold for detection of the disease was set at 5% of the herd showing clinical signs, which was based on the percentage of naturally occurring lameness on swine and cattle farms (24, 25). A sensitivity analysis on the detection threshold (re-analyzed at 2.5 or 10%) was performed for an exemplar scenario (swine herd of 5,000 head) to ensure that time to detection distributions were not overly sensitive to changes in this threshold (**Supplementary Figure 1**).

Once the disease was detected at a premises, it was assumed that a depopulation protocol would be initiated by disease management officials. Total time from detection to beginning depopulation was estimated by adding each time interval by using the following equation:

$$\text{Total time} = t_{det} + t_{conf} + t_{sdep}(h) \tag{3}$$

where, t_{det} is the time elapsed to detect FMD post-infection depending on the farm size, t_{conf} is the time interval between detection of clinical signs in a particular premises to the official laboratory confirmation of a positive sample, and t_{sdep} is the time interval between laboratory confirmation to starting depopulation. All the time intervals were expressed in hours.

Expert opinion was solicited via email from five national experts in emergency management and depopulation procedures working in academia, industry and government settings to provide estimates on time intervals for laboratory confirmation after the detection of an infected premises and for starting the depopulation protocol (**Supplementary Table 1**). It was assumed that the time to complete indemnity or time to find disposal options were not included in the estimation of total time from infection to depopulation. Two scenarios (index case and subsequent cases) were given to the experts for estimating the time to start the depopulation procedure (t_{sdep}). Input values of equation 3 for swine, dairy and beef cattle as the index case are shown in **Tables 2–4**. A Pert distribution was used to characterize the variability among experts' responses (26). The worst-case scenario was selected to populate the distribution by identifying the longest time interval estimates among all the experts for the minimum, most likely and maximum values. For subsequent cases, the time from disease detection to laboratory confirmation and the time from confirmation to beginning depopulation were each set at 24 h. A Monte Carlo simulation was carried out by using @Risk 6.2 for Excel (Palisade Corporation, NY). The analysis was performed using 1,000 iterations with Latin-hypercube method. Outputs were expressed by the mean and 90% prediction intervals as calculated by the 5th and 95th percentile values. The proportion of viremic and recovered animals at the

TABLE 2 | Input values to estimate timings for depopulation procedure in case of FMD outbreak in swine premises.

	Stochastic disease spread model	**Expert elicitation**		
Herd size	**Time to detect disease post-infection (h)***	**Time from disease detection to laboratory confirmation (h)**	**Time from confirmation to starting depopulation (h)**	**Depopulation rate (head/h)****
500	PERT (102, 135, 228)	PERT (24, 48, 72)	PERT (24, 48, 72)	PERT (30, 140, 600)
2,000	PERT (120, 155, 246)			
5,000	PERT (132, 172, 270)			
10,000	PERT (144, 183, 282)			

*Beta-PERT distributions represent minimum, most likely, and maximum values. *5% detection level. **Using three crews (8 men each) during 3 working shifts (20 + 4 h cleaning) and two side discharge alleys with two loaders.*

TABLE 3 | Input values to estimate timings for depopulation procedure in case of FMD outbreak in dairy premises.

	Stochastic disease spread model	**Expert elicitation**		
Herd size	**Time to detect disease post-infection (h)***	**Time from disease detection to laboratory confirmation (h)**	**Time from confirmation to starting depopulation (h)**	**Depopulation rate (head/h)****
100	PERT (42, 82, 192)	PERT (24, 48, 72)	PERT (24, 48, 72)	PERT (18, 36, 60)
500	PERT (54, 93, 192)			
1,000	PERT (60, 97, 192)			
2,000	PERT (60, 107, 216)			

*Beta-PERT distributions represent minimum, most likely, and maximum values. *5% detection level. **Using three crews (8 men each) during 3 working shifts (20 + 4 h cleaning) and two cow side discharge alleys (10 cows each) with two loaders.*

TABLE 4 | Input values to estimate timings for depopulation procedure in case of FMD outbreak in beef cattle premises.

	Stochastic disease spread model	**Expert elicitation**		
Herd size	**Time to detect disease post-infection (h)***	**Time from disease detection to laboratory confirmation (h)**	**Time from confirmation to starting depopulation (h)**	**Depopulation rate (head/h)****
5,000	PERT (66, 109, 216)	PERT (24, 48, 72)	PERT (24, 48, 72)	PERT (18, 36, 60)
15,000	PERT (72, 117, 210)			
30,000	PERT (78, 120, 216)			
50,000	PERT (78, 128, 240)			

*Beta-PERT distributions represent minimum, most likely, and maximum values. *5% detection level. **Using three crews (8 men each) during 3 working shifts (20 h + 4 h cleaning) and two cow side discharge alleys (10 cows each) with two loaders.*

time of starting depopulation was predicted from the disease transmission model at the time elapsed between infection and starting the depopulation.

RESULTS

The disease spread model estimated the time to reach 5% of clinical animals in the herd (threshold for FMD detection by active observational surveillance). Time to detection (5 and 95th percentile values) was estimated at 102–282 h for all swine farm sizes (500–10,000 head), from 42 to 216 h for all dairy cattle premises sizes (100–2,000 head), and from 66 to 240 h for all beef cattle premises sizes (5,000–50,000 head). A sensitivity analysis of the detection threshold demonstrated that the distributions for time to detection were not sensitive to the threshold.

A sensitivity analysis was carried out to identify the time interval that had the greatest influence on the total time (from detection to finalized depopulation). As it can be seen in **Figure 2**, the detection time was the input variable with the greatest influence for dairy and swine premises. However, given the size (i.e., large number of animals on beef premises), the time to depopulate a farm was the interval with the greatest influence on beef premises.

Total time from infection to depopulation (90% prediction interval) for the first FMD infected case was estimated to be 8.5–14.3 days for a 3,000 head swine herd, 6.0–12.8 days for a 2,000 head dairy herd and 6.0–12.8 days for 5,000 head beef cattle premises (**Tables 2–4**). Total time estimated for subsequent FMD cases is reported in **Table 5**. A sizable proportion of animals in the herd (34–56% of swine, 48–60% of dairy cattle, and 47–60% of beef cattle for the first case, and 49–60% of swine, 55–60% of

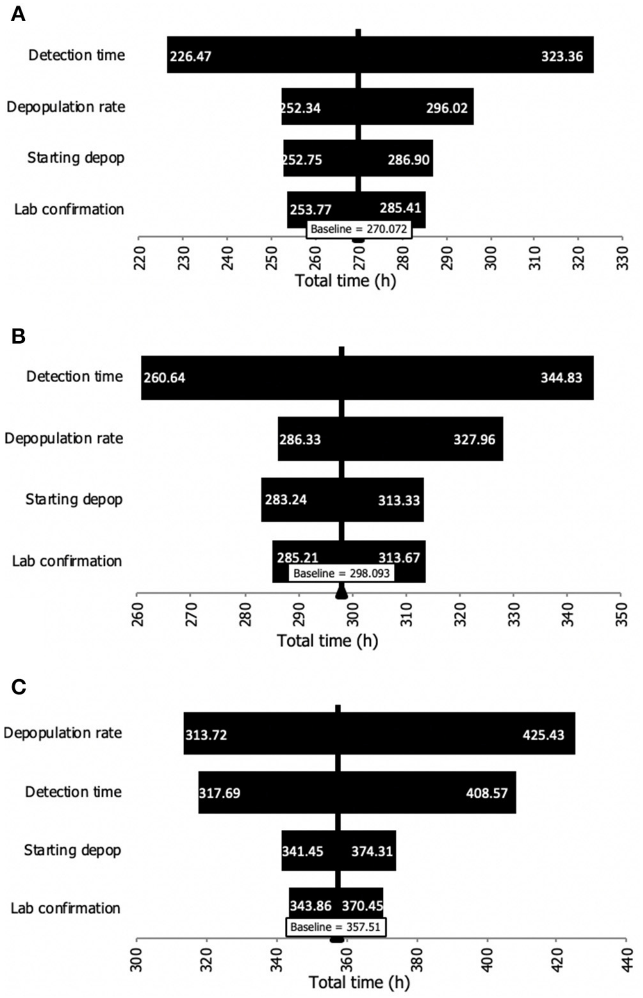

FIGURE 2 | Sensitivity analysis of the influence of the input time intervals on the total time from detection to depopulation of premises during an FMD outbreak. **(A)** Dairy premises. **(B)** Swine premises. **(C)** Beef cattle premises.

TABLE 5 | Total time from infection to beginning depopulation.

Type of farm	Total time (days)*	
	First index case	**Subsequent cases****
Swine (3,000 head)	10.8 (8.5–14.3)	8.8 (6.8–12.3)
Dairy (2,000 head)	8.5 (6.0–12.8)	6.5 (4.3–10.8)
Beef cattle (5,000 head)	8.6 (6.0–12.8)	6.6 (4.5–10.5)

**1,000 iterations (mean, 5th and 95th percentile values).*

***Time from detection (including disease confirmation) to starting depopulation was set at 48 h for subsequent FMD cases.*

dairy cattle, 56–59% of beef cattle for subsequent cases) would be viremic at the time of depopulation (**Table 6**).

TABLE 6 | Number of viremic and recovered animals at the start of depopulation.

	First index case		
	Time elapsed before depopulation (days)*	**Percentage of viremic animals (pre-clinical + clinical) (%)**	**Percentage of recovered animals (%)**
Swine (3,000 head)	10.8 (8.5–14.3)	46 (34–56)	46 (28–62)
Dairy cattle (2,000 head)	8.5 (6.0–12.8)	55 (48–60)	34 (22–45)
Feedlot cattle (5,000 head)	8.6 (6.0–12.8)	55 (47–60)	37 (22–47)
	Subsequent cases**		
Swine (3,000 head)	8.8 (6.8–12.3)	56 (49–60)	15 (13–18)
Dairy cattle (2,000 head)	6.5 (4.3–10.8)	57 (55–60)	12 (10–14)
Feedlot cattle (5,000 head)	6.6 (4.5–10.5)	58 (56–59)	12 (10–14)

**1,000 iterations. Reported values represent mean, 5th and 95th percentile values **Time from detection (including disease confirmation) to starting depopulation was set at 48 h for subsequent FMD cases.*

DISCUSSION

Model outputs suggest that if a herd is depopulated when 5% of animals show active clinical signs, a large proportion of the herd will be viremic at the time of beginning depopulation. Even in subsequent cases where it is assumed that the time to from disease detection to depopulation will be shorter (48 h), the proportion of viremic animals remains relatively unchanged. Moving infected carcasses represents a real risk for FMDv spread during an outbreak. However, in the event that "stamping out" is employed, off-site disposal is likely to be required due to the size of beef, dairy, and commercial swine premises in the US and the large amount biomass resulting from depopulation.

Virus could escape from a load of carcasses in leaked fluid, expelled fomites (e.g., dirt, feces), or jostled carcasses from the load, or via aerosolization of virus-laden particulate matter. The likelihood of a spill or aerosol event is unknown, however it is likely that even a small volume of escaped fluid may contain an infectious dose of virus. The average concentration of FMDv in a carcass in experimental inoculation studies was 10^3 PFU/g for a pig carcass and 10^6 PFU/g for a cattle carcass (27–40). Consultation with rendering industry experts revealed that for transportation of fresh, intact carcasses under normal conditions, most body fluids remain inside the carcass (personal communication, 2013). In a full load of a standard rendering truck (29–1,000 carcasses), experts estimated the amount of fluid leakage from carcasses at 20 L per load. Assuming that 1 mL of leakage contains equivalent virus to 1 g of carcass material, 1 mL of body fluids could contain 10–100,000 times higher virus quantity (10^3-10^6 PFU) than the minimum infectious dose by oral ($1.4 \times 10^4 - 1.4 \times 10^6$ PFU) and inhalation route (7–357 PFU) for pigs and cattle (41, 42). Of note, these estimates are based on literature review and experimental studies; virus loads in tissues may be different among virus strains and subtypes or in non-experimental conditions, however, this data was not available for extrapolation.

The environmental conditions which favor airborne FMDv spread are high humidity, low precipitation, low to moderate wind speed, and flat terrain (43). Suitable conditions of relative humidity (RH) above 60% and temperatures below 33°C (91°F) are needed for long-range airborne transmission to be possible. FMDv bioaerosols degrade quickly in RH below 55% due to desiccation (44). Precipitation generally reduces atmospheric bioaerosol concentrations, while high levels of turbulence temporarily increase aerosolized concentrations when dust is raised (45). In longer-range airflows, turbulence eventually causes dilution of FMD bioaerosol concentrations and higher gravitational sedimentation, especially in particles smaller than 10 micrometers (46). Sunlight has minimal effect on the aerosol spread of FMDv, and instead mostly affects survival on surfaces (46). While beyond the scope of this study, further work on the risks of aerosol spread may be warranted if off-site carcass transportation is considered.

A standard rendering truck is outfitted with sealed tailgate and tarp cover to prevent spills or aerosolization, however, it is unlikely that this will completely mitigate risk of virus escape from a load. In the event of an outbreak, other truck types may be employed due to increased demand for timely carcass disposal. A standard rendering truck, roll-off, or dump truck without tarp covering would have an increased likelihood of spillage, due to the proximity of carcasses and other contaminated debris to the top of the trailer in a full load. The use of a sealed plastic bag suitable for the disposal of biological residues is an option provide full protection against spillage and aerosolization. In the event that new or different types of equipment are employed, or that new personnel lacking adequate training are used during an outbreak, the potential that standard mitigation measures may be misused due to human error cannot be underestimated.

Due to the proactive nature of this assessment, some assumptions in calculations were made which may limit this model's applicability in the event of an outbreak. For example, in estimating the time until FMD detection on a farm, only direct animal-animal contact was considered in disease spread, however, in some geographies or production systems, aerosol or fomite (contaminated person/equipment) may also contribute to spread. In addition, the presence of segregated or sub-herds within a population would change the contact rate and the number of animals with viremia at different time points. However, an analysis by Kinsley showed that adding within-farm population structure did not substantially influence time to detection or time to the peak of the epidemic (47). Additionally, although a change in time to detection (either shorter or longer) could influence our results, we did not find time to detection to be influenced by the detection threshold (percent of animals clinical). Part of the reason for this is the high transmission rate of the virus. By the time 5% of the animal are clinical, transmission is in its exponential growth phase (48), and the difference between time until 5 vs. 10% are clinically infected is very small. In addition, our results for time to detection, derived from the stochastic model, were consistent with an analysis of real-world data from the UK epidemic, where the probability of a farm escaping detection fell sharply at around 7 days and was negligible by 12–13 days (49).

In the event of an especially large infected premises, such as a feedlot operation or an integrated farrow to finish swine operation, depopulation (even at efficient speeds) may last weeks to months. The proportion of viremic animals near the end of a depopulation effort and after significant time has elapsed in disease progression is likely markedly different than that which was calculated at the start of depopulation. Further modeling of this disease progression is an area for further work which may be instrumental in planning for management of large infected premises.

In calculating length of time to depopulation, it was assumed that the disposal site was identified and secured before the outbreak, and no additional delays in depopulation or transportation of carcasses occurred as a result of having to locate an acceptable disposal site. It was assumed that the time from depopulation to movement of carcasses to the disposal site would be very short (a matter of hours), so the potential for body fluids to escape from carcasses (leakage) will be minimized. In the event that depopulation or movement of carcasses from euthanasia location into transport vehicle is delayed, it is likely that larger amounts of body fluids may be present, and risks associated with leakage from carcasses may become more significant. Additional delays in transportation or increased duration of transportation to distant disposal sites can be expected to have similar effects on increased leakage as additional body fluids and products of autolysis escape from a carcass.

Finally, this study did not consider issues related to capacity, resource availability, and resource depletion. A large number of infected premises over an extended time period would have the potential to deplete available resources as well as capacity. This would likely result in longer delays in identification, depopulation and disposal. In this event, the herds continue to progress toward a recovered stage, and the proportion of the herd which is viremic will continue to decrease, while the potential for viral contamination of the premises will increase. Issues of logistics and animal welfare must be balanced with the potential for depopulation to decrease the number of potential animal hosts in a local area.

CONCLUSION

In the event of an FMD outbreak in the US, significant time will lapse between infection of a livestock premises and beginning depopulation. During this time, disease continues to spread throughout a herd, and it is likely that a large proportion of animals will be viremic at the time of depopulation, even if disease confirmation and beginning depopulation occurs in a timely manner. Given that even a small amount of leakage from viremic carcasses is likely to contain FMDv concentrations that will exceed the minimum FMD infective dose for pigs and cattle by several degrees of magnitude, it appears that leakage from vehicles transporting viremic carcasses to off-site disposal locations represent a real risk for virus spread during an outbreak. Delays in identification, depopulation and disposal will likely result in greater number of animals that are in the recovered stage.

This study can inform the risk assessment of FMD transmission during the movement of infected carcasses, and should be valuable for risk managers when considering emergency response options. In addition, this can help federal and state agencies to adopt additional risk mitigation measures to reduce the likelihood of infection of susceptible livestock during an FMD outbreak in the US.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

TG and FS led project development and provided oversight for this work. FS, SM, and KV developed the modeling components for this study. JM participated in drafting initial reports and literature review. EW updated and synthesized previous work and wrote the manuscript. All authors reviewed and provided critical feedback on the manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2019.00501/full#supplementary-material

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Uptake of Diagnostic Tests by Livestock Farmers: A Stochastic Game Theory Approach

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Game theory examines strategic decision-making in situations of conflict, cooperation, and coordination. It has become an established tool in economics, psychology and political science, and more recently has been applied to disease control. Used to examine vaccination uptake in human medicine, game theory shows that when vaccination is voluntary some individuals will choose to "free-ride" on the protection provided by others, resulting in insufficient coverage for control of a vaccine-preventable disease. Here, we use game theory to examine farmer uptake of a new diagnostic ELISA test for sheep scab—a highly infectious disease with an estimated cost exceeding £8M per year to the UK industry. The stochastic game models decisions made by neighboring farmers when deciding whether to adopt the newly available test, which can detect subclinical infestation. A key element of the stochastic game framework is that it allows multiple states. Depending on infestation status and test adoption decisions in the previous year, a farm may be at high, medium or low risk of infestation this year—a status which influences the decision the farmer makes and the farmer payoffs. Ultimately, each farmer's decision depends on the costs of using the diagnostic test vs. the benefits of enhanced disease control, which may only accrue in the longer term. The extent to which a farmer values short-term over long-term benefits reflects external factors such as inflation or individual characteristics such as patience. Our results show that when using realistic parameters and with a test cost around 50% more than the current clinical diagnosis, the test will be adopted in the high-risk state, but not in the low-risk state. For the medium risk state, test adoption will depend on whether the farmer takes a long-term or short-term view. We show that these outcomes are relatively robust to change in test costs and, moreover, that whilst the farmers adopting the test would not expect to see large gains in profitability, substantial reduction in sheep scab (and associated welfare implications) could be achieved in a cost-neutral way to the industry.

Keywords: game theory, sheep scab, disease control, stochastic game, Nash equilibrium, social optimum

INTRODUCTION

Effective policies for livestock disease control and surveillance ideally require that we take into account individual decision-making and behavior. Even so, new diagnostic tests and control measures are typically developed without an assessment of whether they are likely to be taken up by the farming community. An example of current importance is the potential uptake of a new diagnostic test for sheep scab (Psoroptic mange), which is one of the most important diseases in terms of welfare and economic impacts for sheep farmers in the United Kingdom (UK) (1).

Sheep scab is a highly contagious disease, caused by infestation with an ectoparasitic mite (*Psoroptes ovis),* prompting an allergic reaction and intense irritation to the animals resulting in rubbing and scratching behavior that leads to large and painful skin lesions (2, 3). Psoroptic mange is not only a major animal welfare concern but also imposes a significant economic burden on livestock industries in many locations worldwide (1). In the UK, incidences of sheep scab dramatically increased following the deregulation of compulsory sheep scab preventative treatment in 1992, with the number of outbreaks rising from just under 100 per year to an estimated 7,000 in 2003 and 2004 (4–6). Since then, infestation by the parasite has been made notifiable in many countries and, in Scotland, the Scottish Government has collaborated with industry through the Scottish Sheep Scab Initiative to enable control of the disease since 2004.

Transmission of sheep scab typically occurs through direct contact with an infested animal or by contact with contaminated fomites in an infested environment, for instance with fence posts, farm machinery, or contaminated wool. Importantly, continuous incursions of infestation happen between neighboring farms (7, 8), particularly when these farms keep sheep in adjacent fields with shared rubbing areas or when there are gaps in common fence-lines. Because of this, it is typically recommended that neighbors should treat at the same time to achieve maximum effect and protection. Currently, sheep scab can only be diagnosed at the late clinical stage, meaning that infestation is able to spread between animals and between farms prior to detection and treatment. At present, farmers use various chemicals to treat the sheep, including organophosphate plunge dipping or injection with macrocyclic lactones (ML) (3). This has the potential to be detrimental to the environment and, crucially, it has been shown that mites have evolved to become resistant to ML chemicals (9, 10). It is well-established that clinical infestation with sheep scab substantially reduces growth and productivity and, if left untreated, can even kill.

If farmers were able to diagnose and effectively treat sheep strategically, at an early stage of infestation, this would not only benefit the health and welfare of the sheep, but it would also avoid farmers' financial losses from rearing poorly performing animals, as well as reducing transmission to neighboring flocks. One new control option is a recently developed diagnostic blood test (an ELISA test), which can detect sheep scab infestation in sub-clinically infested animals (11, 12). This ELISA test employs a single recombinant antigen, and importantly, is capable of accurately detecting *P. ovis* infestation in sheep at the subclinical stage (12). Such a test would allow the infestation to be identified before the advent of clinical signs, reducing the risk of developing clinical disease and also limiting spread.

The question of whether individuals are likely to adopt an intervention can be studied using game theory. Game theory is a mathematical approach to decision making which captures at its core the idea of strategic interactions, where "strategic" refers to the fact that the decision made by one individual is influenced by the decisions made by others, with classic examples being bargaining or bluffing in cards games. Game theory is such a powerful tool that it has been used to examine a wide range of strategic interactions in social, economic and biological systems, such as conflicts over fishing rights, weapons arms races, pricing strategies among competing firms, and the uptake of interventions in human medicine (13–17). For example, application to the uptake of vaccines in human medicine has shown that if there is any risk or cost associated with vaccination then individual self-interest can prevent eradication of a vaccine-preventable disease (14).

The origins of game theory are typically attributed to the mathematical proof of the minimax theorem by von Neumann in 1928, which established what was later called *Nash equilibrium* for strictly competitive games (18, 19). In general, game theory describes strategic interactions of two or more rational decision makers (or players), where each individual's decision (or actions) jointly determine an outcome that affects them all.

The most prominent and well-known example for a simple strategic game is what is known as the *prisoner's dilemma* (20). Two prisoners (A and B) are accused of a crime, for instance robbing a bank together. They are kept separate by the police and are individually presented with a bargain. If prisoner A confesses while prisoner B does not, the one who confesses will be released immediately and the other will spend 6 years in prison. If neither confesses, each will be imprisoned for just 0.5 years; this outcome which has the lowest combined sentence for both players is known as the *social optimum* (shown in red in **Figure 1**). If both confess, they will each be jailed 4 years. Crucial to determining the outcome is the observation that although neither prisoner knows whether the other has confessed, each prisoner knows

		Player 2 (column player)	
		Confess	Keep quiet
Player 1 (row player)	Confess	4, 4	0, 6
	Keep quiet	6, 0	0.5, 0.5

FIGURE 1 | The *prisoner's dilemma* in which (i) if prisoner A confesses while prisoner B does not, the one who confesses will be released immediately (0 year sentence) while the other receives a 6 year sentence, (ii) if neither confesses, each receives just a 0.5 year sentence, and (iii) if both confess, they each receive a 4 year sentence.

that whatever the behavior of the other, they can improve their outcome by confessing (see **Figure 1**).

The outcome arrived at when each prisoner acts in their own self-interest is known as the *Nash equilibrium* (shown in blue in **Figure 1**). However, in these circumstances, when each prisoner acts in their own self-interest, both end up worse off (a 4 year sentence) than if they had acted in accordance with the best solution for all (the *social optimum* which corresponds to a sentence of just 0.5 year).

In the context of veterinary disease control, relatively little research has applied game-theoretic techniques, mostly using the standard static strategic-form game approach (21, 22). Here, we combine epidemiological and economic parameters in type of game called a *stochastic* game that aims to analyse the adoption of the new diagnostic ELISA test for sheep scab in Scotland, where sheep scab is a notifiable disease requiring treatment upon confirmatory diagnosis.

Stochastic games extend traditional strategic-form games (18, 23), such that they are responsive to dynamic situations where the environment changes in response to players' choices. Stochastic games were first introduced by Shapley in 1953 who established the idea of multiple states, and at each stage of the play the players chose an action in the game dependent on the current state (24, 25). The set actions (or *strategies*) that each player decides on, together with the current state, determine not only the stage *payoff* that each player receives but also the probability distribution governing the transitions between states. Thus, stochastic game theory provides a suitable mathematical framework for assessing if, and under which circumstances, farmers are likely to adopt the new diagnostic test for subclinical sheep scab by providing a mathematical framework which enables us to capture different risk states inherent to epidemiological problems and probabilistic transitions between these states.

Our aim is to use a stochastic game to answer the question whether farmers will use the newly available diagnostic test and treat early or whether they will wait and treat on clinical diagnosis only. Here, the term stochastic means that we are analyzing a game with different states of *infestation risk*s—states of high, medium, or low risk of infestation. The current state depends on the previous state and the test adoption decision by the farmers. Because sheep scab can spread between neighboring flocks, the decision a farmer's neighbor makes affects their risk of infestation. Therefore, whether a farmer believes his flock might be infested and should be tested will depend to some extent on the decisions his neighbor takes. If a neighboring farm had sheep scab last season the farmer's flock might be at high risk of being infected this year, whereas if his neighbor was free of infestation, the farmer might consider his flock to be at low risk of being infected this year. Moreover, in this situation, strategic interactions arise because the farmer may consider his animals at low risk if his neighbor controls infestation by using the diagnostic test. He may "free-ride" on the protection afforded by his neighbor and choose not to adopt the test. Such outcomes can be suboptimal for disease control in the population as a whole.

The paper is organized as follows: First we introduce the basic assumptions underpinning our sheep scab model. We then introduce the basic game-theoretic concepts and definitions for a simple strategic game. This we then extend to a stochastic-game set-up, which we illustrate with a simple example. Finally, we present our multi-state sheep scab test-adoption game, along with our findings in terms of economic and epidemiological implications as well as a discussion of the limitations of the current approach.

CHARACTERIZATION OF THE GAME

Before describing the stochastic game in mathematical terms, we introduce our underlying assumptions: The stochastic game presented here is designed to capture the decisions made by two neighboring farmers when confronted with the choice of either adopting the diagnostic test for subclinical sheep scab or not. We assume that a farmer believes his flock to be (i) at high risk of infestation in the current year, if either he or his neighbor suffered clinical sheep scab in the previous year, (ii) at low risk of infestation if both farms were free of infestation last year, (iii) and at a medium risk of infestation if sheep scab was diagnosed using the new test and then treated at the subclinical stage.

The basic game-theoretic concepts are *players* (the decision makers, i.e., the farmers), *strategies* (alternatives among which each player chooses), and *payoffs* (such as financial gains) among the possible outcomes of the game. Fundamentally it is assumed (i) that all players have consistent preferences and behave rationally in the sense of consistently choosing an option that maximizes their individual payoffs based on their beliefs and knowledge at the time of decision-making and (ii) that the specification of the game and the players' payoffs and rationality are common knowledge among the players.

There are multiple factors that may influence whether farmers adopt a new test, such as (i) the cost of the test, (ii) the expected cost of the disease, (iii) and the cost of treating sheep scab. We assume that the current treatment protocol is that sheep are treated when clinical signs are observed, which involves physical examination of individual sheep, locating lesions, followed by diagnosis through skin-scraping by a veterinary surgeon.

The financial profits (*payoffs)* made by a farmer depend on the revenue from his sheep, which will be reduced if they become diseased, together with the costs of testing and treating the animals. At the time when the farmer decides whether to adopt the new diagnostic test, he does not know whether his flock is infected. Hence, he will have to make his decision based on the payoff he *expects*, which will depend on whether he considers his flock at *high, medium* or *low risk* of infestation. The problem can be presented as a stochastic game matrix, with a *high, medium,* and *low risk* state and farmer *payoffs* that depend on the state and their chosen actions (to adopt the test or not to adopt the test). Key to the decisions made by the farmers is also how they weigh up the immediate costs and benefits of adopting the test, which may not pay off in the current year if test costs are high, vs. the long-term benefits of moving to a lower risk state, should both farmers adopt the test. The extent to which a farmer values the short term vs. the long term can be captured by including a *discount factor*. The discount factor captures the farmer's preference for a reward now vs. a future reward (also known as a time preference). Game theory then tells us the decision they arrived at when individuals act according to rational self-interest, known as the *Nash equilibrium*, and also whether this represents the best outcome for both farmers, and we refer to the outcome with the highest combined payoffs for both farmers as the *social optimum*. In the case of the stochastic game, the solution (*Nash equilibrium* or *social optimum*) not only specifies the decision opted for but also determines the relative amount of *time* spent in each state over the long run.

NOTATIONS, BASIC DEFINITIONS, AND STOCHASTIC GAMES

Basic Definitions

Throughout the paper we apply standard terminology and notation from classical game theory. Before defining how to solve a stochastic game it is useful to illustrate how to solve a standard static game: A simple two-player game is defined by a matrix pair (A, B), specifying the *payoffs* for the row player (player 1) and the column player (player 2), respectively. It is assumed that all game matrices A and B are *n* by *n*, corresponding to a set of *n* strategies available to the players.

For example, the *prisoner's dilemma* game described above (**Figure 1**) has two strategies available to the players which are "Confess" or "Keep quiet." Formally, the game is represented by the matrices A (for the row player) and B (for the column player)

$$A = \begin{pmatrix} 4 & 0 \\ 6 & 0.5 \end{pmatrix} \qquad B = \begin{pmatrix} 4 & 6 \\ 0 & 0.5 \end{pmatrix}$$

The decisions made by each player are represented by vectors of probabilities over the available strategies. In this case, the strategy vectors $(1,\ 0)$ and $\begin{pmatrix} 1 \\ 0 \end{pmatrix}$ for the row and column players, respectively, represent the Nash equilibrium.

The strategies "Confess" or "Keep quiet" are examples of what are known as *pure strategies*. In general, a player's strategy may be a probability distribution over the available options, known as a *mixed strategy*, which in the above case could be represented by the strategy vectors $(x,\ 1-x)$ and $\begin{pmatrix} y \\ 1-y \end{pmatrix}$. Here, the strategy vector (1,0) indicates that the row player will play the first pure strategy "Confess" with probability 1 and the second pure strategy "Keep quiet" with probability 0. Similarly, the strategy vector $\begin{pmatrix} 1 \\ 0 \end{pmatrix}$ indicates that the column player will play the first pure strategy "Confess" with probability 1 and the second pure strategy "Keep quiet" with probability 0. Thus, the Nash equilibrium is both players confessing (**Figure 1**, blue payoffs), with payoff of 4 for each player. The strategy vectors $(0,\ 1)$ and $\begin{pmatrix} 0 \\ 1 \end{pmatrix}$ represent the *social optimum* (both players keeping quiet, **Figure 1**, red payoffs).

Returning to the general case of *n* available strategies, if the row player chooses the strategy *x* and the column player chooses the strategy *y*, player 1 receives payoff A(*x,y*) and player 2 receives B(*x,y*). The strategy vectors X^* and Y^* represent a Nash equilibrium when

$$\left(AY^*\right)_i \le X^*AY^* = v^1 \tag{1}$$

$$\text{and} \qquad \left(X^*B\right)_i \le X^*BY^* = v^2 \tag{2}$$

where v^1 is the value to player 1 and v^2 the value to player 2 at the Nash equilibrium. The term $(AY^*)_i$ is the *i*th element of AY^*, giving the payoff to player 1 playing the *i*th action against player 2 playing Y^*. Similarly $(X^*B)_i$ is the payoff to player 2 playing the *i*th action against player 1 playing X^*.

The inequalities state that the value to player 1 playing a pure strategy against player 2 playing their Nash equilibrium strategy is always less than or equal to player 1's optimal value, v^1 (and vice versa). This is because player 1 will not do better than earn v^1 against player 2 playing Y^* by definition of the Nash equilibrium (and vice versa). Therefore, these inequalities must be satisfied by a Nash equilibrium and hence are a necessary condition for a Nash equilibrium.

To exclude the possibility that strategies other than a Nash equilibrium might satisfy the inequalities, we also show that the inequalities are *sufficient* i.e., that *if* they are satisfied, they represent a Nash equilibrium. To demonstrate this, we consider any old strategy $X = (x_1,\ x_2,\ x_3,\ x_4, .., x_n)$ where $\sum x_i = 1$ and multiply Equation (1) by each x_i and sum the equations to obtain

$$\sum\nolimits_{i=1}^{n} x_i \left(AY^*\right)_i \le \sum\nolimits_{i=1}^{n} x_i\, X^*AY^* \tag{3a}$$

i.e.,

$$\sum\nolimits_{i=1}^{n} x_i \left(AY^*\right)_i \le\ X^*AY^* \tag{3b}$$

i.e.,

$$XAY^* \le X^*AY^* \tag{3c}$$

Consequently, the value to player 1 when playing X^* is always greater than or equal to the associated with any old strategy *X*. This demonstrates that X^* is the best response to Y^*. A similar line of reasoning [multiplying Equation (2) by y_i, the elements of Y where Y is any old strategy adopted by player 2] demonstrates that Y^* is the best response to X^*. Therefore, the inequalities 1 and 2 are a necessary and sufficient condition, meaning that (X^*, Y^*) is a Nash equilibrium if and only if the inequalities are satisfied.

The Stochastic Game

Overview and Example

A stochastic game differs from a static game (outlined above) in three respects: (i) payoffs are specified for multiple states of the system, (ii) transition probabilities between states need to be specified, (iii) the value to a player depends not just on the payoff from the current state but on the discounted sum of payoffs from future states visited. This third component requires an additional parameter, the *beta discounted reward parameter* (β) (here also referred to as *discount factor*), which can take on values between 0 and 1. This parameter is the weight given to next year's payoff relative to the current payoff. Taking the extreme cases, if $\beta = 0$, next year's payoff carries no weight in the decision making. If $\beta = 1$, next year's payoff carries equal weight to the current payoff (see the **Appendix** for further details).

The example illustrated in **Figure 2** shows a 2-state stochastic game. The diagram shows the payoffs for each player in each state and for each pair of player choices. In this example, for simplicity, the payoffs in state 2 are proportional to the payoffs in state 1 (determined by a scaling factor s). **Figure 2** also shows the transition probabilities. For example, the top left box for state 1 shows that if each player makes choice 1, they will each receive a payoff of 4, and given these choices, the probability of remaining in state 1 is 1 and the probability of transitioning to state 2 is 0.

We have chosen a simple example so that in either state choice 1 always gives a lower payoff than choice 2. We can view choice 1 and choice 2 as being "Moderate" or "Greedy" in the case of competition for resources. For $s < 1$, state 1 is the state with high resource levels and state 2 with low resource levels. Both players being "Moderate" in state 1 results in remaining in state 1, whereas if both players are "Greedy" there is a transition to state 2. Conversely, both players being "Moderate" in state 2 means a transition to state 1, whereas both being "Greedy" means remaining in state 2. Whenever one player is "Moderate" and the other "Greedy" there is a 0.5 probability of transitioning to the other state.

