Transmission modelling of environmentally persistent zoonotic diseases: a systematic review

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Transmission of many infectious diseases depends on interactions between humans, animals, and the environment. Incorporating these complex processes in transmission dynamic models can help inform policy and disease control interventions. We identified 20 diseases involving environmentally persistent pathogens (ie, pathogens that survive for more than 48 h in the environment and can cause subsequent human infections), of which indirect transmission can occur from animals to humans via the environment. Using a systematic approach, we critically appraised dynamic transmission models for environmentally persistent zoonotic diseases to quantify traits of models across diseases. 210 transmission modelling studies were identified and most studies considered diseases of domestic animals or high-income settings, or both. We found that less than half of studies validated their models to real-world data, and environmental data on pathogen persistence was rarely incorporated. Model structures varied, with few studies considering the animal–human–environment interface of transmission in the context of a One Health framework. This Review highlights the need for more data-driven modelling of these diseases and a holistic One Health approach to model these pathogens to inform disease prevention and control strategies.

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Introduction

WHO defines zoonotic diseases as diseases that can transmit naturally between vertebrate animals and humans.[1] Such zoonoses can be transmitted either directly from animals to humans, or indirectly via food or the environment. Diseases that can be transmitted indirectly via the environment, such as leptospirosis and hantavirus disease, are particularly challenging to control as the natural environment also acts as a reservoir. For this reason, it is important to consider this additional dimension of the transmission process within a One Health framework, which accounts for interconnectedness between the health of humans, animals and their environment.[2–4] These diseases at the animal–human–environment interface are the focus of this Review.

Understanding disease transmission processes at the animal–human–environment interface is an increasingly important issue, especially because climate change, loss of biodiversity, land use, and land-cover change alter and often increase pathogen transfer to, and from, the environment. The multihost and environmental persistence of such pathogens can lead to complex disease dynamics.[5] For example, many different factors drive the transmission of leptospirosis; there are numerous exposure routes (ie, occupational, recreational, and socioeconomic circumstances) and many animals are known to be involved, including both rodents and domestic animals.[6] Understanding the underlying disease dynamics can enable insight into how anthropogenic change will affect transmission. Furthermore, because of these complex transmission dynamics, these diseases can be difficult to control, with several possible interventions. Many of these diseases will not be controlled using just one intervention, but instead with multimodal control programmes, targeting vaccination, health education and disease awareness, and improved sanitation and environmental hygiene. Dynamic models can be used to explore the underlying transmission dynamics, answer questions as to the effect of environmental change on transmission and provide insight into the most effective interventions. Furthermore, formulating models within a One Health framework provides an integrated approach for understanding these transmission processes.[3,4]

Dynamic disease transmission models can be used to improve understanding of the disease transmission process, predict the risk of disease outbreaks, and inform the development of effective control policies. In a basic dynamic transmission model, a population is divided into epidemiological classifications (eg, susceptible, infected, and recovered) and populations can be tracked over time.[7,8] Unlike non-communicable diseases, the risk of infectious disease transmission depends not only on individual risk factors, but also on the infectious state of others in the population. Because of this epidemiology, it is important to understand how the infectious state of the population changes over time. Compartmental models

Key messages

- We identified a group of environmentally persistent zoonotic diseases, which share similarities in their transmission dynamics and appraised the methodological approaches used to develop transmission dynamic models
- We highlight the need for more data-driven modelling for this class of diseases, particularly neglected tropical diseases and diseases with a wildlife host
- The full transmission process was often not considered, and models were rarely formulated using a One Health framework, including interactions between humans, animals, and the environment
- We identified gaps in our knowledge about the environmental pathogen burden, despite it being a major source of transmission to humans for many of these diseases
- Moving forward, it will become increasingly important to consider the effect of environmental change and global heating, particularly because of the environmental pathogen burden many of these diseases are climate sensitive and expected to increase their range in the future

	Pathogen species	Pathogen class	Animal reservoirs or hosts	Primary animal reservoir or host	Climate sensitive	Human–human transmission	Primary transmission route	Environmental transmission pathway	Duration environmental persistence	Considered to be an NTD*
Anthrax[18-21]	*Bacillus anthracis*	Bacteria	Domestic and wild animals, including cattle, sheep, goats, antelope, and deer	Domestic and wild animals	Changing range as a result of climate change	No	Direct transmission with infected animal, or environmental transmission	Inhalation	Up to 48 years	No
Brucellosis[22-24]	*Brucella abortus, B melitensus, B suis, B neotomae, B ovis, and B canis*	Bacteria	Domestic and wild animals, including cattle, swine, goats, dogs, and bison	Domestic animals	Yes	Rare	Multiple routes; primary route unknown	Inhalation	21 days–8 months	No
Campylo-bacteriosis[25-27]	*Campylobacter jejuni* and *C fetus*	Bacteria	Domestic and wild animals (eg, cattle, poultry, and rodents)	Domestic animals	Yes	Rare	Foodborne	Ingestion via contaminated water	2–14 days	No
Crypto-sporidiosis[28-30]	*Cryptosporidum parvum* (most common zoonotic species, but many others exist)[31]	Protozoan	Mammals	Domestic and wild animals	Yes	Yes	Multiple routes; primary route unknown	Ingestion of contaminated water and food	Several months	Yes (by PLoS)†
Echinococcosis[31,32]	*Echinococcus granulosus and E multilocularis*	Helminth (cestode)	Dogs, sheep, and foxes	Domestic and wild animals	Yes	No	Direct transmission from an infected animal, or environmental transmission	Ingestion food, water or soil	Up to 1 year	Yes (by WHO and PLoS)
E coli[33,34]	*Escherichia coli*	Bacteria	Predominantly cattle, but also other mammals and birds	Domestic animals	Yes	Rare	Foodborne	Ingestion via contaminated water or food	1 day–1 year	Yes (by PLoS)
Erysipeloid[35-37]	*Erysipelothrix rhusiopathiae*	Bacteria	Predominantly pigs, but also turkeys, chickens, ducks, emus, and sheep	Domestic animals	Some evidence‡	No	Direct transmission from an infected animal	Environmental transmission from contaminated animal waste and soil	2–35 days	No
Fascioliasis[38-41]	*Fasciola hepatica* and *Fasciola gigantica*	Helminth (trematode)	Domestic and wild ruminants, including cattle, sheep, buffaloes, donkeys, and pigs	Domestic and wild animals	Yes	No	Environmental transmission	Environmental transmission via ingestion of contaminated aquatic plants or water	Several months	Yes (by WHO and PLoS)
Giardiasis[42-44]	*Giardia duodenalis*	Protozoan	Cats and dogs	Domestic animals	Yes	Yes	Multiple routes; primary route unknown	Ingestion contaminated water and food	Several months	Yes (by PLoS)
Glanders[45-47]	*Burkholderia mallei*	Bacteria	Primarily horses, but also donkeys, mules, goats, dogs, and cats	Domestic animals	No	Rare	Direct transmission from an infected animal, or inhalation of the bacteria from the environment	Inhalation of the bacteria from the environment	2–6 weeks	No
Hantavirus[48-52]	*Puumala* spp, *Seoul* spp, *and Sin Nombre* spp	Virus	Rodents	Wild animals	Yes	Rare	Environmental transmission	Inhalation	Up to 18 days	Yes (by PLoS)
Leptospirosis[6,12,53]	*Leptospira* spp	Bacteria	Domestic and wild animals including rodents, cattle, sheep, and dogs.	Domestic and wild animals	Yes	No	Multiple routes; primary route unknown	Ingestion or via cuts and abrasions in the skin from contaminated water or soil	1–12 months	Yes (by PLoS)

