Reviewing age-structured epidemiological models of cattle diseases tailored to support management decisions: Guidance for the future

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Abstract

Mechanistic simulation models are being increasingly used as tools to assist with animal health decision-making in the cattle sector. We reviewed scientific literature for studies reporting age-structured cattle management models in application to infectious diseases. Our emphasis was on papers dedicated to support decision making in the field. In this systematic review we considered 1290 manuscripts and identified 76 eligible studies. These are based on 52 individual models from 10 countries addressing 9 different pathogens. We provide an overview of these models and present in detail their theoretical foundations, design paradigms and incorporated processes. We propose a structure of the characteristics of cattle disease models using three main features: [1] biological processes, [2] farming-related processes and [3] pathogen-related processes. It would be of benefit if future cattle disease models were to follow this structure to facilitate science communication and to allow increased model transparency.

Keywords

Epidemiology, Model, Mechanistic, Transmission, Cattle, Bovine, Disease, Review

1. Introduction

Contagious cattle diseases such as bovine viral diarrhoea or Johne´s disease are prevalent in many food-producing countries worldwide (Garcia & Shalloo, 2015; Richter, Lebl, Baumgartner, & Obritzhauser, 2017). In countries where these and other diseases are present, the economic impact through direct (reduced milk yield, etc.) and indirect (vaccination campaigns etc.) financial losses can be substantial (Otte & Chilonda, 2000). In response, government agencies and livestock industries in many countries have sought to develop and refine appropriate policy and management actions. The development of epidemiological models capable of representing the spread of infectious diseases in cattle populations is an effective tool for policy support and to assist with animal health decision-making (Singer, Salman, & Thulke, 2011).

It is well acknowledged that epidemiological models should always be designed according to the questions to be answered and be as complex or as simple as the objective requires (Garner & Hamilton, 2011). It is well recognised that different models could be developed for the same disease following the exact purpose of the modelling and the modellers capabilities (EFSA, 2009).

Early epidemiological models introduced the SIR-based compartmental framework (Kermack & McKendrick, 1927). Using this approach, each individual in a population is allocated to one of three infection states: susceptible (S), infected (I) or recovered (R), with transitions between these states describing the transmission process. However, recent advances in computational power and theoretical understanding have facilitated the development of more system-oriented, mechanistic models which describe dynamic systems by their mechanisms (Cabral, Valente, & Hartig, 2017). These models have been used to represent the spatio-temporal dynamics of infections in populations to support animal-health decision-making (Thulke, 2011). In the cattle sector, mechanistic modelling has become an important tool for policy support and enhanced decision-making. Although there has been ongoing development of mechanistic cattle disease models in recent decades, there is as yet no overview of the methods that have been used to represent cattle systems and associated processes in these models. To address this gap, we conducted a systematic literature review on mechanistic age-structured cattle disease models tailored to support management decisions.

The goal of this study is to provide an overview of these models regarding their theoretical foundations, design paradigms and incorporated processes. In particular, we ask which model elements are used in literature when cattle management was investigated for the purpose of disease related decision support. Thus, we consider models of minimum complexity to allow at least representation of age-related cattle management activities. We acknowledge the huge fundus of cattle disease management models on regional networks of farms, i.e. for Foot-and-mouth disease (FMD) (e.g. Boklund et al. (2013), Keeling et al. (2003) & Tildesley, Smith, & Keeling (2012) and Vector-borne diseases (VEC.-BORNE) (e.g. Gubbins et al. (2008) & Szmaragd et al. (2009)). However, these models are implemented at the herd scale without considering herd management processes and are therefore out of scope of this review.

Our intention was not to judge these models based on their structure and complexity. Rather we were interested in providing a summary of the processes that were considered in the models and how these processes were modelled. Our objective resulted from the intention to design a cattle disease model using most recent state of art in the field of epidemiology.

Results from this study may serve as a guide for future model development and contribute to good modelling practice. Our review differs from previous, disease-specific syntheses (Álvarez et al., 2014; Courtejoie,

Zanella, & Durand, 2018; Marcé et al., 2010; S. S. Nielsen et al., 2011; Viet, Fourichon, & Seegers, 2007) by providing a comprehensive picture of what has been achieved over approximately three decades of cattle disease modelling for decision support while addressing recommendations for the development and documentation of upcoming models.

2. Materials & Methods

2.1. Systematic Search Strategy

Web of Science (WOS) databases were searched electronically on 26 July 2018, by applying a search strategy with four individual components (see Table 1). We linked inclusion terms within each component using the "OR" operator. Whole components were linked using "AND". Whenever search terms appeared in the titles, abstracts or keywords, the articles were retrieved and subjected to further inclusion criteria. We used the wildcard character (asterisk *, Table 1) to include all context combinations of search terms guaranteeing maximum coverage of relevant papers.