The procedure for determining the Nash equilibrium and social optimum for a stochastic game such as this is outlined in the **Appendix**. Here, we illustrate the concepts by discussing the solution for $s = 1.0$, 0.8, 0.6, 0.4, and 0.2 (see **Figures 3A–E**).

- When $s = 1.0$ (**Figure 3A**), the Nash equilibrium and social optimum for both players is to be "Greedy" in either state. The long-term equilibrium is for the players to be in state 2, both earning the maximum reward of 8 at each time point.
- When $s = 0.8$ (**Figure 3B**), payoffs in state 2 are 0.8 those of state 1 but the Nash equilibrium and social optimum remain at "Greedy" for both players in each state.
- When $s = 0.6$ (**Figure 3C**), the social optimum shifts in state 2 from being "Greedy" to being "Moderate" for high values of the discount factor β i.e., the players can achieve greater payoffs by being "Moderate" in state 2 when β is large. For ease, consider the case $\beta = 1$. Under the Nash equilibrium of being "Greedy," in the long-run both players remain in state 2 earning a payoff of 8s (=4.8). Under the social optimum of both being "Moderate," the players flip between a payoff of 8 and 4s, giving an average payoff of $(8 + 4s)/2$ (= 5.2). The social optimum is not a Nash equilibrium as shown by the following argument: If one player were to defect from the social optimum and be "Greedy" in state 2, their payoff would increase to 8s in state 2. Under this scenario, both players spend 1/3 their time in state 1 and 2/3 in state 2. Thus, the long-term payoff for the defecting player would be $8(1 + 2s)/3$. This exceeds their payoff at the social optimum $(8 + 4s)/2$ provided $s > 0.4$. Since a player can increase their payoff by defecting from the social optimum, it cannot be a Nash equilibrium.
- When $s = 0.4$ (**Figure 3D**), we see a change in the Nash equilibrium with the Nash equilibrium now coinciding with the social optimum for $\beta = 1$.
- When $s = 0.2$ (**Figure 3E**), the Nash equilibrium and social optimum continue to coincide when $\beta = 1$.

THE SHEEP SCAB TEST ADOPTION GAME: A MULTISTATE MODEL SET-UP

For the stochastic game we assume voluntary test adoption of the new diagnostic ELISA test under a given perfect test regime, assuming a perfect test sensitivity and test specificity [see **Supplementary Material** for implementation of a multi-state setup under an imperfect test regime (26)]. Based on infestation status and test adoption decisions taken the previous year, a farm may be at high, medium, or low risk of infestation this year. In the model, last year's decisions and infestation status determine the decisions the farmer takes this year, and along with the resulting farmer payoffs.

To determine the payoffs, we used epidemiological parameters and estimated costs associated with sheep scab prevalence, which were derived from the literature (2, 5, 11) and are summarized in **Tables 1**, **2**. Traditional treatment costs were obtained for two different treatments, organophosphate plunge dipping and an

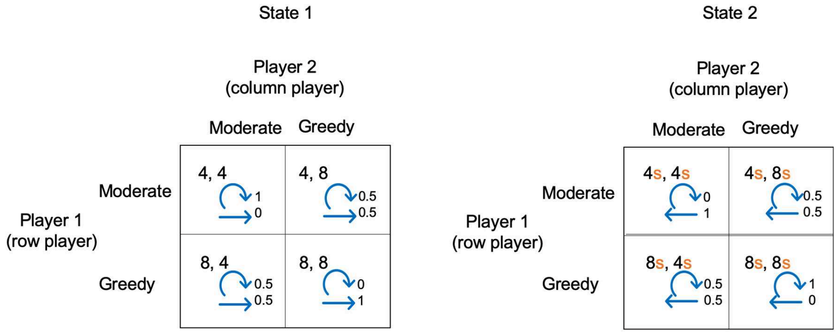

FIGURE 2 | A simple stochastic game for resource competition. The players' pure strategy set is to be "Moderate" or "Greedy." For $s < 1$, state 2 is the low resource state and state 1 the high resource state. Each quadrant contains the payoffs to each player, plus annotated arrows. The straight arrows are annotated with the probability of moving to the alternative state and the curved arrows are annotated with the probability of remaining in the current state.

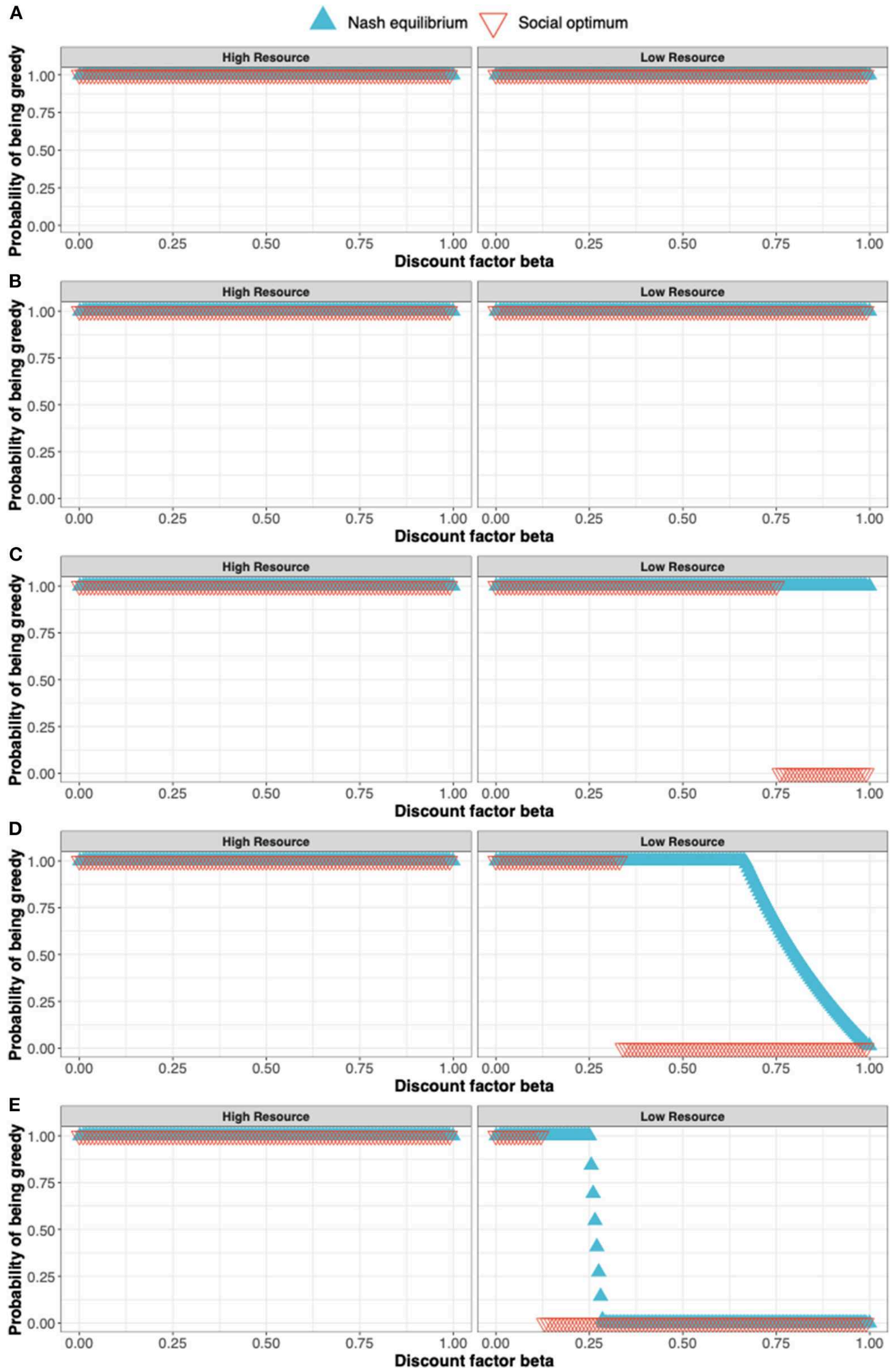

FIGURE 3 | The solution to a simple stochastic game representing resource competition showing the Nash equilibrium (blue triangles) and social optimum (red triangles). The states of the stochastic game are a high resource and low resource state and the pure strategies available to the players are to in either state to either be a Greedy or Moderate user of the resource. The solutions shown in **(A–E)** correspond to $s = 1.0, 0.8, 0.6, 0.4$, and 0.2 where s is the parameter determining the payoff in the state 2 (the low resource state) relative to the payoff in the high resource state.

TABLE 1 | Sheep scab economic costs and epidemiological parameters derived from literature.

Parameter	Description	Default value	Source
C_{Diag}	Cost per head of clinical diagnosis (£100 per flock)	0.21	ADAS (2)
C_{Test}	Cost per head of new subclinical test (£160 per flock)	0.33	
C_{Treat} (dipping)	Cost per head of dipping	0.61	ADAS (2)
C_{Treat} (injected)	Cost per head of injecting	0.65	ADAS (2)
$\text{Subclinical}_{severity}$	Fraction of revenue lost in subclinical infestation relative to clinical infestation	0.15	ADAS (2)
Disease_{cost}	Disease cost per clinical infestation	6.54	ADAS (2)
ϕ_1	Proportion of flock becoming infested (subclinical or clinical)	132/160	Burgess et al. (11)
ϕ_2	Proportion of flock progressing to clinical infestation	27/160	Burgess et al. (11)

TABLE 2 | Assumed or derived parameters.

Parameter	Description	Default value
C_{Test}	Cost of new subclinical test	$1.6{*}C_{Diag}$
R_H	Revenue from a healthy animal	20
R_C	Revenue from clinical animals	$R_H - \text{Disease}_{Cost}$
R_S	Revenue from a subclinical animal	$R_H - \text{Subclinical}_{Severity}\,\text{Disease}_{Cost}$
R_{TT}	Revenue from treated animal	$0.8\,R_H + 0.2R_S$
θ_L	Probability of flock being infested in the low risk state	0.0138 [fitted to Rose et al. (5)]
θ_H	Probability of flock being infested in the high risk state	0.585 [fitted to Rose et al. (5)]
θ_M	Probability of flock being infested in the medium risk state	$0.5(\theta_L + \theta_H)$

injectable formulation using a macrocyclic lactone. Subsequent results are presented for the slightly cheaper option of dipping.

The cost associated with the traditional approach of diagnosing at the subclinical stage is the vet's call-out fee (assumed to be £100 per flock). The cost associated with using the new subclinical diagnostic test is assumed to be the vet's call-out fee plus an additional £60 per flock (27). Costs per head in **Table 1** are derived from reported flock costs (2). Thus, the new test is 1.6× more expensive than the *status quo* clinical diagnosis cost.

Note that the values for the stage payoffs are determined by what the farmer perceives his risk of infestation to be, which may not be an accurate reflection of reality. We considered four scenarios for the test-adoption game:

1) The farmer's flock is **uninfested** and he **does not** adopt the new ELISA test with payoff
2) The farmer's flock is **infested** and he **does not** adopt the test.
3) The farmer's flock is **uninfested** and he **does** adopt the new ELISA test.
4) The farmer's flock is **infested** and he **does** adopt the new ELISA test.

Expected Payoffs

Under scenario 1, the payoff P_1 is represented by $P_1 = R_H$.

Under scenario 2, a proportion of the farmer's flock $(\varphi_1 - \varphi_2)$ will be subclinically infested with revenue R_S, of which proportion φ_2 progresses to clinical infestation with revenue R_C. At this point infestation will be identified and the whole flock will be treated at cost C_{Treat}. Therefore, under scenario 2, the farmer's payoff, P_2, would be

$$P_2 = (1 - \varphi_1)\, R_H + (\varphi_1 - \varphi_2)\, R_S + \varphi_2 R_C - \left(C_{Diag} + C_{Treat}\right)$$

Under scenario three, the test costs C_{Test} are included for the calculation of the stage pay-off P_3, where

$$P_3 = R_H - C_{Test}$$

Under scenario 4, using the diagnostic test and treating infested animals prevents the flock from progressing to the clinical state. Assuming revenue from flock R_H and test and treatment costs C_{Test} and C_{Treat}, the stage payoff, P_4 will be

$$P_4 = (1 - \varphi_1)\, R_H + \varphi_1 R_{TT} - (C_{Test} + C_{Treat})\,.$$

Calculating Expected Payoffs

Another consideration is that because the farmer does know whether his flock is infested or not, he derives his decision to adopt the test or not from what he *anticipates* his payoff to be. Here, we assume that the farmer is risk neutral and therefore that expected payoffs are a linear combination of the payoffs for an infected and uninfected flock. For instance, suppose he thought there was 30% chance (probability of 0.3) that his flock is infected (i.e., a 70% chance or 0.7 probability that it is uninfested). If he decides to adopt the test, his anticipated (or expected) pay-off would be a weighted average of that under scenarios 3 and 4 i.e., the expected pay-off would be $0.7P_3 + 0.3P_4$. In general, if the farmer thinks his flock has a probability θ of being infested and he does adopt the test, his expected pay-off is

$$(1 - \theta)\, P_3 + \theta P_4$$

Conversely, if the farmer thinks his flock has a probability θ of being infested, and he does not adopt the test the expected pay-off is

$$(1 - \theta)\, P_1 + \theta P_2.$$

Risk of Infestation and Payoff Matrices

We distinguish the 3 states by the probability θ_K of the flock being infested in each state with state probabilities $\theta_K = \{\theta_L, \theta_M, \theta_H\}$ denoting the low, medium and high risk states, respectively.

The payoff matrices stating the expected payoffs (the weighted mean across the uninfested and infested scenarios) for a given action in a given state $(\theta_L, \theta_M, \theta_H)$ are defined in **Table 3**.

The infestation probabilities, θ_L and θ_H were estimated by fitting a Markov chain (see **Supplementary Material**) to 10 years

TABLE 3 | Payoff matrix stating the expected payoffs for a chosen action in a given state (θ_L, θ_M, θ_H), where θ_K represents the probability of the flock being infected in low, medium, and high risk states, respectively ($\theta_K = \{\theta_L, \theta_M, \theta_H\}$).

		Farmer 2	
	Risk state	**Does not adopt**	**Adopts**
Farmer 1	Does not adopt	$(1-\theta_K)P_1+\theta_K P_2$, $(1-\theta_K)P_1+\theta_K P_2$	$(1-\theta_K)P_1+\theta_K P_2$, $(1-\theta_K)P_3+\theta_K P_4$
	Adopts	$(1-\theta_K)P_3+\theta_K P_4$, $(1-\theta_K)P_1+\theta_K P_2$	$(1-\theta_K)P_3+\theta_K P_4$, $(1-\theta_K)P_3+\theta_K P_4$

of historical sheep scab outbreak data in the UK, comprising approximately 400 farms in total (5). The data available for these farms was their current infection status and the number of outbreaks in the previous 10 years [illustrated in Figure 1 of (5)]. A Markov chain was simulated for a pair of farms in which the probability of infestation is low (θ_L) if neither were infected in the previous year, or high (θ_H) if one or both were infested in the previous year. Maximum likelihood was used to determine the values of θ_H and θ_L that provided the best fit to the observed distribution of outbreaks. This model fitting therefore exploits the temporal autocorrelation in these data. No information on θ_M[1] could be obtained as the subclinical test was not in use. Thus, θ_M was set equal to the mean of θ_H and θ_L.

Outcome Probabilities

In order to decide whether the farmers will consider themselves in a high, medium, or low risk state next season depends on the possible outcomes for this season which in turn depend on the farmers' actions. At the end of the season, the four possible outcomes (allowing for an imperfect test) for a flock are:

(1) clinical infestation is observed and treated,
(2) subclinical infestation is correctly identified with the new test and treated,
(3) subclinical infestation is incorrectly identified with the new test and treated, and
(4) the absence of infestation is correctly identified.

Outcome 1 (clinical infestation is observed and treated) will occur if a flock is infected and also progressed to clinical infestation without the farmer having tested the flock. Outcome 2 (subclinical infestation is correctly identified and treated) will happen if the flock was infected and tested positive. Outcome 3 (subclinical infestation is incorrectly identified) will occur if the flock was uninfected and testing results in a false positive. Outcome 4 (no infestation is observed) will happen if the flock is uninfected and testing returns no false positives.

Given the probability θ of a flock being infected, $A_1(\theta)$, $A_2(\theta)$, $A_3(\theta)$, and $A_4(\theta)$ represent the probabilities of outcomes 1, 2, 3, and 4 if the farmer adopts the test. Similarly, $DA_1(\theta)$, $DA_2(\theta)$, $DA_3(\theta)$, and $DA_4(\theta)$ represent the probabilities of outcomes 1, 2, 3, and 4 if the farmer does not adopt the test.

Here, we specify the vectors $A(\theta)$ and $DA(\theta)$ for the case of a perfect test. If the farmer *does not adopt* the test, infestation can only be identified at the clinical stage. Thus, the only possible outcomes are 1 (clinical infestation) and 4 (no infestation) which occur with probabilities θ and $1-\theta$. If the farmer *does adopt* the test, the only possible outcomes are 2 (subclinical infestation identified) and 4 (no infestation) which again occur with probabilities θ and $1-\theta$, respectively. Thus, the vectors of outcome probabilities for adopting the test $A(\theta)$ and not adopting the test $DA(\theta)$ are

$$A(\theta) = \begin{pmatrix} 0 \\ \theta \\ 0 \\ 1-\theta \end{pmatrix}, DA(\theta) = \begin{pmatrix} \theta \\ 0 \\ 0 \\ 1-\theta \end{pmatrix}.$$

Transition Probabilities Between High, Medium, and Low Risk States

The outcomes described above determine whether a farmer is in a high, medium, or low risk state *next* season. In other words, the outcomes determine the probabilities of transitioning to the high, medium or low risk state. We assume that **H, M,** and **L** are 4 × 4 matrices, which satisfy $L_{ij} + M_{ij} + H_{ij} = 1$. $\boldsymbol{L}_{ij}$ gives the probability of transition to the **low** risk state next season given outcome *i* for the farm 1 and outcome *j* for the farm 2. Similarly, $\boldsymbol{M}_{ij}$ gives the probability of transition to the **medium** risk state next season given outcome *i* for the farm 1 and outcome *j* for farm 2. $\boldsymbol{H}_{ij}$ gives the probability of transition to the **high** risk state next season given outcome *i* for the farm 1 and outcome *j* for the farm 2.

One option for specifying ***H, M,*** and ***L*** is as follows: We assume that if either farm experiences clinical infestation (i or $j = 1$), both farms transition to the high-risk state next year, represented as follows:

$$H = \begin{array}{cc} \begin{matrix} 1 & 2 & 3 & 4 \end{matrix} & \\ \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} & \begin{matrix} 1 \\ 2 \\ 3 \\ 4 \end{matrix} \end{array}$$

We assume that if either farm correctly identifies subclinical infestation but neither clinical infestation ($i = 2$, $j \neq 1$ or $j = 2$, $i \neq 1$), both farms transition to the medium-risk state next year, represented as follows:

$$M = \begin{array}{cc} \begin{matrix} 1 & 2 & 3 & 4 \end{matrix} & \\ \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix} & \begin{matrix} 1 \\ 2 \\ 3 \\ 4 \end{matrix} \end{array}$$

If both farms are uninfested or they incorrectly identified subclinical infestation ($i = 3$ or 4, $j = 3$ or 4) both farms transition

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[1] A farm is at a medium risk of infestation if sheep scab was diagnosed using the new test and then treated at the subclinical stage.

to the low risk state next year, represented as follows:

$$L = \begin{array}{c} \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{pmatrix} \end{array} \begin{array}{c} \\ 1 \\ 2 \\ 3 \\ 4 \end{array}$$

Hence, the transition probabilities for the stochastic game are:

$$H = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \quad M = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix} \quad L = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 \end{pmatrix}$$

As an example, consider a scenario in which neither farmer adopts the test. Suppose farm 1 had outcome *i* and farm 2 had outcome *j*, then the probability of this combination is $\mathrm{DA_i}(\theta_H) \times \mathrm{DA_j}(\theta_H)$. Therefore, the probability of these observations and followed by transitioning to the high-risk state next season would be

$$\mathrm{DA_i}\,(\theta_H)\;\mathrm{DA_j}\,(\theta_H)\;\mathrm{H_{ij}}$$

Thus, the overall probability of transition to the high-risk state will be obtained by summing over all *i* and *j*, i.e.,

$$\sum_{i=1}^{4}\sum_{j=1}^{4} DA_i\,(\theta_H)\,DA_j\,(\theta_H)\,H_{ij}$$

or, equivalently,

$$\sum_{i=1}^{4} DA_i\,(\theta_H) \sum_{j=1}^{4} H_{ij} DA_j\,(\theta_H)$$

Given that H_{ij} refers to the elements of a 4 × 4 matrix **H** and $\mathrm{DA}_i(\theta_H)$ are the elements of a vector $\mathbf{DA}(\theta_H)$ of length 4, the sum over *i* and *j* is equal to multiplying the vector $\mathbf{DA}(\theta_H)$ by the matrix **H** and then multiplying the result by vector $\mathbf{DA}(\theta_H)$ i.e.,

$$\mathbf{DA}\,(\theta_H)\,\mathbf{H}\cdot\mathbf{DA}\,(\theta_H)$$

Accordingly, for the complete stochastic game, the final payoff matrices and transition probabilities for the high risk state (blue), medium risk state (orange), and low risk state (green) are defined in **Table 4**. Note that the risk of being infected takes on $\theta_K=\{\theta_L, \theta_M, \theta_H\}$, depending on the respective risk state of the farm last year, and **H** (high risk), **M** (medium risk), and **L** (low risk) represent the state-specific transition matrices.

RESULTS

We first examined the test adoption decision for each assumed risk state (*high, medium, low*) in terms of the Nash equilibrium and as a function of the extent to which farmers value future profits. This is captured in terms of the discount factor β. When $\beta = 0$, only immediate returns (i.e., within the season) factor into the farmers' decision and can be thought of as a short-term outlook; at the other extreme, when $\beta = 1$, all future returns are valued equally and can be thought of as taking a long-term outlook. At intermediate values of β, the further into the future a payoff comes, the less it is valued.

TABLE 4 | Matrix notation of the complete stochastic game.

		Farmer 2	
	Risk state	**Doesn't Adopt**	**Adopts**
Farmer 1	**Does not Adopt**	$(1-\theta_K)P_1+\theta_K P_2$, $(1-\theta_K)P_1+\theta_K P_2$ $\mathbf{DA}(\theta_K)\ \mathbf{H}\ \mathbf{DA}(\theta_K)$, $\mathbf{DA}(\theta_K)\ \mathbf{M}\ \mathbf{DA}(\theta_K)$, $\mathbf{DA}(\theta_K)\ \mathbf{L}\ \mathbf{DA}(\theta_K)$	$(1-\theta_K)P_1+\theta_K P_2$, $(1-\theta_K)P_3+\theta_K P_4$ $\mathbf{DA}(\theta_K)\ \mathbf{H}\ \mathbf{A}(\theta_K)$, $\mathbf{DA}(\theta_K)\ \mathbf{M}\ \mathbf{A}(\theta_K)$, $\mathbf{DA}(\theta_K)\ \mathbf{L}\ \mathbf{A}(\theta_K)$
	Adopts	$(1-\theta_K)P_3+\theta_K P_4$, $(1-\theta_K)P_1+\theta_K P_2$ $\mathbf{A}(\theta_K)\ \mathbf{H}\ \mathbf{DA}(\theta_K)$, $\mathbf{A}(\theta_K)\ \mathbf{M}\ \mathbf{DA}(\theta_K)$, $\mathbf{A}(\theta_K)\ \mathbf{L}\ \mathbf{DA}(\theta_K)$	$(1-\theta_K)P_3+\theta_K P_4$, $(1-\theta_K)P_3+\theta_K P_4$ $\mathbf{A}(\theta_K)\ \mathbf{H}\ \mathbf{A}(\theta_K)$, $\mathbf{A}(\theta_K)\ \mathbf{M}\ \mathbf{A}(\theta_K)$, $\mathbf{A}(\theta_K)\ \mathbf{L}\ \mathbf{A}(\theta_K)$

*For each strategy (adopts/does not adopt) chosen by each farmer (row values = Farmer 1; column values = Farmer 2), the upper triangle depicts the respective payoffs, whereas the lower triangle state the probabilities of transitioning to another risk state, shown in blue for transition to the high-risk state, orange for the medium-risk state and green for the low-risk state. Here, **H**, **M**, and **L** represent the transition matrix for each individual risk state (high, medium, low), which is multiplied by each farm's outcome vector of either adopting the ELISA test [A(θ_K)] or not adopting the test [DA(θ_K)].*

When applying realistic economic and epidemiological parameters and an assumed cost for the new ELISA test of around 50% more than the *status quo* clinical diagnosis cost, we found that test adoption depends on the farmer's assumed infestation status (see **Figure 4**). Whenever a farmer considers their farm to be at high risk, i.e., if either farm had been diagnosed with clinical sheep scab the previous year, the diagnostic test will always be adopted. Whenever a farmer considers their farm to be at low risk, i.e., if neither farm had sheep scab the previous year, the test will never be adopted. However, when a farmer considers their farm to be at medium risk i.e., if either farm used the new ELISA test to diagnose and treat animals at the subclinical stage in the previous year, test adoption depends on the discount factor. In this case, mixed adoption can also be observed, meaning that the farmer will adopt the test with some probability between 0 and 1.

These outcomes are relatively robust toward the cost of the new ELISA test (see **Figure 5A**). The test costs would need to more than double before test adoption is not always observed in the high-risk state (see **Figure 5B**), and would need to be very low before test adoption can be seen in the low-risk state (see **Figure 5C**).

We found that the Nash equilibrium strategy does not always match the social optimum. For the same parameters as for **Figure 4** (i.e., a new ELISA test cost 1.5× that of the *status quo* clinical diagnosis cost), in the high and low-risk states

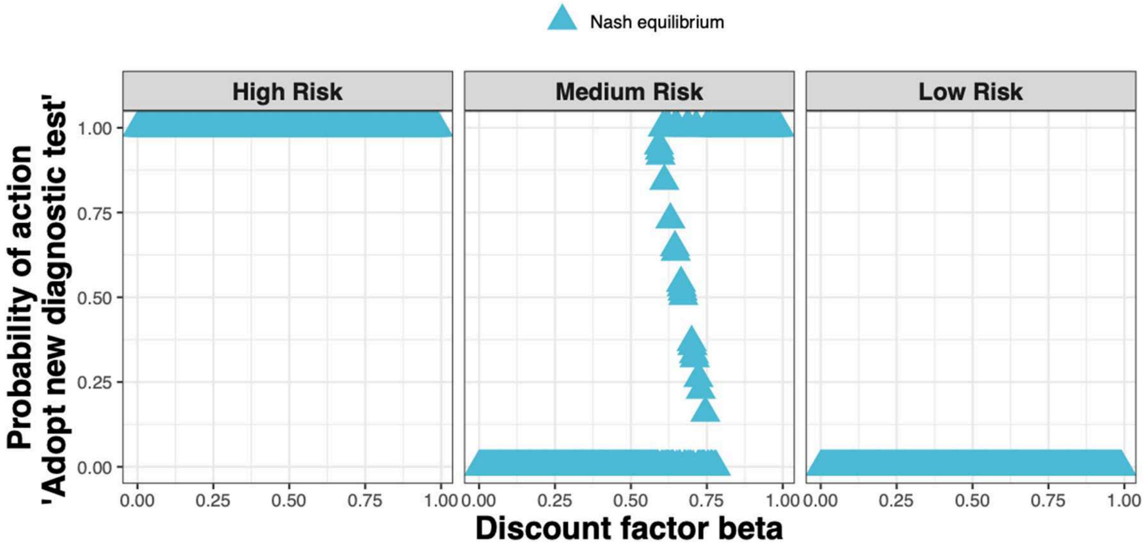

FIGURE 4 | The Nash equilibrium probability in each of the three states (high, medium, and low risk) of adopting the new ELISA test when the cost is 1.5× the *status quo* clinical diagnosis cost, as a function of the discount factor.

the strategies associated with the Nash equilibrium and social optimum agree; in the medium-risk state however, test adoption for the social optimum occurs at lower values of the discount factor than for the Nash equilibrium (**Figure 6**).

The test adoption decision determines the amount of time spent by the farms in the high-, medium-, and low-risk states (**Figure 7**). At the Nash equilibrium (**Figure 7**, blue triangles), compared to the status quo (*Never adopt*), less time is spent in the high-risk state, and more time spent in the medium and low-risk states. Compared to the Nash equilibrium, the social optimum (**Figure 7**, red triangles) either equals the Nash equilibrium or improves upon it by spending less time in the high-risk state and more time in the medium- and low-risk states.

The epidemiological impacts can be observed in terms of the decrease in the proportion of infected farms when going from the *status quo* "*Never adopt*" (with a corresponding baseline proportion of infected farms of just under 0.1) to either the Nash equilibrium (**Figure 8**, blue triangles) or social optimum (**Figure 8**, red triangles), either of which result in a reduction in the proportion of infected farms of around a half.

Contrasting the extreme cases of a discount factor of 0 (a short-term outlook) and a discount factor of 1 (a long-term outlook), shows the epidemiological outcome to be relatively robust to the discount factor. Under test adoption in the high-risk state only, the best strategy for a short-term outlook (**Figure 9A**, highlighted in red), the annual incidence rate is expected to drop to around 5%. If farmers take a long-term outlook and choose to also adopt the new ELISA test in the medium-risk state, the annual incidence rate is expected to drop further to 4% (**Figure 9B**, highlighted in red).

The expected profits per head are greatest for the strategy of adopting the test in the high and medium risk state (the Nash equilibrium and social optimum for the long-term outlook; **Figure 10**). The gains are relatively small, but nevertheless these results show that substantial reductions in annual incidence can be achieved without increasing costs to the farmer.

DISCUSSION AND FUTURE WORK

The transmission and control of infectious diseases strongly depends on both the individual and joint decisions people make with regard to control measures and treatments. In this paper, we applied a game-theoretic model to examine the outcome of strategic interactions between neighboring farms, surrounding decisions to adopt a diagnostic test. The term *strategic interaction* is used because each farmer's decision and payoff depends on the decision made by their neighbor.

Specifically, the game-theoretic model applied in this paper was a stochastic game used to assess whether farmers are likely to adopt the new *P. ovis* diagnostic ELISA test for subclinical sheep scab and how this decision depends on whether a farmer considers their farm at high-, medium- or low-risk of infestation as well the costs and benefits of adopting the new test. Via the discount factor, a stochastic game also allows us to account for farmer preferences in terms of whether they take a short-term or long-term outlook and correspondingly whether they only factor immediate payoffs into their test adoption decision, or whether they factor in future benefits.

In Scotland, the *status quo* is that sheep scab diagnosis happens through skin scraping by a veterinary surgeon. The costs are assumed to come from just the veterinary surgeon call-out fee (here assumed to be £100 per flock), without a laboratory fee as this is currently paid for by the Scottish Government. The cost associated with using the new subclinical diagnostic test is assumed to be the vet call out fee plus laboratory costs (here assumed to be £60 per flock, assuming 12 animals are tested at £5 each). Thus, our assumptions here are that using the new ELISA

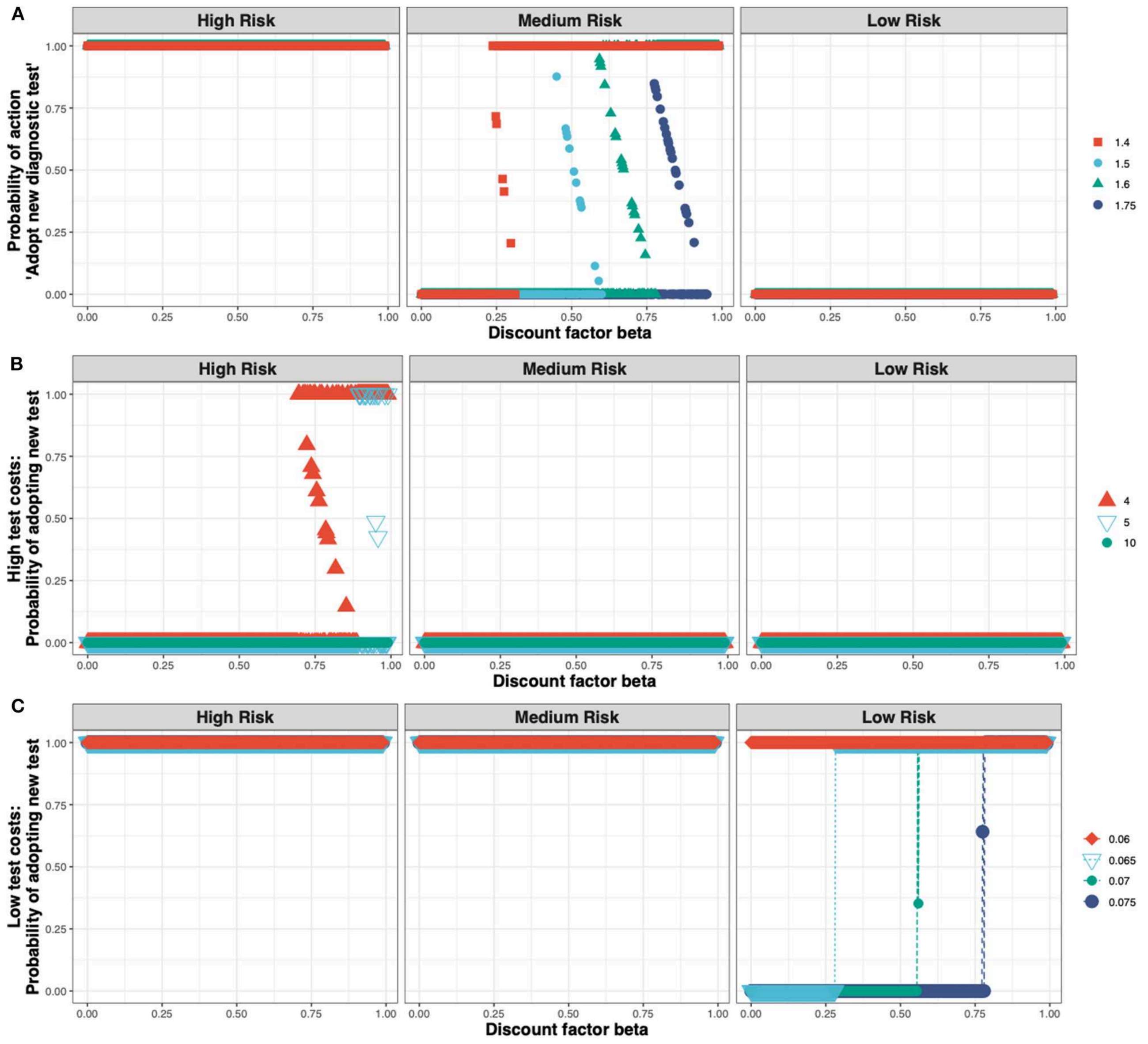

FIGURE 5 | The Nash equilibrium probability in each of the three states (high, medium, and low risk) of adopting the new ELISA test as a function of the discount factor for different multiples of the status quo clinical diagnosis cost **(A)** medium test costs, shown for multiples of 1.4×, 1.5×, 1.6×, 1.75×; **(B)** high test costs, shown for multiples of 4×, 5×, 10×; and **(C)** low test costs, shown for multiples of 0.075×, 0.07×, 0.065×, 0.06×.

test would come to around £160 per flock vs. the £100 per flock for the *status quo* clinical diagnostic test.