(Table 1 contines on next page)

	Pathogen species	Pathogen class	Animal reservoirs or hosts	Primary animal reservoir or host	Climate sensitive	Human–human transmission	Primary transmission route	Environmental transmission pathway	Duration environmental persistence	Considered to be an NTD*
(Continued from previous page)										
Melioidosis[54,55]	*Burkholderia pseudomallei*	Bacteria	Domestic and wild animals, including sheep, goats, swine, cattle, and rodents	Domestic and wild animals	Yes	No	Multiple routes; primary route unknown	Contact, inhalation, or ingestion	Up to 7 days	Yes (by PLoS)
Nipah virus[56,57]	*Nipah virus*	Virus	Pigs, dogs, goats, cats, horses, and sheep; the virus is thought to be maintained in nature by bats	Domestic and wild animals	Some evidence‡	Yes	Direct transmission from an infected animal	Environmental transmission as a result of ingesting food contaminated with bat saliva and urine	Several days	Yes (by PLoS)
Q fever[58-60]	*Coxiella burnetii*	Bacteria	Predominantly cattle, sheep, and goats	Domestic animals	Some evidence‡	Rare	Multiple routes; primary route unknown	Inhalation	Up to 3 years	Yes (by PLoS)
Salmonellosis[61-63]	*Salmonella enterica* Dublin, *S enterica* Enteritidis, *S enterica* Typhimurium, *S enterica* choleraesuis	Bacteria	Domestic and wild animals, including poultry, pigs, cattle, and cats	Domestic animals	Yes	Yes	Foodborne	Ingestion of contaminated water or food	7 weeks	Yes (by PLoS)
Toxoplasmosis[64-66]	*Toxoplasma gondii*	Protozoan	Domestic animals and wild animals (eg, cats, pigs, sheep, and goats)	Domestic and wild animals	Climate change might increase cases	Yes	Foodborne	Ingestion of contaminated soil, water, or food	Up to 24 months	Yes (by PLoS)†
Toxocariasis[67,68]	*Toxocara canis and T cati*	Helminth (nematode)	Cats and dogs	Domestic animals	No	No	Multiple routes; primary route unknown	Ingestion contaminated soil	Several months	Yes (by PLoS)
Tularaemia[69,70]	*Francisella tularensis*	Bacteria	Rabbits, rodents, squirrels, and other small mammals	Wild animals	Climate change might increase cases	No	Multiple routes; primary route unknown	Inhalation or ingestion of contaminated water and soil	Several weeks	No
Yersinosis[71,72]	*Yersinia enterocolitica* and *Y pseudotuberculosis*	Bacteria	Predominantly rodents, but also sheep and pigs	Wild animals	No	Rare	Foodborne and contaminated water	Ingestion of contaminated water or food	7–36 days	No

NTD=neglected tropical disease. PLoS=Public Library of Science. *Based on the WHO list of NTDs[73] and PLoS list of major Neglected Tropical Diseases.[74] †Classed as on the cusp; which is defined by PLoS as diseases that could be classed as NTD's depending on the availability of disease estimates for that condition, and whether they occur in resource-poor settings.[74] ‡Some available studies suggesting the disease might be climate-sensitive, but the link has not yet been clearly established.

Table 1: **Summary of diseases included within the systematic review**

can include more than one population, or in the case of zoonotic diseases, models can include both humans and animal reservoirs.[9] Additionally, individual-based models can be formulated to track individuals, rather than populations, over time. We can further distinguish between models, describing them as deterministic, in which the same results are always obtained from a given set of parameters, and stochastic, in which chance has a role in governing events.[7,8,10,11]

In their simplest form, models can be used theoretically to understand observed patterns and behaviours in different systems, for example, they can be used to find theoretical thresholds for disease elimination or the existence of an endemic equilibrium. Modelling also allows exploration of different scenarios, such as the comparative effectiveness of different control measures, a comparison that can be ethically or logistically unfeasible during a real-world outbreak.[7,8,10,11] Advances of computational capabilities and advances in statistical software has enabled the development of more complex models, and for real-world data to be used to validate or calibrate models, allowing these models to predict disease outbreaks and directly inform policy and interventions.[7,9] Because of these advancements, methods of analysis and fitting models to data have improved, becoming more refined and better able to incorporate real-life complexity.[8] In this Review we define model validation as the comparison of model simulations with observed data, even qualitatively, whereas model calibration takes this definition further