2.2. Inclusion & Exclusion of Papers

Relevance screening was conducted on papers identified by the systematic search (Figure 1). In accordance with guidelines for systematic reviews and meta-analysis as proposed in the PRISMA statement, inclusion and exclusion of papers was undertaken using a multi-stage approach (Liberati et al., 2009). First, a relevance screening procedure was applied to the abstracts that had been identified through the search strategy as outlined in Table 1. Here, we retained those papers that applied or developed mechanistic models, which simulate infectious diseases in cattle populations in assistance of animal health decision-making. In a second step, a full text screening was conducted on all articles retained to this point. We applied an additional inclusion criterion to further refine the scope of this study, namely the retention of those papers in which the proposed models were at least age-structured. Models were classified as having an age structure if either the herd was grouped in age-related compartments (e.g. calves, heifers, cows) without tracking the age of individuals or if the age of individuals was explicitly modelled and animals could be grouped accordingly. Unstructured SIR models were not retained for further analysis. The motivation here was that models of interest must at least be usable to represent minimum farm management e.g. the handling of age groups. In a final step, the reference lists of the eligible papers were scanned for additional literature. For the sake of consistency, the screening process was conducted by a single researcher. External validation was approached by random inclusion testing based on expert input or a targeted literature search by the authors' team. In order

to validate how comprehensive was the conduct of the data extraction process, the whole procedure was repeated twice. Extracted papers of both data extraction processes matched one by one. Only few classification details were refined according to what we found more appropriate.

2.3. Information Extraction

Data were extracted from eligible papers into a standardized Microsoft Access database, designed to document: [1] general model characteristics, [2] cattle related processes, [3] farming related processes and [4] disease transmission characteristics. Data analysis and visualization was conducted entirely in R (R Core Team, 2018).

3. Results

3.1. Screening Process

Our search strategy identified 1290 publications (Figure 1). Abstract screening excluded 1118 papers, yielding 172 articles for full text review. Through full text screening, a further 97 papers were excluded, most commonly because the model(s) lacked complexity with regard to the modelled age structure (e.g. excluding unstructured SIR models). Reference and citation searches identified one additional article for inclusion; therefore 76 papers were eligible for the systematic review. However, not all of these papers were proposing novel system models. In 24 of the 76 retrieved papers, earlier peer-reviewed models were applied (Figure 2B). Hence, the following data summarizes the characteristics of 52 individual cattle disease models (see Table 2) applied to multiple problems (Figure 2B).

3.2. General Model Characteristics

3.2.1. Overall Model Background

Overall, age-structured disease models for cattle populations were developed for 10 countries but almost 80% of all models were calibrated for three countries, namely USA, UK and France (Figure 2A). USA took the lead in the international comparison regarding the number of developed models (16/52). No models originating from Australia, Africa or Asia (except Japan) were encountered. Surprisingly, no age-structured cattle disease models were developed for India, Brazil or China, even though these countries are home to more than 60% of the world´s cattle population (Gilbert et al., 2018).

Nine different diseases/pathogens were the subject of the reviewed models (Figure 2B). Models simulating the spread of MAP and BVDV are the most frequent, collectively accounting for almost 70% of the reviewed models. bTB was the third most often modelled pathogen (6/52), followed by *E. coli* (4/52). Several other

diseases/pathogens have been considered less frequently by the reviewed models, including Salmonella, vector-borne diseases, BLV, brucellosis and mastitis.

The publication of mechanistic age-structured cattle disease models has increased over the past 27 years (Figure 3C). Almost 70% of all reviewed models were published in the last 10 years. However, we did not encounter pathogen-specific differences between the reviewed models.

3.2.2. Model purpose

Based on recommendations from EFSA (2009), three general objectives were distinguished: [1] proof of model, [2] process understanding and [3] comparison of control or surveillance strategies. 17 of the 52 studies reported a model (i.e. [1] proof of model) without an application in the same paper (Figure 3A). Studies that focussed on calibration or parameterization were also assigned to this category. More frequently, the model purpose was improved understanding of a system´s complexity (23/52 i.e. [2]). In particular the question of how infection spreads was addressed in 14 studies. Least frequently (8/52), studies applied the presented model to assess the economic impact of pathogens/diseases. Twelve models were intended to undertake comparison of different strategies i.e. [3]. Of these, the majority (8/12) evaluated and compared different control strategies (e.g. test-and-cull vs. vaccination). Two further models (2/12) assisted with decision-making for the purpose of comparing the effectiveness of multiple post-eradication surveillance strategies (Fischer, Van Roermund, Hemerik, Van Asseldonk, & De Jong, 2005; Yamamoto, Tsutsui, Nishiguchi, & Kobayashi, 2008). The remaining two models (2/12) aimed at optimizing a single control strategy (R. L. Smith, Al-Mamun, & Gröhn, 2017; Thulke et al., 2018).