We analyzed the test adoption outcomes (*Nash equilibria*) and showed that that they are strongly-dependent on the assumed risk state (*high, medium, low*), and also that they are modulated not just by the costs of the new diagnostic test but also by how much short-term profits are preferred over long-term benefits. When applying realistic economic and epidemiological parameters and using an expected test cost of around 50% more than the current clinical diagnosis via skin scraping, we observed test adoption in the high-risk state, no test adoption in the low-risk state, and mixed strategies in the medium risk state that depended on the preference for short-term over long-term profits. We found the outcomes in terms of test adoption to be relatively robust to the cost of the test, with substantial increases or decreases in test cost required to change the overall pattern of test adoption.

Individual decisions in game-theoretic models are based on assumptions of rational self-interest and do not necessarily correspond to a socially optimal outcome. However, in our analysis, we found that test adoption decisions at the Nash equilibrium were socially optimal for most calculated outcomes. Specifically, whenever a farmer considered their farm to be at

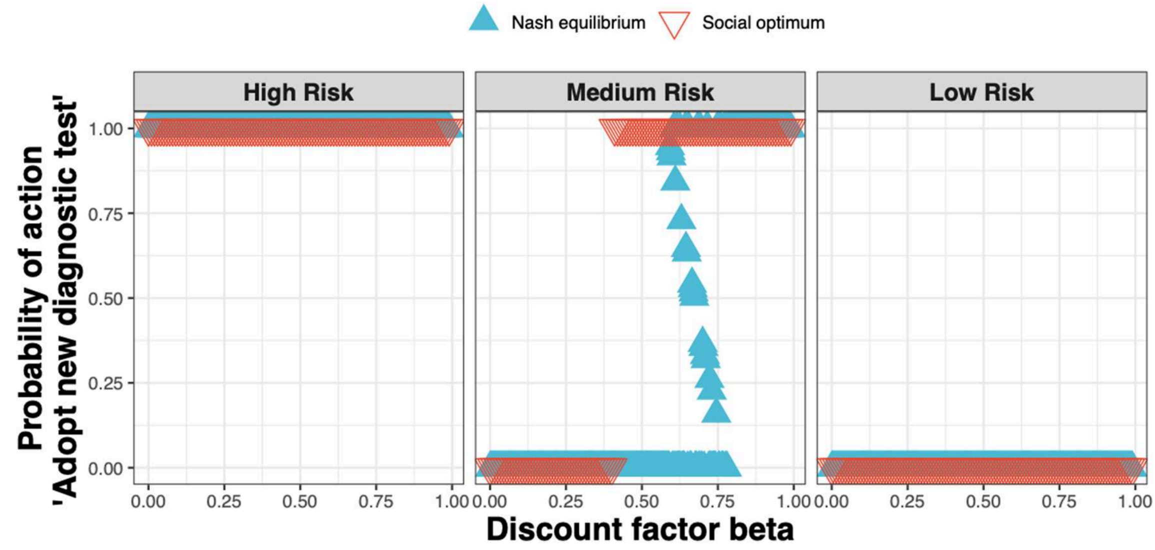

FIGURE 6 | The Nash equilibrium (blue triangles) and the social optimum (red triangles) for a test cost 1.5× that of the *status quo* clinical diagnosis cost, as a function of the discount factor.

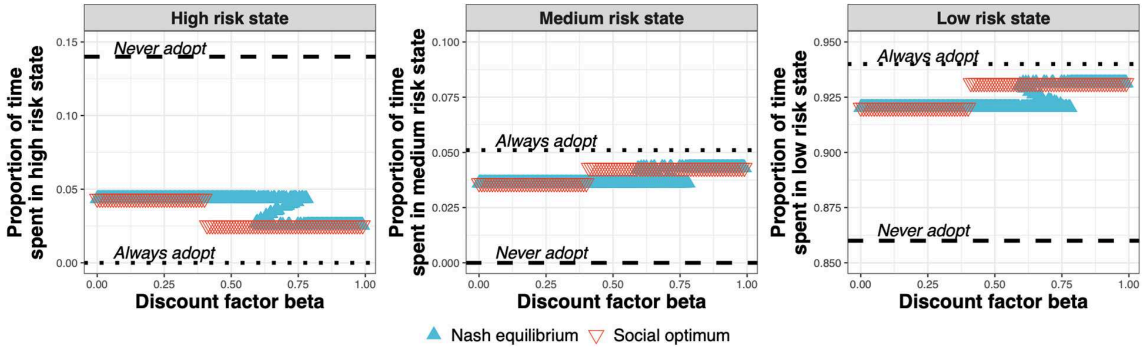

FIGURE 7 | Proportion of time spent in the high-, medium-, and low-risk states for the Nash equilibrium (blue triangles), for the social optimum (red triangles), the status quo solution "*Never adopt*" and the solution "*Always adopt*" for test costs 1.5× that of the *status quo* clinical diagnosis cost, as a function of discount factor.

high risk based on last year's infestation status of themselves or their neighbor's they always chose to adopt the new diagnostic test. Analogously, whenever a farmer considered their farm to be at low risk given that neither farm had sheep scab the previous year, the test was never adopted. For our default parameters—an expected test cost of around 50% more than the current clinical diagnosis via skin scraping—we found discrepancies between the Nash equilibrium and the social optimum in the medium risk state, for intermediate values of the discount factor (the parameter specifying the preference for short-term over long-term gains). One reason for this is that adopting the new diagnostic test is freely chosen by the individual farmers and individual choices do not necessarily align with the public interest. Also, some individuals may free-ride on the protection provided by their neighbor, which is at odds with the socially optimal outcome. In light of this any new policy intervention promoting the use of the new diagnostic ELISA must address the divergence between private and public consequences of actions and, ideally, motivate individual free choice toward a social optimum (28). This could be achieved for example by offering private incentives and encouraging cooperative schemes among farmers.

However, when viewing the outcomes in terms of the prevalence of infestation, we see that the outcomes are largely robust to whether the Nash equilibrium or social optimum is adopted. The primary benefits are seen in the drop in prevalence from the baseline of just under 10% to around 5% following adoption of the test in the high-risk state, or 4% following adoption in the high- and medium risk state.

The financial benefits to the farmer are not substantial; however, what these results show is that substantial reductions in sheep scab incidence should be achievable without additional costs to the farming community. Moreover, the results suggest that the primary goal should be to facilitate test adoption amongst

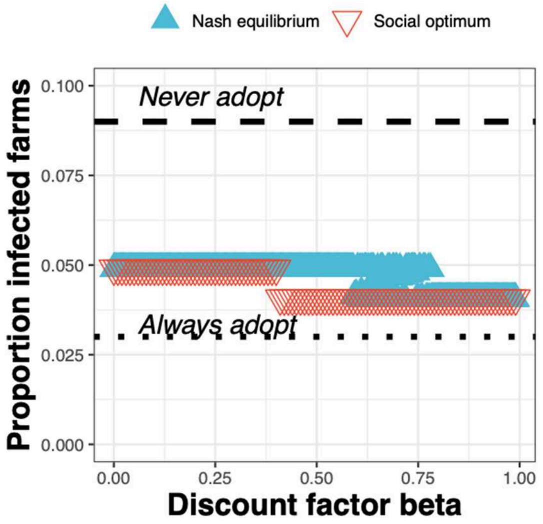

FIGURE 8 | The proportion of infected farms at equilibrium for the Nash equilibrium (blue triangles), the social optimum (red triangles), the *status quo* "*Never adopt*" and the solution "*Always adopt*" for a test cost 1.5× than the *status quo* clinical diagnosis cost, as a function of the discount factor.

farms at high-risk of infestation, as this would provide most of the epidemiological benefits.

However, there are limitations to this modeling framework. Firstly, the framework does not account for the fact that the external risk to farms should decline as the expected prevalence of infestation in the farms adopting the test declines. Whilst capturing this would be desirable, it is not something that can readily be done within the stochastic game framework. We therefore view our results as a conservative assessment of the benefits of the adopting the test, since widespread adoption would reduce the external risk to farms. Thus, cooperative behavior among the farming community should provide additional benefits, first by encouraging the social optimum rather than just the Nash equilibrium outcome, and secondly, by reducing the external risk of infestation and therefore the expected prevalence of infestation following widespread test adoption.

A second limitation is that the model considers a two-farm system only and the above scenario of widespread adoption should ideally be assessed by extending the analysis to include multiple farms as well as multiple farmer strategies. In this paper we chose to examine this simple two-farm set-up in order to allow

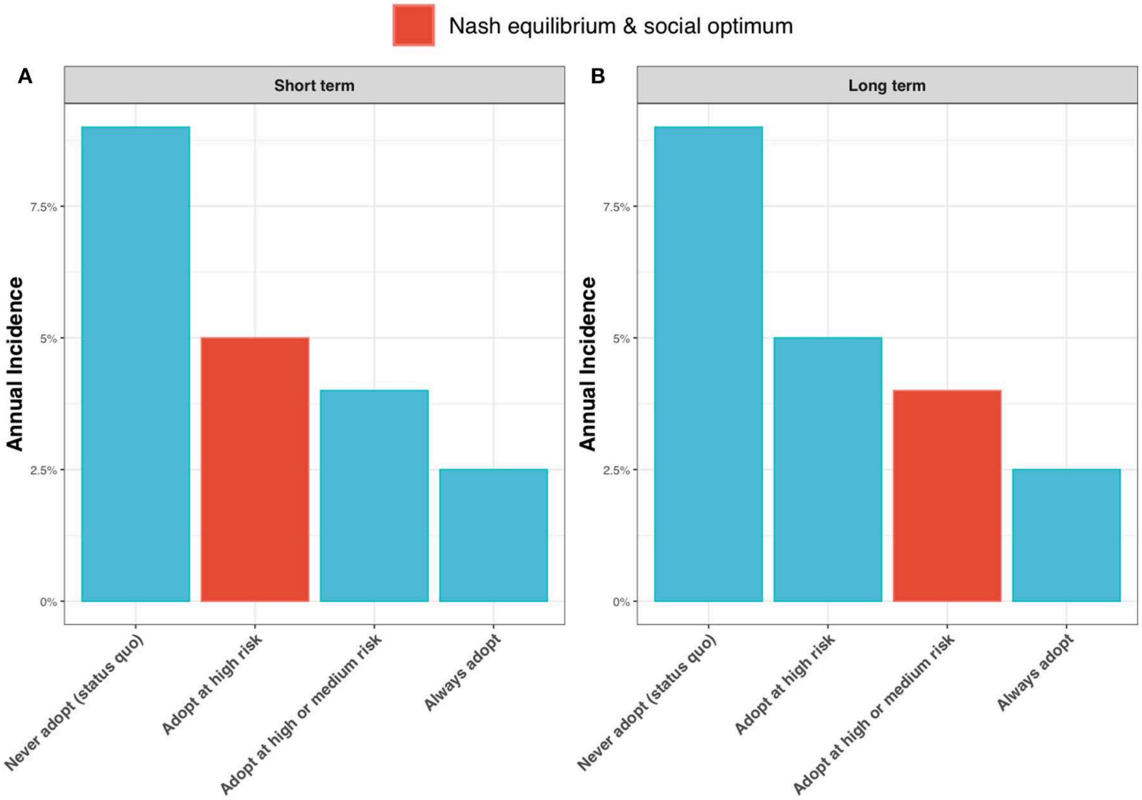

FIGURE 9 | Annual incidence rate for **(A)** a short-term outlook (discount rate, $\beta = 0$) and **(B)** a long-term outlook (discount rate, $\beta = 1$) under alternative scenarios for adoption of the new ELISA test: the status quo (i.e., never adopting the test); always adopt the test (irrespective of risk state); adopt the test only in the high risk state; and adopt the test in the high and medium risk state. When $\beta = 0$, the Nash equilibrium and social optimum coincide (shown as red bar) and are to adopt the test in the high risk state (see **Figure 6**). When $\beta = 1$, the Nash equilibrium and social optimum coincide (shown as red bar) and are to adopt in the high and medium risk states (see **Figure 6**).

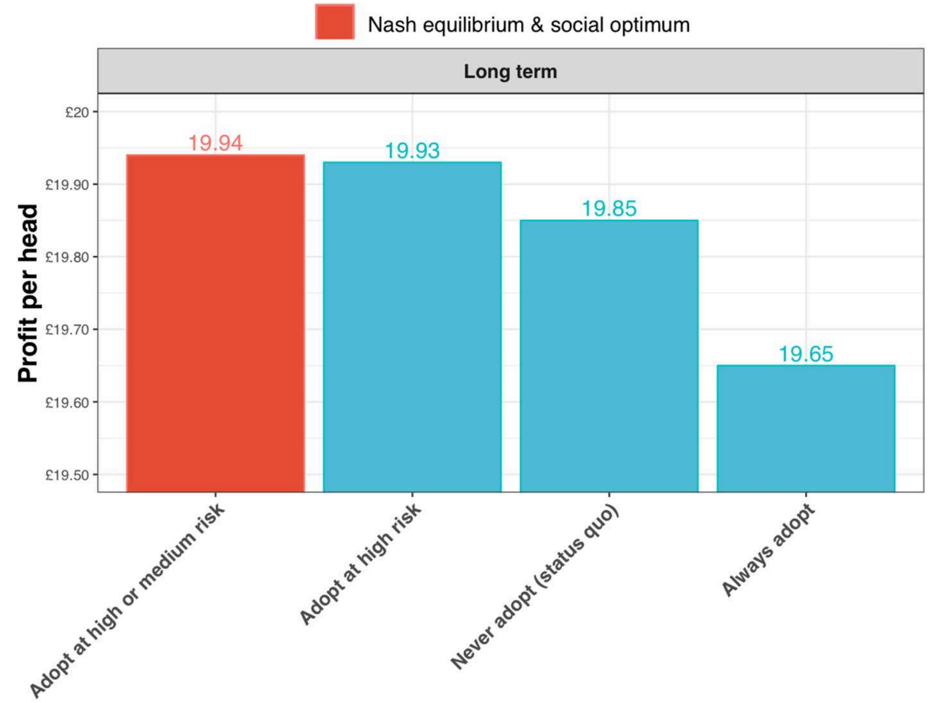

FIGURE 10 | Expected profits per head for a long-term outlook (discount rate, $\beta = 1$) under alternative scenarios for adoption of the new ELISA test: the status quo (i.e., never adopting the test); always adopt the test (irrespective of risk state); adopt the test only in the high risk state; and adopt the test in the high and medium risk state. In this case of the long-term outlook, the Nash equilibrium and social optimum coincide at test adoption in the high and medium risk state (shown in red).

a game-theoretic approach. However, to capture multiple farms with realistic farm to farm heterogeneity and features such as explicit import of infested sheep (as opposed to capturing this via the fixed background risk) would require a much more flexible framework. Such future work would be more amenable to an agent-based approach, following, for example (29). This could offer a more flexible and potentially more realistic approach for modeling individual farmer decisions that allows farmers to learn from their infestation history, risk status, and past payoffs. The approach in this paper necessarily assumes a perfect mixing of populations, and is not able to capture farm heterogeneity and differences in behavior, not only socially but also in terms of spatially-driven interactions. Particularly for the latter, where players interact with their immediate neighbors more than with randomly chosen individuals and the payoff becomes a function of the risk state and preferred choices of more than two players, agent-based methods on a network or a grid-based scenario provide a potential next step.

Third, the costs used in these analyses were current at the time of publication of the ADAS report and some changes may have occurred. Nevertheless, the robustness of the results to test cost would suggest that we would expect a similar picture with current figures.

It should also be noted that the results shown here assume a test with perfect sensitivity and specificity—a reasonable assumption given that estimates for flock level sensitivity and specificity are very high at 0.98 and 0.97, respectively. However, the framework can be used in the case of an imperfect test (as described in the **Supplementary Material**). When we assume an imperfect test, we obtain broadly similar results, albeit with slightly lower payoffs and slightly higher incidences of infestation. Small improvements in outcome were observed for a scenario in which the farmer *does not know* that the test is imperfect, vs. a scenario whereby the farmer is assumed to be able to captured changes to payoffs due to an imperfect test in the calculation of the Nash equilibrium.

In summary, we have presented a novel use of a stochastic game which provides advantages over the more commonly used static games [e.g., (21)], especially in an epidemiological context where it is useful to be able to capture dynamic changes in risk. Together our findings provide strong support for the new diagnostic test whilst also indicating that further benefits could be accrued through flock health schemes that encourage and facilitate cooperation between farmers. Our key finding however, remains that adopting the new diagnostic ELISA test for subclinical sheep scab could significantly reduce prevalence of sheep scab and improve animal welfare in a cost-neutral way to the industry.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

SM wrote the manuscript, ran simulations, conducted analysis, and interpreted the results. RB, AN, SB, RR, MD, TP, SM, RZ, and LM developed the methodology, performed analysis, and contributed to the manuscript. RR and MD provided R code for the analyses. All authors reviewed the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00036/full#supplementary-material

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Cross-Validation of Generic Risk Assessment Tools for Animal Disease Incursion Based on a Case Study for African Swine Fever

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In recent years, several generic risk assessment (RA) tools have been developed that can be applied to assess the incursion risk of multiple infectious animal diseases allowing for a rapid response to a variety of newly emerging or re-emerging diseases. Although these tools were originally developed for different purposes, they can be used to answer similar or even identical risk questions. To explore the opportunities for cross-validation, seven generic RA tools were used to assess the incursion risk of African swine fever (ASF) to the Netherlands and Finland for the 2017 situation and for two hypothetical scenarios in which ASF cases were reported in wild boar and/or domestic pigs in Germany. The generic tools ranged from qualitative risk assessment tools to stochastic spatial risk models but were all parameterized using the same global databases for disease occurrence and trade in live animals and animal products. A comparison of absolute results was not possible, because output parameters represented different endpoints, varied from qualitative probability levels to quantitative numbers, and were expressed in different units. Therefore, relative risks across countries and scenarios were calculated for each tool, for the three pathways most in common (trade in live animals, trade in animal products, and wild boar movements) and compared. For the 2017 situation, all tools evaluated the risk to the Netherlands to be higher than Finland for the live animal trade pathway, the risk to Finland the same or higher as the Netherlands for the wild boar pathway, while the tools were inconclusive on the animal products pathway. All tools agreed that the hypothetical presence of ASF in Germany increased the risk to the Netherlands, but not to Finland. The ultimate aim of generic RA tools is to provide risk-based evidence to support risk managers in making informed decisions to mitigate the incursion risk of infectious animal diseases. The case study illustrated that conclusions on the ASF risk were similar across the generic RA tools, despite differences observed in calculated risks. Hence, it was concluded that the cross-validation contributed to the credibility of their results.

Keywords: African swine fever, cross-validation, livestock diseases, generic model, introduction risk, model uncertainty, risk assessment

INTRODUCTION

Increasing globalization and international trade contribute to rapid expansion of infectious animal diseases, as illustrated by the recent outbreaks of bluetongue (BT), African swine fever (ASF), lumpy skin disease (LSD), and peste des petits ruminants (PPR) in Europe (1–3). Introduction of exotic animal diseases into naive livestock populations can result in large-scale epidemics with serious economic and socio-ethical impact (4–6). Hence, preparedness is warranted to prevent, detect, and control outbreaks of exotic animal diseases. To make decisions on risk management of exotic animal disease threats, it is necessary to know which animal diseases pose the highest threats and should therefore deserve more attention.

Risk assessment is a useful tool for prioritization of diseases with respect to their incursion risk, the results of which can be used to assign resources for prevention and surveillance to those diseases posing the highest risk or to identify targets for additional research. Most commonly, risk assessments are developed to assess the risk for a single disease and introduction pathway. In recent years, however, several generic risk models or frameworks have been developed that can be applied to assess the incursion risk for multiple animal diseases (7–15). In contrast to bespoke models, these generic risk assessment (RA) tools allow for a more rapid response to a variety of newly emerging or re-emerging diseases.

Generic RA tools, however, tend to have a lower resolution in their algorithms to allow the assessment of risk over multiple diseases that differ with respect to the species of animals affected, transmission modes, and epidemiological and economic impact. Furthermore, uncertainty and variability are not always considered in much detail. To parameterize generic RA tools, global databases are preferred, as these contain information over multiple countries, diseases, and/or introduction pathways. Application of results from generic RA tools vary from a rapid response to new emergencies to horizon scanning and prioritization of diseases, pathways, or regions.

A shared problem of generic tools with bespoke models is the validation of their results. Most import risk assessments estimate the probability of rare events occurring in an ever-changing world, leaving the use of a long range of historical data for this purpose useless. Validation of import risk assessments is, nevertheless, an important step in their development to ensure the plausibility of results. Sensitivity analysis to address parameter uncertainty by varying the values of uncertain input parameters in a plausible range contributes to the internal validation of risk assessments (16, 17). With several generic RA tools having been developed in recent years in Europe that all can be used to assess the incursion risk of notifiable animal diseases such as ASF, LSD, and BT, opportunities arise to address model uncertainty by comparing results obtained with different tools. The objective of this study was to explore the opportunities for cross-validation of generic RA tools, where cross-validation was defined as the validation of model results by comparing them with results of other models that addressed the same question. ASF was selected as a case study given its rapid spread in Europe in recent years (18–20).

ASF is a viral disease of pigs and wild boar caused by the ASF virus, the only member of the family *Asfarviridae* (21–23). ASF virus (genotype 2) was introduced into the Caucasus region in 2007 and has subsequently spread into Belarus, Russia and Ukraine and then to the European Union in 2014 with infection having been reported from Estonia, Latvia, Lithuania, Poland, Czech Republic, Romania, Hungary, Bulgaria, and Belgium in recent years (2, 3). Prevention of ASF introduction is a high priority for European countries still free from the disease as introduction of the disease can have severe consequences for the domestic pig sector and the wild boar population due to an extremely high case fatality rate (up to 100%) (24). Rigorous measures are needed to control the disease including culling of infected herds and movement bans, and there are difficulties in eradicating the disease once it has established itself in the wild boar population (24, 25). There is currently no vaccine available against ASF infection and infection continues to spread through various pathways, including movement of infected wild boar and human mediated routes.

Results of risk assessment studies are an important input into risk management decisions to prevent ASF spread to new regions and several bespoke models for ASF have been developed in the last decade (26–31). All generic RA tools of this study can also be used to assess the ASF incursion risk with the major advantage that results can easily be updated when outbreaks are reported from new regions in Europe. However, because of their generic character, validation is an even more essential step to ensure plausibility of results.

To cross-validate the generic RA tools of this study, all tools were used to assess the incursion risk of ASF to two European countries, the Netherlands and Finland. These countries were chosen because of their opposite risk profiles when considering their ASF risk, with the Netherlands being a trading country not only exporting millions of pigs annually, but also importing over a million of live pigs each year (32), whereas Finland has hardly any international trade in live pigs (33). Finland, on the contrary, was geographically much closer to observed outbreaks of ASF in Europe at the time this study was initiated (before the ASF outbreaks in wild boar in Belgium in September 2018).

MATERIALS AND METHODS

Definitions

Although an assessment of the incursion risk would ideally address both the probability of incursion of disease and its subsequent consequences, not all generic RA tools of this study had incorporated a consequence assessment. Therefore, in this study *incursion risk* is used as a generic term to indicate any metric to estimate the risk of exotic diseases entering a new territory, varying from entry only to a full risk assessment including epidemiological and economic consequences.

Regarding the probability of incursion, four separate steps are distinguished in this study. In the *entry* step the probability that an infectious agent enters a new territory (hereafter called:

TABLE 1 | Brief outline of seven generic RA tools.

RA tool	Objective	Prioritization	Data available in tool	Number of diseases in tool	Number of pathways in tool	Variability/ uncertainty included	Software	Developer	More information
SPARE	Early warning of disease incursion risks	Target areas	Yes	4	5	None	R	APHA, UK	(14, 35)
COMPARE	Identification of hotspots for risk-based surveillance	Target areas, pathways	No	3	5	Variability	R	APHA, UK	(15, 36–38)
RRAT	Identification of high priority exotic notifiable diseases	Pathways, diseases	Yes	10	3	None	R, SQLite	WBVR, NL	(39)
MINTRISK	Comparison and prioritization of vector-borne diseases	Target areas, diseases	No	NA[a]	NA[b]	Uncertainty	C#, Visual Studio	WBVR, NL	(10, 11, 40, 41)
IDM	Identification of high priority exotic notifiable diseases	Diseases	Yes	34	7	None	Excel	Defra, UK	(8, 11)
NORA	Rapid risk assessment to respond to new disease events	Pathways	No	NA[a]	9	None	Excel	Ruokavirasto, FI	(12)
SVARRA	Rapid risk assessment to respond to new disease events	Pathways	No	NA[a]	8	Uncertainty	Word, Excel	SVA, SE	(11)

[a] *These tools have no underlying database with disease-specific data and can evaluate any disease.*
[b] *MINTRISK can evaluate any pathway.*

target area) by any pathway is evaluated, without assessing subsequent exposure of susceptible animals in the target area via this pathway. In the *exposure* step the probability that a susceptible native host animal in the target area is exposed to the infectious agent is evaluated given its entry into the target area, without assessing the probability that such exposure would result in infection. In the first *infection* step the probability that contact with the infectious agent results in infection of a first native host in the target area (= index case) is evaluated given its entry into the target area and exposure of the host animal. In the *establishment* step the probability that the infectious agent will start spreading in the target area is evaluated given it has entered the target area and resulted in a first infection of native host animals. Establishment is an important step when evaluating the incursion risk of vector-borne diseases, where an infection of a native host animal can be a dead-end if, e.g., no competent vectors are present in the target area or if climatic conditions impede subsequent transmission.

Consequences of disease incursion have been separated into epidemiological and economic consequences. *Epidemiological consequences* have been defined as the expected spread of the infectious agent in the native (susceptible) population in the target area or further geographical spread from the target area to new regions, considering, e.g., the epidemic size and geographic area affected. *Economic consequences* have been defined as the expected monetary losses resulting from an outbreak with the infectious agent in the target area due to, e.g., morbidity and mortality, production losses, control measures and trade restrictions.

Generic Risk Assessment Tools

Seven generic RA tools, all developed by the G-RAID[1] consortium (34), were included in the cross-validation study. Selection criteria for inclusion were (i) the tool was developed to assess the incursion risk of multiple diseases rather than a single disease, and (ii) the tool focused on the veterinary risk of animal diseases rather than public health. Although all seven tools can be used to address the incursion risk of exotic animal diseases, they were originally developed for different purposes ranging from immediate response to new disease events to prioritization of diseases and horizon scanning. As a consequence, input, algorithms, and endpoints of the tools differed. The seven generic RA tools included two quantitative tools (SPARE, COMPARE), four semi-quantitative tools (RRAT, MINTRISK, IDM, NORA) and one qualitative tool (SVARRA). A brief overview of all tools is given in **Table 1**. More details are available in **Supplementary Material 1**.

All seven RA tools were built to be flexible with respect to the animal diseases to be evaluated, although MINTRISK was primarily designed to assess the risk of vector-borne diseases. The total number of diseases evaluated so far with each of the tools varies greatly, as does the level of resources (expertise, data, time) needed to complete a risk assessment. For all tools, the assessment is less rapid if the disease has not been evaluated before with the tool, because additional data collection and parameterization is required. The RRAT and the IDM tool have the data required to perform the risk assessment readily available in the tool for

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[1] Generic approaches for Risk Assessment of Infectious animal Disease introduction.

TABLE 2 | Introduction pathways embedded in each of the generic RA tools.

PATHWAY	SPARE	COMPARE	RRAT	MINTRISK[a]	IDM	NORA	SVARRA
Live animals	X	X	X	X	X	X	X
Products of animal origin	X	X	X		X	X	X
Germplasm			X		X	X	X
Vectors	X	X			X	X	X
Wildlife	X	X		X	X	X	X
Human travel	X	X				X	X
Transport					X	X	X
Laboratory material and samples					X		
Feed and bedding						X	X
Airborne spread						X	

[a] *MINTRISK can deal with any pathway, but none are embedded in the tool; these are the pathways that were evaluated for the ASF case study.*

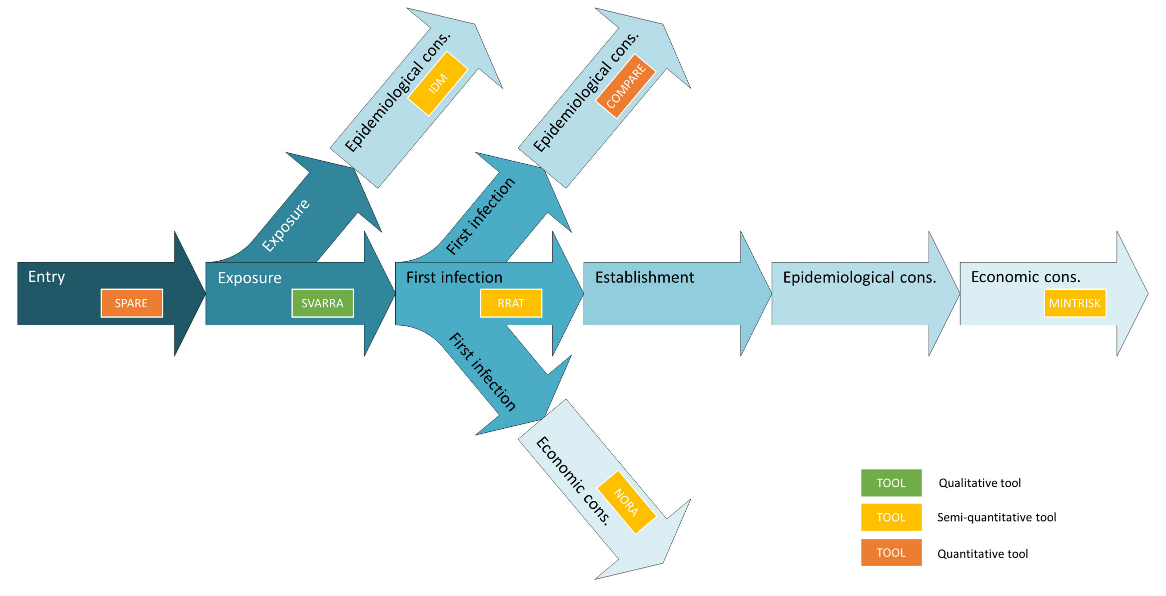

FIGURE 1 | Outline of the steps involved in assessing disease incursion risks indicating the entirety of the generic RA tools.

a multitude of diseases. SPARE and COMPARE have only been parameterized for a few diseases, although the data available on disease prevalence worldwide in these tools can theoretically be used to assess the risk of any OIE-listed disease. MINTRISK, NORA, and SVARRA come mostly without underlying databases and have to be filled by the risk assessor.

The tools also differ widely with respect to the number of introduction pathways that can be evaluated (**Table 2**). Legal trade in live animals and imports of products of animal origin are considered by each tool, although these pathways were not always consistently defined across the tools. For example, some tools consider trade in livestock animals only, whereas other tools also consider trade in pets and exotic animals. Most tools also address windborne vector spread and wild animal dispersion including migratory birds. All tools but MINTRISK have predefined pathways built in. MINTRISK asks the risk assessor to define relevant pathways for the disease considered, either related to vertebrate host animals and their products, vectors, or humans. In general, the tools with relatively uncomplicated algorithms, such as the qualitative tool SVARRA and the semi-quantitative tools IDM and MINTRISK, are most flexible to include additional pathways.

The outline of all seven generic RA tools is primarily based on the OIE import risk assessment framework (42). However, the RA tools differ widely with respect to the steps that are included to assess the disease incursion risk (**Figure 1**). Endpoints of the tools differ alike. MINTRISK is the most complete tool considering entry up to establishment, and epidemiological and economic consequences. SPARE on the contrary only considers entry. All tools use the basic principles of the Binomial model (43) to assess entry of pathogens into new areas, combining information on pathway numbers (N) with probabilities of infection (p) based on prevalence levels. All tools that evaluate epidemiological consequences (COMPARE, MINTRISK, IDM)

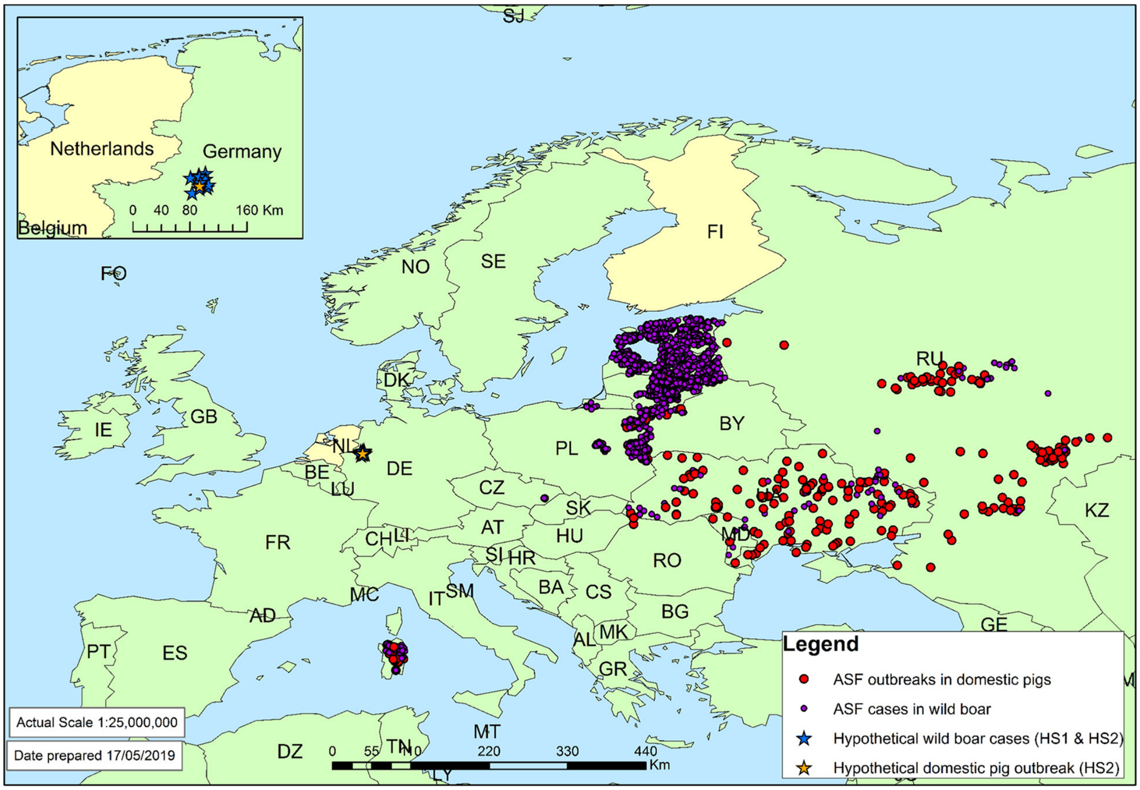

FIGURE 2 | ASF cases in domestic pigs and wild boar in 2017 as reported to the OIE (2). Target countries of the case study (the Netherlands and Finland) have been colored yellow. Inset: location of hypothetical ASF cases in Germany.

do so by estimating the basic reproductive number R_0 (44) and implementing it into their model calculations.