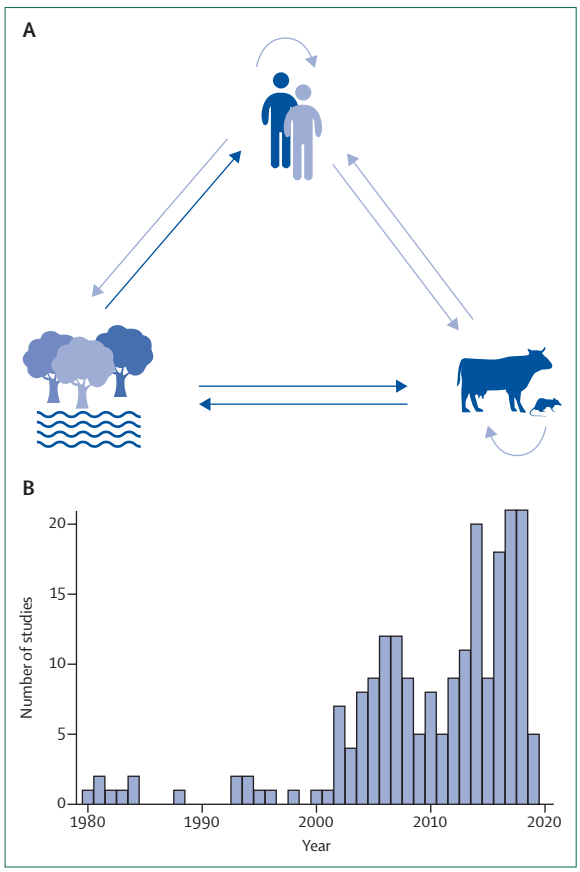

Figure 1: **Transmission pathways and studies included in the systematic review**

(A) Transmission pathways of the diseases included within this study; solid arrows show shared transmission routes across all diseases, dashed arrows show transmission routes that only occur in some diseases. (B) Number of studies (n=208) identified in the systematic review from 1980 to 2019, studies which present models on more than one disease are only included once.

See Online for appendix

and fits models to observed data to estimate key unknown biological parameters (eg, by using methods such as Markov chain Monte Carlo to estimate parameters).[7] Studies will have different aims and purposes, and the model should only be as complex as needed to fulfil the intended objective.

In this Review, we critically appraise studies that have attempted to model infectious diseases at the animal–human–environment interface to quantify traits of models across diseases and identify studies that have adequately accounted for these three One Health components. Previous reviews of modelling studies have focussed on vector-borne diseases or zoonotic diseases generally[9,12,13] and, to the best of our knowledge, this is the first review that focusses specifically on environmentally persistent pathogens. Of particular interest is the way by which models are validated or calibrated, and the data that have been used to do so. First, we identified diseases in which indirect transmission can occur from animals, more specifically land mammals, to humans via the environment. This human–environment transmission could be the only transmission route, or there might be multiple transmission routes to humans, of which environmental transmission is just one. Second, we reviewed modelling studies using a systematic approach. For each paper, we extracted information on the type of model, the data used, and the quality of model validation and calibration attempts. Finally, using this information, we evaluated the current state of transmission modelling studies and identified key themes and best practices, which could be incorporated in future disease transmission analyses and shared between different diseases.

Methods

Disease selection

Two criteria were used to select diseases for inclusion in the study: the disease must be zoonotic (transmissible from animals to humans, specifically affecting land mammals), and the pathogen must persist in the environment for at least 48 h and then remain able to cause subsequent human infections.

Vector-borne diseases and fungi were excluded. Lists of zoonotic diseases were obtained from Public Health England,[14] the European Centre for Disease Control,[15] and WHO.[1] Following these criteria, 20 diseases that had free-living pathogens were identified. We considered free living to mean the pathogen could survive in the environment for more than 48 h outside of a host. We focussed on land mammals as we were particularly interested in animals that live alongside humans in the same environment, and as a result of our criteria very few diseases were excluded (appendix pp 1–3). For example, rabies was excluded because transmission to humans occurs via direct contact with an infected animal or human, and there is no evidence of environmental transmission to humans. Ebola was excluded as, although there is some evidence of environmental persistence, transmission to humans occurs via an infected animal, or human–human transmission, and not via the environment. Although Lassa fever and Bolivian haemorrhagic fever anecdotally have the ability to survive in the environment, no evidence was found of this, and so these diseases were also excluded from this Review.[16,17] A summary of each disease is presented in table 1 and a generalised schematic representation of the transmission pathways for the diseases is shown in figure 1A.

There are many different serovars of *Salmonella enterica* subspecies *enterica*, not all of which are zoonotic. Therefore, four common zoonotic serovars were selected for the study, *S enterica* serotype Dublin, *S enterica* serotype Enteritidis, *S enterica* serotype Typhimurium, and *S* serotype Choleraesuis. Melioidosis is not always considered a zoonotic disease because transmission to humans occurs primarily via the contaminated environment;[75] animals can be the source of the environmental contamination, but not necessarily so.

However, because environmental transmission to humans is of key interest for this Review, this disease matched our inclusion criteria and was included.

Inclusion and exclusion criteria

To qualify for inclusion, studies had to model one of the 20 diseases described (table 1) and include a dynamic population model (ie, models that track populations over time), both compartmental and individual-based models were included.

The following studies were excluded from the review: PhD theses, grey literature (including conference abstracts), statistical models (including time-series analysis, regression, and ARIMA [Auto Regressive Integrated Moving Average] models), within-host models, models using cellular automata, and review articles (unless new models were presented).

Search strategy

In June, 2019, we searched Embase, MEDLINE, and Web of Science for articles published between January, 1970, and June, 2019. Only articles in English were included. We used disease specific and model-specific search terms (appendix pp 4–5). An example search strategy used in the database Embase for leptospirosis is shown (appendix p 6). We aimed to identify all published articles that included population dynamic models of the 20 diseases. To ensure all relevant papers were captured, EMR examined the title, abstract and keywords of known modelling studies to identify relevant search terms, and these were discussed and finalised with other coauthors (AM, AKJ, and RL). Each disease was included as a search term and as a keyword.

