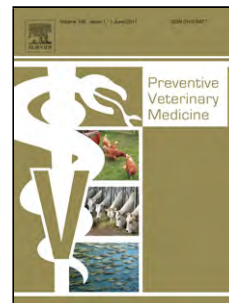


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Using multi-criteria risk ranking methodology to select case studies for a generic risk assessment framework for exotic disease incursion and spread through Europe

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Abstract

We present a novel approach of using the multi-criteria pathogen prioritisation methodology as a basis for selecting the most appropriate case studies for a generic risk assessment framework. The approach uses selective criteria to rank exotic animal health pathogens according to the likelihood of introduction and the impact of an outbreak if it occurred in the European Union (EU). Pathogens were evaluated based on their impact on production at the EU level and international trade. A subsequent analysis included criteria of relevance to quantitative risk assessment case study selection, such as the availability of data for parameterisation, the need for further research and the desire for the case studies to cover different routes of transmission. The framework demonstrated is flexible with the ability to adjust both the criteria and their weightings to the user's requirements. A web based tool has been developed using the RStudio shiny apps software, to facilitate this.

Keywords: risk ranking; risk assessment; disease incursion

Introduction

The threat of incursion of exotic animal pathogens is ever present for individual countries currently free of such diseases. This threat has become enhanced due to factors such as increased reliance on global trade markets and fluctuations in the immigration patterns of both people and traded goods such as live animals and animal products. Consequences of an incursion, such as subsequent disease outbreak in a naïve animal population, can go on to have adverse implications for a country's animal health and welfare, human health, trade and productivity. Strategies to combat such an incursion can, however, be costly and so, under a risk based paradigm, pathogens should ideally be prioritised to target resources at those pathogens which have the highest risk of both incursion and impact (Hasler et al., 2011).

Pathogen prioritisation can be carried out using a formalised risk ranking process that ranks pathogens according to weighted criteria that are specifically selected to meet a required objective (McFadden et al., 2016). The process has previously been used in both public health and veterinary health spheres (Cardoen et al., 2009; Havelaar et al., 2010; Balabanova et al., 2011; Caribvet, 2012; Ciliberti et al., 2015; McFadden et al., 2016; Roelandt et al., 2017), ensuring that limited resources are allocated to areas such as prevention, early warning surveillance or control measures regarding disease incursion. Previously developed risk ranking tools, (McKenzie et al., 2007; Caribvet, 2012; Humblet MF, 2012; D'Hondt et al., 2015; Gibbens et al., 2016; Discontools, 2017; Roelandt et al., 2017), are wide ranging with a high level of variability in methods and number and weighting of criteria suggesting that methods developed for specific circumstances may not always be transferable between situations (Krause and Working Grp, 2008). A recent review conducted by the European Food Safety Authority (EFSA) concluded that there is no universal

methodology for risk ranking (EFSA Panel on Biological Hazards (BIOHAZ), 2012), but that risk ranking exercises should take a structured approach and be transparently and consistently documented so as to be reproducible. Similarly, a European Centre for Disease Prevention and Control (ECDC) report on best practices in ranking emerging infectious disease threats concluded that the choice of risk ranking tool should reflect the specific study objectives (ECDC, 2015).

Risk ranking is, therefore, already recognized as a useful tool to assist government decision makers in targeting restricted resources to combat pathogen incursion where they are needed most. In this paper, the application of the risk ranking approach was expanded and further developed for use in the selection of case studies to inform a generic quantitative spatial risk assessment which aimed to explore the introduction and transmission of exotic animal pathogens within Europe (SPARE, 2016). Generic risk assessment frameworks have previously been used in several European Union (EU) wide projects (Antigone, 2016; Compare, 2016) and have benefitted from the use of case studies to demonstrate that the frameworks were as broad and universal as possible; selection of appropriate case studies was, therefore, essential to the successful communication of these generic assessments.

The objective of this work was to develop and apply a multi-criteria ranking model to animal pathogens which were regarded as relevant threats to Europe. The approach described here shows how risk ranking can be used as a basis for a case studies selection process, adapting the selected criteria to the aims of the risk assessment as required. The ranking process developed was similar to that used by government stakeholders, i.e. selecting a full list of pathogens of concern for ranking, identifying the assessment criteria, weighting criteria, scoring diseases against those criteria, and producing a ranked list of diseases. A key element of this project, however, was to identify case studies which could represent

incursion by as many transmission routes as possible; a qualitative assessment of the prioritised pathogens was therefore carried out as a final stage of the process to fulfil this requirement.

Methods

The framework for the risk ranking methodology is set out in Figure 1. The process is divided into three stages comprising: initial selection of pathogens to be ranked, risk ranking of pathogens according to weighted criteria and qualitative assessment of pathogens against selective criteria.