Only a few of the generic RA tools have embedded uncertainty and/or variability in their risk assessment. COMPARE is the only tool addressing variability in calculating the incursion risk using stochastic calculations, including primarily the variability in disease prevalence in traded animals/products but also variability in other disease parameters. MINTRISK and SVARRA are the only tools that explicitly ask the risk assessor for his/her uncertainty in estimating the input parameter values, and only MINTRISK uses stochastic simulation to address this uncertainty. NORA also acknowledges that risk assessors cannot be expected to know everything and offers the "I don't know" option in answering the questions. This uncertainty is reported in the results of the tool by counting the number of questions that were given this answer. Despite the fact that uncertainty is not embedded in the other RA tools, most of them offer the opportunity to consider uncertainty via scenario analysis.

Risk Question and Scenarios

To explore the opportunities for cross-validation of the generic RA tools, all seven tools were used to assess the risk for a selected case study considering several African swine fever scenarios. The risk question considered the ASF virus strain responsible for European cases in 2017 as the hazard and was formulated as: Given the history of ASF cases reported in Europe in 2017, as well as trade patterns in 2017, what is the predicted incursion risk of ASF to (a) the Netherlands and (b) Finland from any country where the virus strain circulates? In addition, the same question was answered considering two hypothetical scenarios in which ASF cases were reported in Germany. In the first hypothetical scenario (HS1), it was assumed that on 30/12/2017 10 separate cases of wild boar found dead, infected with ASF, were reported from the Munster region of Germany at a distance of ∼50 km from the Dutch border (**Figure 2**). In the second hypothetical scenario (HS2), it was assumed that on 30/12/2017, as per scenario HS1, ten separate cases of ASF in wild boar were reported from the Munster region of Germany, and that one outbreak on a single commercial mixed (breeding and fattening) farm had been reported in the same region with 2,500 pigs on it, 18 of which were found infected and all 2,500 were immediately culled (**Figure 2**). In both hypothetical scenarios, the history of ASF outbreaks and reported trade patterns were assumed to be the same as in the 2017 scenario. Furthermore, hypothetical ASF cases in scenarios HS1 and HS2 were assumed to behave in a similar way to the other cases in Europe in 2017 with regards to characteristics such as infectious period and transmission rate.

Input Data for the African Swine Fever Case Study

The majority of the data required for the generic RA tools can be broken down into four categories: (1) pathway movements from source areas to the target area; (2) disease prevalence in source areas; (3) susceptible animals in the target area; and (4) disease-specific parameters. For the case study, input data used by the tools were harmonized wherever possible to ensure that differences in results would result from model uncertainty rather than input parameter uncertainty. An overview of input data shared between the tools is available in **Supplementary Material 2**.

Pathway Movements

Data on pathway movements are relevant to the entry stage of the risk assessment and focus on how many units (animals, products etc.) will reach the target area from different source areas, regardless of whether or not they are infected. All generic RA tools derive data on pathway movements predominantly from global databases on international trade. For the legal trade pathways, all of the tools can use one or more of TRACES (45), Comext (33), or Comtrade (46). For movement of wild animals and illegal trade, global datasets are obviously not possible to obtain. However, most tools incorporate global datasets of travel statistics (47) or population abundance maps in order to either model or estimate a score for how much illegal trade or wild animal movements are to be expected.

For the case study, all of the generic RA tools used Comext trade data for 2017 (33) to assess the numbers of animals, products (including germplasm and laboratory material), and travelers entering the Netherlands and Finland. However, the selection of CN codes (Combined Nomenclature) (48, 49) included in the tools depended on how pathways were defined and was not the same across all tools, especially when considering the legal trade in animal products. Population abundance maps (50) were used to either model or estimate a score for how many wild boar movements were to be expected. The quantitative tools (SPARE, COMPARE) applied mechanistic approaches (in which a complex problem is broken down to the underlying mechanisms) to determine the movement of wild boars and harmonized the parameters within these tools as far as possible, e.g., percentage of wild boars that move long distances and how far they move.

Disease Prevalence

Data on disease prevalence are also relevant to the entry stage of the risk assessment and are used to estimate the probability that animals/products are infected. Disease prevalence in source areas is primarily based on information on disease occurrence derived from the World Animal Health Information System (WAHIS) (2), although Empres-i (51) and the Animal Disease Notification System (ADNS) (52) are also used across the tools. Furthermore, the more qualitative tools might also include information derived from reports and mailings from the European Commission.

For the case study, all generic RA tools were fed with data from WAHIS (2) on the number of ASF outbreaks and the number of cases by species (domestic pigs, wild boar) on the country level for 2017 and previous years. An overview of ASF cases reported to OIE in 2017 is given in **Figure 2**. To estimate disease prevalence in the source countries, information on pig and wild boar populations in those countries were also derived from WAHIS. The RA tools used, however, different approaches to convert the WAHIS data into disease prevalence estimates. Whereas some of them included all historical data available from the OIE website, others only considered information on disease outbreaks in a recent period (e.g., a 1-year period or the high-risk period, i.e., the period from introduction of disease into an area until its detection). Furthermore, some tools had built-in algorithms to correct for non-reporting or underreporting, or to include a probability of disease presence despite current absence, whereas other tools based their prevalence estimates on the actual situation reported to OIE only. In addition, the more qualitative tools had the ability to include additional information derived from, e.g., ADNS and reports and mailings from the European Commission, especially when assessing the infection probabilities of wild boar populations.

Susceptible Animals

Data on susceptible animals relate to the probabilities of disease transmission to susceptible populations in the target area. For this category of data input, more variation is observed between the seven tools due to contrasting choices made to model contact between susceptible animals and infected animals/products. Whereas some tools include detailed data on number of animals and farms or livestock densities in the target area derived from global databases such as WAHIS (2) and FAOSTAT (53), other tools distinguish between different farm types based on size and biosecurity level or include information on disease susceptibility only. One of the tools, SPARE, has not included information on susceptible animals in the target area at all, because it only evaluates entry of the pathogen, and not subsequent exposure or infection.

As a result, harmonization of data on susceptible animals in the Netherlands and Finland was difficult. COMPARE used maps on wild boar abundance (50), whereas most tools did not need data at this spatial scale and used data on wild boar presence and abundance from Dutch and Finnish sources (54–56).

Disease-Specific Parameters

The category of disease-specific input parameters includes all parameters specific to the disease, such as duration of the latent and infectious period, transmission probabilities, severity of clinical signs, test sensitivities, and decay rates in products. For this category of data input, the tools differ in whether and how they incorporate these parameters; however, all of them primarily used published literature and expert opinion to find relevant parameter values.

For the case study, disease-specific parameters were sourced individually by each tool from published literature [e.g., (57–61)] and expert opinion. Parameter values were shared to enable harmonization of input data over the RA tools if the same input parameters were used (**Supplementary Material 2**).

Comparison of Results

Although ideally both the probability of incursion of disease and its consequences are evaluated in assessing the incursion risk of exotic diseases, results of the generic RA tools for the ASF case study could only be compared for the probability

TABLE 3 | Risk of ASF incursion as evaluated by the seven generic RA tools.

RA tool	Endpoint	Output type	Output parameter
SPARE	Entry	Quantitative	Number of entries per year
COMPARE	First infection	Quantitative	Annual probability
RRAT	First infection	Semi-quantitative	Risk score (from 0 to 1)
MINTRISK	Establishment	Semi-quantitative	Annual rate
IDM	Exposure	Semi-quantitative	Risk score (from 0 to 60)
NORA	First infection	Semi-quantitative	Risk score (from 0 to 1)
SVARRA	Exposure	Qualitative	Qualitative probability level

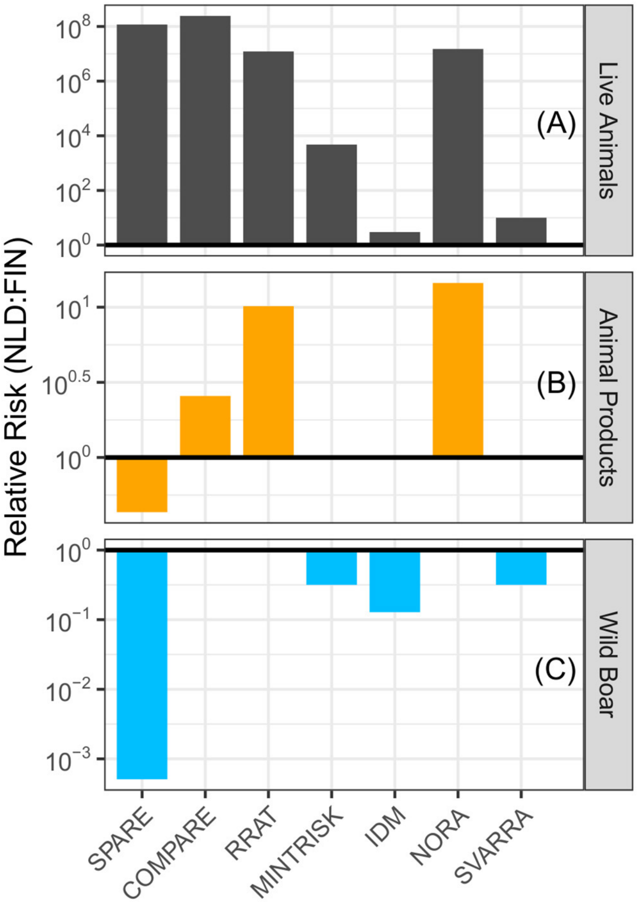

FIGURE 3 | Relative risk of introducing ASF into the Netherlands compared to Finland in the baseline scenario (2017 situation) by **(A)** trade in live animals, **(B)** trade in animal products, and **(C)** movement of wild boar. A relative risk above 1 (bold line) denotes the Netherlands has a higher risk than Finland, while a relative risk below 1 denotes Finland has a higher risk. Please note the different scales used on the y-axes.

of incursion, because consequences were only assessed by some tools. A comparison of absolute results obtained by the seven generic RA tools was not possible though, because endpoints for the probability of incursion varied from entry to establishment (**Table 3**). In addition, the tools had different output parameters (**Table 3**) and evaluated different numbers and types of introduction pathways (**Table 2**). All tools assessed the ASF risk from legal trade in live animals and six out of seven tools assessed trade in animal products (all but MINTRISK) and wild boar movements (all but RRAT). Therefore, for each tool, relative risks were calculated by country and scenario for the three pathways most in common to enable comparison of results. These were compared to see if the tools agreed on the directions and magnitudes of the relative risks resulting in a similar prioritization of countries and scenarios. In addition the pathways within each RA tool were compared against each other to identify the pathways contributing most to the ASF risk to the Netherlands and Finland.

The relative risk across the two countries ($RR_{c_{ij}}$) for each tool i was calculated for each pathway j as:

$$RR_{c_{ij}} = R_{NLD_{ij}} / R_{FIN_{ij}}$$

where $R_{NLD_{ij}}$ is the calculated risk by tool i to the Netherlands for pathway j and $R_{FIN_{ij}}$ the calculated risk by tool i to Finland for pathway j. Calculations were done for the baseline scenario (2017 situation) only.

Relative risks across scenarios ($RR_{HS1_{ijk}}$ and $RR_{HS2_{ijk}}$) for each tool i were calculated for each pathway j and each country k as:

$$RR_{HS1_{ijk}} = R_{HS1_{ijk}} / R_{Base_{ijk}} \text{ and } RR_{HS2_{ijk}} = R_{HS2_{ijk}} / R_{Base_{ijk}}$$

where $R_{Base_{ijk}}$ is the calculated risk by tool i for pathway j and country k for the baseline scenario (2017 situation), $R_{HS1_{ijk}}$ is the calculated risk by tool i for pathway j and country k for the first hypothetical scenario (ASF in wild boar in Germany), and $R_{HS2_{ijk}}$ is the calculated risk by tool i for pathway j and country k for the second hypothetical scenario (ASF in wild boar and domestic pigs in Germany).

In order to calculate relative risks for the qualitative RA tool SVARRA, qualitative probability levels were converted to numerical values using a log-scale, where negligible = 1, very low = 10, low = 100, etc. The in-between probability level negligible/very low was given a numerical value of $\sqrt{10}$. All other RA tools provided numerical results, either representing absolute risk estimates or semi-quantitative risk scores (see **Table 3**), making it possible to calculate relative risks. The only exceptions were scenarios resulting in a negligible or zero result. To enable the calculation of relative risks, negligible and zero results were set equal to 10^{-10}, based on the lowest results that were calculated by the tools (7×10^{-10} for the risk of the live animal trade pathway to Finland as calculated by RRAT).

RESULTS

Relative Risks Across Countries

For each of the generic RA tools, the ASF incursion risk to the Netherlands was compared to Finland for the pathways (a) trade in live animals, (b) trade in animal products, and (c) wild boar movements. Results for the baseline scenario (2017 situation) are given in **Figure 3**. A calculated relative risk above 1 indicates that the ASF risk was higher to the Netherlands than Finland.

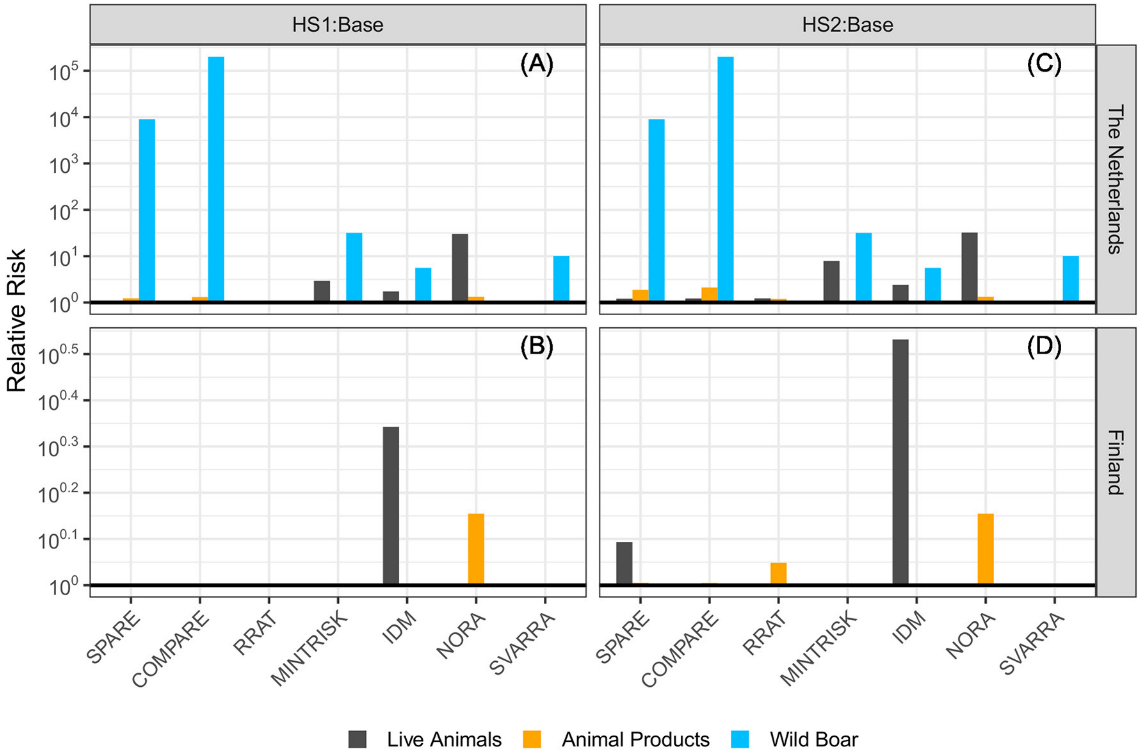

FIGURE 4 | Relative risk of introducing ASF into **(A)** the Netherlands and **(B)** Finland in the hypothetical scenario with ASF reported in wild boar in Germany (HS1) and **(C)** the Netherlands and **(D)** Finland with ASF reported in wild boar and domestic pigs in Germany (HS2) compared to the baseline scenario (2017 situation). A relative risk of 1 (bold line) denotes no differences in risks among the scenarios. Please note the different scales used on the y-axes.

From **Figure 3A** it can be seen that, for each of the RA tools, the evaluated risk of the live animal trade pathway was higher to the Netherlands than Finland. In particular SPARE, COMPARE, RRAT and NORA predicted a much higher risk (i.e., over 10^7 times higher).

Six of the seven RA tools evaluated the animal products pathway (MINTRISK did not) (**Figure 3B**). COMPARE, RRAT, and NORA predicted a higher incursion risk to the Netherlands than Finland for this pathway, although differences in risks were much smaller than for the live animal trade pathway. IDM and SVARRA predicted an equivalent risk for both countries, whereas SPARE uniquely predicted that the risk was lower to the Netherlands than Finland.

Again, six of the seven RA tools evaluated the wild boar pathway (RRAT did not) (**Figure 3C**). COMPARE and NORA predicted an equivalent, very low to negligible incursion risk resulting from this pathway to both countries. All other tools had a relative risk below 1, which indicates that the predicted ASF risk was higher to Finland than the Netherlands.

Relative Risks Across Scenarios

For each of the generic RA tools, the ASF incursion risk of both hypothetical scenarios was compared to the baseline scenario. Results for the Netherlands and Finland are given in **Figure 4**. A calculated relative risk above 1 indicates that the ASF risk was higher in the hypothetical scenario than in the baseline scenario.

The hypothetical situation in which ASF cases were reported in wild boar in Germany (HS1) resulted in an increased risk to the Netherlands compared to the baseline scenario, especially for the wild boar pathway. In particular SPARE and COMPARE predicted a much higher risk (i.e., over 10^3 times higher). NORA was the only tool of those evaluating the wild boar pathway that did not predict an increased risk for this pathway in HS1 to the Netherlands. The addition of a single ASF outbreak at a domestic pig farm (HS2) resulted in a slightly increased risk to the Netherlands for the live animal trade pathway compared to HS1 for MINTRISK, IDM and NORA, and a slightly increased risk for both the live animal trade pathway and the animal products pathway for SPARE, COMPARE and RRAT. SVARRA indicated that the ASF outbreak at a domestic farm in Germany (HS2) did not further increase the ASF risk to the Netherlands compared to HS1.

Most RA tools agreed that the presence of ASF in wild boar in Germany (HS1) did not increase the risk to Finland compared to the baseline scenario. Only IDM and NORA predicted a slightly increased risk for the live animal trade pathway and the animal products pathway, respectively. The addition of a single ASF outbreak at a domestic pig farm (HS2) resulted in a slightly increased risk to Finland for the live animal trade pathway compared to HS1 for SPARE and IDM, and a slightly increased risk for the animal products pathway for SPARE, COMPARE, and RRAT. MINTRISK and SVARRA indicated

TABLE 4 | Pathways contributing most to the ASF incursion risk for each tool[a] per country and scenario (indicated in red)[b].

RA TOOL	Scenario	The Netherlands			Finland		
		Live animals	**Animal products**	**Wild boar**	**Live animals**	**Animal products**	**Wild boar**
COMPARE	Baseline		🟥			🟥	
	HS1		🟥			🟥	
	HS2		🟥			🟥	
RRAT	Baseline		🟥	▨		🟥	▨
	HS1		🟥	▨		🟥	▨
	HS2		🟥	▨		🟥	▨
MINTRISK	Baseline		▨	🟥		▨	🟥
	HS1		▨	🟥		▨	🟥
	HS2		▨	🟥		▨	🟥
NORA[c]	Baseline		🟥			🟥	
	HS1	🟥				🟥	
	HS2	🟥				🟥	
SVARRA[d]	Baseline	🟥	🟥			🟥	
	HS1	🟥	🟥	🟥		🟥	
	HS2	🟥	🟥	🟥		🟥	

[a] *It was not possible to compare pathways in the SPARE and IDM tools.*

[b] *The gray cells indicate that this pathway was not evaluated by the tool.*

[c] *In NORA, the human travel pathway had the highest risk for Finland in all three scenarios; the animal products pathway ranked second.*

[d] *Equal contribution of several pathways in one scenario.*

that the presence of ASF in wild boar and/or domestic pigs in Germany did not increase the ASF risk to Finland compared to the baseline scenario.

Pathway Contribution

Table 4 presents an overview of the three most commonly investigated pathways in the tools (i.e., trade in live animals, trade in animal products and wild boar movements), indicating the pathway that contributed most to the ASF incursion risk to the Netherlands and Finland in the baseline scenario and the two hypothetical scenarios. Results for SPARE and IDM are not included here, because a relative comparison of estimated pathway risks was not possible for these tools. In SPARE the units in which the risks are expressed differ over the pathways being numbers of infected animals for the live animal trade and wild boar pathway and numbers of infected kilograms for the animal products pathway (**Supplementary Material 3**). In IDM the semi-quantitative risk scores assigned to each of the pathways have not been scaled to allow for a comparison between the pathways.

Overall, most tools agreed that (when considered) animal products constituted the highest risk to Finland for all three scenarios, and to the Netherlands in the baseline scenario. For both hypothetical scenarios the animal products pathway was still predicted to have the highest risk to the Netherlands by COMPARE and RRAT. However, NORA indicated a change in risk such that trade in live animals became the pathway with the highest risk for ASF incursion when the disease was assumed to be present in Germany. Under all scenarios the SVARRA tool did not have a single pathway constituting the highest risk to the Netherlands resulting from the lack of resolution available with a qualitative approach when risk estimates are close. The presence of ASF in Germany resulted in an increased risk estimate for the wild boar pathway in SVARRA, such that all three pathways had an equal risk level in the hypothetical scenarios. MINTRISK was the only tool not to consider animal products and concluded that from those that were included (trade in live animals and wild boar movements), wild boar was the pathway associated with the highest risk, for both the Netherlands and Finland.

Some of the tools included more pathways than the three investigated here (**Table 2**). When taking into account these additional pathways, only in NORA the pathway ranking top for Finland was changed from trade in animal products to human travel for all three scenarios (**Supplementary Material 3**).

DISCUSSION

Cross-Validation Based on the ASF Case Study

Validation of generic RA tools is a challenging task for which no gold standard is available. In this study, we explored the opportunity to cross-validate seven generic RA tools by universally applying them to a predefined case study on the incursion risk of ASF. Comparison of the absolute results from the tools was not possible for several reasons, including their differing objectives, endpoints, outputs, and risk pathways considered. However, by comparing relative risks it was possible to cross-validate the generic RA tools across the different pathways, between the two countries of interest (Netherlands and Finland) and between the three scenarios that were evaluated.

In general, the tools agreed on the ranking of the target countries for the pathways evaluated, although the magnitude of relative risks calculated differed widely (**Figure 3**). All of the tools estimated that the live animal trade pathway posed a (much) higher risk to the Netherlands than Finland in the baseline scenario (2017 situation). The large differences in risk relate to the extremely low or even negligible incursion risk of trade in live animals to Finland rather than to a high risk to the Netherlands (absolute results for each tool are provided in **Supplementary Material 3**). In 2017, only 300 live pigs were transported to Finland compared to 1.9 million pigs to the Netherlands (33). All of the tools which included the animal products pathway agreed that the risk of this pathway to the Netherlands was higher than or equal to Finland in the baseline scenario with the exception of SPARE. This might be explained by the relatively large amount of pork and pork products imported by Finland from Estonia (33) and SPARE being the only tool not considering exposure, first infection or establishment, having entry as an endpoint. Hence, these imports from Estonia, which is an ASF-infected country, contributed largely to the estimated incursion risk by SPARE. For the wild boar pathway, all of the tools including this pathway agreed that the risk to Finland was higher than or equal to the Netherlands, although differences in risks between the countries were less pronounced than for the live animal trade pathway. SPARE calculated a high relative risk of this pathway to Finland if compared to the other tools, which again might be explained by the fact that this tool had entry as an endpoint. A lot of uncertainty was included in the predictions for the wild boar pathway, especially in the estimated risk to Finland, due to uncertainty on the presence of wild boar in the border region of Finland and Russia and the spatial distribution of ASF cases in wild boar in Russia.

When comparing the hypothetical scenarios to the baseline all of the RA tools indicated an increased risk to the Netherlands due to presence of ASF in wild boar and/or domestic pigs in Germany, especially for the wild boar pathway, whereas most tools agreed that the risk to Finland would stay at the same level or increase slightly. However, differences were observed between the tools on the extent to which the live animal trade pathway contributed to the increased risk to the Netherlands.

Investigating the ranking of risk pathways, comparisons could only be made for five of the seven tools, as the risk estimates for individual pathways in SPARE and IDM were given in different units and at a different scale, respectively. Comparisons of rankings were further complicated by the different numbers and types of pathways evaluated by each of the tools. Although **Table 4** indicates that most tools agreed that the animal products pathway constituted the highest risk to both countries in the baseline scenario, this is actually only true for three out of the five tools that could be compared (COMPARE, RRAT, and SVARRA), with MINTRISK not having evaluated this pathway and NORA estimating a higher risk for the human travel pathway for Finland (**Supplementary Material 3**). In NORA, the human travel pathway includes the risk of ASF incursion via animal products carried for own consumption. Bringing products from Estonia was assumed to be common practice in Finland due to easy accessibility of wild boar products in Estonia at low prices, contributing largely to the high estimate of the risk of the human travel pathway to Finland. Lastly, it should be noted that SVARRA evaluated the risk of the live animal trade pathway equal to the animal products pathway for the Netherlands.

Differences in calculated relative risks over countries and scenarios between the tools can be largely explained from (i) differences in endpoints considered when evaluating the risk of ASF incursion, (ii) different quantitative scales on which the risk estimates were scored, and (iii) differences in the definition of pathways.

SPARE was the only tool that evaluated the entry of ASF into the target area without considering exposure or first infection of native animals. This has probably contributed to the differences observed between SPARE and the other RA tools when evaluating the relative risk from the animal products and the wild boar pathways to the Netherlands compared to Finland in the baseline scenario (**Figure 3**). No such differences between SPARE and the other tools were observed for the live animal trade pathway, where entry is more directly linked to exposure, first infection and establishment if animals are imported for life.

All tools but SVARRA produced numbers to express the incursion risk of ASF to the Netherlands and Finland, although the quantitative scales differed among the tools (see **Table 3**). Absolute results from SPARE and MINTRISK could in theory run from zero to infinity, even though most estimates were below 1 given the relatively low risk of disease incursion. Again, as SPARE evaluated entry rather than exposure, first infection or establishment, its results were relatively high for the animal products pathway (**Supplementary Material 3**). Absolute results from COMPARE, RRAT and NORA were bounded by 0 and 1. Thus, for all these five tools, whether absolute results were given from 0 to 1 or from 0 to infinity, calculated relative risks could run from zero to infinity and some tools indeed had extremely high relative risk scores (**Figures 3**, **4**), especially if the denominator was estimated to be negligible or zero. Results from IDM, on the contrary, are semi-quantitative risk scores ranging from 0 to 60 for the overall risk, with maximum scores for individual pathways being < 60. As risk scores of IDM are discrete values (at an interval of 0.5), calculated relative risks were in general relatively low compared to those from other tools. Qualitative probability levels from SVARRA were converted into quantitative numbers using a log10 scale. Although this would have allowed the calculated relative risks to vary from 10^{-4} to 10^{4} with a scale consisting of five levels (ranging from very low to very high), the relative risks estimated by SVARRA never exceeded 10, since differences in risk were always equal to or less than one probability level.

Differences in calculated relative risks over countries and scenarios might also have originated from how pathways were defined in the tools. Trade in live animals was most uniformly defined, although some tools (SPARE, RRAT, IDM) not only included trade in domestic livestock animals, but also trade in horses, pets, and exotic mammals and birds. This will, however, not have resulted in differences for the ASF risk, since the only animals affected by ASF are porcine species (including wild boar and warthogs) (21, 22, 59, 62). Trade in animal products differed to a larger extent, with some tools only including pork and pork products for human consumption (SPARE, COMPARE), whereas other tools also included other products derived from slaughtered pigs, such as hides and bristles (RRAT, IDM). In IDM, NORA and SVARRA, this pathway even included illegal trade, whereas that was separated out in the other tools. The different definitions of the animal products pathway might have lead to different estimates of the absolute incursion risk of this pathway by the different tools, especially from source countries from which imports of fresh and frozen meat are not allowed. Also when considering the relative risks, the generic tools agreed least on the animal products pathway (**Figure 3**). Although the wild boar pathway was uniformly defined among the tools to be the incursion of ASF due to wild boar movements, this pathway was modeled differently among the tools, with some tools estimating the risk based on geographic proximity of infected wild boar populations at the country level (SPARE, MINTRISK, IDM), whereas one tool modeled the spatial distribution of wild boar and their movements based on habitat suitability (COMPARE).

MINTRISK is the only tool in which pathways are not predefined. The risk assessor can thus decide upon the pathways to include in the risk assessment and will preferably include those that are deemed most important given the transmission mechanisms of the disease. Although trade in animal products was considered an important route for ASF, the risk assessors decided not to include it because of lack of information on whether animal products were derived from domestic pigs or wild boar. The other tools did not offer the opportunity to distinguish between products from domestic pigs and wild boar and included both in the animal products pathway. The asset of having user-defined pathways in MINTRISK thus created another level of uncertainty in the results of the risk assessment which is beyond parameter and model uncertainty.

Differences in (implicit) modeling assumptions between the generic RA tools might have further contributed to the observed differences in the evaluated ASF incursion risk between the tools, although it is difficult to predict their impact on the calculated relative risks. For instance, the level of detail at which contact with susceptible animals in the target area was modeled varied widely among the tools, with some of them only using an overall probability estimate (RRAT, MINTRISK, IDM, NORA), while others explicitly modeled how different animal species (COMPARE) or livestock farms (SVARRA) would be exposed. Another example is that RRAT and NORA used worst case assumptions to evaluate the ASF incursion risk whereas the other tools used more realistic assumptions. Furthermore, the time period for which the risk assessment was performed differed among the tools. Most tools used an annual timescale and thus assessed the ASF incursion risk using data from a 1-year period (here: 2017). However, NORA and SVARRA considered a 3-month period to account for the high-risk period of newly infected territories, when no trade restrictions are in force yet. For some tools, decisions on these issues were embedded in the model structure, and could thus be attributed to model uncertainty, whereas for other tools, decisions were taken by the risk assessor performing the ASF case study.

The ultimate aim of these generic RA tools is to provide risk-based evidence to support risk managers in making informed decisions on reducing the incursion risk of infectious animal diseases by, e.g., preventive actions, targeted surveillance, and contingency planning. While absolute risk estimates contribute to the decision on whether any preventive actions are required or not, relative risk estimates are useful for prioritization of risk management options. Prioritization of diseases, pathways and/or target areas is an important output of all seven generic RA tools in this study (**Table 1**). Comparing the results of the tools for the ASF case study indicated that the tools largely agreed upon the direction of the relative risks and thus on prioritization of countries and scenarios. All tools concluded that the ASF risk of trade in live animals was lower to Finland than the Netherlands in the baseline scenario (2017), and that the risk of wild boar movements to Finland was equal to or higher than the Netherlands. Furthermore, all tools concluded that the presence of ASF in Germany (hypothetical scenarios) had little or no impact on the ASF risk to Finland, but did increase the ASF risk to the Netherlands. Thus, we concluded that the cross-validation contributed to the credibility of the results obtained with the generic RA tools.

Further validation of generic RA tools could be achieved by comparing their outcome for a specific risk question with results from bespoke models that were specifically developed to address this risk question. Although several bespoke models were developed for ASF in recent years (26–31), results of these models could not be used directly for comparison purposes as they addressed the ASF incursion risk for different years and/or countries than we did. Updating, re-parameterizing and re-running these models for the ASF case study was beyond the scope of this study. Two bespoke models were, however, developed that addressed the same risk question as the generic RA tools, one model assessing the probability of a first ASF infection in a new territory resulting from trade in live animals and the other model assessing the probability of entry of ASF virus in a new territory due to wild boar movements (63). Both models were parameterized to assess the ASF risk to the Netherlands and Finland in the 2017 situation and for the two hypothetical scenarios with ASF present in Germany. Results for trade in live animals indicated a higher risk to the Netherlands than Finland in the baseline scenario, with the calculated relative risk being in the same order of magnitude as those of the generic RA tools (**Supplementary Material 4**). The bespoke model for trade in live animals predicted an increased risk only to the Netherlands for HS2, i.e., when ASF cases were also reported in domestic pigs, with a calculated relative risk just above 1 if compared to the baseline scenario. Again, this is in agreement with the results from the generic RA tools (**Supplementary Material 4**). Results of the bespoke model for the wild boar pathway indicated an equally negligible risk to the Netherlands and Finland in the baseline scenario. In HS1, the risk of this pathway was increased to the Netherlands with no further increase in HS2. The hypothetical scenarios did not result in an increased risk to Finland for the wild boar pathway. These results are in agreement with results from the generic RA tools, with none of them predicting an increased risk to Finland for the wild boar pathway under the hypothetical scenarios and all of them but one predicting an equally increased risk under HS1 and HS2 to the Netherlands (**Supplementary Material 4**).

Application of the tools for a prolonged period might create an opportunity for external validation using field data. Some of the generic tools have been up and running for at least 5 years now. IDM was first released in 2011 and has intensively been used in the UK by Defra and the Scottish Government's Center of Expertise on Animal Disease Outbreaks (EPIC) to prioritize their risk levels for incursion of disease at different times of the year. SVARRA was first used in 2013 and has been used for several rapid risk assessments including ASF, BT, LSD, and avian influenza (AI). However, one of the difficulties in validating models evaluating the incursion risk of exotic diseases is that the adverse events being modeled have a low probability of occurrence resulting in too few data points for validation, even when used for a prolonged period.

Model Uncertainty

This study clearly illustrates the impact of model uncertainty on risk assessment results. Although the generic RA tools agreed on the direction of the relative risk of ASF to the Netherlands and Finland, the magnitudes of these relative risks varied largely, especially for the live animal trade and wild boar pathways. The range of results obtained when considering the results of all generic RA tools could be interpreted as an indication of the uncertainty included in the risk estimates. The results of the bespoke models fell well within this uncertainty range.

Several methods exist to combine the results of different models that predict similar metrics, such as ensemble modeling, structured decision making and model averaging (64). Although widely applied in, for example, weather prediction (65), ensemble modeling is still at its infancy in veterinary epidemiology (64, 66). Methods like structured decision making and ensemble modeling can only be applied to models that produce similar metrics to compare results accross models. It was thus not possible to combine the model outputs of the generic RA tools involved in this study to produce an uncertainty distribution of the modeled ASF risk as output parameters represented different endpoints, varied from qualitative to quantitative, and were expressed in different units. To make an integrated risk estimate from the generic RA tools possible, output parameters would need to be harmonized first. A further impediment to the integration of risk estimates obtained by the generic RA tools is the difference in pathways evaluated by each of the tools. Nevertheless, a mere comparison of results of different tools can already be helpful in obtaining a more complete picture of the risk and the uncertainties involved as illustrated by this study.