We combined and stored the results from database searches using Mendeley reference manager, and duplicates were removed manually. We screened the titles and abstracts of all papers to remove irrelevant studies (eg, experimental animal models). Subsequently, abstracts and full texts of potentially relevant papers were independently reviewed by two reviewers (EMR and AM), and any conflicts were resolved through discussion. Any additional studies identified from the reference lists of these studies were also included (appendix p 7).

Data extraction

To compare studies, we extracted information (including model structure, model type, and model features) from each study (table 2). For studies including models for more than one relevant pathogen, we extracted information separately for each disease.

Results

Overall, 20 different diseases were identified that matched the disease inclusions criteria (table 1). After removal of duplicates, a total of 13420 studies were identified using the search terms, and these were screened by title and abstract. A further full-text screen was done for 504 studies, and in total 208 studies were found as meeting all inclusion criteria (table 3; appendix pp 9–33). For papers that included multiple models of relevant diseases, data extraction was done for each disease individually, resulting in 210 models being included in this Review. As expected, the number of published studies has increased over time (figure 1B), with an average of 0·7 studies published per year between 1990 and 2000, rising to 6·8 studies per year from 2000 to 2009 and 13·5 studies per year from 2010 to 2019. Although the overall number of studies has increased over time, the proportion of studies that have included model validation has not changed (figure 2b). The number of studies that had model validation varies considerably by disease and is more common in diseases where domestic animals are the predominant host (figure 2B). When interrogated by study region, model validation is more common for diseases studied in Europe and Asia (figure 2C).

There were no modelling studies identified for Glanders, Nipah virus, erysipeloid, yersinosis, and toxocariasis. Overall, more studies (n=96) were identified for diseases for which domestic animals are the predominant host species (eg, brucellosis, echinococcosis, and *Escherichia coli*) rather than wild animals (n=27; figure 2A). Five diseases were found to have fewer than five studies identified: Q fever, tularaemia, melioidosis, giardiasis, and fascioliasis. 165 (79%) of 210 studies were deterministic, compartmental based models (table 3), with only 55 (26%) of 210 studies using stochastic

	Description
Components	
Animals	Animals included in the model
Environment	Environmental pathogens included in the model
Humans	Humans included in the model
Structure of the model	
Deterministic or stochastic	Model structure of the model was deterministic or stochastic
Compartmental or IBM	Model structure of the model was ODE-based or an IBM
Model Features	
Data-driven parameters	Parameters informed by empirical data
Model validation	Model outputs compared with data in any way, even qualitatively
Model calibration	Model fitted to data to estimate parameters
Prediction	Model used to generate predictions about future cases (limited to studies that compared their model with data)
Control measures	Were any control measures included within the model, examples include vaccination and culling
Climate factors	If applicable, were any climate factors (eg, temperature and rainfall) included within the model
Data sources	
Data used	What data was used for model validation (if applicable), including information on type of data, time period, and whether data was for animals, humans, the environment, or a combination of these three factors
Country	Country the study was done in (if applicable)

IBM=individual-based model. ODE=ordinary differential equation.

Table 2: **Summary of information recorded from all studies**

	Anthrax (n=19)	Brucellosis (n=37)	Campylo-bacteriosis (n=8)	Crypto-sporidiosis (n=6)	*E coli* (n=24)	Echino-coccosis (n=23)	Fascio-liasis (n=5)	Giardiasis (n=2)	Hantavirus (n=25)	Lepto-spirosis (n=23)	Melioi-dosis (n=1)	Q fever (n=4)	Salmonella (n=20)	Toxoplas-mosis (n=11)	Tularaemia (n=2)	Total (n=210)
Components																
Animals	17 (89%)	37 (100%)	6 (75%)	1 (17%)	20 (83%)	23 (100%)	5 (100%)	1 (50%)	24 (96%)	23 (100%)	0	4 (100%)	19 (95%)	9 (82%)	2 (100%)	191 (91%)
Environment	15 (79%)	14 (38%)	1 (13%)	5 (83%)	18 (75%)	12 (52%)	5 (100%)	2 (100%)	9 (36%)	4 (17%)	0	4 (100%)	13 (65%)	6 (55%)	1 (50%)	109 (52%)
Humans	6 (32%)	8 (22%)	4 (50%)	5 (83%)	4 (17%)	4 (17%)	0	2 (100%)	5 (20%)	18 (78%)	1 (100%)	0	1 (5%)	5 (45%)	1 (50%)	64 (30%)
Model type																
Deterministic	18 (95%)	29 (78%)	7 (88%)	5 (83%)	8 (33%)	19 (83%)	3 (60%)	2 (100%)	19 (76%)	22 (96%)	1 (100%)	0	11 (55%)	9 (82%)	2 (100%)	155 (74%)
Stochastic	1 (5%)	6 (16%)	1 (13%)	1 (17%)	14 (58%)	4 (17%)	2 (40%)	0	3 (12%)	1 (4%)	0	3 (75%)	8 (40%)	1 (9%)	0	45 (21%)
Deterministic and stochastic	0	2 (5%)	0	0	2 (8%)	0	0	0	2 (8%)	0	0	1 (25%)	1 (5%)	1 (9%)	0	9 (4%)
Model structure																
Compartmental	18 (95%)	33 (89%)	8 (100%)	5 (83%)	18 (75%)	19 (83%)	3 (60%)	2 (100%)	23 (92%)	23 (100%)	1 (100%)	1 (25%)	20 (100%)	10 (91%)	2 (100%)	186 (89%)
IBM	1 (5%)	3 (8%)	0	1 (17%)	5 (21%)	4 (17%)	2 (40%)	0	2 (8%)	0	0	3 (75%)	0	1 (9%)	0	22 (10%)
Compartmental and IBM	0	1 (3%)	0	0	1 (4%)	0	0	0	0	0	0	0	0	0	0	2 (1%)
Model features																
Data driven parameters	15 (79%)	28 (76%)	8 (100%)	6 (100%)	24 (100%)	19 (83%)	5 (100%)	2 (100%)	19 (76%)	15 (65%)	1 (100%)	4 (100%)	19 (95%)	8 (73%)	2 (100%)	175 (83%)
Model validation	6 (32%)	15 (41%)	6 (75%)	5 (83%)	19 (79%)	8 (35%)	3 (60%)	2 (100%)	7 (28%)	5 (22%)	1 (100%)	3 (75%)	12 (60%)	0	1 (50%)	93 (44%)
Model calibration	5 (26%)	14 (38%)	5 (63%)	5 (83%)	14 (58%)	6 (26%)	0	1 (50%)	4 (16%)	2 (9%)	1 (100%)	2 (50%)	6 (30%)	0	0	65 (31%)
Prediction	2 (11%)	4 (11%)	2 (25%)	2 (33%)	0	2 (9%)	3 (60%)	0	1 (4%)	0	0	0	1 (5%)	0	0	17 (8%)
Control measures	8 (42%)	29 (78%)	2 (25%)	3 (50%)	11 (46%)	10 (43%)	4 (80%)	1 (50%)	4 (16%)	7 (30%)	0	3 (75%)	5 (25%)	6 (55%)	1 (50%)	94 (45%)
Climatic factors	..	4 (11%)	2 (25%)	2 (33%)	3 (13%)	2 (9%)	2 (40%)	0	4 (16%)	2 (9%)	0	0	1 (5%)	..	..	22 (10%)
Data																
Animals (domestic)	0	7 (19%)	3 (38%)	0	13 (54%)	2 (9%)	1 (20%)	0	0	1 (4%)	0	3 (75%)	11 (55%)	0	0	41 (20%)
Animals (wild)	5 (26%)	2 (5%)	0	0	0	4 (17%)	0	1 (50%)	5 (20%)	3 (13%)	0	0	0	0	1 (50%)	21 (10%)
Environment	0	0	0	0	3 (13%)	0	2 (40%)	0	0	0	0	0	0	0	0	5 (2%)
Humans	1 (5%)	7 (19%)	3 (38%)	5 (83%)	3 (13%)	2 (9%)	0	2 (100%)	2 (8%)	1 (4%)	1 (100%)	0	1 (5%)	0	0	28 (13%)