FIGURE 1 HERE

Stage 1: Preliminary identification and selection of pathogens to be ranked

An initial list of 66 animal health pathogens was compiled from the World Organisation for Animal Health (OIE) and European Commission (EC) lists of notifiable diseases and then condensed to include only pathogens that are not normally found within the EU, i.e. have previously only caused sporadic outbreaks of disease in livestock or only occurred in isolated controlled zones over the past 10 years. These pathogens were defined as 'exotic'. Conversely, endemic pathogens were defined as those that are maintained within an EU livestock population without the requirement for external inputs and that are regularly reported to the national authorities; these pathogens were removed from the list. Pathogens which may be considered endemic in wildlife populations such as wild birds, wild boars or ticks, but not in livestock populations were not defined as endemic. Each pathogen was assessed as either endemic or exotic, using numbers of previous outbreaks within each member state (MS) from the OIE World Animal Health Information System (WAHIS) dataset

(OIE, 2015), information from the EU Animal Disease Notification System (EU, 2015) and expert opinion (Animal and Plant Health Agency (APHA) disease experts pers. comm.).

Pathogens were also assessed according to transmission pathways or routes. A shortlist of nine key routes, for which robust evidence was thought to exist, was drawn up in consultation with disease experts (Table 1). A semi-quantitative score was assigned to each pathogen/transmission route combination to describe how likely the route is as a transmission pathway given the possibility of multiple routes for one pathogen. The scores were devised by the authors using evidence available from published literature and in consultation with APHA disease experts. The scoring system was between 1 and 4, with 1 = A major key route for the pathogen with proven documented evidence; 2 = The route can transmit the pathogen but is less of a key route; 3 = An indication that the route can transmit the pathogen but evidence is limited; and 4 = A negligible chance of transmission by this route with no existing evidence.

Table 1: Shortlist of key pathogen transmission pathways or routes

Key transmission routes	Description
1. Arthropod vector	Biological or mechanical transmission of pathogens via arthropods i.e. mosquitoes, ticks, midges, flies etc.
2. Import of live animals	The illegal or legal import of an infected animal with the potential to onwardly transmit disease
3. Wildlife	The movement of infected wildlife e.g. birds, mammals, bats with the potential to onwardly transmit disease
4. Import of animal products	The illegal or legal import of an infected animal product (e.g. meat, hides, semen) with the potential to onwardly transmit disease
5. Human travel (including pets)	The movement of pathogens via humans or via pets associated with their owners travel to a location where onward transmission is possible

6. Vehicle movement	The movement of contaminated vehicles e.g. livestock trucks or transport of infected vectors on planes
7. Import of non-animal products	The illegal or legal import of a non-animal product (e.g. tyres, flowers, animal feed) with the potential to onwardly transmit disease
8. Windborne spread	Movement of airborne pathogens via natural air currents to a location where onward transmission is possible
9. Accidental/deliberate release	The accidental or deliberate release of pathogens from source laboratories or deliberate release by an independent body as an act of bioterrorism

Stage 2: Risk ranking model

Selection, weighting and scoring of criteria

Six criteria, *N1:N6*, for the risk ranking assessment were selected based on those regarded by animal health experts as the most relevant to the risk and consequence of an exotic animal health pathogen incursion within the EU (Table 2). Initially, all exotic pathogens were evaluated against three criteria: zoonotic potential (*N1*), number of domestic species involved (*N2*) and presence of a wildlife reservoir (*N3*), using a binary scale. All binary scores were 0 and 1 with the exception of the scores for “*Number of domestic species involved*” which were 0.5 and 1. By doing this the option ‘0’ is avoided which would nullify the influence of this criteria if only 1 species was susceptible.

Five animal health experts from three European institutes (SAFOSO, APHA & IZSTO) then scored each pathogen according to three further criteria: expected probability of entering EU (*N4*), potential impact on production at EU level (*N5*) and impact on international trade (*N6*). These criteria were initially scored on a scale of 0-3 corresponding to negligible to high. For each pathogen, the expert’s scores were summed and an average score was calculated. These average scores were then ranked over all pathogens and quartiles were calculated;

pathogens in the top quarter of average scores were assumed to have a high risk and were assigned a score of 3, while those in the lowest quarter assumed to have a negligible risk and assigned a value of 0. To get the final score, these quartile scores were then divided by 3 to put them onto a 0-1 scale, in line with the other criteria.

The panel of five experts evaluated and scored each of the pathogens using their own expertise, global information datasets and existing ranking tools previously developed for EU wide or National prioritisation (OIE, 2015; Gibbens et al., 2016; Discontools, 2017; FAO, 2017). The assessment was revisited in a few cases as new evidence emerged during the evaluation process (e.g. an outbreak of Lumpy skin disease occurred for the first time in the EU while the assessment was being completed).