In this section we additionally considered 24 excluded model application papers in order to provide a comprehensive overview of model purposes. Papers that applied previously published models mainly focused on strategy comparison ([3] see Figure 3B). In five of these 24 papers, the authors sought to provide an improved understanding of relevant processes [2] through the application of mechanistic cattle disease models.

3.2.2. Technical Model Characteristics

The 52 models differed in relation to their technical characteristics. Almost one-third of all reviewed models were deterministic, meaning that outcomes are calculated according to the model equations and parameter

values, while excluding stochasticity (Table 3). The remaining two-thirds were stochastic, i.e. they include a certain degree of randomness.

Model paradigms were 3-fold. Compartmental models, in which the population is divided into subgroups, with the assumption that every individual in the same compartment has the same characteristics, were the predominant model type among the reviewed models (33/52). More recently, beginning in 2004, individual-based models (IBMs) have been developed (15/52), e.g. (Viet, Fourichon, Seegers, Jacob, & Guihenneuc-Jouyaux, 2004). In IBMs (sometimes also referred to as agent-based models) each animal is represented explicitly, thereby allowing for an incorporation of complex patterns of interactions and individual heterogeneity. The application of IBMs requires sufficient computing capacity (Cabral et al., 2017). Hence, hybrid models (4/52), which overcome this problem by coupling compartmentalisation and IBMs have been developed (e.g. Damman et al., 2015). In the hybrid models, most often individual-based sub-models were integrated into a compartmental model basis.

Three different spatial scales in which the models operate were encountered during the review process (Table 3). 78% of all models included in the review were simulating cattle populations for a single herd. Nine models were found to be pseudo-regional (e.g. Courcoul & Ezanno, 2010). Models were termed as pseudo-regional if a meta-population of multiple animal populations were considered without taking into account real geographic information on their locations. In these models, spatial positioning was either determined using a random process or was not applied at all. Finally, two models simulated cattle populations at the regional scale, incorporating real spatial data, such as locations of farms, farm-to-farm movement by date and age cohort etc. (Thulke et al., 2018; Widgren et al., 2016). Similar proportions of models represented herds with open and closed trading statuses.

Two-thirds of the included models provided complete documentation of their considered processes and related parameters (Table 3). We classified model documentation as complete when the information provided in the respective papers and supplementary material would facilitate reimplementation of the model. Accordingly, documentation of 16 models out of 52 were categorised as not complete. Two of the 52 model descriptions followed the ODD protocol (Robins et al., 2015; Thulke et al., 2018). The ODD (overview, design concepts, and details) protocol, proposed by Grimm et al. (2006), is a standardized scheme designed to produce a transparent and comprehensive model description following a generic structure.

3.3. Structuring Cattle Disease Models

In the cattle disease models that were reviewed in this study, a herd was typically split into different cohorts, based on age or production status. Animals in these cohorts were described by state variables determining their common properties (sex, age, pregnancy status, disease status etc.). Sub-models addressed biological (ageing, mortality), farming-related (grouping, insemination, culling) or pathogen-related processes that altered the state variables according to the time steps in which the models operated. Based on the alteration of the state variables, animals e.g. grew or died, became pregnant and gave birth to a calf or suffered from infection.

In the following sections the processes of the cattle disease models are structured according to the categorization biological, farming-related and pathogen-related.

3.3.1. Biological Processes

Several aspects of a bovine's biological lifecycle were taken into account over the 27 years of modelling. The review identified seven different biological processes that were represented in at least one of the 52 models. An overview of these processes and their proportional consideration is shown in Figure 4A. Ageing and calving were simulated in all of the 52 reviewed models. Ageing was always modelled via the simulation steps: with each simulation step the age of the animals increased accordingly. Calving was instead either modelled explicitly by means of a calving rate or emerged from the pregnancy and/or fertility sub-model. The decision as to whether certain biological processes were included or not in the models related to the modelled pathogen (e.g. Figure 4B). Reproductive processes, such as fertility and pregnancy, were considered in more than 85% of models of BVDV, whereas only a few (20%) of the reviewed bTB models represented fertility and neglected pregnancy as the disease is not transmitted vertically. Other examples of pathogen-specific process selection can be read from the Supplementary Material.