No studies were identified for toxocariasis, Nipah virus, erysipeloid, glanders, or yersinosis. IBM=individual-based model.

Table 3: **Summary of data extraction by disease**

models, and 24 (11%) studies using stochastic or individual-based models, or both.

93 (44%) of the 210 included studies validated their models against real-world data, 65 (30%) calibrated their models to data, and 17 (8%) used the model to predict future disease transmission (figure 2A; table 3).

Of the 93 studies validated against real-world data, 62 (67%) used animal data, with 28 (30%) studies using human case data (figure 2D). Of the 62 studies with animal data, 41 (66%) concerned domestic animals. Five (5%) of the 93 validated studies included data on the environmental pathogen prevalence (table 3). Data on the environmental prevalence was only considered for fascioliasis and *E Coli*; including field studies that investigated cow pat sampling (*E Coli*) and faecal egg counts from dairy cows (fascioliasis).

While similarities exist, many of the selected diseases have unique transmission pathways. For example, campylobacter and *E coli* infections are usually a result of foodborne transmission,[25,76] whereas leptospirosis transmission can occur either by contaminated water or soil, or through direct contact with the urine of an infected animal.[77] Therefore, differing modelling structures have been chosen to model these diseases, with varying degrees of complexity (table 3; figure 3A; appendix p 8). For most diseases, animals were included within the models (191 [901%] of 210 studies). The environmental reservoir, was included within the model less often (109 [52%] of 210 studies), and humans less frequently still (64 [31%] of 210 studies). Looking specifically at the inclusion of the environmental reservoir, we found five diseases (brucellosis, leptospirosis, campylobacteriosis, Hanta virus, and tularaemia) by which less than half of published models did not include the environmental component (figure 3B). Regarding the proportion of studies that validated and calibrated their models to data by the number of components included (ie, animal, human and, environmental components), there was little difference in model validation by number of components, but a slightly higher proportion of model calibration in modelling studies that included all three components (figure 3C). In total, 17 (8%) of the studies included all three modelling components; of these studies, nine (4%) validated their models to data, and six (3%) calibrated their models to data.

Of the diseases that are climate sensitive, very few models considered the climatic factors within their models (22 [12%] of 178 studies; figure 3D).

Approximately half of studies included control measures within their models (94 [44%] of 210 studies). Control measures investigated included vaccination strategies, disposal of infectious carcasses and contaminated material, livestock movement restrictions, and environmental controls such as water treatment.