The choice for one or more generic RA tools to answer a specific risk question will depend on the primary objective of the risk assessment, the diseases and pathways that need to be evaluated, the resources and expertise available, and the timescale at which the risk assessment has to be completed (see **Tables 1, 2** and **Supplementary Material 5**). Some of the tools allow for a rapid risk assessment in response to a new disease event (NORA, SVARRA), whereas others can be used for a continuous assessment of incursion risks over time making them suitable for horizon scanning (SPARE, COMPARE, RRAT, IDM). The latter tools could, for instance, be used to monitor the incursion risk of ASF for a specific target area by comparing results obtained for previous years with the current situation. Some of the tools come with a prefilled database for specific diseases and pathways and can easily be used to perform updates of risk assessments for these diseases (SPARE, COMPARE, RRAT, IDM), whereas other tools do not come with an underlying database and have to be filled by the risk assessor (MINTRISK, NORA, SVARRA). For these tools, disease expertise is a prerequisite to perform the risk assessment, whereas some of the prefilled tools mainly require computing expertise. Generally speaking, SVARRA and MINTRISK are most flexible as to which pathways and diseases to include. SVARRA is very well-suited for rapid risk assessments in response to disease events such as the incursion risk of ASF in wild boar in Belgium in September 2018 (2). MINTRISK was primarily developed to evaluate the incursion risk of vector-borne diseases. Although ASF can be transmitted by soft ticks of the genus *Ornithodoros*, these vectors do not seem to play a role in ASF virus transmission in Europe (23). Hence, MINTRISK is not a preferred tool to evaluate the risk of ASF. Some of the generic RA tools can rapidly assess the risk of multiple diseases for a target area given the diseases have been included in the tool (SPARE, COMPARE, RRAT, IDM). Results of these tools can be used to evaluate the relative risk of ASF compared to the risk of other notifiable diseases that might threaten the target area on a regular basis. Most of the generic RA tools can break down results to provide more detail on source areas and pathways contributing most to the risk or to indicate regions in the target area most at risk of incursion of a new disease, all of which is essential information for disease prevention and surveillance purposes. Communication of results from generic RA tools to risk managers should therefore aim at a proper understanding of the risks and the uncertainties involved by indicating underlying mechanisms rather than at communicating the absolute value or level of risk predicted.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

CV and ES initiated and conceptualized the research. RS provided harmonized data from Eurostat and WAHIS. RS performed the case study in SPARE. RT and ES performed the case study in COMPARE. AK, MC, and AB performed the case study in MINTRISK. RP, MS, and CV performed the case study in RRAT. HR performed the case study in IDM. TL and LS-L performed the case study in NORA. CH, KS, and AC performed the case study in SVARRA. SN developed the bespoke models to evaluate the ASF incursion risk. CV did the analysis of results and drafted the manuscript. All authors reviewed and edited the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00056/full#supplementary-material

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EPIC, Scottish Government's Centre of Expertise in Animal Disease Outbreaks: A Model for Provision of Risk-Based Evidence to Policy

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EPIC, Scottish Government's Centre of Expertise on Animal Disease Outbreaks, offers a successful and innovative model for provision of scientific advice and analysis to policy-makers in Scotland. In this paper, we describe EPIC's remit and operations, and reflect on three case studies which illustrate how the Centre of Expertise Model provides risk-based evidence through rapid access to emergency advice and analyses, estimating disease risks and improving disease detection, assessing different disease control options, and improving future risk resilience. The successes and challenges faced by EPIC and its members offer useful lessons for animal health researchers and authorities, working in contingency planning for animal health security in other countries.

Keywords: risk-based evidence, animal health, contingency planning, disease outbreaks, risk communication

BACKGROUND

Global challenges, such as animal disease outbreaks, are complex multi-faceted problems which demand cross-cutting interdisciplinary collaboration to find scientific and technical solutions which also take into consideration the political and societal dimensions of these events. In Scotland, the Government has invested in four Centre of Expertise models of science-policy exchange to support evidence-based decision-making for environmental, plant and animal/public health risks[1]. EPIC, Scottish Government's Centre of Expertise on Animal Disease Outbreaks (www.epicscotland.org), is funded to develop and provide research capacity to assist in the prevention of, preparation for and eradication of important notifiable animal diseases.

EPIC has been funded by the Rural and Environmental Science and Analytical Services (RESAS) of the Scottish Government since 2006 as a collaborative interdisciplinary research consortium between major scientific research institutions that focus on animal health in Scotland, including both universities and other research providers[2]. The consortium aims to foster a culture in which

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[1] EPIC, Scottish Government's Centre of Expertise on Animal Disease Outbreaks; ClimateXChange, Scotland's Centre of Expertise on Climate Change; Crew, Scotland's Centre of Expertise for Waters; Centre of Expertise on Plant Health.

[2] The University of Edinburgh [The Global Academy of Agriculture and Food Security, Royal (Dick) School of Veterinary Studies and The Roslin Institute], The University of Glasgow, Scotland's Rural College, Moredun Research Institute, The James Hutton Institute and Biomathematics and Statistics Scotland.

Case Study 1. Estimating risks.

Contingency planning for FMD disease outbreak response

To ensure business continuity and avoid economic losses in the event of future outbreaks, and to respond to SG queries about whether countryside closures were proportional to the risk, EPIC veterinary epidemiologists conducted veterinary risk assessments (VRAs) to assess the risks of recreational activities requiring access to the countryside during an outbreak of FMD. VRAs were developed to estimate the risks associated with 12 activities including walking, cycling, canoeing, fishing, horse riding, staging events on agricultural land, stalking deer and shooting birds, which necessitate access to the countryside in an outbreak (5, 6). The VRAs were assessed by SG and the UK National Experts Group on FMD and shared with other risk assessment teams as a model of good practice in outbreak preparedness. It is anticipated that these VRAs would help to avoid costs associated with the collapse of rural economies and tourism observed during the FMD outbreak in UK in 2001, due to "the countryside being closed" for disease control purposes, which reached £3billion (7).

researchers from different disciplinary and professional domains (i.e., veterinary medicine, epidemiology, genetics, physics, mathematics, statistics, social science, and economics) come together to address policy-relevant questions in "peace-time" as well as during animal disease emergencies.

The original rationale for EPIC was based on the need to improve scientific capacity to respond to animal disease risks and threats which have the potential to cause significant socio-economic harm to the UK. The demand for this capacity was writ large after the Foot-and-Mouth Disease outbreak in 2001 (1). The first important test for EPIC occurred not long after, when in 2007 it was requested by Scottish Government to provide evidence to underpin negotiations with local stakeholders and the European Commission to reopen livestock markets after FMD was detected in England (2). The response to this request helped forge EPIC's reputation for delivering robust, timely policy-relevant outputs in anticipation of, and during, disease outbreaks. This, in combination with EPIC's explicit consideration of best-practice at the science-policy interface (3), resulted in UK-wide recognition of EPIC as "a good model of how to secure the best available scientific advice to inform government policy on reducing the impact of animal disease outbreaks (4)."

In this paper, we describe the EPIC remit and, through a series of case studies, illustrate its operational (**Case Study 1**), tactical (**Case Studies 2A** and **2B**) and strategic work (**Case Study 3**). We conclude with a discussion about the opportunities and challenges of this exemplar model for the provision of scientific and other interdisciplinary research evidence and expertise for policy.

THE EPIC MODEL FOR PROVIDING RISK-BASED EVIDENCE FOR POLICY

EPIC comprises 40 or so scientists who work as part of the EPIC team either full time, or part-time alongside other research and other commitments. The multi-disciplinary expertise of EPIC's members means that it has the capacity for delivering interdisciplinary research to policy-makers to address questions which range from the very applied (e.g., operational or tactical decisions regarding disease control) to the very strategic (e.g., foresighting activities, research and development of innovative methodologies). EPIC has a programme of research agreed with government, to be conducted when no disease outbreak is occurring. This work programme is proposed at the start of each 5-years funding cycle, but is reprioritized as necessary to respond to requests from Scottish Government for specific analyses. In the event of an outbreak, as many EPIC scientists as are required convert to work which informs the outbreak response. The ability to provide a rapid response to emergency outbreak events is facilitated by trusted partnerships between consortium members and Scottish Government veterinarians, scientists and policy officials, and has been underpinned by sustained funding over multiple policy-cycles. The latter has been essential to build meaningful, long-lasting relationships with policy-makers. EPIC's activities at the science-policy interface have been strengthened by integration of EPIC scientists at Government-facilitated stakeholder group meetings to foster knowledge exchange with industry leads and the public. Explicit engagement between EPIC scientists, the Animal and Plant Health Agency (APHA) and Department for the Environment, Farming and Rural Affairs (Defra) also occurs at a UK level to ensure that EPIC's work adds value, avoids unnecessary duplication and is complementary to UK priorities. The relationships between GB and Scottish disease control structures are outlined in the Scottish Government Exotic Disease Contingency Framework Plan [(15), p. 30].

RESEARCH PRIORITIES

EPIC's research priorities align to four strategic foci which are important to Scottish Government and Defra:

1. Risk communication: Providing rapid access to emergency advice and analyses in the event of disease outbreaks, and knowledge exchange.
2. Estimating risks: Characterizing disease risks and improving disease detection.
3. Informing risk management: Assessing different disease control options.
4. Improving future risk resilience: Developing advice on challenges and opportunities presented by local and global societal, technical, economic, environmental, and political developments.

Risk Communication: Rapid Access to Emergency Advice and Analyses

Academic researchers can struggle to engage with policy through a lack of understanding of how policy-making works, or a lack of ability to communicate science in the most effective way for policy-makers (16). Similarly, policy-makers may not access relevant evidence for policy (or request such evidence to be provided) because they do not know the appropriate academics to approach or the correct questions to ask. Furthermore, there can be a disconnect between the temporal scales of traditional academic research which often looks to the future, and policy need which is often "here and now." EPIC has addressed this potential dissonance through its investment in experienced knowledge brokers who are embedded in both academia and the SG Animal Health and Welfare Division (AHWD) policy environment to ensure rapid and effective communication across the science-policy interface within and outwith disease emergencies (3). EPIC members work alongside policy-makers in AHWD offices to facilitate effective science-policy translation and knowledge exchange both in "peace-time" and in disease emergencies. These knowledge-brokering roles have been an effective means of communication and co-construction of policy-relevant scientific endeavors. The emphasis placed on understanding animal health policy and governance as a means to improving delivery of relevant scientific evidence, has enabled mutual understanding and trust to grow between the scientific and policy "poles" of EPIC's business. In doing so, there is greater appreciation, on both sides, of the other's pressures, abilities and needs, and the properties of what will be useful outputs. Investment in this science-policy interface has resulted in an agile research model, which enables researchers to navigate successfully between operational and tactical policy-responsive work and longer term strategic and other "blue-sky" research. The former forms the basis of advice to policy-makers whilst the latter is essential to sustain the experience-base, quality and credibility of the science available to inform policy.

Estimating Risks: Characterizing Disease Risks and Improving Disease Detection

EPIC has dedicated resources to improving preparedness and outbreak response for exotic diseases such as Foot-and-Mouth disease, Highly Pathogenic Avian Influenza, and African Swine Fever via epidemiology, economics and risk assessment (**Case Study 1**) and is one of few non-government members with representation on the UK's National Emergency Epidemiology Group (formed during exotic disease outbreaks to provide epidemiological input on the determinants and distribution of disease to inform decisions on disease control) and the "5 Nations Veterinary Risk Assessment (VRA) forum" which includes leaders from all relevant agencies and governments from England, the other UK devolved administrations and Republic of Ireland.

EPIC members work with animal and human health surveillance data providers in Scotland to add value to existing data collection systems, develop methodologies to analyse and integrate surveillance datasets and develop risk-based approaches to surveillance to improve disease detection. Horizon scanning tools have been developed in collaboration with Defra to monitor salient disease threats—in particular Bluetongue virus (BTv), African Swine Fever (ASF), and Highly Pathogenic Avian Influenza (HPAI) in order to expedite assessments of risks posed by animal import to other livestock (Bessell et al., under review). This work is notable for its cross-sectoral involvement and multi-disciplinary approach which is important for identifying surveillance gaps and future emerging threats, whether in the form of specific pathogens, or vulnerabilities such as industry practices.

Case Study 2A: Informing risk management.

Informing options for FMD control

In response to the FMD outbreak in 2007, EPIC developed animal movement models to provide Scottish Government with evidence to underpin a decision to reopen livestock markets (2). In subsequent years, EPIC models have been developed to explore cost-benefits of alternative FMD contingency plans specified under EU legislation (Directive 90/423/EEC)[3], including a reactive vaccination-to-live policy targeting cattle in Scotland. EPIC's analyses highlighted the potential for cost-savings in large (but not small) outbreaks when vaccination is used (8–11). Further, they quantified the negative impact of suboptimal vaccine dose availability and resultant stocking delays on outbreak control costs. EPIC's assessment of the role of livestock haulage vehicles on the spread of diseases has demonstrated the importance of this route of transmission on the spread of FMD and other diseases and highlighted the need to improve cleaning & disinfection protocols in the UK. EPIC scientists estimated that sharing haulage vehicles limited the efficacy of the standstill regulation that was put in place to prevent widespread FMD outbreaks, resulting in a 10-fold increases in the size of the largest outbreaks.

Case Study 2B: Informing risk management.

Transmission and tracking of Bovine Viral Diarrhea: The value of endemic disease models to inform exotic disease preparedness

Although EPIC's principal focus is on preparedness for, and response to, exotic animal disease outbreaks, endemic disease models for livestock can also offer valuable insights into the interaction between infectious pathogens and various animal species within a local context and enhance EPIC's capability and capacity to respond quickly and effectively in the event of an emergency. The Scottish BVD Eradication Scheme has provided EPIC with a unique opportunity in this regard. EPIC scientists, in collaboration with stakeholders (Biobest laboratories, SAC consulting), sequence BVDV isolates obtained from animal samples to inform the latter stages of the Scottish eradication campaign. Over two thousand samples have been archived and genotyped, providing a reference database for Scotland. Preliminary phylodynamic analysis demonstrates multiple BVDV strain movements between Scotland and the rest of GB. Synthesis of this work with EPIC's experience and familiarity with working with data rich mechanisms of disease spread, such as animal movements, together with insights into farmer and stakeholder experiences (12) provides an important resource that will improve our understanding of BVDV transmission and should inform the final stages of Scotland's BVDV eradication policy (13). EPIC scientists' experience with the methodologies for integrating phylodynamics with other data types for endemic disease provide important resilience in responding to exotic disease outbreaks where similar approaches are valuable.

Informing Risk Management: Assessing Different Disease Control Options

EPIC uses epidemiological modeling and economic approaches to assess disease control options, which are ground-truthed through interactions with livestock industry experts (**Case Study 2A**). Endemic disease models also offer instructive exemplars of how to improve exotic animal disease preparedness

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[3] Council Directive 90/423/EEC of 26 June 1990 amending Directive 85/511/EEC introducing Community measures for the control of foot-and-mouth disease.

Case Study 3: Improving future risk resilience.

Anticipating the future of veterinary surveillance in Scotland

EPIC has a strategic research portfolio which includes participatory foresighting activities (such as scenario planning) led by multidisciplinary, multi-partner teams of researchers, decision-makers and practitioners from different disciplinary domains. Scenario planning is a formal approach used by the private and public sectors and academics (in the social science disciplines in particular) to structure thinking around long-term planning in response to uncertainty. In 2017, the outputs of scenario planning work coincided with a disruptive political shock: the decision of UK to leave the European Union, known as Brexit (14). The scenarios generated from the workshop were co-produced with stakeholders and later shared with the British Veterinary Association Surveillance Working Group; key findings were presented to Scotland's Strategic Management Board for Veterinary Surveillance, the Scottish Futures Group and the British-Irish Parliamentary Assembly Committee inquiry into the implications of Brexit for the agri-food sector. Importantly, the scenarios offer an opportunity for a positive and strategic feedback loop within EPIC to "future-proof" its programme of research and tailor it to anticipate and adapt to future possibilities and uncertainties.

(**Case Study 2B**). EPIC's modeling expertise and experience is therefore always current and routinely adapted to policy- and industry-specific queries which means that there is readiness to respond to new and emergent threats such as Schmallenberg Virus (17) and ASF (18), #muckfreetruck campaign[4], when/if they occur.

Improving Future Risk Resilience

Developing advice on challenges and opportunities presented by local and global societal, technical, economic, environmental, and political developments.

EPIC utilizes novel combinatorial approaches, including the application of social science and business management tools such as scenario planning to integrate interdisciplinary expertise and create transdisciplinary solutions [**Case Study 3**, (14, 19)]. Scenario planning exercises have been held with a wide range of cross-sectoral stakeholders and decision-makers to consider and co-create credible long-term futures in order to enhance opportunities and mitigate challenges to facilitate earlier diagnoses and detection of exotic, endemic, and novel animal and zoonotic diseases in different industry sectors. This participatory method offers an opportunity for inclusive and reflexive approaches which enable up-stream engagement with research beneficiaries. It also enables positive feedback loops within EPIC to "future-proof" risk assessment tools and encourage improved risk communication.

CHALLENGES AND SUCCESSES FOR EPIC

EPIC illustrates a model of research provision for policy-making that utilizes academic partners, working closely with Government policy-makers, to contribute to evidence-based decision-making. EPIC's continued funding over more than 10 years has provided the opportunity to develop and refine EPIC's remit and operations. As a result, EPIC researchers have been able to deliver tangible policy-relevant outcomes (e.g., **Case Studies 1**, **2**, **3**) via a broad range of outputs (**Figure 1**). EPIC's successes have come from building long-term sustained relationships with policy-makers that allow for meaningful and genuine engagement. The specific impacts of this type of approach are hard to quantify as they go beyond traditional academic metrics (of peer-reviewed publications and patents) and include broader conceptual changes about how the scientists and policy-makers interact, moving further toward a co-production approach (20), illustrated by the case studies presented.

One of the challenges of this model is that academics value quality scientific publications, which take time to develop, whilst policy-makers need timely, trusted information to inform policy decisions. Responding to requests from policy-makers helps academics to produce more impactful science, but does not always lead to the scientific publications that they and/or their employers, desire. Focusing on policy-oriented research can therefore be a barrier to career progression within academic organizations. The increased emphasis on "research impact" that has emerged over the last few years (21) is helpful in promoting the value of academics engaging in policy-oriented work, although it potentially rewards a rather simplistic view that research leads directly to policy, rather than a more nuanced co-production approach (20). A real benefit of initiatives such as EPIC is in building up a cohort of personnel with the technical capacity to provide analyses in outbreak situations, but careful consideration is needed to ensure the structures do not inadvertently inhibit personal career development.

CONCLUSIONS

Risks to animal health and welfare have changed rapidly, and will continue to evolve and become increasingly complex in future. The increasing liberalization of trade combined with a changing climate has resulted in an increase in the velocity and volume of people, animals and animal products moving around the globe (22). This, in combination with the translocation of non-native disease hosts and vectors as a result of climate change and urbanization, creates the potential for new and (re)emerging transboundary disease outbreaks of significant socio-economic importance (22). These risks are illustrated by the current threat of ASF. This lethal pig disease has already taken hold in Europe and Asia, and is having far-reaching effects in global health and food security, that are likely to be felt long after the initial outbreak has subsided.

The current global ASF outbreak illustrates the importance of coordinated interdisciplinary efforts which consider systems-approaches to animal disease preparedness. EPIC's current governance and organizational structure offers a framework for the effective deployment of interdisciplinary capabilities in the natural sciences, social sciences, economics and the humanities, in an enduring and resilient way to support a coordinated vision for animal health policy through appropriate risk prioritization, analysis and communication. In the UK, and in particular in Scotland, this approach has helped to reduce research wastage through avoidance of duplication

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[4] #MuckFreeTruck. Available at: http://www.npa-uk.org.uk/_MuckFreeTruck_campaign_launched_to_encourage_better_lorry_washing.html.

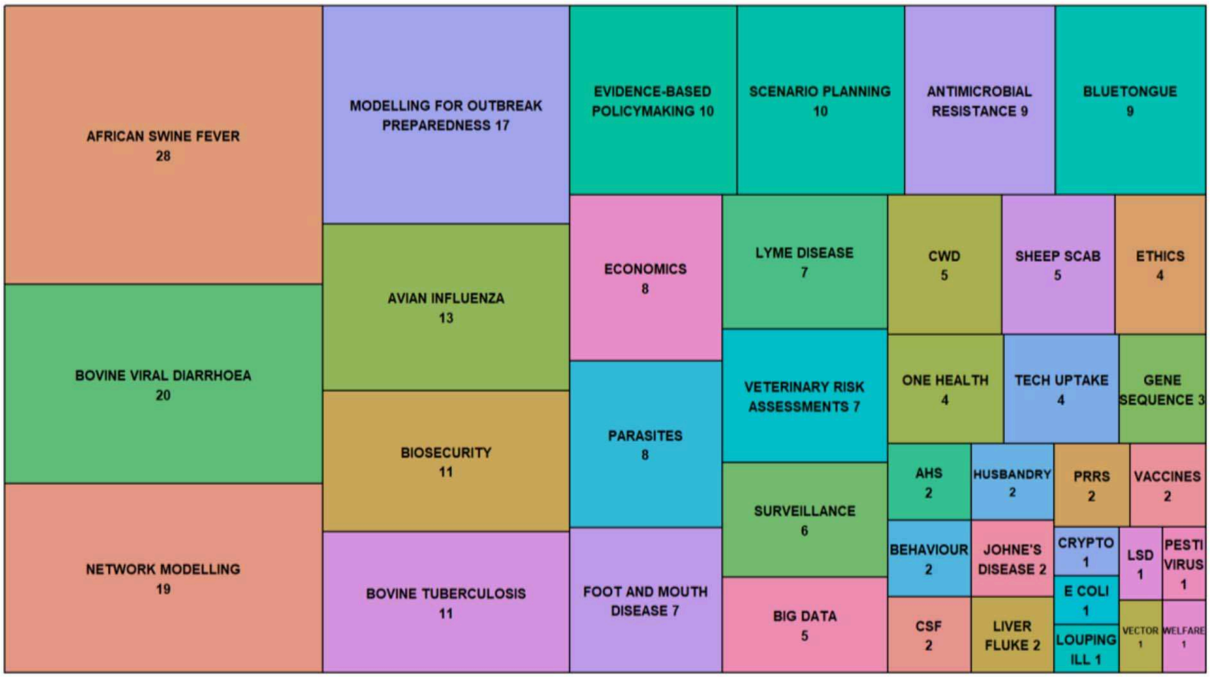

FIGURE 1 | Treemap of a sample of EPIC's knowledge exchange outputs between March 2016 and 2019 to illustrate the range of EPIC work. In total, EPIC researchers recorded 486 KE-related outputs during this time period. In this graph, we present a subset of those that referenced a specific policy focus, animal disease topic or methodology ($n = 253$). These outputs included peer-reviewed publications, policy and research briefs, stakeholder meetings, technical reports for government, conference presentations, and posters. Due to space constraints, some words and terms in the figure have been abbreviated: AHS, African Horse Sickness; Crypto, Cryptosporidiosis; CWD, Chronic Wasting Disease; *E. coli, Escherichia coli*; LSD, Lumpy Skin Disease; PRRS, Porcine Reproductive and Respiratory Syndrome; Tech uptake, Technology uptake; Vector, Vector-borne Disease; Welfare, Animal Welfare.

of efforts, build research skills and capacity, and generate targeted evidence to improve cost-effective interventions ensuring the long-term resilience of animal health policy and food security.

DATA AVAILABILITY STATEMENT

Datasets are in a publicly accessible repository. The datasets generated for this study can be found at https://figshare.com/articles/Treemap_data/11918967.

AUTHOR CONTRIBUTIONS

LB was responsible for the conception of the paper. LB and HA wrote sections of the manuscript. All authors contributed to manuscript revision, are accountable for the accuracy and integrity of this work and have approved the final manuscript for publication.

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ORIGINAL RESEARCH
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A Tool for Prioritizing Livestock Disease Threats to Scotland

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There are a number of disease threats to the livestock of Scotland that are not presently believed to be circulating in the UK. Here, we present the development of a tool for prioritizing resources for livestock disease threats to Scotland by combining a semi-quantitative model of the chance of introduction of different diseases with a semi-quantitative model of disease impact. Eighteen key diseases were identified and then input into a model framework to produce a semi-quantitative estimate of disease priorities. We estimate this through a model of the potential impacts of the infectious diseases in Scotland that is interpreted alongside a pre-existing generic risk assessment model of the risks of incursion of the diseases. The impact estimates are based on key metrics which influence the practical impact of disease. Metrics included are the rate of spread, the disease mitigation factors, impacts on animal welfare and production, the human health risks and the impacts on wider society. These quantities were adjusted for the size of the Scottish livestock population and were weighted using published scores. Of the 18 livestock diseases included, the model identifies highly pathogenic avian influenza, foot and mouth disease in cattle and bluetongue virus in sheep as having the greatest priority in terms of the combination of chance of introduction and disease impact. Disregarding the weighting for livestock populations and comparing equally between industry sectors, the results demonstrate that Newcastle disease and highly pathogenic avian influenza generally have the greatest potential impact. This model provides valuable information for the veterinary and livestock industries in prioritizing resources in the face of many disease threats. The system can easily be adjusted as disease situations evolve.

Keywords: livestock, disease, introduction, risk, horizon scanning

INTRODUCTION

Since 2000 there have been incursions of high profile diseases such as Foot and Mouth Disease (FMD), Classical Swine Fever (CSF) and Bluetongue virus (BTV) in the United Kingdom (UK) that have caused large outbreaks with high impacts, resulting in high costs (1–3). The UK has also had a number of incursions of highly pathogenic avian influenza (HPAI) that resulted in smaller outbreaks, but with the potential for great impact should HPAI become established (4, 5).

There is an ongoing outbreak of African Swine Fever (ASF) in Europe (6) and there have been outbreaks of lumpy skin disease, sheep pox, and peste des petits ruminants in the Balkans (7–10). Policymakers can take actions to reduce the chance of incursion, or to prepare for potential disease outbreaks, but have to prioritize between different pathogen threats. Assessing the risks posed by such threats requires consideration of both the chance of incursion and the impact following the arrival of the disease.

The potential impacts of some diseases have been assessed using mathematical models of disease spread (11–14) but comparable mathematical modeling frameworks are not available for all diseases. In the absence of a single consistent modeling framework the impacts of an infectious disease can be evaluated with respect to a number of criteria. These include the potential extent of spread of the disease in terms of the likely numbers of animals that may become infected. This effect is offset by the mitigating factors that may exist such as the availability and effectiveness of vaccines, the seasonality of the pathogen, and whether there are potential reservoirs of infection in vectors and wildlife. A disease outbreak will have direct impacts on animal health, welfare and productivity as well as potential secondary effects on human health. There are also indirect impacts on international trade and impacts on society as a whole. This includes both the costs of controlling the disease and wider impacts on rural economies as seen during the 2001 FMD outbreak (1).

Estimating the chance of incursion of a particular disease is important in prioritizing the threat from that disease. Defra has developed a tool for assessing and assigning a risk ranking on the incursion of different diseases (15). The tool combines the current known global distribution of diseases with data on the likelihood of different pathways of introduction, the products that are traded and existing risk mitigation measures that are in place. The diseases are classified according to the EFSA risk level classification scale shown in **Table 1**, which provides a consistent mapping from the estimated levels of risk to a scale of probabilities, which we will interpret as being the chances of an incursion leading to an appreciable outbreak.

Two methods have been developed for comparing potential impacts directly and consistently between diseases. Defra has developed the Disease briefing, Decision support, Ranking and Risk assessment (D2R2) database (17) and the DISCONTOOLS Project that aims to identify knowledge gaps in diseases (18). Whilst the methods underlying both methods are different, both are essentially based on expert elicitation.

The aims of this paper are to demonstrate the value of a model to prioritize disease threats to Scotland based on estimates of their chance of incursion (hereafter denoted by r) and potential impact following introduction. Such a model can be used by industry and government veterinary agencies to prioritize surveillance and preparedness resources. The tool will use data from DISCONTOOLS and D2R2 to derive an index of disease impact. This will then be combined with the chance of incursion based on the risk of incursion scores defined in Roberts et al. (15) to develop a risk matrix capturing variability across the two contributory axes, namely chance of introduction and disease impact. To compare our measure to the impact as perceived by the scientific research community, we examine the estimated impact of the diseases against a metric which seeks to measure the extent of scientific research into each pathogen.

MATERIALS AND METHODS

In discussion with the Animal Health and Welfare Department (AHW) at the Scottish Government, a list of 18 priority diseases was identified (**Table 2**). Rather than a static list the priority diseases were refined over a period of years between 2012 and 2019 as new threats emerged and the priorities of the AHW department changed, for example, in response to the emergence of lumpy skin disease in the Balkans. Some of the diseases affect multiple host species; these were treated separately when modeling the impact in different species. Both low pathogenic and high pathogenic avian influenza were included, due to their differing impacts and epidemiology. Bluetongue virus (BTV) has clinical presentations that are both highly pathogenic and less pathogenic, here we consider a more highly pathogenic presentation (19). Caprine diseases were not included because the population of goats in Scotland is small (20).

Livestock Populations

To allow for differences in the size of the population and the values of animals of different species and ages, species population data were taken from the Scottish agricultural census from June 2018 (21). The horse population is an estimate from Horse Scotland (22). The Scottish Agricultural census breaks

TABLE 1 | The risk classification scale used in the Defra risk of incursion tool (15, 16).

Probability	Score	Definition from EFSA	Expanded description
Negligible	0–10	Event is so rare that is does not merit consideration	The chance of the event occurring is so small it does not merit consideration in practical terms; it is not expected to happen for many years, if at all
Very low	10–20	Event is very rare but cannot be excluded	The event is not expected to occur (very rare) in the next few years but it is possible
Low	20–30	Event is rare but does occur	The event may occur occasionally (rare) but could occur in the next few years
Medium	30–40	Event occurs regularly	The event is possible within the next year
High	>40	Event occurs very often	The event is expected to occur within the next year

TABLE 2 | Diseases included in these analyses.

Disease	Domestic species affected	Zoonotic	History of occurrence[a]	Mode of transmission
Brucellosis (*B. abortus*)	Cattle	Yes	2003 (Scotland) 2004 (England)	Direct, indirect contact—fetal material, uterine discharges, milk
Enzootic bovine leukosis (EBL)	Cattle	No	1999 (UK)	Direct, indirect, vertical
Lumpy skin disease (LSD)	Cattle	No	Never	Biting flies, mosquitoes
Bluetongue Virus (BTV)	Cattle, sheep	No	2007 (England)	Vector—Culicoides
Foot and mouth disease (FMD)	Cattle, sheep, pigs	No	2007 (England)	Direct, indirect contact
African Swine Fever (ASF)	Pigs	No	Never	Direct contact, vector–exotic soft ticks
Aujeszky's Disease	Pigs	No	Eradicated 1989	Direct, indirect contact
Classical Swine Fever (CSF)	Pigs	No	2000 (England)	Direct, indirect contact
Swine Vesicular Disease (SVD)	Pigs	No	Eradicated 1982	Direct, indirect contact
Porcine Epidemic Diarrhea (PED)	Pigs	No	Eradicated 1982	Fecal-oral, fomites, germplasm, airborne
Sheep pox	Sheep	No	Eradicated 1866	Direct contact
Peste des petits ruminants (PPR)	Sheep	No	Never	Direct, indirect contact
Low Pathogenic Avian Influenza (LPAI)	Poultry	Yes	2018 (Scotland)	Direct, indirect contact, wild birds
Highly Pathogenic Avian Influenza (HPAI)	Poultry	Yes	2018 (Scotland)	Direct, indirect contact, wild birds
Newcastle Disease (ND)	Poultry	Yes	2006	Direct, indirect contact, wild birds
African Horse Sickness (AHS)	Equines	No	Never	Vector–Culicoides
Equine Infectious Anemia (EIA)	Equines	No	2012 (England)	Mechanical vector–Tabanids
West Nile Virus (WNV)	Equines	Yes	Never	Vector–Mosquitoes

[a] *If there has been an outbreak in Scotland this is recorded, otherwise the most recent outbreak elsewhere in GB is given.*

down the animals of each species to different age groups and production classifications (e.g., dairy vs. beef). Each age group and production classification has a value for livestock grazing comparison units based on the Defra Farm Business Survey and cited in Nix (23). By mapping the data from the Scottish Agricultural census to livestock units, we calculate a total value in terms of livestock units for the population of each species in Scotland and in **Table 3** we present the mean number of livestock units per head of each species. We then take the square root of these population livestock units as the transformed population for livestock species i (Pop_i^T) (**Table 3**). In so doing, we are up-weighting the relative importance of smaller populations when evaluating overall impact. This is reasonable, since we believe that it is unlikely that impact will increase *pro-rata* to the population size.

TABLE 3 | Populations of livestock in Scotland transformed by the number of livestock units assigned to that species by Nix (23).

Species	Population	Population livestock units	Mean livestock units per head	Transformed population (Pop_i^T)
Cattle	1,755,318	1,125,158.84	0.641	1,060.7
Horses	100,000	80,000	0.800	282.8
Pigs	316,736	60,179.84	0.190	245.3
Poultry	14,541,621	101,791.347	0.007	319.0
Sheep	6,593,410	402,198.01	0.061	634.2

Disease Impact

The source of the estimates of disease impact was the DISCONTOOLS project, informed by the Defra D2R2 system. Impact is scored based on 6 sub-categories in three broad categories:

1. Extent of spread:
   a. Rate of spread.
   b. Mitigation factors including the availability of effective vaccines, wildlife reservoirs, vector reservoirs and opportunities to control the disease through biosecurity and through movement bans.
2. Health and welfare:
   a. Animal welfare (including morbidity) and animal mortality.
   b. Human health.
3. Indirect impacts
   a. Wider society to include the impacts of the disease on restrictions to human activities, the industry sector, and government finances.
   b. International trade.

The parameters that were derived from DISCONTOOLS and D2R2 (17, 18) are described in **Tables S1–S3**.

The metrics in **Tables S1–S3** are combined in a single impact model for disease *d* in species *i*:

$$r_{di} = Pop_i^T \beta_{di} p_{di} (a_{di} + h_{di}) c_{di} t_{di}$$

In this equation, $Pop_i^T \beta_{di} p_{di}$ scales the impact with respect to the extent of spread of the disease in the specific transformed population; β_{di} quantifies the potential for spread and p_{di} summarizes and adjusts for the impact of mitigation measures on the potential for spread. The second block of terms, a_{di}, h_{di}, sum to give the direct impact score in terms of animal morbidity and mortality and human health, respectively. All the terms contribute multiplicatively, with the exception of the direct impacts on animal morbidity and mortality and human health a_{di}, h_{di}, which each make an independent additive contribution to the impact score. This is to reflect the discreet impacts of disease on human and livestock populations and to scale the sum of these to be between 0 and 2, recognizing that most of the diseases have no human health impact and therefore give rise to a factor taking values between 0 and 1. In this way, the effect of direct impacts is consistent with the effects of indirect impacts on society and trade c_{di}, t_{di} that are each also scaled to be between 0 and 1.

The corresponding estimate of impact in species *i*, when we do not adjust for the livestock population is:

$$r^*_{di} = \beta_{di}(1 - p_{di}) \left(a_{di} + h_{di}\right) c_{di} t_{di}.$$

We will illustrate the approach to quantifying individual terms by considering the potential for spread (β_d) of disease *d*. This is estimated as the sum of scores over the set of relevant determining factors in species *j* (s_j) (**Table S1**) normalized relative to the maximum possible sum of factor scores:

$$\beta_d = \frac{\sum_j s_{jd}}{\sum_j \max(s_j)}.$$

A similar formulation based on a weighted sum of scores was used for each of the other parameters (**Tables S1–S3**): effect of mitigation factors (p_{di}), animal health factors (a_{di}), human health factors (h_{di}), wider society (c_{di}), international trade (t_{di}), each being calculated and scaled using the specific determining factors for that metric, for that disease and species. In the equation we multiply by $(1 - p_{di})$ because values of 1 for p_d correspond to strong mitigation and values of 0 to no mitigation. An example of the calculation of impact is given in **Supplementary Information S2**.

Chance of Incursion

The chance of incursion of each pathogen is taken from the risk of incursion tool (15) (update from March 2019). This takes into account the current global distribution of the diseases, possible routes of entry (including migrating birds) and disease mitigations that are in place in the country or region of origin.