The six criteria were also weighted by the same animal health experts, taking into consideration the significance of that criterion to the overall risk evaluation and the variability of the impact of a particular criterion between different EU MSs. Each expert's weighting score for each criterion was then summed up and the average was calculated and used to express the final score.

Table 2: Assessment criteria selected for risk ranking model with weightings and consideration points for scoring

N	Assessment criteria	Weighting (W)	Scale	Qualifiers	References
<i>N1</i>	Zoonotic potential	$W1=2$	No = 0; Yes = 1	Binary	(Discontools, 2017)
<i>N2</i>	Number of domestic species involved	$W2=4$	1 = 0.5; >1 = 1	Binary	(Discontools, 2017)
<i>N3</i>	Wildlife reservoir	$W3=3$	No = 0; Yes = 1	Binary	(Discontools, 2017)

<i>N4</i>	Expected probability of entering EU	<i>W4=4</i>	<p>Quartile score: 0 =Negligible; 1 = Low; 2 = Medium ; 3 = High</p> <p><i>N4</i>=Quartile score/3</p>	<p>Negligible: Negligible risk of transmission into the EU Low: Non-negligible risk of transmission into the EU Medium: occurring regularly in a country where there may be frequent transmission into EU by the key transmission mode High: Incursion in the EU in the last 10 years</p>	(OIE, 2015; Gibbens et al., 2016; FAO, 2017)
<i>N5</i>	Potential impact on production at EU level	<i>W5=2</i>	<p>Quartile score: 0 = Negligible; 1 = Low; 2 = Medium; 3 = High</p> <p><i>N5</i>=Quartile score/3</p>	<p>Number of species affected (single or multiple); Value of the industry at EU level; speed of transmission; time to clinical signs and diagnosis or subclinical; impact of control measures post-outbreak; vaccine availability</p>	(Gibbens et al., 2016; Discontools, 2017)
<i>N6</i>	Impact on international trade	<i>W6=1</i>	<p>Quartile score: 0 = Negligible; 1 = Low; 2 = Medium; 3 = High</p> <p><i>N6</i>=Quartile score/3</p>	<p>Impact on racing/sport due to movement restrictions; meat and live animal export; scale of outbreak and number of infected premises; number of species affected</p>	(Gibbens et al., 2016; Discontools, 2017)

A Microsoft Excel based prioritization disease framework was developed to assess each pathogen from Stage 1 against the generic criteria. The final score assigned to exotic pathogen, j , $R2(j)$, was given by

$$R2(j) = (N1(j) * W1) + (N2(j) * W2) + (N3(j) * W3) + (N4(j) * W4) + (N5(j) * W5) + (N6(j) * W6).$$

Scenario Analyses

To investigate the impact of the decisions made in deriving the overall score for the selection Stage 2, a number of scenarios where the methodology was adapted were investigated (Table 3). These scenarios help illustrate the importance of the contribution of some of the

criteria to the ranking of the pathogens and the potential influence that bias, incurred by the use of expert opinion, could have on the weightings of criteria. Scenarios included removal of zoonotic potential ($N1$) and presence of a wildlife reservoir ($N3$) (to assess the influence of these transmission routes in addition to domestic species), using an average of the expert's scores for $N4:N6$ instead of quartiles and altering the weighting of criteria, including giving higher weighting to the factors related to entry to the EU and trade and removing all weightings.

Table 3: Scenario analyses considered

Scenario	Description
Baseline	The methodology used for the main results using the equation for $R2(j)$ and applying the weights as stated in Table 2 ($N6=1$; $N1$ and $N5=2$; $N3=3$; $N2$ and $N4=4$)
S1	No weighting of the criteria ($W1:W6 = 1$)
S2	Remove $N3$ (Wildlife reservoir)
S3	Remove $N1$ (Zoonotic potential)
S4	Use average of experts score for $N4$, $N5$ and $N6$ instead of quartiles
S5	Multiply $W4:W6$ by 2
S6	Multiply $W4:W6$ by 3

Statistical Analyses

To compare the level of agreement in the scores between the experts for criteria $N4-N6$ statistical analyses were conducted. Firstly, a simple calculation of the percentage of diseases where there was agreement was carried out. For this calculation it was assumed that there was agreement between experts if there was a difference of no more than 1 across all the expert's scores. Secondly, the level of agreement was assessed using Fleiss' weighted kappa (Fleiss JL., 1971; Gwet, 2014) which takes into account the differences in

scores among the experts, such that 1 is "less" different from 2 and "more" different from 3 i.e. it allows for varying degrees of agreement between scores. There is no universally accepted method for interpreting kappa values but the interpretation devised by Landis and Koch (Landis, 1977), ranging from $k < 0$ = "poor agreement" to $k = 0.81-1$ = "almost perfect agreement", was used here.