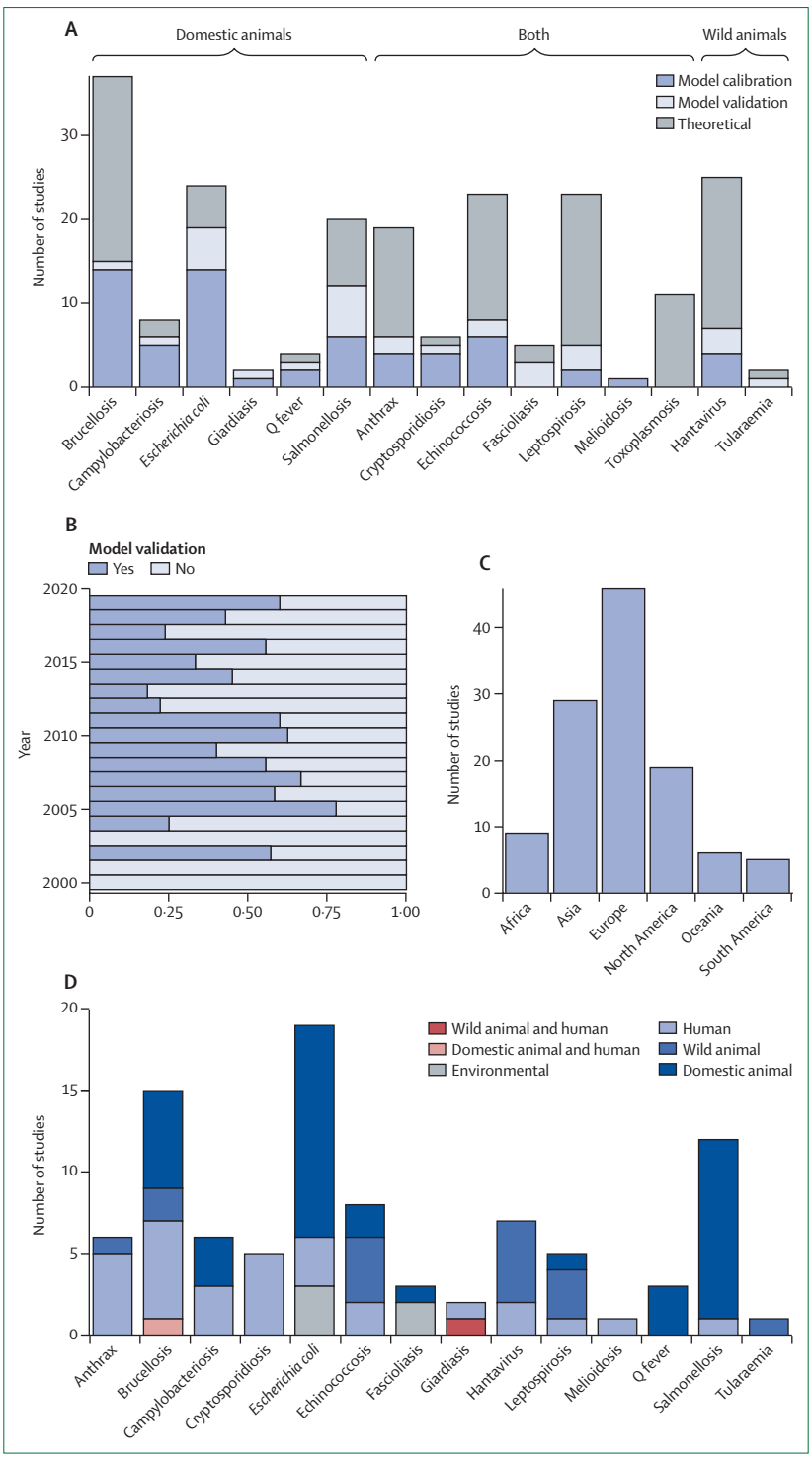

Figure 2: **Summary of model validation and calibration for all included studies**
(A) Number of studies by disease (n=210). Theoretical studies had neither model validation nor calibration; all studies that include model calibration also include model validation. (B) Proportion of studies that include model validation for all diseases, between 2000 and 2019 (n=195). (C) The number of studies by case study region (n=114). (D) Types of data used for model validation by disease (n=93).

Discussion

This Review provides biological and epidemiological insights into modelling approaches used to study

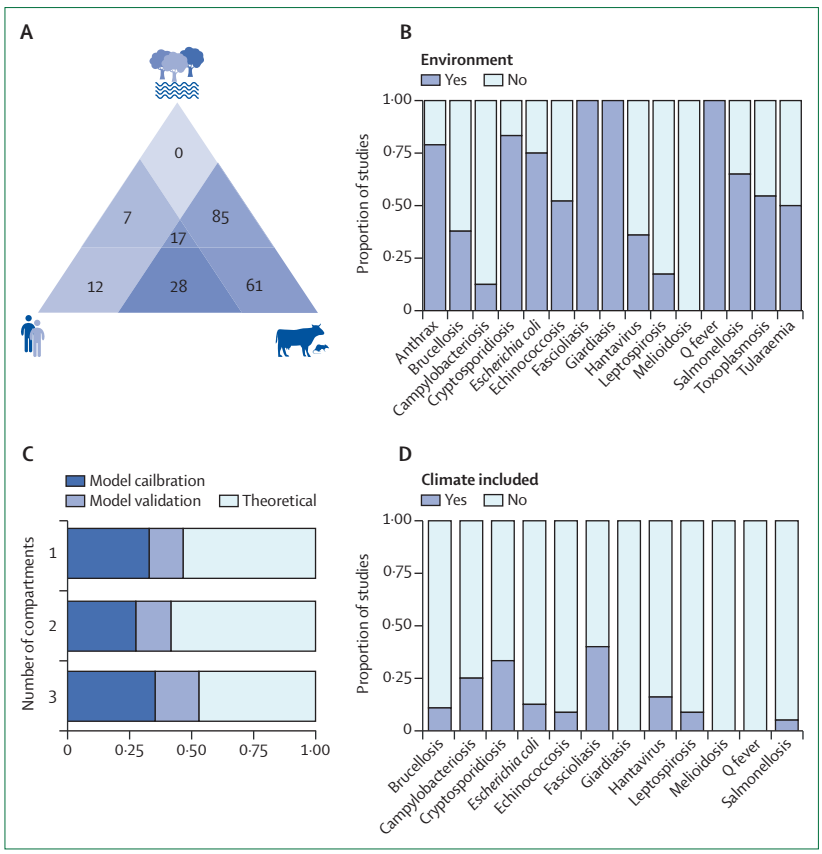

Figure 3: **Models included in systematic review**
(A) Studies by transmission (ie, human, animal, and environmental) factors. The different triangles represent the different components included within the model, with 17 studies including all three components. (B) Proportion of studies that included the environment in their models, by disease (n=210). (C) Proportion of models that validated or calibrated their models by the number of components included within the study (n=210). (D) Proportion of studies that included climate information within their studies (n=178; three diseases excluded because they are not considered to be climate sensitive).

diseases at the human–animal–environment interface, and highlights best practice methodological approaches, which can be applied to lesser studied diseases that have similar transmission dynamics. Environmentally persistent zoonotic diseases vary considerably, occurring in different regions in the world, with different animal hosts and different transmission pathways. However, two key similarities link them together: being a zoonosis, and the capacity of pathogens to survive in the environment for extended periods of time. By contrast with directly transmitted human infections, such as measles, different approaches are required to model this class of human–animal–environment diseases to fully capture the biological processes involved, which could have hindered technical progress. Furthermore, the persistence of pathogens in the environment provides an additional layer of complexity that needs to be considered when studying these diseases. There are many different potential transmission routes; therefore, interventions need to be formulated using a One Health framework to develop effective control programmes, but first this requires a good understanding of the underlying transmission dynamics. The problem is further compounded by the fact that many diseases included in this category are considered to be neglected tropical diseases (NTDs),[73] which typically receive less funding and resources. The transmission process of NTDs is often ambiguous, and, particularly for diseases with wild animal hosts, little is known about the behaviours and environmental interactions exhibited by these animals.