RESULTS

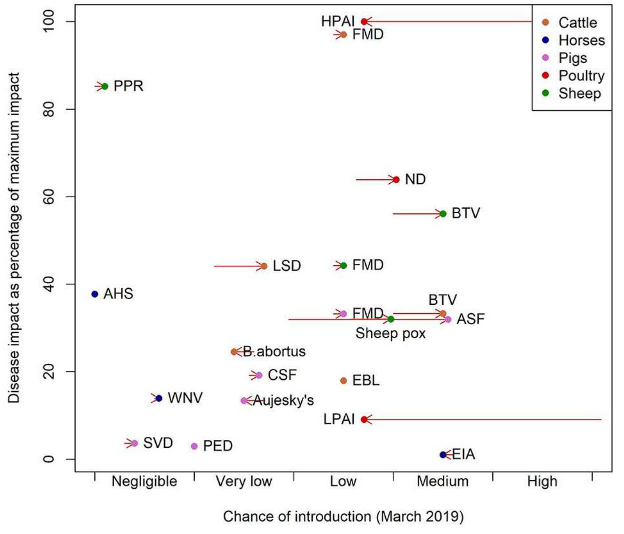

FIGURE 1 | Chance of introduction against impact as of March 2019. Impact is presented as the percentage of the impact of the disease with greatest impact. The arrows represent the change in the chance of introduction from the position in March 2017 to chance of introduction in March 2019.

Examining the pattern of estimated potential impacts relative to the specific chance of incursion (**Figure 1**), diseases can be categorized and hence prioritized. HPAI, BTV in sheep, FMD in cattle and ND are diseases with high impact and a low or medium chance of introduction (top right hand corner of **Figure 1**). BTV in cattle and ASF both have medium chances of introduction, but slightly lower impact and EIA a very low impact (**Figure 1**). PPR has a negligible chance of introduction but is a disease with potentially high impact (**Figure 1**). The decomposition of these scores is provided in the (**Figures S1–S4**).

Comparing the changes in risk between March 2017 and March 2019 shows a large decrease in the relative importance of avian influenzas and increases in risks of ASF, BTV, ND, sheep pox and LSD (**Figure 1**). These are driven by the change in their chance of introduction driven by changes in the distribution of the pathogens in Europe.

A sensitivity analysis in which the indirect impact scores (impacts on wider society and international trade) are included additively rather than multiplicatively results in BTV in sheep becoming the most impactful disease. This high impact is driven by the high potential for spread of the disease (**Figure S5**). Disregarding the size of livestock population so that impacts are considered irrespective of sector, leads to the relative impact of cattle and sheep diseases reducing and the impact in pigs and poultry diseases increasing (**Figure 2**).

DISCUSSION

This framework provides a novel way to combine and interpret independent metrics of animal disease impacts. The selected metrics of disease impact were similar in both DISCONTOOLS (18) and D2R2 (17) and were loosely classified as disease spread, impacts on animal and human health and indirect impacts on wider society and international trade. The methodology was

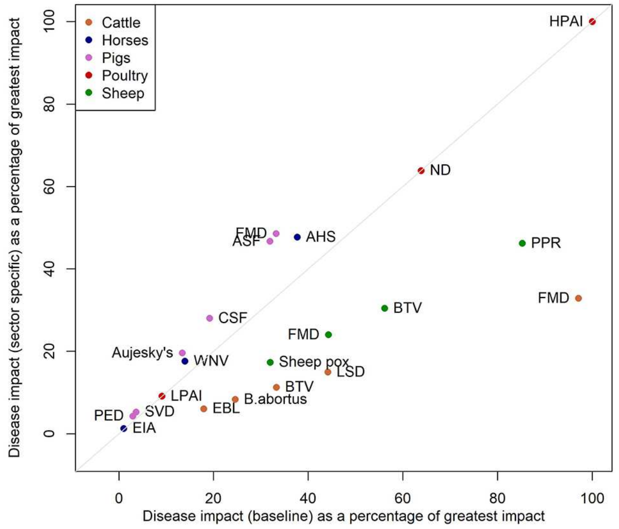

FIGURE 2 | Scatterplot of the impacts from the baseline model against the impacts from a model where we do not include the livestock population sizes in the model.

implemented over a range of diseases, selected by discussion with policy-makers because the diseases are exotic to Scotland (most are notifiable) and pose a potential threat. Further diseases can be bought in as the model is further developed.

The diseases with the highest overall impact (**Figure 1**) are cattle FMD, PPR, HPAI, ND, and sheep BTV, but their high impact scores are driven by different factors. In the case of FMD in cattle the indirect factors are key and for HPAI and ND the impacts are driven by the direct factors. For BTV the main driver is the large potential extent of spread due to the fact that it is transmitted by midge vectors (**Supplementary Information S1**). The impact of BTV is further impacted by the wide range of strains which affects the potential severity of infection and the potential to control disease through vaccination. The purpose of this approach is to summarize disease properties succinctly and effectively: some diseases have high impact in just one area. For example in the case of WNV the impact is predominantly on human and animal health, but WNV has low potential for spread and low indirect impacts and so is assigned a lower overall impact score. Cattle diseases: FMD, BTV, LSD, and brucellosis (*B. abortus*), had the greatest overall estimated impact scores due to the size and relative value of the cattle sector in Scotland. Pig diseases, by contrast, had lower overall impact, given the relatively small pig population in Scotland, estimated at 320,000. Hence the sector-specific impact of FMD and ASF in pigs and AHS in horses is high, but when, in this model framework, the impact is adjusted for the size of the Scottish populations, the overall estimated impact is low due to the small size of the populations of these species. The estimated impact of BTV in cattle is low when population size is not considered because the disease impacts of BTV in cattle are typically relatively mild, although cattle may act as a reservoir species (24) (**Figure 1**).

Multi-host diseases were assessed individually for each potentially affected sector. However, a real-world incursion would probably impact on all sectors. So for example, FMD has a high estimated impact in cattle alone, but when sheep and pigs are also considered, the estimated impact of FMD considerably outweighs that of all other diseases.

At the time of writing, the diseases with the highest potential impact and highest risk of incursion were BTV (sheep), FMD (cattle), HPAI and ND (**Figure 1**). This is largely due to the extent to which these pathogens were circulating in Western Europe and as the fact that the generic model for incursion weights imports of live animals and the vector or wildlife pathways most highly. ASF is increasing in terms of risk of introduction as it spreads in Western Europe, but the impact remains low due to the small pig population in Scotland. AHS is a disease with an impact that is similar to ASF but with a negligible chance of introduction, due to it being restricted to Sub Saharan Africa, in countries with no direct trade links to the UK (25). However, the global pattern of livestock diseases is constantly changing; LSD and PPR are good examples of diseases that until recently had never been reported in Europe (7–9). In addition, the global distribution of disease vectors is changing, for instance, *Aedes albopictus* larvae were found in Southern England for the first time in 2016 (26). Vector distributions are factored into the model, but a changing distribution of vectors could change the estimated impacts of vector borne diseases.

The relative chance of disease introduction changes with time, particularly as the global distribution of diseases changes or as disease regulations change. There are also seasonal variations associated with vector borne diseases or with annual variations in bird migrations. Whilst the chance of introduction is quite dynamic, the risks arising from the diseases are quite static, changes only result from changes to the size of the population at risk, or possibly to changes in our understanding of the pathogenicity of the disease.

The matrix emphasizes the importance of focusing on species for which Scotland has the largest populations. Whilst swine diseases are very high impact, they are less prominent in the matrix than cattle and sheep diseases for which Scotland has a very large population. The matrix also emphasizes how the same disease can affect different sectors in different ways. This particularly applies to FMD in cattle relative to sheep or pigs.

CONCLUSION

We have presented a simple model framework that can be used to explore the interplay of the chance of disease incursion and the likely disease impact: the two components of risk assessment. The framework allows users to prioritize and assign risks to individual diseases. We have demonstrated that the outcomes are sensitive to purely local considerations such as the balance of species in the livestock population. The model focuses the relative impacts of different diseases beyond the individual animal or farm and compares populations as a whole.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

PB, IM, BB, HA, and LB contributed conception and design of the model. HR contributed the risk of incursion database. All authors reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00223/full#supplementary-material

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Meat Safety in Northern Tanzania: Inspectors' and Slaughter Workers' Risk Perceptions and Management

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Through a social scientific lens, this paper considers the risk perceptions and "risk-based decision-making" of two key groups in a northern Tanzanian context: (1) frontline government meat inspectors and health officers charged with ensuring that red meat sold commercially is safe for people to consume, and (2) the workers who slaughter and process cattle and red meat prior to its sale in rural butcheries. In contrast to techno-scientific understandings of disease risk and "rational" approaches to its management, this paper foregrounds the role of social, economic and institutional context in shaping the perceptions and practices around meat safety of these actors whose daily, close proximity to meat means they play a significant role in mitigating potential meat-borne disease. We show how limited resources, and a combination of scientific and local knowledge and norms result in "situated expertise" and particular forms of risk perception and practice which both enhance and compromise meat safety in different ways. Actors' shared concerns with what is visible, ensures that visibly unsafe or abnormal meat is excluded from sale, and that infrastructure and meat is kept "clean" and free of certain visible contaminants such as soil or, on occasion, feces. While such contaminants serve as a good proxy for pathogen presence, meat inspectors and especially slaughter workers were much less aware of or concerned with invisible pathogens that may compromise meat safety. The role of process and meat handling did not figure very strongly in their concerns. Microorganisms such as *Salmonella* and *Campylobacter*, which can easily be transferred onto meat and persist in slaughter and meat sale environments, went unacknowledged. Although health officers expressed more concern with hygiene and meat handling, their influence over slaughter process and butchery operations was unclear. Ultimately, recognizing the perceptions and practices of frontline actors who engage with meat, and the ways in which social, material and institutional realities shape these, is important for understanding how decisions about risk and meat safety are made in the complexity and context of everyday life, and thus for finding effective ways to support them to further enhance their work.

Keywords: meat safety, risk perception, Tanzania, slaughter, foodborne disease, *Salmonella*, *Campylobacter*

INTRODUCTION

Tanzania hosts Africa's third largest national population of livestock, upon which millions at least partially depend for their livelihoods. Despite policies to modernize the livestock sector through improved and intensified farming mechanisms, it is estimated that 88% of cattle in the country continue to be held in small-scale peri-urban farms and/or large-scale traditional pastoral systems. Such cattle provide the majority of domestically consumed cattle-derived food products, as population growth and rising per capita income increase demand (1–3). Despite the presence of urban abattoirs and some rural slaughterhouses, many cattle destined for slaughter and for the commercial sale of meat are killed at small, rural, concrete slaughter slabs, usually owned by local butchers, where they are slaughtered by a few workers with simple tools (such as knives, cleavers and ropes)[1]. Before meat is transported to butcheries, it must be inspected by a certified government meat inspector (MI) and stamped to indicate fitness for human consumption, or otherwise condemned. MIs (many of whom also provide livestock extension services), alongside health officers (HOs), are also charged with ensuring infrastructural and hygiene standards at slabs and in butcheries are met.

Emerging evidence suggests that the extent and burden of food-borne disease (FBD), including meat-borne disease, in low- and middle-income countries (LMICs) is substantial. A landmark WHO study concluded that Africa suffers the highest per capita burden of FBD globally (5), and the World Bank recently estimated FBD costs LMICs at least 110 bn USD annually (6). Many FBDs, such as salmonellosis, can be transmitted from animals to humans through the handling or consumption of meat and other animal products (although contamination of animal products by human or environmental pathogens is also possible).

Explanations for why LMICs have high burdens of FBD frequently highlight the predominance of small, informal actors, poor infrastructure, and weak regulation and capacity for enforcement in LMICs (7). Lack of awareness of presence and transmission risks of disease-causing organisms among food handlers and consumers is also oft cited, but numerous studies have demonstrated that provision of the "right" information does not necessarily lead to behavior change or adoption of more "rational" risk-based decision-making in relation to food safety, whether in low, middle or high income countries (8). Rather, perspectives from the social sciences highlight how people's risk perceptions and behaviors in all contexts, are highly situated and shaped by a range of psychological, social and economic factors (9).

This paper offers a rare social science contribution to the study of risk-based decision making in relation to meat safety in a low-income country context. Little information on risk perception in LMICs is available, which creates an opportunity to take greatest advantage of qualitative analysis. Through observation and semi-structured interviews, which "communicate experiences and opinions in an articulate, expressive and reflective manner" (10) and are therefore excellent for eliciting rich and candid responses from interviewees, this paper explores the perceptions of meat safety and its management among two key sets of actors in Tanzania. These are: (1) state employees with direct roles in ensuring meat safety, namely MIs and HOs, (together henceforth referred to as inspectors) and (2) people involved in the slaughter process at small slaughter slabs and slaughterhouses in rural areas, many of whom also own and/or work in small local butcheries (hereafter termed slaughter workers). By approaching "risk" as a variable, socially constructed notion, rather than an objective scientific measure of probability that legitimates particular technical control measures, this paper presents a contextually embedded analysis of how meat safety actually "happens" in the complexity of the everyday lives of these "risk managers" (11). In doing so, we recognize the broader social economic systems and conditions in which inspectors and slaughter workers operate, and how for instance, available resources influence their perceptions, inclinations and capacities to act (12, 13). More specifically, we illustrate how local conceptualizations of risk emphasize animal health, the appearance of meat, and certain infrastructural and hygienic aspects of slaughter and butchery environments while downplaying others, such as how meat is handled. Such perspectives help to elucidate the strengths of existing practice, as well as areas where contextually embedded risk managers, like the inspectors and slaughter workers considered here, can be supported to further enhance meat safety in realistic and appropriate ways. These insights are vital for meat safety policy in LMICs, but can also potentially inform high-income countries where those who work in close proximity to meat may also hold different forms of knowledge and are subject to variabilities of context.

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[1] Slaughterhouses, characterized as roofed or enclosed buildings, are larger than slaughter slabs with more systematic and formal operating procedures, infrastructure (drainage systems and running water) and equipment (such as hooks). Abattoirs are urban and are the most formal and mechanized facilities in Tanzania (4). The Tanzania Food and Drugs Authority records that there are 1,084 slaughter slabs and 85 slaughterhouses in Tanzania (4). In Moshi municipality and Moshi district, there are five slaughterhouses and an estimated 260 slaughter slabs.

Background: Understanding and Managing Food Safety

The intensification of production, the complex elongation of value chains and the rise in demand for animal products has led to increasing concern over the possibilities of food safety breaches with potentially devastating and far-reaching effects [cf. (14)]. In high-income countries, governments and private industry actors have reoriented meat safety policies and practice toward risk-based preventative approaches seen to be more effective, particularly against pathogens and hazards undetectable through traditional sensory inspection regimes (such as *Salmonella* and *Campylobacter*) (15–17). However, highly formalized preventative risk-based approaches, such as Hazards Analysis and Critical Control Points (HACCP) and Good Management Practices (GMPs), have not proven easily adoptable for smaller scale operations, or for producers in low-resource contexts (18–20). Yet, food safety policy and regulation in LMICs is often modeled on international and regional standards, export markets and "best practices" associated with particular food value chains. In addition, governments are urged to undertake their own "risk analysis." This involves expert "risk assessors" identifying hazards, quantifying and comparing their prevalence, probabilities and impacts, and possibly testing control measures. In combination with scientific understandings of how particular pathogens or contaminants enter and move through value chains, this information is seen as crucial to ensuring food safety, as is its effective communication to "risk managers" who, armed with this "objective data," can make "rational decisions" about biosecurity and control (11, 21, 22). "Risk managers"—in this paper considered to be those government employees undertaking day-to-day assurance of food safety, as well as private sector actors engaged in small-scale slaughter and raw meat sale—are expected to take decisions in accordance with this technical risk knowledge as it is embedded in policy (23). These expectations however, rely on a set of assumptions, including that such information reaches relevant actors, that they understand, accept and prioritize the information in expected ways, and that they have the capacity to act on it.

Social science approaches recognize "risks" as nebulous, socially variable notions of what is hazardous, of cause and effect, and of whether and how control should occur or caution be taken (24). Research in the cognitive psychology tradition has drawn a distinction between "expert" and "lay" perceptions of risk, emphasizing in relation to the latter, "affective" human responses to different characteristics of particular risks such as voluntariness, controllability, or dread. For instance, Jensen et al. illustrated in 2005 that experts perceived lay concern in Denmark over bovine spongiform encephalitis (BSE) as "irrational" because it diverted attention and resources away from *Salmonella* prevention which, while less immediately frightening to the public, was far more common and had significant, if diffuse, societal impacts (25). Anthropological approaches to risk have highlighted the socially constructed nature of risk perceptions, situating "risk" within social, cultural, economic, and political systems (9, 26–28). In other words, people's risk perceptions, responses to risks, and even "risks" themselves are shaped by interacting and dynamic contextual factors and constraints. Furthermore, risk perceptions can vary considerably from person to person in the same context. Considering risk from a primarily technical perspective and failing to take socio-cultural contexts, structural realities, and resources and power into account, has the effect of casting blame upon individuals and/or cultures for their own vulnerability to, or role in generating, risk (29).

While structural and contextual factors shape risk perceptions and responses in key ways, it is also important to recognize individual agency (30). With their formal training[2] on public health risk and associated regulations and specific responsibility for meat safety, inspectors in northern Tanzania occupy uniquely powerful positions through which they can and do mitigate meat safety risks, sometimes in unexpected ways. Furthermore, as "street-level bureaucrats," these government staff have considerable discretion, often bringing their own values, priorities and understandings to bear when implementing policy (33, 34). This has been framed both as problematic divergence from high-level policy goals, but also, as creative and necessary to operate effectively in complex, messy realities—especially in the face of limited resources (35, 36). Slaughter workers also have substantial influence over meat safety given their daily activities of slaughter and dressing, and based on their own knowledge, concerns and priorities, deploy their own forms of risk-based decision-making. While they learn some elements of technical risk knowledge and control through their contact with inspectors, who also explain what regulations they must follow, slaughter workers' understandings and management of risk are also shaped by on-the-job experience and a wide range of other influences. As Sjölander-Lindqvist and Cinque (12) argue, personal experiences, feelings and beliefs inform decision-making even in situations where decision-makers are expected to rationally assess the effects of their choices and strategies. In addition to being an emotionally complex process which draws on individuals' experience and intuitive knowledge, it is also often a shared, collaborative activity in which individuals make assumptions about the commitments, priorities and assumptions of others. It is a fluid social phenomenon, shaped by "contextualized processes of interaction between individuals, authorities, and social structures" (37).

Despite the daily and intimate interfacing between inspectors, slaughter workers and meat and thus the importance of understanding the ways in which these actors perceive, construct, prioritize, manage and make decisions about risk in relation

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[2] Due to resource constraints, ongoing training is not typical and thus continuing formal communication to inspectors about what constitutes "risk" and what should be done to manage it happens primarily through legislation and policy communicated in meetings and via communiques. MIs generally have a certificate or diploma in animal health, and may have taken optional courses on HACCP-style risk-based approaches (personal comms. Sindiyo). Similarly, HOs hold certificates or diplomas in environmental health, and some in our study reported having studied meat safety specifically. The Ministry of Health and Social Work estimated, in 2012, that there were 2047 Environmental Health Officers and Assistant Officers in Tanzania. Of these, 94 worked in the Kilimanjaro region, within which Moshi falls (31). The Department of Veterinary Services reported, in 2014, that there were 1,350 MIs in Tanzania, although only about half of these were fully qualified. These are "assigned to the slaughter slabs of Regions and Districts" (32). In Moshi municipality and Moshi district, there are an estimated 40 HOs and 56 MIs.

to meat safety, research has tended to focus on the risk perceptions of meat consumers (38–40). This paper expands our understanding of inspectors' and slaughter workers' perceptions, priorities and practices in relation to meat safety in northern Tanzania, asking what lies behind them, and what this might mean for meat safety and technological paradigms of risk management.

METHODS

This paper is based on two sets of relatively open-ended, semi-structured interviews. This type of open-ended interview, often used in qualitative research, encourages respondents to share their experiences and viewpoints (10) in ways that reveal information not usually sought in structured surveys or questionnaires, thereby creating opportunities for unanticipated insights to emerge both in the interviews and through the analysis (41). The interviews were conducted by a Tanzanian interviewer (BM) in northern Tanzania as part of a multi-disciplinary project to understand hazards associated with zoonotic enteric pathogens in emerging livestock meat pathways (HAZEL). One set ($n = 19$), taking place between February 2017 and February 2018 was conducted with MIs ($n = 10$), and HOs ($n = 9$), the latter of whom are also charged with ensuring food establishments, including butcheries, comply with food safety standards through inspection and enforcement[3]. Half were conducted with respondents from five urban wards in Moshi Municipality, and half were conducted in five rural wards of Moshi District, both in the Kilimanjaro Region of Tanzania's Northern Zone. Moshi, in north eastern Tanzania, was chosen because it offered the possibility to study both traditional and emerging livestock meat pathways in an agro-ecological setting (with scope to explore urban, peri-urban, mixed crop and livestock and pastoral-wildlife interfaces) as well as providing opportunities to work with policy actors to identify areas for improvement in food safety policy and practice in Tanzania. Respondents were asked about their work and duties, challenges, perceptions of policy, experiences with animal disease and meat safety, and related expectations and recommendations for the future. Where meaningful differences between the responses of urban and rural inspectors have been observed, this is noted in the paper.

The other set of interviews was conducted with people working at slaughter slabs ($n = 13$) and slaughterhouses ($n = 2$) in the same five rural wards in northern Tanzania in which rural inspectors were interviewed, between August 2017 and September of 2018. These respondents had between one and 30 years of experience as slaughter workers, with only three having <7 years' experience. Cattle were the primary animals slaughtered at these sites. Most slaughter workers explained that the most affordable, healthy animals were purchased by butchery owners or their representatives from traders at cattle markets in the region (they were less sure where animals originated prior to auction), and occasionally from local farmers. The decision to focus on rural wards was based on the observation that rural sites, and the inspectors who serve them, face potentially greater challenges (such as long distances between sites) than their urban counterparts (36). All slaughter workers interviewed were directly involved in slaughter activities, and ranged from cleaners, skinners, and slaughterers, to slab owners who frequently also owned and operated butcheries (often adjacent to slabs). Some slabs were used by more than one butcher, and were sometimes rented to others on agreed days and times. Two respondents from rural slaughterhouses were interviewed, namely a manager who oversaw operations at a government-owned facility, and an individual who carried out the majority of slaughter work and cleaning in a smaller, privately-owned slaughterhouse. Butchers operating within reasonable distance from slaughterhouses were expected to have their animals slaughtered in these facilities, while those beyond reasonable distance used their own slabs. These interviews included questions on slaughter workers' routines and practices, aspects of the slaughter environment, its management and change over time, understandings of meat safety, and relationships with inspectors.

Interview participants were selected to cover a range of workers fulfilling a diversity of roles associated with meat and slaughter. The interviews attempted to capture contextually rich depictions of respondents' routines, experiences, perceptions, priorities and practices in the complex context of everyday life (24) as a central premise of this research is that these aspects are constitutive of "decision-making" and cannot be understood independently of this. As researchers, we draw on anthropological understandings that highlight the complex, fluid, interactional and situated dimensions associated with decision-making rather than reifying rational and calculated individualized choices (12, 37). All interviews were conducted, recorded and transcribed in Kiswahili before being translated into English by the interviewer (BM). Field notes were also taken by researchers (GP, LW, TH) during visits to the study area between March 2015 and March 2018. Data analysis of the interviews was conducted through a primarily inductive approach by the authors (TH, LW). Interviews were thoroughly read to gain a sense of overarching themes related to our research questions:

1. What are the perceptions, priorities, and practices of inspectors and slaughter workers in relation to risk and meat safety?
2. What might explain these perceptions, priorities and practices?

An initial coding structure was created based on these broad themes and then interviews were coded in an iterative, cyclical process using NVivo 12 (QSR International, Australia). The coding structure developed and evolved as familiarity with the data deepened and new patterns and connections were noticed

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[3] Both HOs and MIs are employed directly by Local Government Authorities, but have technical remits under different government authorities. While HOs answered to the Ministry of Health and the Tanzania Food and Drug Authority (TFDA) during the time of the research, MIs are accountable to the Ministry of Livestock and Fisheries Development. Technically, MIs are responsible for ante-mortem and post-mortem inspection before and immediately after slaughter. Thereafter, the product is considered to be food and its safety (including handling, transportation, and storage) becomes the responsibility of the HO.

(41). This process was documented in internal analytical memos. Quantitative observational data (noting infrastructural provision and hygiene practices) collected during visits to nine of the slabs and both slaughterhouses, are triangulated with qualitative observations in this paper.

Research was approved by the Tanzanian National Institute of Medical Research (Ref. NIMR/HQ/R.8a/Vol. IX/2028 and extension Ref. NIMR/HQIR.8cNol. 11/1069); the Kilimanjaro Christian Medical Centre (KCMC) Ethics Committee (Research Ethical Certificate No. 832); the Ethics Committee of the College of Medical, Veterinary and Life Sciences at the University of Glasgow, Glasgow, UK (Refs. 200140183 and 200140152) and the Human Research Ethics Committee at the University of Otago, Dunedin, New Zealand (Ref. H15/069). In accordance with the Ethical Approval process and documentation and the standard "Framework for Research Ethics" produced by the UK Economic and Social Research Council, interviewees gave recorded, verbal consent to participate. Researchers ensured that respondents knew that their involvement was entirely voluntary, and that they could terminate their involvement at any point.

RESULTS

This section presents respondents' understandings, priorities and practices, and thus their decision-making, —in relation to risk and meat safety under three major themes: (1) unsafe meat and disease; (2) infrastructure and equipment; and (3) hygiene and cleanliness.

Unsafe Meat and Disease

One indicator of respondents' risk perceptions and priorities in relation to meat safety was the set of pathogens or diseases they referred to during their interviews (see **Table 1**). Anthrax, endemic in East Africa, and causing visible abnormalities to carcasses and meat as well as recognizable symptoms in humans, was foremost in respondents' minds. It was mentioned 80 times by 16 of 19 inspectors—more than four times as much as African swine fever, the next most frequently mentioned disease (which is not zoonotic and does not pose a direct threat to human health). Although slaughter workers primarily processed cattle, inspectors' activities were not limited to cattle as reflected by mention of diseases affecting other animal species (rabies, African swine fever, Newcastle disease).

Inspectors recounted experiences with anthrax when asked about their successful prevention of animal-to-human disease transmission. These experiences included attending to a specific case after hearing about a suspicious livestock death from community members, and arriving at a slaughter slab for inspection and finding that workers had slaughtered an infected animal:[4]

TABLE 1 | Specific diseases and conditions mentioned by inspectors and slaughter workers.

	Inspectors ($n = 19$)		**Slaughter workers ($n = 15$)**	
Diseases/ pathogens mentioned	**Times mentioned**	**No. respondents mentioning this**	**Times mentioned**	**No. respondents mentioning this**
Anthrax	80	16	14	8
African swine fever	18	5	0	0
Rabies	16	9	0	0
Tuberculosis (or "TB")	16	8	0	0
Brucellosis	6	3	0	0
Liver flukes/Fasciola	6	5 (only 1 used "*Fasciola*")	1 ("fluke")	1
Cysticercus bovis	8	4	1 (colloquial term: "*fini*")	1
Foot and mouth disease	6	3	0	0
Liver cirrhosis	6	2	1	1
Newcastle disease	5	3		
Ebola	2	1	0	0
Trypanosomiasis	3	2	1 ("sleeping sickness")	1

> *We discovered this when the animal was slaughtered and I observed the blood. The owner claimed the animal was crushed by others in a truck from auction. The blood didn't clot. I gave an order to stop the skinning and took a sample for diagnosis. It was confirmed to be anthrax. I immediately condemned the animal and dug a deep hole to bury it with lime to prevent bacteria migrating to the surface.* (urban MI)

> *The animal died suddenly and people decided to butcher it [...]. They thought it died from a normal disease. I was informed and went to see it. You know anthrax has very obvious signs. The blood was still fresh, I quickly understood it was anthrax. I stopped all procedures. They were lucky we responded quickly. Some were taken to hospital and the carcass was condemned and buried.* (rural HO)

In addition to describing real-life encounters with the disease, anthrax was also frequently used to illustrate hypothetical situations, and respondents' corresponding responsibilities in relation to meat safety.

> *My role is to inspect meat at slaughter sites and certify it is safe to eat. If not, I will condemn it. If it has anthrax for example, I won't allow the carcass out of the area. All people involved will be required to go for treatment at the nearest dispensary. The meat will be condemned and buried.* (rural MI)

Inspectors emphasized that anthrax was "*very obvious*" and easy to identify and they frequently drew on anthrax signs when explaining how they knew meat was unsafe for consumption.

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[4] Signs commonly associated with anthrax in dead animals include dark blood that does not clot, bleeding from the mouth, nose, and other orifices, subcutaneous swelling, rapid bloating and an absence of rigor mortis. In live animals, "fever, dyspnea, agitation, and convulsions" occur before sudden death (42).

Anthrax was also the most commonly referenced specific disease among slaughter workers, who mentioned it disproportionately to other animal diseases, with eight out of 15 referencing it 14 times (see **Table 1**). Four described signs of anthrax, while two noted they had learned to identify it from inspectors.

> *We have been taught by the MI that, if the blood doesn't clot after slaughter, not to touch the animal and to wash our hands with kerosene. It has anthrax.* (rural slaughter worker)

When asked what they felt the future held for zoonotic disease and meat safety, most inspectors ($n = 16$) and slaughter workers ($n = 12$) reported that disease would continue to decline. This conclusion was "evidenced" by the perception that incidents and outbreaks of anthrax had slowed or ceased.

> *I think major problems regarding zoonotic diseases are declining. For example, this year I have not heard of any serious animal disease outbreak like anthrax.* (rural MI)

In addition to anthrax, inspectors also expressed concerns about a range of different types and degrees of health risks, including bovine tuberculosis (bTB), brucellosis and *Cysticercus bovis* among others. While slaughter workers did not often name particular diseases, almost all ($n = 13$) were confident they could tell when live animals were ill. "*Lungs that bulge out,*" "*standing hair,*" unusual breathing or salivation, and weakness were cited as indications.

Many slaughter workers also claimed to be able to identify inner organs which looked "*unusual,*" such as with "*swells and accumulations of fluids*" or having "*threads or worms.*" Visibly diseased—even "*completely destroyed*"—livers, lungs and kidneys were considered unsafe for human consumption and it was recognized that these would be condemned by the inspectors.

> *Given our experience, we can see when an organ appears differently. You know some animals drink contaminated water from ponds and they become sick… We can see things like worms in the intestine and other organs. When the MI comes, we tell him what we have seen.* (rural slaughter worker)

As illustrated in the above examples, MIs and slaughter workers emphasized visible signs of disease when considering meat safety, and well-known and easily visually identified diseases like anthrax. Invisible organisms such as *Salmonella* and *Campylobacter*, which are often present as commensals in the digestive systems of healthy cattle but do not cause abnormalities in meat or organs, and can be introduced onto meat through slaughter and handling, went unmentioned. As shown in the above quote and **Table 2**, when asked what *caused* meat to become unsafe, slaughter workers primarily identified animal disease caused by livestock consuming "*poisonous*" food or "*dirty*" water, particularly at cattle markets or in transit, or by livestock keepers' poor practices such as failure to vaccinate and treat animals.

TABLE 2 | Slaughter workers' responses to the question "what causes meat to become unsafe for people to eat"?

What causes meat to become unsafe for people to eat?	Number of slaughter workers reporting this ($n = 15$)
Animal drinking contaminated/standing water	8
Animal consuming grass, bad food, or grazing in the bush	7
Livestock keeper practices	7
Animal exposed to insect vectors	2
Contact with other animals	2
Don't know	1
Starvation	1
Climate change	1
Slaughtering, skinning and chopping	1

FIGURE 1 | A government stamp indicating that meat from this carcass was inspected and thus deemed safe for human consumption. Photo: Mary Ryan.

> *Animals come with infections from the source. There is no problem here. After all, they stay for only a few days before being slaughtered.* (rural slaughter worker)

Although not specifically asked about the causes of unsafe meat, many inspectors similarly associated livestock keepers and their practices (lack of vaccination; poor treatment of animals; low levels of awareness; poverty; and/or unwillingness to make investments) with animal disease, and thus, unsafe meat.

When asked what they did to ensure meat from their establishments was safe for human consumption, slaughter workers' most frequent response was that they ensured meat was inspected and marked safe with a government stamp by an official MI (see **Figure 1** and **Table 3**, discussed in more detail below). They regarded MIs as experts, trusted their judgements, and saw the stamp as an important visual signifier that their meat was safe.

> *We have no reported case of affected customers after buying meat from our butchery. This has not happened because we rely on the*

TABLE 3 | Number of inspectors indicating they enforced particular infrastructural or equipment provisions, and/or pointed to their adoption as evidence of positive change.

Infrastructure/ equipment	Urban MIs ($n = 5$)	Rural MIs ($n = 5$)	Urban HOs ($n = 5$)	Rural HOs ($n = 4$)
Tiles on floors, walls, counters	5	5	4	4
Glass windows/doors	5	4	3	2
Uniforms	5	2	5	3
Water available (not necessarily running water)	3	3	3	4
Plastic chopping boards	5	1	4	0
Handwashing facilities	0	2	2	3
Meat saws	1	2	4	0
Ceiling boards	1	0	1	1
Freezers	1	0	0	0

FIGURE 2 | This rural butchery, situated in a permanent structure, featured a tiled counter, walls and floors and even a sink, but no running water. We also observed few rural butcheries with glass windows. Photo: Tabitha Hrynick.

> *MI's report after inspection. We don't sell uninspected meat.* (rural slaughter worker)

MIs also emphasized their meat inspection duties. Indeed, all devoted more time and detail to describing this aspect of their responsibilities at the outset of the interview (*vis a vis* their roles as providers of livestock extension services and, as discussed in the next section, as enforcers of infrastructural and equipment standards). Cross checking for the stamp in their own inspections ($n = 6$) or encouraging customers not to purchase unstamped meat ($n = 2$) was also mentioned by HOs.

FIGURE 3 | A rural slaughter slab with a pole mounted roof and a wooden pallet. Photo: Linda Waldman.

Infrastructure and Equipment

A number of Tanzanian national laws outline the responsibilities of government ministries to draw up regulations "for any matter in relation to slaughter and slaughter facilities which appears [...] necessary for the proper maintenance of quality standards in respect of meat intended for human consumption"[5]. In addition to requiring ante- and post-mortem inspections, there are infrastructural, procedural, and personnel standards to be followed in premises where slaughter or meat sale occur. While not always in possession of published regulations, inspectors seemed clear about their responsibilities which, they assured us, were clearly spelled out in by-laws and "directives"[6].

As interviews progressed, MIs emphasized their responsibilities and efforts beyond meat inspection to ensure that certain elements of physical infrastructure were present and that particular pieces of equipment were used by workers. HOs also mentioned these provisions. In relation to butcheries, such infrastructural standards included easy to clean tiled walls and floors, glass doors and windows (to prevent flies and dust), and although less frequently mentioned, facilities for hand washing. Urban inspectors were particularly concerned with staff uniforms and plastic chopping boards (although the appropriateness of the latter was questioned by some).

When asked about whether there had been any change in slaughter or meat sale practices in the last 5–10 years, inspectors frequently pointed to improved infrastructure and adoption of equipment as evidence of positive change. **Table 3** shows the number of inspectors who claimed to enforce or encourage infrastructural elements or equipment in butcheries,

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[5] The Tanzania Food and Drug Authority (TFDA) Act of 2003, The Animal Disease Act of 2003, the Meat Industry Act of 2006 and the Public Health Act of 2009.