Stage 3: Risk Assessment case study selection

Case study selection was a qualitative process in which only the ten highest ranking pathogens identified from Stage 2 were considered. Criteria for the assessment of pathogens for the identification of case studies were selected by the project consortium as relevant to the aims of the SPARE project (Table 4). The EU Community Research and Development information Service (CORDIS) database was used to determine those pathogens which were already being studied by other EU funded projects (N7), along with expert opinion of consortium members regarding current ongoing projects. For the criteria 'expression of interest by funding body' (N8), policy makers from the consortium governing bodies were asked to score the pathogens according to how important they felt the pathogens were in terms of threats to the individual countries production and trade capabilities.

Table 4: Assessment criteria for qualitative assessment of case study selection

N	Assessment criteria	Scale	Qualifiers
N7	Pathogens targeted by other EU projects	Yes =1; No=0	Binary
N8	Expression of interest from funding bodies	high interest=1; low interest=0	Binary
N9	Expected data availability	Score 0-4	0=very good data; 1= good data; 2=okay data; 3=poor data; 4= no data

N10	Case studies to cover as many routes as possible	Each pathway assessed as 1= major key route, 2=likely route, but not major, 3=route is possible but unlikely/limited evidence, 4= no evidence for route existing
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To assess the availability of the data necessary to parameterize the release, exposure and consequence models of the SPARE project (N9) each parameter was categorized according to their relative importance as “*necessary for the model*” or “*not necessary (but would improve the model)*”. For each parameter and for each of the selected pathogens, the experts were then asked to assess the data availability (0=very good, 1=good, 2= fair, 3=poor- (data gap), 4= no data (significant data gap)) and give an estimate of the uncertainty of the assessment (0=no uncertainty, 1=low, 2= medium, 3=high) for each parameter. The uncertainty score was added multiplicatively to the data availability score, before the scores (release, exposure, consequence) were summed up.

Results

Stage 1: Preliminary selection of pathogens

A total of 33 pathogens of potential relevance out of the initial 66 were selected for inclusion in the assessment based on the criteria described in the methods i.e. defined as exotic. These pathogens were assessed according to their primary routes of transmission which were ranked from 1-4 (Table 1). Any pathogen/route combination with a score of 4 was not considered further, while a score of 1 was considered essential to include (see Table 5). Note that the score refers to how likely the route is as a transmission pathway, assuming that the pathogen is present, not to the probability of the pathogen entering Europe via these routes.

Table 5: List of selected pathogens and assessment of transmission pathway scores for pathogens, 1= major key route, 2=likely route, but not major, 3=route is possible but unlikely/limited evidence, 4= no evidence for route existing. Cells were shaded in tones of grey: from light grey = 1 to dark grey = 4.

Pathogen	Vector	Live animal Imports	Wildlife	Import animal products	People movement and pets	Vehicle movement	Non-animal products	Windborne spread	Accidental/deliberate release
African Horse Sickness	1	2	3	2	4	3	4	4	4
African Swine fever	2	1	2	1	4	3	4	4	4
Aujeszky's disease	3	1	2	2	4	3	4	3	4
Avian influenza Highly Pathogenic	3	2	1	2	4	3	4	3	4
Avian Influenza Low Pathogenic	4	2	1	2	4	3	4	3	4
Bluetongue	1	2	3	3	4	3	4	4	4
<i>Brucella ovis</i>	4	1	4	1	4	4	4	4	4
<i>Burkholderia mallei</i> (Glanders)	4	1	3	2	2	3	4	4	3
Classical Rabies	4	4	1	4	1	4	4	4	4
Classical Swine Fever	4	1	2	1	4	3	4	3	4
Crimean Congo Haemorrhagic Fever	1	3	2	4	3	4	4	4	4
<i>Ehrlichia ruminantium</i> (Heartwater)	1	2	2	4	4	4	4	4	4
Enzootic bovine leucosis	4	1	4	3	4	4	4	4	4
Epizootic haemorrhagic virus	1	4	2	4	4	3	4	4	4
Equine encephalomyelitis – Eastern and Western	1	3	1	4	3	3	3	4	4
Equine infectious anaemia	1	1	3	3	4	4	4	4	4
Equine influenza	4	1	2	4	4	4	4	4	4
Foot and Mouth Disease	4	1	2	2	3	3	4	3	4
Japanese encephalitis	1	2	2	2	3	3	3	4	4
Lumpy skin disease	1	2	4	2	4	3	3	4	4
<i>Mycoplasma capricolum</i> subsp. <i>Capripneumoniae</i> (contagious caprine pleuro pneumonia CAPP)	4	1	3	4	4	4	4	4	4
<i>Mycoplasma mycoides</i> subsp. <i>mycoides</i> (small colony) (Contagious bovine pleuro pneumonia CBPP)	4	1	4	4	4	4	4	4	4
Nairobi sheep disease	1	2	4	4	4	4	4	4	4
Newcastle Disease	3	2	1	2	4	4	4	3	4
Nipah Virus	4	2	1	2	3	4	2	4	4
Peste des petits ruminants	4	1	2	2	4	4	4	4	4
Rift Valley fever	1	1	3	2	3	3	3	4	4
Sheep pox and goat pox	3	1	4	2	4	4	4	4	4