We identified several key areas for progress in the modelling of zoonotic environmental diseases. First, there was substantial variation in the extent of model validation and calibration across pathogens and studies. Overall, less than half of all studies included in this review undertook any kind of model validation (ie, comparing model outputs to observed data), a trend that has not changed over time. This trend can be partly explained by the inclusion of theoretical models in this Review. The aim of such models is to explore transmission dynamics and generate hypotheses, and these models are the foundation for the development of data-driven models. Validating and calibrating models to data is an important step to ensure adequate realism, not only to estimate biological parameters and understand transmission, but also to predict disease outbreaks.[7,8] However, model validation and calibration is a necessary but not sufficient criteria for model realism; the specific choice of data, the implementation methods used, and the model structure are also key decisions. There is substantial future work to be done in this regard, including making testable predictions about real-life epidemics that later be assessed. Additionally, engaging with multidisciplinary and local experts to ensure that the model adequately captures the local environment and situation is an important consideration. The main reason for the lack of extensive model validation is likely to be one of complexity. Some of these diseases have very complex transmission pathways, which means little data exist to understand the full transmission process and, historically, modelling studies have tended to focus on diseases with simpler transmission pathways that are easier to calibrate and validate. In this systematic review, models that included two or three components (ie, animal, human, or environmental) generally included a similar quality of model validation or calibration compared with simpler, and intuitively easier to fit, models that just included one component. Nevertheless, the number of studies validating and calibrating their models was still low, and this highlights the need for more research into these pathogens to provide data to inform models, policy, and important planetary health questions related to landscape change and environmental degradation. This research is likely to require increased transdisciplinary collaboration and coordination between policy makers, mathematical modellers, epidemiologists, ecologists, and veterinarians to overcome the shortfalls of studies to date.

We found that model validation was more common for diseases that affect high-income countries (eg, for example, *E Coli* infection and salmonellosis), and for diseases by which domestic animals are the predominant host. By contrast, fewer models exist for diseases that affect predominantly low and middle-income countries (eg, melioidosis, fascioliasis, giardiasis, and yersinosis) despite a high global burden of disease. This validation discrepancy likely reflects a focus on global research and public health, which in turn means an absence of epidemiological data on the precise number of human cases. Few diseases included within this Review occur primarily in wild animals, most diseases occur in both wild and domestic animals. However, diseases that occur in wild animals (eg, tularaemia and yersinosis), which have low spillover into human populations, tend to be less studied, or do not have model validation and calibration.[9] It is known that wildlife hosts act as major reservoirs of disease, and more effort should be placed on understanding their behaviour and disease transmission potential. However, there are some exceptions. Hantavirus is a disease that is only found in wild animal reservoirs, but there have been a number of outbreaks of hantavirus in Europe, and this is reflected in the number of studies that exist for this disease.[78,79] Additionally, wildlife in national parks are often closely monitored—eg, brucellosis transmission in bison (*Bison bison*) and elk (*Cervus canadensis*) in Yellowstone National Park, USA,[80] and anthrax transmission in Kruger National Park, South Africa.[81,82] A study published in 2020 (ie, after our search was completed), investigated Nipah virus in bats in Bangladesh.[83] Bats were sampled over a 6-year period and a model developed and fitted to seroprevalence data. This study provides a good example of repeated monitoring of a wildlife population and combining this data along with a compartmental model to understand transmission dynamics.

Ideally, data for model validation would be obtained from experiments or field studies specifically designed with modelling as a potential application, with modellers working as part of an interdisciplinary team. There are examples of this collaboration in livestock, such as studies of *Campylobacter* in broiler chickens,[84] *E coli* in pigs[85,86] and cattle,[87,88] *Salmonella* in cattle,[89,90] and examples from wildlife populations, such as echinococcosis in fox populations.[91,92] An illustrative example is a study that originally aimed to look at breeding strategies in female mice.[93] In 2012, there was an outbreak of tularaemia in this study population, allowing for optimal monitoring of this outbreak and a model was subsequently developed using this data. However, often model validation is limited by the data available, and it is not always possible or practical to do experimental studies. For many of these diseases surveillance systems exist, particularly in high-income countries, which monitor the numbers of reported cases in both animals and humans, and these data can then be used to inform and parameterise models. Nevertheless, the existence of surveillance systems varies extensively, not only by disease but also by setting. These surveillance systems tend to focus on human and animal cases, with very little focus on surveillance of the natural environment.

The vast majority of studies that validated their models to data used animal or human data, with few studies including data on the environmental reservoir, which could be explained by the difficulties in collecting such data. Only two diseases included data on the environmental pathogen prevalence, *E coli* and fascioliasis. Some of these studies necessary qualitatively compared their model outputs to environmental data; however, other studies took this further by comparing or fitting their models to observational data. For example, Turner and colleagues[94] compared their model with *Fasciola hepatica* faecal egg counts sampled from dairy cows. Similarly, Mathews and colleagues[95] fitted their model to the prevalence of *E coli* O157 in cow faeces sampled monthly over 1 year. However, transmission to animals and humans is affected by the duration of pathogen survival outside of its host and the extent of spatial dispersal, and for many of these pathogens this is not well understood, highlighting the need for further research and empirical data. For disease systems with little observational epidemic data, experimental estimates (eg, from in vitro or in vivo studies) can be used to parameterise models, which in turn can be used to explore dynamics. There are many examples, but a useful example is Bontje and colleagues[96] who modelled Q fever in Dutch dairy goat herds. The parameters used a wide range of studies, particularly those parameters relating to *Coxiella burnetii*.