[6] Respondents used the term "directives" in a general sense, implying that these came "from above." Respondents may have been generally referencing all relevant legislation at all levels, or more specific local bylaws, national regulations, or *ad-hoc* orders from ministries or other authorities.

or highlighted their adoption as evidence of positive change over the past 5–10 years.

Butcheries which made these legislated upgrades—built permanent structures, tiled walls, and installed glass doors and windows or other screens—were described as "*modern,*" "*clean,*" and "*attractive*" (see **Figure 2**). They were contrasted with "*dirty,*" "*very simple*" structures of the past—temporary wooden shacks or meat simply hung from tree branches for sale—and by implication, were seen as more facilitative of meat safety.

> *You can see newly-constructed, rehabilitated slabs and butcheries. Good number of butcheries now have tiles and are very modern. The old dirty butcheries are no longer there [. . .]* (rural MI)

Getting butcheries to make these upgrades was described by inspectors as a slow and ongoing process which they perceived to be largely the result of their active, consistent enforcement and efforts to persuade butchers, and their ability to eventually "*use force*" to close the establishment if necessary.

> *When a new directive comes, the response is slow. Not much change is done voluntarily. [. . .] When we asked them to fix tiles and glass windows and doors they didn't understand. They complained it was too costly. But after some months of strong follow-up, they responded as you can see.* (rural HO)

As suggested in the above quote, inspectors recognized that butchers resisted or could not easily afford to make expected changes, and thus gave them time to adapt.

As **Table 3** indicates, not all infrastructural and equipment mandates were given equal weight. Despite guidelines for hot running water onsite, and even apparently for freezers and electric meat saws, inspectors did not take the same hard line on these issues as they took in relation to tiles or glass barriers—especially in rural areas. Another rural/urban difference stemmed from urban by-laws which mandated butchers to use plastic chopping boards. Some urban inspectors insisted these were more "*sanitary and hygienic*" than traditional wooden blocks. It seemed there was either no corresponding requirement in rural areas, or it was not a priority among rural inspectors. Only one rural MI mentioned that some butchers had them and that this represented an improvement.

Infrastructure and equipment at slaughter slabs seemed generally to be of less concern to inspectors. Although four rural MIs and three HOs (two rural and one urban) mentioned telling slab owners to improve infrastructure or checking these structures were kept clean, slab conditions were generally regarded as poor and relatively unchanged, and this enforcement was not described with the same enthusiasm as that applied to butcheries. While some acknowledged the characteristically modest concrete platforms, outfitted with simple drainage systems and sometimes pole-mounted roofs, were indeed improvements over previous practices, a dissatisfaction with the extent of change was also expressed.

> *Before cattle were slaughtered on the ground covered with few leaves of bananas and timber, but we advised them to use concrete slabs. However, they are not yet to the recommended standards. Some are dirty, but we ask them to wash the slabs often. So we can say that there are positive changes.* (rural HO)

Four slaughter workers also mentioned that slabs were poor or had not improved. Two of these noted that inspectors were "*more serious with butcheries*" and that they were not pushed to make slab improvements. One worker of 30 years commented:

> *The slab structure has not changed at all. The system is still the same. We've been asked to fence the slab but haven't done it yet, we can't afford to. [. . .] Different people from different authorities come here for inspection, they see the situation, and they are satisfied with the way we process meat here. They don't say anything.* (rural slaughter worker)

Despite the comparative lack of perceived change at slabs, six slaughter workers saw their use of wooden pallets—for laying carcasses upon to be skinned or chopped—as improved infrastructure and practice contributing to meat safety (see **Figure 3**).

> *I think the meat is safe now, as we were feeding dirty and unhygienic meat to our customers. Then we said no this is not proper we decided to use better slabs, concrete slabs and wooden pallets.* (rural slaughter worker)

This linking of infrastructure and equipment to meat safety, or at least to general notions of "improvement" in slaughter and meat sale, does suggest understandings and beliefs that link meat safety to aspects such as exposure to "dirty" surfaces, and thus goes beyond the visible presence of abnormalities in animals and meat. And while dirt and dust may be good visible proxies for pathogens, there is no indication in the interviews that respondents were referring to anything other than dirt and dust in their responses. In keeping with the above-described lack of attention to pathogens, most respondents underplayed or overlooked the role of process—how slaughter was performed, meat handled, and infrastructure and equipment kept clean—in mediating meat safety. This is discussed in the next section.

Meat Handling, Hygiene and Cleanliness

Slaughter workers and MIs tended to emphasize meat inspection and, as discussed above, the former in particular focused on upstream determinants of meat safety (such as livestock keeper practices and conditions at cattle markets). Only one respondent (see **Table 2**) explicitly linked slaughtering, skinning and chopping to meat safety. However, all slaughter workers reported it was important to keep their work environments "*clean and hygienic*" in a general sense, and six linked this to meat safety.

The details of keeping slaughter slabs and slaughterhouses clean varied from site to site. The public slaughterhouse manager explained that cleaning was conducted continuously throughout the slaughter process, with fresh water being used to constantly wash blood off floors to avoid contamination between carcasses[7].

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[7] Unlike at slabs, multiple animals were slaughtered each day at the slaughterhouses.

This respondent did not mention fecal matter or concerns to ensure viscera remained intact during slaughter.

Although none of the slabs had running water onsite (both slaughterhouses did), this was only identified as a challenge by three slaughter workers. Most respondents explained that slabs were brushed down using soap and water carried from a nearby domestic point, only at the beginning and end of a slaughter day. Some slaughter slab workers explained that slabs were simply swept of dirt just prior to slaughter, having been washed after the previous slaughter. All slabs reported usually slaughtering only one animal a day, but many reported processing two or three during periods of higher demand. Although only two slaughter workers described slab cleaning between each animal on these occasions, and only one verbalized the possibility of "*contamination from one animal's meat to another,*" this was not framed as a major concern. Furthermore, one slab worker justified washing the slab between animals, not for hygiene, but for ensuring animal placidity:

> *After the first slaughter, we wash the slab before bringing the next animal. This is because if the animal smells the blood of the first, it may become angry and hurt people.* (rural slaughter worker)

The act of cleaning—whatever this entailed—was described as a routine, necessary part of daily business operations, and workers often expressed confidence in their practices. However, only four slaughter slab workers, and both slaughter house workers, mentioned cleaning in response to a question about what they did to ensure meat from their establishment was safe. In this way, cleanliness was less explicitly linked with meat safety than was meat inspection by most slaughter workers.

> *I don't have any problems. I perform my duties well. I clean the slab at the end of business. It looks clean as you have seen it today. I am not responsible for ensuring the meat is safe to eat or not. There are people with that obligation, especially the MI.* (rural slaughter worker)

Slaughter workers' confidence in their own cleaning practices was not necessarily shared by all inspectors. HOs, who are responsible for inspecting many types of establishment and often emphasized the importance of cleanliness and hygiene in eateries, claimed to also actively seek assurance that butcheries and slabs were clean and meat handled hygienically. Indeed, they commented on these aspects more frequently than MIs who did not always see enforcement of general hygiene standards to be within their roles, and as discussed above, this is in keeping with their formal remits. This contrast between MIs and HOs is evident in the following quotes.

> *[...] after meat inspection, the rest of the work is done by the HO and other staff. I don't want to follow business people that much [...].* (urban MI)

> *We also visit butcheries to witness the physical environment and the condition of butchers themselves. How they appear, are they clean, what equipment do they use etc. The meat may have been inspected, but the way it's handled determines its safeness.* (rural HO)

TABLE 4 | Slaughter workers' responses to a specific question asking how they ensured meat safety.

Ways of ensuring meat safely	Slaughter slabs ($n = 13$)	Slaughter houses ($n = 2$)
Reliance on Inspection and the Government Stamp as a guarantee of meat safety	11	2
Ensure the slab/SH is very clean	4	2
Sponge the meat to ensure it is dry/clean	5	0
Wear uniforms	2	0
Avoid contaminants (from the ground, or by covering meat)	1	1
Shorten or delay slaughter date according to an animal's health	1	0
Only slaughter healthy animals	1	0
Observe the organs for signs of disease/abnormality before Inspectors arrive	1	0
Ensure blood is drained away to avoid cross-contamination between animals	0	1

HOs and, to a lesser extent MIs, also expressly associated meat safety with slaughter workers' or butchery staffs' clothing, health and personal hygiene. All HOs claimed to ensure workers had clinically issued health certificates while only one MI mentioned this. "*Very dirty clothes,*" lack of bathing, and human disease were also interpreted as risks to meat safety. Indeed, as evidenced by **Table 3**, uniforms were of concern to most inspectors. In contrast, while most slaughter workers ($n = 11$) mentioned they were expected to wear uniforms and several reported doing so, only two explicitly linked this to meat safety (**Table 4**). Rather, they primarily saw this as something inspectors expected of them. Even those that acknowledged dirty clothing as a possible meat safety risk, did not necessarily comply. One described, for instance, the "*dirty clothes and flip flops [sandals]*" that other slaughter workers wore, claiming *"meat contamination starts there."* Later however, this worker admitted:

> *It is required I put on an apron when handling meat, but I ignore this and wear it only when an inspector comes. When they leave, I take it off.* (rural slaughter worker)

Researchers also frequently observed butchers or slaughter workers either not wearing uniforms, or donning them only when prompted by inspectors. During systematic observations, no personnel were seen wearing uniforms.

Indeed, and as reflected in **Table 2**, slaughter workers infrequently suggested that their own slaughtering, skinning and chopping activities might lead to meat contamination when asked what caused meat to become unsafe. Apart from the following exceptional statements from two slaughter workers, one of which was an afterthought at the end of the interview, most did not recognize the role of process and handling as relevant to meat safety.

> *Meat can also be contaminated during preparation process such as slaughtering, skinning, chopping, transportation, selling and even food preparation.* (rural slaughter worker)

> *Contamination of meat mostly occurs during preparation time, so we have to be careful.* (rural slaughter worker)

Five slaughter workers recognized other pathways to meat contamination. This included dogs, chickens or wild birds accessing the slaughter site although some felt that their cleaning practices were sufficient to mitigate this. At nine of 11 sites, we observed dogs roaming freely. In one slaughterhouse, it was emphasized that carcasses were suspended from railings and "*didn't touch the floor or anything dirty*." At slabs, some ($n = 5$) explained that skin was removed as animals were suspended. Others ($n = 8$) mentioned that carcasses and meat would be chopped or placed upon an animal's splayed skin, and/or on "*modern wooden pallets*" (described in the previous section and illustrated in **Figure 3**). These practices were seen as hygienic alternatives to direct contact with the slab surface or ground. One slaughter worker explained how the wooden pallet they used was kept inside his butchery overnight "*to minimize contamination*"; another claimed that while his team did not use one, it was "*a good idea*" which could save skin from damage and "*keep the meat clean*." Respondents did not, however, talk about cleaning pallets. While this does not necessarily indicate they were not cleaned, it suggests this was not closely associated with meat safety or with daily routine.

Five slaughter workers described "washing," "drying," or "clearing" meat of blood (and feces in one case) with a sponge when explaining how they ensured that meat processed at their site was safe to eat.

> *We ensure the slaughter slab is very clean. We also wash off blood and faces from the meat using a sponge.* (rural slaughter worker)

> *After the animal is skinned and opened, we dry the meat with sponges. The aim is to ensure all blood is removed, and the meat appears clean and attractive. If you wash it using water, the meat will be destroyed and nobody will buy it.* (rural slaughter worker)

As the second quote suggests, this practice was regarded necessary not only to "clean" meat, but for aesthetic reasons. While one respondent said that sponges were soaked in clean water, no other details were offered regarding whether or how sponges themselves (see **Figure 4**) were kept clean. Inspectors did not mention the sponges.

Whether, how, and when tools such as knives, uniforms or hands were cleaned seldom figured in the verbalized concerns of all respondents in relation to meat safety, despite regulations mandating this. These practices went widely unmentioned or were downplayed barring a few exceptions. One slaughter worker, for instance, offered the following statement:

> *After skinning we have to wash our hands and knives before opening the animal. We cannot use dirty knives to chop meat. There is a lot of sand here, it sticks on the meat, so we have to be careful not to use dirty knives. You cannot remove sand from meat, people won't buy it.* (rural slaughter worker)

FIGURE 4 | A sponge used to "dry" and "clean" meat on the counter of a rural butchery. Photo: Tabitha Hrynick.

In systematic observations at the nine slabs, authors noted workers making efforts to wipe knives with damp cloths or sponges after they had been dropped on the ground surrounding the slab, but not necessarily after being placed on the slab, cutting skin or viscera.

As MIs tended to arrive at slabs for meat inspection after slaughter was complete, they were unable to, and perhaps less interested in, observing the actual process and ensuring, for instance, that tools were cleaned or that care was taken to isolate gut contents and feces. In our systematic observation of the slaughter process, feces were observed on meat at six out of 11 sites (including one slaughterhouse). In two of these instances, workers were observed scraping it off with a knife, and in four, wiping it off with a damp sponge or a cloth.

Handwashing, in contrast to wiping or scraping, was seldom witnessed. Although one slaughter worker noted that the inspector "*reminds us every time he comes here*" to "*keep hands and equipment clean,*" only one MI related handwashing to meat safety in his interview. Although included in the regulations, handwashing was generally not prioritized and, as one urban HO lamented:

> *...here we do [animal slaughter] manually with dirty hands on poor slaughter sites. Meat contamination comes from the way the meat is handled, people may have bacterial infections, and consumers will be affected.* (urban HO)

One slaughter worker suggested that handwashing was required, but in general, slaughter workers did not imply it was something they practiced or were inclined to do.

Despite researchers' presence during some interactions between butchery workers and inspectors, and despite the presence of hand washing facilities in most locations (usually suspended buckets with spigots, although not necessarily soap), inspectors did not remark on attendants serving multiple consecutive customers without washing hands or utensils and while handling money, plastic bags, and other objects in addition to meat. As shown above, "cleanliness" and "hygiene" were similarly important to slaughter workers and, although they generally expressed confidence in their practices, they did not always expressly relate them to meat safety. Even when such links were acknowledged, there were indications that breaches to what were considered acceptable standards (whether specified in regulation or shaped by context, social norms and experiential knowledge) were not necessarily seen as problematic enough to take additional biosecurity measures.

DISCUSSION: SITUATED KNOWLEDGE AND EXPERTISE

In this discussion, we argue that inspectors and slaughter workers, with their different incentives, knowledges and priorities, co-construct and enact a situated expertise around meat safety. This situated expertise draws on: technical-scientific understandings of risk as it is rooted in and communicated through regulations and the formal training of inspectors; *and* experiential knowledge and local understandings of disease and risk nested within a particular context of social relations and economic factors related to material and institutional constraints. Indeed, despite conventional understandings of scientific expertise as objective, "all knowledge—including that of science and technology—is situated, partial and embedded" (43). The concept of "situated expertise" encapsulates the manner in which knowledge is contextualized such that it cannot be codified and abstracted from experience and the way in which it is deployed (44).

Despite increasing recognition that scientific expertise should be more attuned to context and local perspectives to enhance its policy relevance (13, 45), little consideration is given to risk managers whose perceptions are shaped both by local understandings and by scientific knowledge. Such work draws on the classic feminist work of Haraway (46) which calls attention to the need to understand what it means for knowledge to be situated, and recommends asking how knowledge operates. This encourages the exploration, not of whether knowledge is objectively true or not, but rather of what the effects of certain kinds of knowledge or pronouncements—believed to be objectively true—might be. In this vein, failing to understand and recognize situated expertise, and the partial knowledges of which it is comprised, resource constraints and the contexts in which people act—and thus relying upon and reifying the superiority of the scientific, the technical and the regulatory—can have the effect of compromising understandings of food safety in both high-income countries and LMICs. Indeed, Cook, drawing on Habermas, argues that "communicative action" and dialogue are necessary to ensure that science can be "untied from the objective claims made" in order to enable the "learning and practice of science" (47). It is through taking account of the multiplicity of partial, situated knowledges that new possibilities for understanding and addressing real-world problems emerge. This challenges the conventional expert-lay binary which conceptually limits *expertise*, in relation to risk, to that which is grounded in technical notions of probability and quantified impact (however measured) to the exclusion of the understandings and flexibility held and practiced by risk managers as they navigate, negotiate and make decisions about risk in real, messy, multi-dimensional contexts. As Corburn (48) argues, conventional "risk-based problem framing and decision-making processes largely ignore evidence that is more informal, experiential, tacit, and explicitly value laden."

Area of Consensus: Meat Matters

Despite estimates suggesting *Salmonella* and *Campylobacter* are among the most common causes of FBD in sub-Saharan Africa (5), many respondents demonstrated a preoccupation with anthrax as a singular threat to meat safety. An officially notifiable and widely-known disease in Tanzania (for both humans and animals), anthrax results in sudden animal death and is easily transmitted to humans through contact or consumption of infected animal products. It has serious implications, including death, if treatment is not promptly sought. Parts of northern Tanzania have been designated anthrax "hotspots" due to environmental, social and economic conditions (42, 49). Although it is not always easy to tell if an animal or meat is infected with *Bacillus anthracis*, the cause of anthrax, all inspectors and many slaughter workers were relatively confident in their ability to identify anthrax in animal carcasses and most recalled direct or indirect experiences with it. Respondents' perceptions of the severity of anthrax, and the social reverberations of their and others' experiences with it likely contribute to a "social amplification of risk," despite in some cases, years-long periods without actually encountering it [c.f. (50)]. This social amplification works to expand the importance of, and to lengthen memories of the disease. Høg et al. used the term "temporalities of risk" to explain risk perceptions in the context of time and experience. Most of their respondents in the Bangladeshi live bird trade did not perceive risk from, or take measures to prevent, avian flu in their stock because they had not heard of or experienced outbreaks in recent years and thus took no biosecurity measures against its prevention (51). In contrast, in Tanzania, despite hearing about occasional isolated anthrax cases, the *absence* of recent widespread or direct experiences, did not temper our respondents' concerns. This may speak to the lasting social and psychological impact of past events, to a high degree of "dread" response to the disease, and to a greater sense of unpredictability and uncontrollability over its emergence (25).

Widespread awareness and concern with anthrax suggests that it has become symbolic of zoonotic and meat-borne disease more broadly for these Tanzanian actors, and it may be contributing to the tendency illustrated in the results to orient attention onto meat itself, and animals' contraction of disease prior to the point of slaughter (and thus, largely outside the control of slaughter workers). Indeed, other conditions of meat with which respondents were primarily concerned were those which were visible, and related to live animals' health conditions. This fosters and reinforces "upstream" understandings of disease and prevailing notions that unsafe meat largely results from poor livestock keeper practices, or conditions and food/water that animals are exposed to during auction at cattle markets and transit.

Leach et al. (52) argue that the ways in which risk is framed have implications for the kinds of mitigation strategies that are seen to be legitimate. Framing meat safety (or lack thereof) as something primarily determined upstream from slaughter, and that can be deduced by sensory observation of animals and meat, legitimates the corresponding—and officialized—strategy of visual inspection and certification by stamp. Unless inspectors equally emphasize the slaughter process itself and how meat is handled thereafter, this upstream and sensory framing serves to obscure the role of slaughter workers in ensuring (or compromising) meat safety, particularly in relation to pathogens and other invisible hazards. Indeed, addressing this is a challenge even in high-income countries where technical risk-based inspection is routinely implemented as the main causes of meat-related FBD continue to be those which are invisible, such as *Campylobacter*, *Salmonella*, *Listeria* and *E. coli* O157:H7 (53, 54).

Assessing the appearance of meat is nonetheless a key component and scientifically-justified aspect of meat inspection and safety (including in high-income countries). Furthermore, MIs' focus on hazards—which can be seen, perceived and understood as such by all—over hygiene and process may be a strategic calculation on the part of MIs who see this as a way of maximizing meat safety within their resource-constrained context, and within the parameters of local knowledge, social norms and expectations (36). For their part, slaughter workers were generally deferential to MIs as "*experts*," respected their judgements, and were open to learning from them. Indeed, many slaughter workers claimed to have learnt from these interactions with MIs how to *"notice if the meat is unsafe to eat by just looking at it."* This convergence of understanding and priorities represents a shared situated expertise based on a combination of scientific and experiential knowledge that facilitates risk-based decisions about slaughter, sale and condemnation that, to some extent, enhances meat safety.

This emphasis upon animal disease, the appearance of meat and its inspection may indeed play a central role in ensuring that meat purchased in butcheries is free from many pathogens, but it does not address the possible presence of enteric pathogens such as *Salmonella* or *Campylobacter*. Meat can become contaminated with these and other organisms during slaughter and subsequent meat handling, and these can persist on surfaces in slaughter and meat sale environments (55, 56). While, as we show in the next section, the priorities, perceptions and practices of inspectors and slaughter workers do include attention to handling, hygiene and facilitative infrastructure, acceptable standards and perceived risks were variable, unclear, and mediated by the social and economic context (in particular, material and institutional constraints).

Navigating Risk Management Beyond Meat

Slaughter workers and inspectors shared concerns about visible abnormalities in animals and meat. However, other aspects of meat safety and risk management—such as what counted as adequate or necessary infrastructure, hygiene and associated practice—were less uniformly understood and implemented. Although inspectors had more scientifically-rooted understandings of meat safety—reinforced and embedded in the regulations they were charged with enforcing—they did not necessarily prioritize ensuring that slaughter workers and butchers followed these precisely or all the time. Rather, inspectors were flexible under the circumstances of the real, messy world in which all faced substantial resource constraints, pressures, and differing incentives, and strove to remain sympathetic to the understandings and capacities of slaughter workers in relation to risk management.

MIs' under-emphasis on hygienic practices at slabs and during the slaughter process is partially explained by the fact that they typically arrived after slaughter had actually taken place, due to understaffing and lack of resources for transport. This lack of attention to hygiene might also be explained as a desire to maintain positive relationships with slaughter workers. As suggested by Hrynick et al. (36), trust was a crucial element in these relationships and necessary for keeping slaughter workers "onside" and receptive to inspectors' meat inspection decisions—perceived by all respondents to be of primary importance for meat safety. Additionally, Tanzania's audit into hygiene control in meat production processes in the country revealed a lack of clear, specific criteria for assessing hygiene in meat production (4). This may be a matter of food control authorities having to prioritize activities as they seek to manage a broad array of risks and to align monitoring to their priorities. In our research, this is evident in inspectors' emphasis on meat inspection and compliance with certain infrastructural requirements.

In butcheries, inspectors' focus on ensuring infrastructural compliance in the form of tiles, screens, and windows—aspects clearly in the remit of the butchers/shop owners—reflects their recognition and accommodation of the latter's practical and economic capabilities. In contrast, infrastructural upgrades for which responsibility is more ambiguously shared with the state (running water, electricity) and/or which require substantial investment, went largely unremarked upon as such expectations were considered unreasonable. Similarly, Bardosh et al. (13) noted that Moroccan MIs recognized slaughter workers could not afford to make all regulated infrastructural upgrades and felt morally unable to insist on complete compliance. Furthermore, in focusing on obvious, visible improvements in butcheries, inspectors may be projecting a desire, or perhaps even be responding to political pressure, to publicly demonstrate implementation of regulations in the public interest. In contrast, although several respondents recognized that slaughter slabs were overlooked and would benefit from improved infrastructure, these small, often out-of-sight structures operated outside regular hours, functioning as "backstage" operations, and were relatively invisible to consumers and public scrutiny (57). As such, slaughter workers' perceptions and practices in relation to hygienic processes and meat safety at these sites are of particular significance as they are key actors who have the ability to influence meat safety through their day-to-day activities and practices.

Slaughter workers' understanding of the causes of unsafe meat as "upstream" has the effect of reducing their sense of agency in relation to risk management for meat safety. As illustrated, hygiene practices and infrastructural improvement tend to be regarded as related, but not central, to meat safety (*vis-a-vis* meat inspection). Thus, at times, compliance with some regulations were heeded primarily to satisfy inspectors and not necessarily perceived as means of mitigating meat safety risks. This does not mean that "cleanliness" was not important to slaughter workers, but their notions of what this meant was shaped by how they understood its relevance. Respondents predominantly linked cleaning to notions of appropriate and smooth business operations, respectability and reputational concerns. How clean premises (or meat) "looked" was seen as an indication of quality. This perception may be reinforced and indeed shared with Tanzanian meat consumers, who, Nandonde et al. (38) suggest, have a regulating effect upon the "hygienic beef retailing environment" through their greater patronization of cleaner looking butcheries.

In keeping with this notion of cleanliness as something visible, slaughter workers' concerns were oriented toward observable contaminants like soil on slab surfaces and knives, fecal matter and sand on meat, and keeping meat from coming into contact with the ground (in one slaughterhouse, concern around contamination included animal blood, which was continuously pushed into drains with the aim of mitigating cross-carcass contamination). Thus, slabs were scrubbed and/or brushed prior to and/or after use, tools dropped on the ground were wiped "clean," and carcasses were suspended where infrastructure would allow. This reveals a widespread understanding about the nature of soil and feces capable of rendering meat unsafe, or at least less sellable. The use of wooden pallets in service of preventing contamination, illustrates a desire to keep meat off the ground, and may suggest a belief in wood, which has been traditionally used for chopping meat, as an appropriate surface on which to dress meat[8].

Although soil (and fecal matter) are good proxies for the presence of pathogenic bacteria, slaughter workers' notions of cleanliness and contamination seemed to preclude an understanding of pathogens such as *Salmonella* and how they might play a role in spreading them. The example of the sponge, seen as necessary by slaughter workers to "clean" and "dry" meat, demonstrates a disjuncture between pathogen-aware notions of hygiene and those articulated through the situated expertise of slaughter workers, which are reinforced by customers' demand for "clean" looking meat and MIs' lack of attention to meat handling. Given the absence of hot, clean, running water, and no explanations as to how or whether these sponges were themselves kept "clean," this practice—from a scientific perspective—likely undermines meat safety (59). Nevertheless, this and other practices described above, were in effect, the result of risk-based decision-making, legitimated by a situated expertise involving particular notions of cleanliness, contamination and meat safety, and mediated by available infrastructure and interacting knowledges.

Both MIs' and slaughter workers' relatively relaxed attitudes toward hygiene may also be related to and reinforced by the fact that incidents of FBD are seldom traced back to food, let alone to raw meat, and may instead be attributed to poor cooking or not attributed to food at all. Indeed, one slaughter worker mentioned never having heard of customers becoming ill as a consequence of consuming meat processed at his slab. The challenge of linking FBD to specific foods and origins is not unique to Tanzania, and is also faced in high-income countries (60), although given the complexity and scale of food systems in these contexts, such challenges may be quite different. Nevertheless, health systems and food surveillance systems in Tanzania and other LMICs are weak and people may not attribute their own experiences of FBD (such as diarrhea) to food, nor seek medical attention (7, 61, 62). Furthermore, eatery operators have reported cooking meat for long periods which raises questions about whether meat is actually a significant source of FBD in Tanzania and thus about the appropriate degree of regulation and intervention. Similarly, although there were concerns about some Tanzanian populations consuming raw meat (49, 63), inspectors, and HOs in particular, mentioned their efforts to remind people to cook meat for long periods. Local practices of doing just this reflect another form of situated expertise held by communities, informed by experience and practical wisdom adapted to life with limited electricity, and capacity to preserve food.

HOs also, for their part, emphasized meat handling and hygiene (of infrastructure, equipment and personnel) and its link with meat safety much more than MIs. However, slaughter workers made far fewer references to these issues and it was unclear how frequently HOs visited slaughter sites as they have many other duties, and unlike MIs, do not necessarily make such visits as a matter of routine. In contrast, and as described above, slaughter workers were clearly highly influenced by MIs who were more inclined to overlook questions of meat handling and hygiene, sometimes seeing this as beyond their remits. Despite indications that MIs and HOs often support each other and at times play overlapping roles given resource constraints, there is no clear mechanisms for encouraging such collaboration and support. There may thus be a case for introducing policy which closes the apparent gap between their remits (both official and perceived) and practices, and strengthens the assemblage of partial knowledges upon which decisions about meat safety and associated risk are made.

CONCLUSIONS

Through their interactions, inspectors and slaughter workers co-construct and enact a situated expertise to manage risk in relation to meat safety. While informed by scientific, technical risk knowledge, this expertise is also shaped by local logics and contextual conditions which bring into consideration material and institutional constraints, local expectations of appropriate business operation and consumer demand, and perceptions of

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[8] This practice at several rural slabs was happening concurrently alongside efforts in urban wards to ban the use of wooden chopping boards in butcheries for reasons of hygiene. There is a lack of scientific consensus on the superiority of plastic chopping surfaces *vis a vis* wooden ones (58).

hygiene, cleanliness and meat quality. This interaction between scientific and experiential knowledge can enhance meat safety. For instance, slaughter workers and inspectors uniformly agree that meat should be inspected and condemned if it exhibits visibly problematic signs, while slaughter workers' concern with soil, feces and maintaining a "clean" environment can help to reduce the risks associated with pathogen contamination.

At the same time, the diverse priorities and practices of different respondents may compromise meat safety. Workers' experiential knowledge and inspectors' (especially MIs') under-emphasis of process and hygiene is at odds with meat safety (and the technical risk paradigm), particularly when hazards affecting meat are not immediately obvious or amenable to redress with available resources. The concern with what is visible, and the preclusion of contaminating pathogens legitimates potentially compromising practices such as wiping soil and feces off meat and tools and the prioritization of public, visible sites of meat production (butcheries) over more private and inconspicuous ones (slaughter slabs). This is reinforced by a lack of feedback connecting ill-health to the process of meat production at the local level. Conversely, HOs' greater concern with hygiene issues, but seemingly limited contact with slaughter workers and sites (alongside MIs' reservations about addressing hygiene), may represent an opportunity to strengthen meat safety at the local level through a more multi-sectoral approach which more explicitly emphasizes context-appropriate hygiene practices and improvements.

It is clear, from the above results and discussion that, in the absence of financial, technological, and scientific investment to revolutionize meat production in LMICs, both technical risk-based knowledge, and situated expertise must be taken into account. Local understandings and practices must be taken seriously as opposed to being seen as evidence of a knowledge deficit, a failure to assess and respond to risk, or as forms of cultural conservatism (13, 64). Exclusive reliance upon technical knowledge, either in an attempt to regulate meat safety or to assess meat safety implementation, will continue to run up against inspectors' and slaughter workers' situated expertise as practice and practicality take priority over theory. Consequentially, this can compromise meat safety or make inspection and regulation, as it plays out in real life, appear profoundly deficient.

Taking situated expertise for risk management seriously involves, as this paper has shown, acknowledging the logics and understandings behind inspectors' and slaughter workers' priorities and practices for meat safety alongside recognition of the particular social, economic and institutional conditions in which they work. It further requires facilitating shared expertise between these actors, in relation to the ways contaminating pathogens are transmitted and spread, and highlighting the importance of hence under-emphasized processes and places associated with meat production. Such encouragement, facilitation and adoption of context-appropriate, multi-sectoral solutions will enable slaughter workers and inspectors to more clearly recognize their own agency in relation to meat safety, collaborate more closely, address the gaps between their roles and responsibilities and take more informed risk-based decisions, predicated on a situated expertise that embraces a broader assemblage of partial knowledges.

The research has the following limitations: qualitative research is time consuming, can be costly and does not seek to ensure representative samples. For these reasons, sample sizes tend to be small and this study is not representative of all slaughter workers in Tanzania. This research is based on qualitative interviews, which included a combination of structured open-ended questions and, in follow-up to each of these questions, relatively unstructured discussion and, interaction. Data saturation was achieved in terms of interviews no longer yielding substantive new information nor new codes; detailed and nuanced data descriptions having been attained (65) and the data having provided substantial insights which theoretically informed the research questions (66). Nonetheless, as the researchers involved in the interviewing assumed a "role of research instrument" (67) through follow-up questioning and discussion, it may be challenging to replicate these findings. As mentioned above, this research forms part of HAZEL, a larger, multi-disciplinary project to understand hazards associated with zoonotic enteric pathogens in emerging livestock meat pathways. Future research will seek to integrate this qualitative assessment of risk perception into a Bayesian belief network (BBN), a form of probabilistic graphical model that allows for integration of information from disparate sources. This will provide information regarding the risks associated with foodborne pathogens in meat supply chains in Tanzania, and show how decisions to optimize food safety are influenced by information supply when economic factors cause changes in patterns of beef production and consumption. Future research should also investigate the molecular epidemiology of foodborne illness in Tanzania and other LMICs.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are currently available from the corresponding author on reasonable request, and will be lodged in a public repository at the culmination of the project.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Tanzanian National Institute of Medical Research (Ref. NIMR/HQ/R.8a/Vol. IX/2028 and extension Ref. NIMR/HQIR.8cNol. 11/1069); the Kilimanjaro Christian Medical Centre (KCMC) Ethics Committee (Research Ethical Certificate No. 832); the Ethics Committee of the College of Medical, Veterinary and Life Sciences at the University of Glasgow, Glasgow, UK (Refs. 200140183 and 200140152) and the Human Research Ethics Committee at the University of Otago, Dunedin, New Zealand (Ref. H15/069). Written informed consent was not provided because, in keeping with the Framework for Research Ethics produced by the UK Economic and Social Research Council, our ethical applications stressed that, in order to ensure no-one is made to feel inadequate where participants are not literate, or in situations where researchers are unsure of the literacy status of respondents, verbal consent would be obtained.

AUTHOR CONTRIBUTIONS

BMm, ES, GP, JC, JS, KT, LW, NM-M, and RZ contributed to the designing of the research and field study. BMa conducted all interviews, translation, and transcription. LW and TH were responsible for literature review, data analysis, formulating key arguments, and drafting the manuscript. BMa, ES, GP, JC, JB, JS, KT, MD, RZ, and SC contributed to the manuscript's critical revision and intellectual development.

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Identifying Environmental Risk Factors for Louping Ill Virus Seroprevalence in Sheep and the Potential to Inform Wildlife Management Policy

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Identifying the risk factors for disease is crucial for developing policy and strategies for controlling exposure to pathogens. However, this is often challenging, especially in complex disease systems, such as vector-borne diseases with multiple hosts and other environmental drivers. Here we combine seroprevalence data with GIS-based environmental variables to identify the environmental risk factors associated with an endemic tick-borne pathogen—louping ill virus—in sheep in Scotland. Higher seroprevalences were associated with (i) upland/moorland habitats, in accordance with what we predicted from the habitat preferences of alternative LIV transmission hosts (such as red grouse), (ii) areas of higher deer density, which supports predictions from previous theoretical models, since deer are the key *Ixodes ricinus* tick reproduction host in this system, and (iii) a warmer climate, concurring with our current knowledge of how temperature affects tick activity and development rates. The implications for policy include adopting increased disease management and awareness in high risk habitats and in the presence of alternative LIV hosts (e.g., grouse) and tick hosts (especially deer). These results can also inform deer management policy, especially where there may be conflict between contrasting upland management objectives, for example, revenue from deer hunting vs. sheep farmers.