Swine vesicular disease	4	1	2	2	4	3	4	4	4
Transmissible gastroenteritis	3	1	2	4	3	4	4	4	4
Venezuelan equine encephalomyelitis	1	2	1	4	3	3	3	4	3
Vesicular stomatitis	1	1	3	4	4	4	4	4	4
West Nile Fever	1	2	1	3	3	3	3	4	4
Total No. of key routes ('1')	14	17	8	3	1	0	0	0	0

Stage 2: Risk ranking model

The results of the risk ranking exercise are shown as the 'Baseline' results in Table 6. After assessing the 33 pathogens against the 6 weighted criteria the poultry diseases Avian influenza (AI) (both highly and low pathogenic) and Newcastle disease (ND) were the top 3 rated diseases whilst the two *Mycoplasma* spp. were the bottom ranked pathogens. The poultry diseases had a maximum score for the criteria N1-N3 as well as scoring highly in the expert opinion scored criteria N4-N6.

Table 6: Heat map of change in rankings of diseases for different scenarios and range of rankings over all scenarios considered. The scores in S1-S6 represent the difference between the ranking in each alternative scenario and the baseline. Blue shading shows a decrease in ranking (light to dark shade with increasing magnitude); red shading shows an increase in ranking (light to dark shade with increasing magnitude)

Disease	Baseline	S1=No weighting of criteria	S2=Remove wildlife reservoir	S3=Remove zoonotic potential	S4=Use average of expert's score for N4-N6	S5=W4-W6*2	S6=W4-W6*3	Range
Avian influenza Highly Pathogenic	1	0	0	0	0	0	0	0
Avian influenza Low Pathogenic	2	0	0	0	0	0	0	0
Newcastle disease	3	0	0	-1	0	-1	-1	1
Bluetongue	4	-1	0	1	-1	1	1	2
Classical rabies	5	-2	0	-3	1	-3	-5	6
Crimean Congo haemorrhagic fever	5	-2	0	-3	-3	-3	-5	5
Rift Valley fever	7	4	0	-3	2	-4	-6	10
Foot and mouth disease	8	3	-2	4	1	3	1	6

West Nile fever	9	-3	-2	-2	0	1	0	4
African swine fever	10	3	-4	4	1	5	5	9
Classical swine fever	10	3	-4	4	-1	5	5	9
Equine encephalomyelitis – eastern and western	12	0	-5	-4	0	-2	-6	6
Nipah virus	13	6	-8	-5	0	-4	-7	14
<i>Ehrlichia ruminantium</i> (Heartwater)	14	-2	-10	2	-6	-7	-8	12
Sheep pox and goat pox	15	-1	7	2	-2	2	3	9
Swine vesicular disease	15	0	-10	2	1	0	-1	12
Transmissible gastroenteritis	15	-5	-10	2	-1	0	-1	12
Vesicular stomatitis	15	1	7	-8	-3	-5	-6	15
Venezuelan equine encephalomyelitis	19	3	-9	-5	4	-4	-10	14
Aujeszky's disease	20	4	8	4	-2	8	12	14
Japanese encephalitis	21	1	8	-6	1	-2	-6	14
African horse sickness	22	2	-8	3	-1	-1	-3	11
Epizootic haemorrhagic virus	22	-3	-8	3	3	-1	-3	11
Nairobi sheep disease	22	-2	6	-7	-2	-7	-9	15
Enzootic bovine leucosis	25	0	8	4	-2	8	11	13
Equine infectious anaemia	25	0	8	4	0	8	11	11
<i>Burkholderia mallei</i> (Glanders)	27	7	7	-4	1	4	3	11
Equine influenza	28	-2	6	4	-2	6	9	11
Peste des petits ruminants	28	3	6	4	0	-1	-1	7
Lumpy skin disease	30	5	3	2	1	2	7	7
<i>Brucella ovis</i> (Contagious epididymitis)	31	1	2	1	0	0	3	3
<i>Mycoplasma mycoides</i> subsp. <i>mycoides</i> (small colony) (Contagious bovine pleuro pneumonia CBPP)	32	0	2	0	0	0	0	2
<i>Mycoplasma capricolum</i> subsp. <i>capripneumoniae</i> (Contagious caprine pleuro pneumonia CCPP)	33	0	0	0	0	0	0	0