There were differences in how the same processes were implemented in different reviewed models. Generally, the biological processes were either implemented explicitly or emerged from other sub-models. Explicitly modelled processes were classified according to how they were implemented, which can either be deterministic (with interaction), stochastic (with interaction) or emergent. For example, fertility was sometimes simulated deterministically by means of a fertility rate. This rate determined the proportion of animals which would conceive given breeding as equal throughout all cattle, independent of age or group. Several models used multiple fertility rates depending on the management group (cow or heifer) or age cohort of the breeding animals which was classified as modelled deterministically with interaction. Other model variants included the effect of chance. Here the fertility rate parameter was interpreted as a central tendency and converted into a

221 stochastic event to become pregnant or not following breeding. Depending on the underlying model paradigm
222 the probabilities were drawn either from binomial distributions (compartmental models) or from a Bernoulli
223 distribution (individual-based models). As before, different fertility parameter values were assumed depending
224 on an animal's age or group membership categorising the model approach as stochastic with interaction. In
225 some of the reviewed models processes that were not modelled explicitly were triggered by other processes.
226 For instance, the change in physiological status from non-pregnant to pregnant was induced as a combined
227 outcome of both the fertility sub-model and the farmer-related breeding sub-model. In this model solution, the
228 event of getting pregnant (conception) was categorised as emergent (Grimm et al., 2006).
229
230 To illustrate these, we developed a parallel coordinates plot (Figure 5) for the MAP models, indicating how
231 physiological reproductive mechanisms were represented on the vertical axis. The plot indicates that the
232 implementation of reproduction processes in models of MAP depended mainly on the underlying model
233 paradigm. Compartmental models often neglected the reproductive processes or alternatively, summarized all
234 the processes into one rate of calving. IBMs of MAP in contrast represented the reproductive processes of a
235 cow with a higher degree of complexity. In these models, the implementation of fertility as an example often
236 showed some degree of stochasticity and triggered other events such as conception and calving time.

237 ***3.3.2. Farming-related Processes***

238 The review identified eight different farming-related processes that were represented in at least one of the 52
239 models (see Figure 4C). In particular, grouping (the allocation of animals in cohorts) and culling appeared as
240 important components of cattle disease models and were included in all of the reviewed models. Another
241 component playing a vital role for disease transmission is whether cattle are indoors or outdoors. Nearly 25%
242 of the models incorporated a change between indoor and outdoor rearing. To the same extent, calving or
243 breeding windows imposed by the farmer were accounted for. Comparing the proportional consideration of
244 processes between models of BVD and MAP, differences were apparent for the farming-related activities
245 regarding breeding (Figure 4D). The remaining processes were considered almost identical.

246 ***3.3.3. Pathogen-related Processes***

247 In all of the reviewed models, individuals or compartments were assigned to discrete health states and
248 transitions between these states represented the infection, disease and recovery process. In the models we
249 reviewed transmission happened via several modes and depended on the biological characteristics of the
250 modelled disease. The epidemiological dynamics that have been used in the reviewed cattle disease models

represent three main modes of pathogen dissemination: direct contact transmission, vertical transmission and environmental transmission.

3.3.3.1. Direct Transmission

Direct transmission corresponds to all processes where the disease is transmitted from an infected host to a susceptible host by direct contact. A so-called force of infection is used to determine the number of newly infected animals per simulation step. Overall, three formulations of the force of infection were used in the reviewed models (see Table 4).

Most often (in 37% of the models that accounted for direct transmission) a deterministic transmission model was used that calculates a transmission rate (calculation indicated in bold font), which is then used to derive the cohort rate of change (ΔI) at which susceptible animals (S) become infected. The way in which the transmission rate is calculated varied, depending on whether a frequency ($\beta I/N$) - or density ($\beta I/1$) - dependent transmission was assumed.

In the density-dependent transmission model it is assumed that force of infection does equally increase with the amount of infectious cattle, independent of herd size. In frequency-dependent transmission models it is presumed that force of infection must not increase with the amount of infectious cattle if the proportion of infected is the same for differently sized farms. The latter is often used to represent limited contact number in short time compared to the assumed overall mixing in the former.

The frequency- or density-dependent transmission rates are standardized to the time step in which the models operate and can each be converted into an individual probability. This is done by using the calculated rate in the following equation: $P_{inf} = 1 - exp^{-(transmission\ rate)}$. An individual probability is estimated and applied to each susceptible animal, which determines an individual's chance of becoming. In 35% of the models that simulated direct transmission, this probability was used.