Keywords: deer, ticks, GIS, habitat management, *Ixodes ricinus*, tick-borne disease

INTRODUCTION

Identifying the risk factors for disease is crucial for developing policy and strategies for controlling exposure to pathogens. This is often challenging, depending on the type of disease system and the complexity of its epidemiology. The prevalence and spread of many livestock diseases are influenced primarily by the densities and movements of the livestock themselves, for example, bovine viral diarrhea (1). The risk factors become more diverse and the epidemiology more complex when the pathogen has alternative reservoir hosts in addition to the livestock, e.g., *Mycobacterium bovis* the causative agent of bovine tuberculosis in domestic cattle, which can have wildlife reservoir hosts including red deer *Cervus elaphus*, wild boar *Sus scrofa*, and European badgers *Meles meles* (2, 3). Similarly, diseases that are vector-borne can be influenced by a range of environmental factors that affect the populations of free-living vectors, e.g., geography, climate, and habitat drive the risk of liver fluke *Fasciola hepatica* infection (fasciolosis) in livestock via their effect on the vector, the mud snail *Galba truncatula* (4, 5). However, the most complex disease systems are those with both multiple vector hosts and multiple pathogen transmission hosts, which makes disease risk difficult to predict and to control, and it is challenging to tease apart the effect of the livestock themselves from wildlife or other environmental factors on disease risk. Prime examples include tick-borne pathogens such as the *Borrelia burgdorferi* sensu lato complex of bacteria that cause Lyme borreliosis and the tick-borne encephalitis complex of viruses, which includes louping ill virus (LIV). In Europe these pathogens are vectored primarily by the most ubiquitous tick in Europe, *Ixodes ricinus,* which is a generalist, parasitizing almost all terrestrial vertebrates. It spends the vast majority of its lifecycle away from its hosts, so its survival and activity is influenced by a multitude of environmental factors [e.g., (6–10)]. This makes identifying the environmental risk factors for such pathogens extremely challenging. For example, the *B. burgdorferi* s.l. complex is transmitted by a huge range of terrestrial vertebrates including birds, rodents, hedgehogs and sheep, but not deer. Unsurprisingly, even after multiple studies, there is still no uniform consensus on how the key players in the transmission cycle interact to drive disease risk to humans. LIV is much less studied than *B. burgdorferi* s.l., and, while not as complex a system, still has multiple transmission hosts including birds and mammals. It causes illness and death in livestock, especially sheep *Ovies aries* (11), and in red grouse *Lagopus lagopus scoticus* (12), an economically valuable gamebird. LIV is prevalent in upland areas of the British Isles, and parts of Norway, Denmark and Spain [reviewed by (13)]. A national scale analysis of environmental risk factors for LIV infection in sheep has not, until now, been conducted.

Sheep can be reservoirs of LIV without the need for any other transmission hosts of tick or LIV (14–16) since sheep are competent transmission hosts (17) and also feed all active stages (larvae, nymphs and adults) of the *I. ricinus* vector (18). Therefore, it may seem reasonable to predict that higher prevalences of LIV occur in areas with higher densities of sheep. However, because *I. ricinus* feed on such a wide range of terrestrial vertebrates, including rodents, birds and deer, and because LIV can be transmitted by other hosts, most notably red grouse and mountain hares *Lepus timidus*, here we test the hypothesis that LIV prevalence in sheep farms is influenced by environmental factors associated with tick abundance and LIV transmission hosts. In Scotland heather moorland is the preferred habitat for LIV transmission hosts, red grouse and mountain hares, while sheep are stocked at much lower densities on moorland than on improved grassland. *I. ricinus* ticks are most abundant in areas with high deer densities (7, 10, 19, 20), and in the North-European context, where the climate is warmer (21, 22). Thus, if wildlife hosts and other abiotic factors are more important risk factors than the sheep themselves, we predict higher LIV seroprevalences in heather moorland than in lowland improved grassland and in areas with higher densities of deer and a warmer climate. Woodland habitats are often associated with higher *I. ricinus* tick densities than open habitats, due to generally higher tick host densities and mild, humid microclimate created by woodland canopies (10, 19, 23–25). Indeed, sheep tick burdens and tick densities on sheep pastures can be higher if they are closer to woodlands or have more tree cover (26). We therefore also predict higher LIV seroprevalences among sheep farms that have a higher proportion of woodland cover. We tested these predictions by combining a randomized seroprevalence survey in sheep farms across Scotland with GIS-based environmental data of each farm's location, with the purpose of identifying environmental risk factors of LIV to inform policy on potential disease mitigation measures. This is the first large-scale cross-sectional study to identify the environmental risk factors for LIV in sheep.

MATERIALS AND METHODS

Sheep Farm Selection and Sample Collection

We conducted a national survey, using a stratified random sampling design based on Scottish Agricultural Census data to ensure random and representative sampling of sheep flocks for all regions over Scotland. Only flocks with at least 50 breeding ewes were included and, on farms that had multiple flocks, only one flock was used. Breeding ewes were chosen to get a representative sample for a location. Younger animals may not have yet seroconverted to endemic pathogens. Tups are likely to have been purchased from elsewhere, so that any seroconversion may have been due to infection picked up in a different location. The inclusion criterion of 50 sheep was chosen because holdings of <50 sheep often do not have the number of breeding ewes we required for sampling ($n = 27$). In addition, this ensured we excluded pet sheep and small-holdings or "hobby-farms," which tend to have different management.

Study farms were initially contacted by mail and then by telephone to confirm which farms were willing to participate, resulting in a sample size of 125 sheep farms. The selection procedure for randomly assigning farms was as follows: A sampling frame of 825 sheep holdings was randomly generated as a random subset of the 2,004 agricultural census data held by the Scottish Government containing a total of approximately 14,400 Scottish sheep holdings. Of these, a spatially representative subset of 251 farms were approached, and 125 were recruited: 28 farms did not meet the selection criteria as they did not have the minimal required flock size of 50 breeding ewes; 91 eligible farms refused participation; on seven farms the flock could not be sampled for a variety of reasons. The final sample size of 125 farms was cross-stratified in line with the proportion of farms across the Scottish Animal Health administrative divisions, as follows: Central (22), North East (13), Northern Isles (14), Highlands (27), South East (18), and South West (22).

Each of the 125 farms was visited between July 2006 and August 2008 and approx. 10 mL of blood was collected from a random selection of 27 sheep per farm (except 26 sheep from 3 farms, and 28 sheep from 1 farm). This sample size allows a 95% confidence interval of <5% for estimating LIV sero-prevalence (15). Farmers were asked whether they had vaccinated the breeding against LIV and, if so, date of last vaccination. In case of inter-annual variation, such as potential LIV cycles, year was controlled for in the statistical models. However, from a study that monitored LIV sero-prevalence in sheep over multiple years there is no evidence for cyclical behavior or stochastic inter-annual variation in LIV (15).

Determination of Positive LIV Samples

Hemagglutination-inhibiting antibody (HIA) tests were undertaken on sheep blood sera using chick red blood cells as described by Clarke and Casals (28). The LIV HIA test is the standard diagnostic test used in the UK to determine a serological response to LIV exposure. The test is known to detect antibody to closely related viruses such as TBE and Yellow a Fever which are not endemic in the UK; the LIV HIA test is not known to have cross-reactivity to any viruses endemic to the UK. Reciprocal HIA titers of at least 20 HIA units (a dilution titer of 1/20 or more) were regarded as sero-positive to LIV infection (29). However, vaccination against LIV had been administered at three of the 125 farms within the 6 months before blood sampling so for these three farms sero-positivity was assumed only for titers >1/160 which is consistent with ongoing exposure (15). One farm had vaccinated 2 years previously, which was assumed to not affect LIV assays as antibody titers from vaccination rapidly decline such that seroposivity after vaccination is typically well below 1/160 (30). For statistical analysis we used the estimated sero-prevalence (the proportion of sheep blood samples that tested positive) for each sheep flock.

Environmental Variables

From GIS databases we extracted data on climate, habitat and tick hosts for the locations of each farm. Climate variables from a GIS database included variables relating to temperature and precipitation on a 1 km or 5 km grid (**Table 1**). All these were from Met Office 1971–2000 long-term averages and derived using the Hawth's Analysis Tools (32). We chose a long period of time for the climate averages to reduce the influence of outlying weather events and to enable generic inference nationally and irrespective of weather in a particular season. Hawth's Analysis Tools is an extension for ESRI's ArcGIS (specifically ArcMap) that performs spatial analysis and functions and is available to download online.

Habitat data were derived from the UK Land Cover Map (2000) in a 50 m grid. They were split into the following categories according to those most commonly occurring around the farms: bracken, blanket bog, heathland (an amalgamation of wet heath, dry heath and unclassified heath), improved grassland, rough grassland, montane, broadleaf woodland, coniferous woodland, mixed woodland and, in addition, we created a generic "woodland" category (an amalgamation of the broadleaf, coniferous, and mixed woodland categories); **Table 1**. For analysis we used the proportion of land area around each farm (within a 5 km radius) that contained each land cover type. A distance of 5 km was chosen because 90% of the farms held their sheep within 5 km of the farmhouse. These habitat values were then arc-sin square-root transformed as they were proportions.

Sheep and cattle density data were obtained from the national agricultural census data (AgCensus), available at the Parish level, at a 2 km^2 grid resolution.

Approximate red deer densities were derived from Deer Commission for Scotland (now Scottish Natural Heritage) count data, based on dedicated observer counts of individual deer from the ground or air, Krigged to a 2 km grid. These data are the best (indeed only) quantitative deer data available, but have several caveats. For example, red deer counts were conducted where the 44 Deer Management Groups areas are, but these cover only around 75–80% of Scotland. Furthermore, the counts for different areas were not always conducted at the same time but, instead, staggered between 2000 and 2006. Therefore, given the level of error in these data, we consider any positive results linking deer density to LIV seroprevalence in sheep to be highly conservative.

Intersect Point tool was used in ArcMap v9.3 (ESRI, 2008) to extract the values of all environmental parameters at the locations of each of the 125 sheep farms from a set of raster and vector maps of environmental data.

Statistical Analysis

To test for environmental variables (habitat, climate and tick hosts) associated with the sero-prevalence of louping ill virus among sheep farms we used general linear mixed models using the glimmix procedure in SAS Version 9.1. The response variable was seroprevalence for each farm expressed as the number of positive serum samples divided by the number of samples assayed for each farm. This is more powerful than using merely a single figure for the proportion of positives because it allows the model to take into account the number of samples taken, which varied from 26 to 29. A binomial distribution was specified. The data distribution was over-dispersed and zero-inflated (i.e., a disproportionate number of zero counts than expected from a Poisson distribution), which is commonly found with disease prevalence data such as these. Therefore, each data point, i.e., individual farm, was entered as a random effect in the model (33) as a way of increasing flexibility of model fit to allow for such overdispersion.

Because of the large number of potential climate-related explanatory variables (**Table 1**) and because many of the climate variables are inter-related, a variable selection procedure was conducted. All related variables within a climate category (temperature or precipitation) were entered into the model separately and we chose which (within each category) had the strongest individual effect in terms of F and *P*-values for the variable and model AIC. We also then entered all climate variables within a category into the model simultaneously to identify which had the strongest overall effect in terms of F and *P*-values and change in AIC. This variable selection procedure selected annual growing degree days (day-by-day sum, over a year, of the mean number of degrees by which the air temperature is more than 5.5°C) from the temperature-related variables, and the number of dry days from the precipitation-related variables.

TABLE 1 | Environmental variables from the GIS database that were originally considered for inclusion in the statistical model to describe louping ill virus seroprevalence.

Variable type	Variable description	Units	Scale	Source
Temperature	Growing degree days	days	5 km	Met office
	Growing season length	days	5 km	Met office
	Average days of air frost annually	days	1 km	Met office
	Average days of ground frost annually	days	1 km	Met office
	Average days of snow cover annually	days	1 km	Met office
	Average daily maximum temperature annually and monthly	°C	1 km	Met office
	Average daily minimum temperature annually and monthly	°C	1 km	Met office
	Average daily mean temperature annually and monthly	°C	1 km	Met office
Precipitation	Average precipitation annually and monthly	mm	1 km	Met office
	Dry days per year	days	5 km	Met office
Hosts	Sheep density—2003–2006	head km^{-2}	2 km	AgCensus
	Cattle density—2003–2006	head km^{-2}	2 km	AgCensus
	Red deer density—approximate average red deer density 2006, then Krigged	head km^{-2}	2 km	DMG
Habitat	Heather moorland (undifferentiated heath, wet heath, dry heath)	%	25 m	Fuller et al. (31)
	Blanket bog	%	25 m	Fuller et al. (31)
	Montane	%	25 m	Fuller et al. (31)
	Bracken	%	25 m	Fuller et al. (31)
	Coarse (rough/acidic) grassland	%	25 m	Fuller et al. (31)
	Smooth and improved grassland	%	25 m	Fuller et al. (31)
	Broadleaf woodland	%	25 m	Fuller et al. (31)
	Coniferous woodland	%	25 m	Fuller et al. (31)
	Mixed woodland	%	25 m	Fuller et al. (31)
	"Woodland" = broadleaf+conifer+mixed	%	25 m	Fuller et al. (31)

The Met Office data were based on 1971–2000 long term average climate data. Growing degree days is the number of days with daily temperature above 5°C. OS is Ordnance Survey, DCS is Deer Commission for Scotland, DMG is Deer Management Group. Habitat categories are derived from the Land Cover Map 2000 categories (31) and are a proportion of a 5 km radius area around the farmhouse location.

Thus, we entered the following selected explanatory variables as fixed effects into the model: easting and northing (to take into account any spatial autocorrelation), time of year that bloods were sampled (December-March, April-July, August-November), year of blood sampling, estimated deer density, estimated sheep density, growing degree days, dry days, and the proportion of land cover that was each habitat category listed in **Table 1**. Because the habitat proportions are not independent of each other (e.g., if there is 90% heathland there cannot be more than 10% of any other habitat; see **Figure 1**) we entered each habitat category separately into the model, i.e., the model never had more than one habitat category at once.

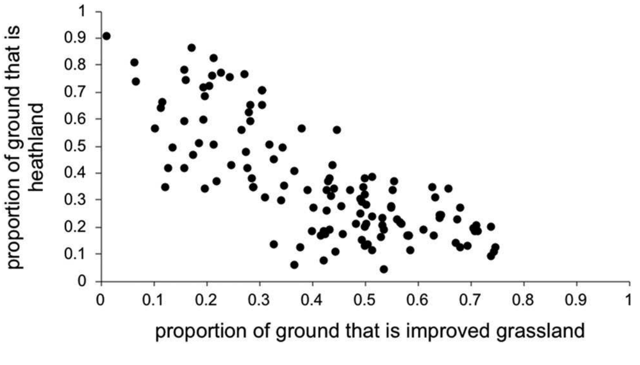

FIGURE 1 | Improved grassland covaried with heathland, so each was entered into the model separately to obtain outputs.

We had expected deer density to covary positively with the proportion of heathland. Also, because areas with more heathland have less improved grassland (**Figure 1**), we expected deer density to negatively covary with improved grassland. However, surprisingly, there was little clear relationship between deer density and the proportion of each of these two key habitat types (**Figure 2**), so we could include deer simultaneously with each separate habitat in the model.

We conducted a backwards stepwise procedure, whereby we sequentially removed from the model all explanatory variables that did not improve the model: we first removed each variable that had very low significance, i.e., $p > 0.1$, and then checked that removal did not adversely affect model fit (increase AIC). If removal had increased AIC, the variable would have been kept in the model, but this did not occur in our procedure. Because such terms were eliminated from the models, we present test statistics for only those fixed effects that remained in the final model.

RESULTS

Of the 125 sheep farms sampled, 28 (22.4%) farms contained LIV seropositive sheep (from the 27 individuals per farm blood-sampled). The proportion of positive farms varied greatly over

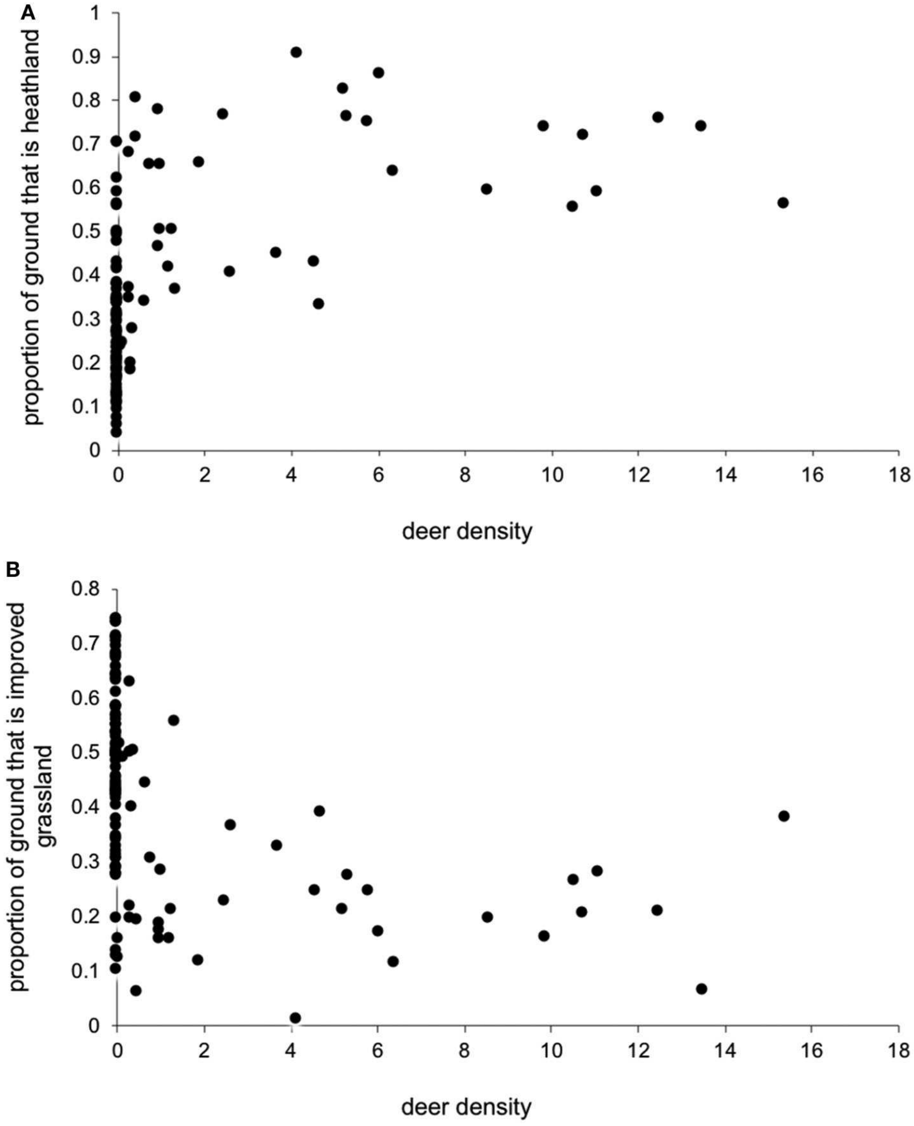

FIGURE 2 | Estimated red deer density (Km^{-2}) and the proportion of land cover that was **(A)** heathland and **(B)** improved grassland within a 5 Km radius of each farm location.

different areas of Scotland (**Figure 3**), with a much higher proportion along the West and North coasts than in other areas.

The national average seroprevalence, including farms that did not have LIV, was 6.39% (range 0–100%; median 0%). If only sero-positive farms are considered, the average seroprevalence was 28.52% (range 3.7–100%; median 25.93%). The frequency distribution of within-farm LIV seroprevalence exhibited a negative binomial distribution typical of disease and count data, with most farms having no or low infection, and a small number having very high infection rates (**Figure 4**).

Sheep farms had higher within-farm LIV seroprevalences (% of ewes within a farm that tested positive) if they were in areas with a warmer climate (more growing degree days per annum), a higher proportion of land that is heath-dominated moorland, a lower proportion of land under improved (smooth) grassland and areas with higher deer densities (**Table 2**; **Figure 5**). There was no association between LIV within-flock seroprevalence and the proportion of land cover that was blanket bog, bracken, montane, coarse (rough) grassland or woodland (either broad-leaved, coniferous, mixed or the generic "woodland" category), nor sheep or cattle density, northing, easting, or time of year, or year the blood sample was taken; all these variables were removed from the model during the backwards stepwise procedure.

DISCUSSION

We aimed to test the hypothesis that LIV prevalence in sheep farms is influenced by environmental factors, especially those associated with tick abundance and LIV transmission hosts.

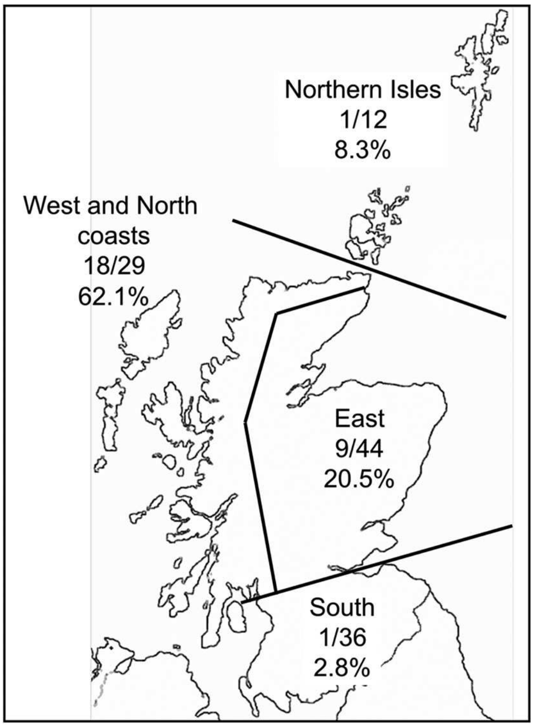

FIGURE 3 | Map of Scotland with the proportion of farms in contrasting areas that had at least one ewe testing seropositive to louping ill virus.

In support of our predictions, sheep farms had higher LIV seroprevalences if they were in areas with a warmer climate (more growing degree days per annum). Higher temperatures increase tick interstadial development rate, oviposition rate, egg development rates and tick activity (34–37), and warmer climates (for example, as studied using altitude) have been associated with higher tick abundance (9, 20, 21, 27, 38, 39) and higher risk of tick-borne diseases (examples from Lyme disease risk or *B. burgdorferi* prevalence: (7, 22, 40). While growing degree days is a variable originating from plant growth, it is a measure of warmth, and is particularly relevant to ticks because the plant growing season aligns well with the tick activity season (usually April-October, depending on the area). One potential source of error with the climate parameters is that the blood samples were taken 6 years after the 1971–2000 time period over which the climate data were derived. However, we would not expect the association between climate and tick populations to change over time, i.e., we still expect more ticks (due to higher tick activity and development rates etc.) in areas with a warmer climate irrespective of the year of blood sampling. A further limitation is the spatial scales for some of the climate parameters, especially those variables at the broadest 5 km spatial scale. However, compared to the large, national-scale patterns we were investigating, they proved useful enough for examining our predicted associations with tick-borne disease infection.

As predicted, there were higher LIV seroprevalences among sheep farms in heather moorland which is the characteristic habitat in upland UK and is the habitat most frequented by wildlife hosts that are competent LIV transmitters: red grouse and mountain hares. Upland areas with more heather moorland had less improved grassland (**Figure 1**). Improved grassland is a habitat more common in the lowlands and more productive farmland areas and was associated in this study with lower LIV seroprevalence. This makes sense, as alternative tick or LIV transmission hosts such as red grouse and mountain hares do not tend to frequent lowland improved grassland habitats and (41) demonstrated fewer ticks on improved pastures compared to upland habitats such as rough hill pastures. Likewise, we expected a strong relationship between deer density and proportion of heathland (positively) and improved grassland (negatively). However, our variable selection procedure found no clear relationship between deer density and the proportion of heathland, nor the proportion of improved grassland (**Figure 2**), Nonetheless, **Figure 2** does indicate that most positive counts of deer are in areas with at least 30% cover of heathland and <50% improved grassland. Including both deer density and % habitat cover in the model simultaneously meant that any effect of deer was over and above the effect of habitat, i.e., the significant effect of deer on LIV seroprevalence was not because there was higher LIV prevalence on heathland. In terms of deducing the mechanism for these effects of habitat and deer on LIV seroprevalence it would have been more informative to include data on densities of red grouse, mountain hares and ticks; however, not enough detailed spatial data were available, hence using habitat as a proxy for these very habitat-specific LIV transmission hosts. More detailed, accurate and extensive deer count data would also be invaluable.

It is particularly interesting to policy and management that we found higher LIV seroprevalences in areas with higher estimated densities of red deer. This was despite the data on red deer being patchy, staggered over several years, and not covering all of Scotland. We therefore consider any result involving a significant effect of deer highly conservative. Thus, although the association between red deer densities and LIV seroprevalence was statistically weak and included a lot of variation, the fact that we found a significant association at all could be indicative of a much stronger association in reality. While red deer do not transmit LIV between ticks (42) deer of various species are often the key drivers of Ixodid tick populations in both Europe (7, 20, 43, 44) and North America (45–50), including red deer in Scotland (10, 19, 21, 24, 40). Because of this, several theoretical models of the LIV system in Scotland predict a key role of deer in the persistence of LIV in ticks and both red grouse and sheep systems (51–54). That deer densities are associated with higher tick abundance and have also been shown in some previous studies to be associated with higher incidence or risk of other tick-borne diseases (both Lyme disease and tick-borne encephalitis: (7, 40, 46, 55, 56), as well as LIV as shown in this study, is highly relevant to policy on disease management. Deer can be managed through various means, most commonly through exclusion from areas using fencing, or by reducing densities through culling. These are common management techniques for the purposes of habitat management for conservation or protection of commercial forestry or crops. Deer management through exclosure fencing and culling have

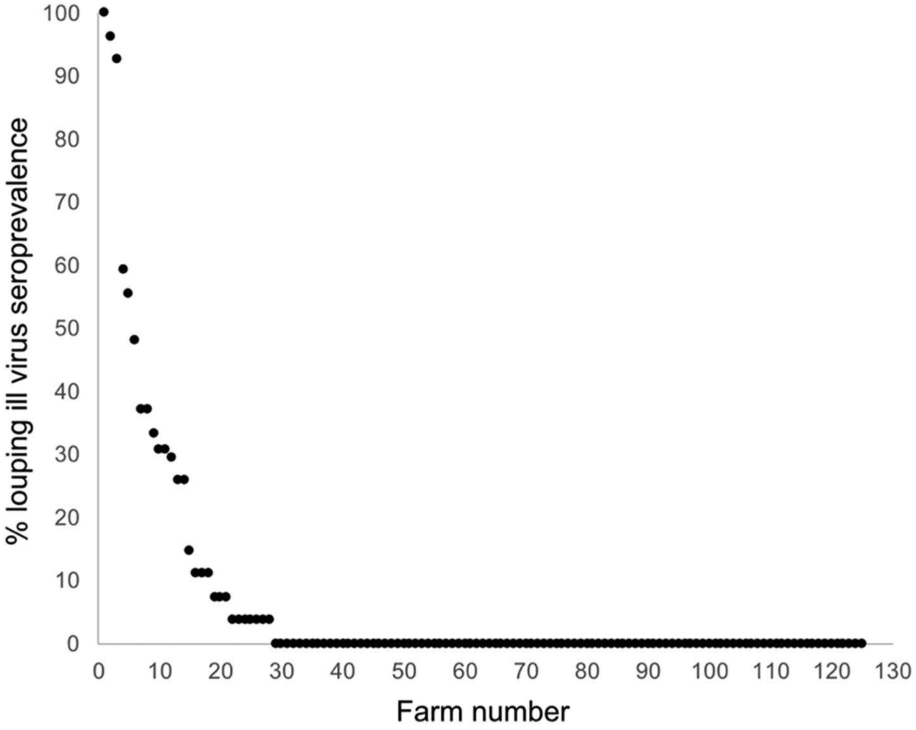

FIGURE 4 | Frequency distribution of LIV seroprevalence across 125 sheep farms randomly stratified around Scotland.

both been found to dramatically control densities of *I. ricinus* ticks in Scotland in both upland heather moorland and forest habitats at a range of spatial scales (10). Reducing deer densities can have impacts not considered in theoretical models, such as increase ground vegetation height (57) and therefore rodent density (58, 59). However, rodents are generally not considered drivers of tick populations, nor competent transmission hosts for LIV (14). It remains possible that reducing deer densities on upland heather moorland could result in an increase in red grouse or mountain hares (LIV transmission hosts), which may potentially dampen the desired reduction of LIV in sheep. However, large-scale field experiments would be needed to test for such unintended consequences, and these would be difficult to achieve in terms of resources, available space and enough replication (e.g., see critique and discussion of a landscape-scale experiment testing the impact of mountain hare control on LIV in grouse: (60–62).

Against our predictions, we did not find a significant association between LIV seroprevalence and the proportion of land cover that was woodland. However, a previous more detailed study of ticks (not LIV) found that (i) distance to woodland and (ii) the proportion of sheep pasture that had tree cover were strong predictors of tick burdens on lambs and tick densities in sheep pastures in Norway (26). One reason for this difference could be potential error with matching our spatial GIS land cover data (5 km buffer zone around the postal address of the farm) with where the sampled sheep actually spent most of their time during the peak tick season in spring/summer. Data from (19) on tick densities on open moorland suggested (non-significantly) higher tick densities only within 50 m from (unfenced) woodland boundaries, and (63) showed striking differences in Lyme disease hazard (the density of ticks infected with *B. burgdorferi*) between woodlands and adjacent open habitats which were often only 50–100 m apart, which suggests that any link between woodlands and tick or tick-borne risk incidence in adjacent open habitats probably operates at a much finer spatial scale than we had access to in this study.

TABLE 2 | Output from the final model identifying environmental parameters that were significantly associated with LIV seroprevalence among sheep farms in Scotland.

	Estimate	SE	df	*F*	*P*
Intercept	−20.606	3.052	101		
Growing degree days	0.000483	0.000105	1, 88	21.23	<0.0001
Deer density	0.276	0.1064	1,83	6.73	0.0112
Heath-dominated moorland	8.0992	1.6500	1,103	24.09	<0.0001
Smooth (improved) grassland	−12.6596	2.4289	1,105	27.16	<0.0001

Growing degree days are the day-by-day sum (over a year) of the mean number of degrees by which the air temperature is more than 5.5°C. Habitats heath-dominated moorland and smooth (improved grassland) were arcsin square-root transformed as they were proportions. Since they are therefore interdependent they were entered separately into the model.

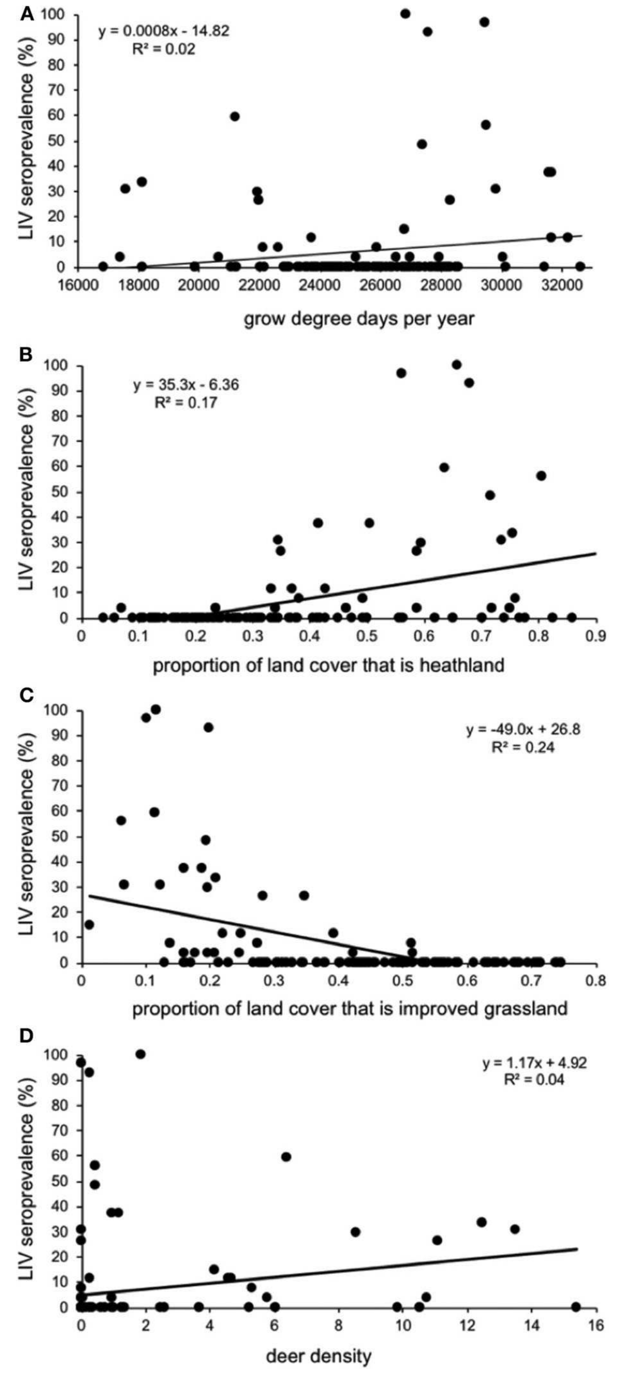

FIGURE 5 | Relationship between seroprevalence of louping ill virus in 125 Scottish sheep farms (% of individuals testing seropositive) and **(A)** growing degree days per year; the proportion of land cover that is **(B)** improved (smooth) grassland and **(C)** heath-dominated moorland; and **(D)** estimated density of red deer in Deer Management Group areas. Each data point represents a sheep farm, and the positions are from the raw unadjusted data, not from the model output.

Geographically, the proportion of farms testing seropositive to LIV was much higher along the West and North coasts of Scotland than in other areas. This might be expected given the warm, humid climate which aids tick survival, activity and development. There was low LIV seroprevalence in the Northern Isles (Shetland and Orkney) which is most likely attributed to very low *I. ricinus* tick densities in most areas of these islands (Gilbert unpublished data). This is likely due to a combination of the lack of deer and the colder climate which inhibits tick activity and development. The eastern regions of Scotland had intermediate seroprevalence. These areas, especially Grampian Region, Speyside and Perthshire, have a particularly heterogeneous landscape, from high quality improved grassland for cattle up to high altitude (1,400 m) montane habitats, with extensive forested areas and heather moorland in between. Some of these heathlands have the highest deer, red grouse and mountain hare densities in Scotland. Here, therefore, we would expect a wide spectrum of LIV seroprevalences, which is reflected by the overall intermediate values over the whole region. South of the Central Belt of Scotland there were even lower seroprevalence than the Northern Isles, even with a good sample size of 36 farms. The main habitats are upland rough grasslands and commercial coniferous forests, with some improved grassland for high density livestock grazing. There are deer, and some mountain hares and red grouse present, although not at the densities found in the East region of Scotland. We would therefore expect lower LIV infection rates than in the East region, but it is not clear why the seroprevalence is as extremely low as it is. This could be due to unconsidered factors such as historical movements of infected sheep and warrants further research.

Although exposure of sheep to ticks can be mitigated by acaricide application to the animals (64) alternative measures to reduce exposure are increasingly being sought, such as management of habitats or wild hosts, separation of livestock from tick-infested areas or the application of biological control agents to the pastures (65). By identifying which areas, habitats and environmental conditions pose the greatest LIV risk we can now start to inform policy on the implementation of these alternative approaches, and more efficiently target standard disease control measures to be prioritized in the highest risk areas, periods of time and conditions.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The study design was reviewed and approved by Moredun Research Institute.

AUTHOR CONTRIBUTIONS

CC and FB initiated and designed the blood collecting sampling strategy as part of a separate study on Ovine pulmonary adenocarcinoma (OPA, also known as jaagsiekte). FB organized farm visits and collected blood samples and KW conducted the LIV serology tests. LG wrote the LIV proposal to Scottish Government, assimilated the separate data sets, analyzed the data and wrote the paper. CC, FB, and KW commented on the manuscript drafts. All authors contributed to the article and approved the submitted version.

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