By including multiple sources of data within models, it can be possible to estimate the relative contribution and importance of these different transmission routes. For example, Zinstagg and colleagues[97] used demographic and livestock field data from cattle and sheep, and human case data over 9 years, to build a transmission model of brucellosis in Mongolia. This is one of only two examples where human and animal data are used together. The other study, Waters and colleagues,[98] did not fit their model formally, instead they qualitatively compared the model results to the data. Other examples include Gautam and colleagues[99] who combined experimental data in cattle with environmental contamination in faeces, and Ebinger and colleagues[80] who used both bison and elk field data to model brucellosis in Yellowstone National Park.

Another key area for future progress will be consideration of these diseases within a One Health framework, with models exploring the disease transmission system as a whole. Only a small proportion of studies (11%) accounted for the full transmission process (human, animal, and environmental components) within their models, including studies examining the long-term trends of echinococcosis, brucellosis,[100,101] and hantavirus.[78,102] However, including the full transmission

process might not be required for particular research questions, and model parsimony should be considered. Detail and model complexity should not be mistaken for realism; a simple model that explains the data well and answers the question of interest is preferred.[8] There are a number of reasons why some studies have chosen to focus on one element of transmission—eg, it can allow models to focus on particular aspects of transmission for which they have detailed data and a comprehensive understanding. Many of the studies included within this Review did not include the environmental reservoir and the decision to include the environment depends on the context. For example, for *Campylobacter*[3] and hantavirus, the duration of environmental persistence is relatively short (2–14 days for *Campylobacter* and 1–18 days for hantavirus)[19,48] and, depending on the timescale of the model, might not require consideration. Furthermore, although all of these diseases have pathogens that survive in the environment, the importance of the environmental reservoir as a transmission route varies considerably, and in many cases, is unknown. For example, foodborne transmission by *Campylobacter* and *E coli* is considered to be the main transmission route, with environmental transmission a secondary transmission route.[76] The decision of whether or not to include the environment can also be due to the difficulty in understanding the environmental reservoir. For many of these diseases, very little is known about the exact duration of environmental persistence of these pathogens, or the effect of environmental factors on pathogens survival.

However, for some diseases the importance of environmental transmission is well established. For example, transmission of leptospirosis to humans primarily occurs via contaminated water and soil with leptospires surviving long periods in the environment, yet most of the models included humans and animals, without considering the role of the environment (only four of 23 models of leptospirosis considered the environmental reservoir). A better representation of the environmental persistence within these models, particularly with the use of empirical data, would allow for a better understanding and management of these diseases systems, particularly because the environmental burden can pose substantial issues when it comes to control strategies and interventions. Inclusion of environmental data would then lay the groundwork for the development of models that address how environmental change will shape transmission. Many studies also excluded humans from their transmission models, with differences observed between diseases. In diseases with only sporadic human cases (eg, anthrax), human cases provide very little information on the underlying dynamics of transmission. However, when there are outbreaks or endemic transmission in humans, data on humans can help understand the transmission dynamics in the animal hosts even if they are not contributing to transmission directly. Additionally, data collection is usually focussed on human cases, which could aid parameterisation of models that have little or no animal data.

Although there are many valid reasons to focus on particular aspects of transmission when modelling these diseases, there is a need for more models that explore the system as a whole. This approach would allow the transmission dynamics and the effect of climate and anthropogenic change on transmission to be fully explored. Diseases rarely occur in closed, isolated populations and failure to take this complexity into account could result in models being unable to replicate the observed transmission dynamics. This is particularly true for diseases that have an environmental component; failure to take this into account can lead to overestimation of the importance of particular transmission pathways over others, and result in the effect of anthropogenic and climate change being underestimated and unexplored. Furthermore, many of these diseases are climate sensitive, with an increase in cases observed as a result of extreme climatic events. For example, outbreaks of leptospirosis are often associated with heavy rainfall and flooding.[6] The inclusion of climatic data can help to explain observed outbreak dynamics, which was done for hantavirus[78] and brucellosis,[103] and this inclusion can be particularly useful when little is known about the animal population. Furthermore, many of these diseases (eg, anthrax, campylobacteriosis, cryptosporidiosis, and leptospirosis) are expected to expand their range as a result of climate and land-use change and modelling studies incorporating climatic data can help identify the effect of climate change on these diseases, such as campylobacter and cryptosporidium in New Zealand.[104] However, only a small number of models considered the effect of climate variables within their models. It is also important to take into consideration spatially varying covariates, which was done for *E coli*,[105] hantavirus,[79] and echinoccosis.[106] An obvious next step is to combine these dynamic transmission models with other tools, such as ecological niche modelling and geospatial approaches.[107]

Conclusions

This systematic review identified four areas for development in the modelling of zoonotic environmental diseases. First, there is a need for more model validation and calibration for many of these diseases, particularly for models of diseases with wildlife hosts and NTDs that often did not have this important component of the model fitting process. It is known that wildlife hosts act as major reservoirs of diseases; therefore, more effort should be placed on understanding their behaviour and disease transmission potential. Furthermore, most emerging pathogens are zoonotic, with the majority emerging from wildlife reservoirs that then spillover to domestic animals and humans.[2,5,108,109] Second, it is

important for more models to be developed that capture the full transmission process. In particular, the environment as a source of transmission was rarely considered, despite being a major source of transmission to humans for many diseases. This environmental pathogen burden can pose substantial issues when it comes to control strategies and interventions and should be included in more of these disease models using a One Health framework. Third, this Review highlighted how little data exists for the environmental pathogen burden of disease, and often little is known about the environmental burden of these diseases. Finally, it is important to consider the effect of climate variability and climate change on these diseases. Because of the environmental burden, many of these diseases (eg, leptospirosis and melioidosis) are climate sensitive and they are predicted to increase their range in the future.[110] It is essential that we combine these considerations to generate robust models using a One Health approach that are capable of predicting outbreak dynamics and changes in disease risk to inform planning and control.

Contributors

EMR, AJK, and RL conceptualised this Review. EMR, AM, AJK, and RL designed the methodology. EMR did the study search and data analysis. EMR and AM did the screening of studies. All authors contributed equally to the discussion and the editing of the final draft.

Declaration of interests

We declare no competing interests.

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