Scenario Analyses

Table 6 shows the ranking for the pathogen prioritization exercise after Stage 2 for both the baseline and the various scenarios analyses. Avian influenza, ND and Bluetongue (BTV) topped the rankings under all scenarios. Equally *Mycoplasma capricolum* subsp. *capripneumoniae* (Contagious caprine pleuro pneumonia CCPP) was consistently ranked the lowest with no change in the ranking for all scenarios assessed. The largest increase in range (i.e. larger variability between scenarios) was found for Vesicular stomatitis and

Nairobi sheep disease (range = 15) both of which were ranked higher if the presence of a wildlife reservoir were removed and ranked lower if zoonotic potential was removed fitting with the biological profiles of these pathogens. Diseases which have no wildlife reservoir or zoonotic potential and only affect one domestic species such as Aujeszky's disease, Enzootic bovine leucosis and Equine infectious anaemia were more sensitive to increasing the weighting of *N4:N6*.

Statistical Analysis

Overall the level of agreement between experts scores for the criteria *N4-N6* was high assuming that agreement equated to a difference of no more than 1 across all the expert's scores (Table 7). Impact on international trade (*N6*) showed the highest level of agreement (in percentage terms: 93.94) whilst probability of entering the EU (*N4*) and impact on production at the EU level (*N5*) showed similar levels of agreement, 81.82% and 78.79%, respectively. For the criteria 'probability of entering the EU', experts opinion for Italy consistently ranked the risk to be higher for vector borne diseases such as Rift Valley fever (RVF) and African horse sickness (AHS).

The level of agreement was also assessed using Fleiss' weighted kappa (Fleiss JL., 1971; Gwet, 2014). Using the interpretation devised by Landis and Koch (Landis, 1977), the values gave "moderate agreement" for *N4* and *N5* and "substantial agreement" for *N6*. The ranking of the criteria by the weighted kappa analysis was the same as that for the percentage agreement between experts; the highest level of agreement using both analyses was for impact on international trade (*N6*).

Table 7: levels of agreement between experts for scoring of the criteria *N4*, *N5* and *N6*. Areas where there was a difference of greater than 1 between expert's scores are highlighted in grey.

Disease	Probability of entering EU (N4)	Impact on production at EU level (N5)	Impact on international trade (N6)
Agreement	81.82%	78.79%	93.94%
Fleiss' kappa weighted value (95% CI)	0.58 (0.47, 0.69)	0.52 (0.40, 0.65)	0.70 (0.63,0.78)
African horse sickness	2	1	1
African swine fever	1	1	1
Aujeszky's disease	1	2	0
Avian influenza Highly Pathogenic	1	1	1
Avian influenza Low Pathogenic	1	2	2
Bluetongue	1	2	1
<i>Brucella ovis</i> (Contagious epididymitis)	1	1	1
<i>Burkholderia mallei</i> (Glanders)	1	1	1
Classical rabies	1	1	1
Classical swine fever	1	1	1
Crimean Congo haemorrhagic fever	1	1	1
<i>Ehrlichia ruminantium</i> (Heartwater)	1	0	0
Enzootic bovine leucosis	1	1	0
Epizootic haemorrhagic virus	1	1	1
Equine encephalomyelitis – eastern and western	2	2	1
Equine infectious anaemia	0	1	1
Equine influenza	1	1	1
Foot and mouth disease	1	0	0
Japanese encephalitis	3	2	1
Lumpy skin disease	0	1	1
<i>Mycoplasma capricolum</i> subsp. <i>capripneumoniae</i> (Contagious caprine pleuro pneumonia CCPP)	1	0	1
<i>Mycoplasma mycoides</i> subsp <i>mycoides</i> (small colony) (Contagious bovine pleuro pneumonia CBPP)	1	1	1
Nairobi sheep disease	1	1	1
Newcastle disease	1	2	1
Nipah virus	1	1	1
Peste des petits ruminants	3	1	1
Rift Valley fever	3	1	1
Sheep pox and goat pox	1	1	2
Swine vesicular disease	1	2	1
Transmissible gastroenteritis	1	1	1
Venezuelan equine encephalomyelitis	3	1	1
Vesicular stomatitis	1	1	1
West Nile fever	1	1	1

Stage 3: Risk Assessment case study selection

The top 10 baseline ranked pathogens from Table 6 were then taken forward to Stage 3 and used to select the case study pathogens for the SPARE project. The sensitivity analyses showed that small changes in some areas could affect the ranking of the pathogens within the baseline top 10, but that there were only a few instances where different pathogens would enter the top 10. Thus, we restricted selection to those 10 pathogens. Assessment of criteria *N7* determined that there was already considerable research being conducted on AI whilst *N8* determined that there was less interest from funding bodies in ND than in many other of the top-ranking pathogens; as such these pathogens were not selected. The highest ranking pathogens were, therefore, Bluetongue and Classical rabies, which were duly selected. As the aim of SPARE was to develop a model to cover distinct transmission routes or pathways (as described in Table 5), it was decided that the final case study pathogen should have a prominent animal product route. The highest ranked pathogens with a significant animal product route, according to Table 5, were African swine fever (ASF), Classical swine fever (CSF) and Foot and mouth disease (FMD); as BTV already covered live cattle imports, it was felt that a pig disease would be of more interest. CSF was therefore selected, heavily influenced by the availability of data, although adapting the model for ASF would also be possible. A summary of the case study selection stage is shown in Table 8.

Table 8: Assessment of the top 10 baseline ranked pathogens with regards to case study selection using criteria 'pathogens targeted by other EU projects' (*N7*), 'expression of interest from funding bodies' (*N8*), 'expected data availability' (*N9*).

Disease	Baseline Rank	Reason for selection
Avian influenza Highly Pathogenic	1	Considerable research already done
Avian influenza Low Pathogenic	2	Considerable research already done
Newcastle disease	3	Of less interest to funding bodies
Bluetongue	4	Selected; vectors, live animal imports
Classical rabies	5	Selected: wild animal dispersion, human travel, pets
Crimean Congo haemorrhagic fever	5	Vector borne, covered by Bluetongue
Rift Valley fever	7	Vector borne, covered by Bluetongue
Foot and mouth disease	8	Equal ranking with CSF, CSF selected
West Nile fever	9	Vector borne, covered by Bluetongue
African swine fever	10	Equal ranking with CSF, CSF selected
Classical swine fever	10	Selected: animal products, live animal imports and wild animal dispersion; good data availability

Discussion

Risk ranking tools are designed to demonstrate the relative importance of pathogens in relation to one another based on chosen criteria, as opposed to absolute importance. The rank assigned to a pathogen is influenced by a number of factors such as the criteria chosen

and the weightings assigned to the criteria. In the ranking approach used here the initial pathogen selection identified those pathogens which were exotic to the EU and the criteria on which the rankings were made were relevant to the risk of incursion and the impact on production and trade at an EU and international level. The ultimate purpose of the ranking approach was to rank pathogens in order to select case studies for a generic risk assessment.

The case study approach is similar to that used in social science where case studies provide a 'detailed examination of an aspect of a historical episode to develop or test historical explanations that may be generalizable to other events' (George & Bennett, 2005). In this instance, the case studies were selected to identify all possible causal transmission pathways within the generic risk framework and to test the feasibility of each contributing dataset to ensure the framework can be applied to any pathogen. Case studies have previously been successfully used in other EU projects to define generic risk assessments (Antigone, 2016), but a structured multi-criteria risk ranking methodology has not, to our knowledge, been applied to this process before. A qualitative assessment of whether the pathogens had been assessed by other EU projects, expected data availability, interest from funding bodies and number of relevant transmission routes was used as the final stage for selection of the case studies. The results of the risk ranking component of the model highlighted AI, ND, BTV, and rabies as important. Taking into account factors specific for the risk assessment in the second stage, the three case studies chosen for the SPARE risk assessment were CSF, BTV and classical rabies. The three selected diseases included different host species and varied transmission routes or pathways (vector; live animal imports; wildlife; imported animal products; people movement and pets).

The weightings and scoring for each criterion used in this tool were based on available evidence and expert opinion. As such they are likely to be dynamic and can be updated as appropriate if new data becomes available or if there is a change in priorities of the stakeholders concerned. Within the assessment, the calculation of the score $R2(j)$ assigned to each exotic pathogen assumes independence of the criteria $N1:N6$. However, for certain pathogen/transmission routes, it can be envisaged that conflict may occur, for example, for pathogens with a significant wildlife reservoir($N3$) in both exporting countries and the EU, such a characteristic might have positively influenced the score given to the probability of entry into the EU ($N4$). This was taken into account during the scoring process. The wording of each criterion was carefully selected and amended through discussion within the project team to reduce any correlation or conflict between the criteria. Clear definition of the scores for each criteria and the use of up to date evidence (OIE, 2015; Gibbens et al., 2016; Discontools, 2017; FAO, 2017) for all pathogens to support the experts decision making meant that potential conflict was also reduced. Ultimately the aim for any prioritisation calculation is to produce a simple and transparent score that can be used to rank pathogens by priority whilst limiting any bias or conflicts. The methodology used strikes a good balance between transparency of the tool and accuracy.

Subjectivity is an issue that all prioritisation methodologies experience because of the use of expert opinion for both selecting criteria and their relative weightings. Whilst the criteria selected were relevant to the aims of the project, the perception of the importance of disease impacts e.g. economic or welfare is likely to vary between decision makers. For instance, there can be bias in favour of prioritising pathogens that have a prior history of being introduced, such as CSF or AI, or receive increased media coverage causing stakeholder's awareness of the disease to be heightened; for example in the UK the threat of Zika and

Ebola received widespread media coverage compared to the actual first incursion of lumpy skin disease in the EU in 2016.

This subjectivity was explored by carrying out sensitivity analyses of the criteria weightings and statistical analysis of the expert opinion to address potential bias and ensure that the ranking tool was as transparent, flexible and practical to apply as possible. The scenario analyses highlighted that the ranking was quite susceptible to change depending on what criteria were included and the weighting of these criteria. The biggest effect on the ranking of individual pathogens varied according to their biological profiles, for example, those pathogens which were zoonotic or were present in a wildlife reservoir were sensitive to the removal of these criteria. Those pathogens with no zoonotic potential or wildlife reservoir, however, were more sensitive to the weightings of criteria *N4-N6*, i.e. potential entry into the EU and impact on production and trade.

Statistical analyses of the agreement between expert opinions on the probability of entering the EU, the impact on production at EU level and the impact on international trade found a high level of agreement with a difference of no more than 1 across all the expert's scores. Analyses using weighted kappa also found moderate to substantial agreement for all 3 criteria; the highest agreement was for impact in international trade (*N6*). As the pathogens considered here were OIE/EU notifiable, the high agreement between experts for this criteria possibly reflects the well documented impact of notifiable diseases with regards to potential embargos on international trade (OIE, 2017). It was of interest that experts from Italy consistently gave a higher rank for the probability of entering the EU for vector borne diseases such as RVF and AHS than experts from Switzerland and the UK. This could be due to the geographical location of Italy i.e. closer to countries where outbreaks of these pathogens have already occurred, the size of the susceptible host population and/or climatic

conditions that are more likely to support competent vectors capable of transmitting these diseases (EFSA Panel on Animal Health and Welfare (AHAW), 2013). Expert's perception of risk of disease entry may also be influenced by consideration of the number of ports or entry points into the country and of the frequency of contact with countries in which infection already exists via trade, workers or tourists. Perception of impact on production or trade may depend on an expert's consideration of the size of a resident domestic species herd and both the size of any wild population at risk and its ability to sustain a reservoir of disease.

Several different methods of pathogen prioritisation exist, the most widely used of which (bibliometric index, the Delphi technique, multi-criteria decision analysis (MCDA), qualitative algorithms and questionnaires) have recently been summarised with regards to their strengths and weaknesses (ECDC, 2015). For ease of use as a model based tool, a multi-criteria ranking model appears to be most suitable as it is able to be fully automated with the ability for the user to alter weightings and scores as appropriate. This approach forms the basis of other ranking tools such as the United Kingdom specific D2R2 (Gibbens et al., 2016) and the web based Discontools (Discontools, 2017).

The top five diseases ranked by the Discontools prioritization model (excluding bovine tuberculosis which is classed as endemic) were: Nipah virus, Peste des petits ruminants, ASF, RVF and FMD. The aim of Discontools was to build a prioritisation model and gap analysis tool enabling the prioritization of research on infectious animal diseases (O'Brien et al., 2017). The emphasis is, therefore, on research needs to fill data gaps, in particular with reference to diagnostic tests and vaccines rather than risk of incursion and impact on trade which is of particular relevance to the SPARE project. Taking the different priorities of the two models into account it is interesting to note that pathogens such as ASF, FMD and RVF ranked high using both methods.

The purpose of this work was to provide an easy to use tool whereby pathogens can be prioritised according to the user's choice of criteria to provide an input into a full risk assessment of the introduction and transmission of exotic animal pathogens into Europe. As such, there is a reasonably high level of uncertainty and so it should not be considered to provide an accurate prioritisation of disease risk (i.e. true risk). The model analysis was initially written in Microsoft Excel but a web based tool has also been developed using the RStudio shiny apps software. The web tool allows the user to adjust the scores for each section of Stage 2 ($N1:N6$) and to modify the original weights ($W1:W6$), to see how this influences the ranking of the pathogens. This tool is available on the SPARE website (https://spare-europe.shinyapps.io/Prioritising_livestock_diseases/).

In conclusion, the framework demonstrated here is flexible with the ability to adjust both the criteria and their weightings to the user's requirements. It is relatively fast, simple to use and automated. Due to its flexibility this framework may represent a valid tool to prioritise pathogens especially in a data scarce environment. The paper describes a novel approach of using the multi-criteria pathogen prioritisation methodology as a basis for selecting the most appropriate case studies for a generic risk assessment framework.

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Figure 1: Framework used to select case studies for SPARE project. Parasites/fungi and endemic diseases were excluded from the selection. Text within balloons in Stage 2 and 3 shows the selection criteria adopted in each phase.