The third way used to calculate the probability of a susceptible animal becoming infected was a Reed-Frost transmission model. In a Reed-Frost model, the probability of infection is expressed as one minus the probability of not being infected. The individual force of infection (see Table 4 second row; indicated in bold) describes the within-contact chance of becoming infected i.e. calculated as $p = ks/N$ in the Reed-Frost model where k is the number of effective contacts made by an individual during one time period, s is the susceptibility

of the individual to acquire the disease and *N* the size of the population at risk of contact with the infective animals.

3.3.3.2. Vertical Transmission

For some diseases (in this review BVDV, MAP and VEC. - BORNE), congenital transmission from dam to calf in utero was considered. Commonly this is termed vertical transmission. If a pregnant dam is infected, various outcomes were modelled, including embryonic death, abortion, congenital defects, birth of an immune calf or birth of an infected calf, depending on the pathogen and other factors (Kendrick, 1971; Whittington & Windsor, 2009). Vertical pathogen transmission was represented in two thirds (35/52) of the reviewed models. Depending on the modelled disease, outcomes were determined either by the age of the foetus at the time of infection or more simply by the infectious state of the dam. Taking models of BVDV as an example, vertical transmission was modelled with two alternative approaches. For 9 of the 13 BVDV models, the pregnancy period was first split between two (Innocent, Morrison, Brownlie, & Gettinby, 1997) and nine (McCormick, Stott, Brülisauer, Vosough Ahmadi, & Gunn, 2010) different stages. Then, deterministic rates or probabilities are assigned to each of the different stages triggering the different possible consequences. In the remaining four BVDV models, the pregnancy period was not divided into different stages. In these models, the infection status of the calf was randomly allocated if susceptible dams become infected during pregnancy.

In the MAP models, vertical transmission was modelled independent of the time of infection during gestation. In these models, the chance that a calf getting infected *in utero* solely depended on the infectious state of the dam. Depending on whether vertical transmission was modelled in a compartmental model or using an IBM, predefined rates or probabilities were used.

3.3.3.3. Indirect Pathogen Transmission

In addition to direct and vertical transmission, disease spread was modelled indirectly via several pathways. Here we use the term “indirect” transmission for all pathways that replace direct animal contacts and require the pathogen to persist in the intermediate environment for a certain period of time (for brevity, we subsume the one vector-borne example but appreciate this approach is debatable). Several types of indirect pathogen transmission were taken into account in the reviewed models, including pathogen transmission by contact with a contaminated object (e.g. boots, clothes, equipment or other fomites,), through the air by aerosols, through faeces in the calving area or ingestion of contaminated milk or colostrum. Here, it is worth mentioning that movement of animals between farm-sections and farms (e.g. animal purchase) is not to be equated with

313 indirect transmission. Rather, these animals have been infected in advance by one of the several transmission
314 modes and are capable of infecting susceptible animals directly.
315
316 The decision on whether or not to incorporate indirect pathogen transmission was associated with the
317 biological characteristics of the modelled pathogen. In the studies reviewed, indirect pathogen transmission
318 was simulated in models of MAP, *E. coli*, vector-borne diseases, Salmonella, bovine leukaemia virus and
319 brucellosis. Generally, the different types of indirect transmission that were taken into account in the reviewed
320 models can be summarized by two major groups: [1] environmental infection and [2] pseudo-vertical
321 transmission. Environmental infection accounts for pathogen transmission by contact with contaminated
322 objects, people or materials that routinely move around or between farms, through the air by aerosols or in
323 some cases transmission across farm boundaries. The processes of infection via the environment were either
324 modelled by including an unspecific term in the infection model, which depended on the number of infectious
325 animals in other groups or neighbouring herds (Ezanno, Fourichon, Viet, & Seegers, 2007), or by explicitly
326 modelling pathogen excretion into a local and/or global environment (Joanne Turner, Begon, Bowers, &
327 French, 2003). Two papers study the impact of the indirect transmission function used on model predictions
328 (Hoch et al. 2008; Ögren & Martin, 2002).
329
330 Pseudo-vertical pathogen transmission refers to neonatal infection of the calf by its dam due to faeces in the
331 calving area or the ingestion of contaminated milk or colostrum. Especially for models of MAP, pseudo-
332 vertical pathogen transmission played a recognised role in the transmission dynamics and is thus accounted for
333 in 90% of the models.

334 **4 Discussion**

335 Over the last three decades, process-oriented mechanistic cattle disease models have been developed to assist
336 with animal-health decision-making about control and surveillance planning. Within this study we provide an
337 overview of the range of model solutions that have been applied, thereby providing insights into the breadth of
338 mechanisms relevant to cattle disease modelling.
339
340 This systematic review benefits from a comprehensive, strategic search routine and categorization of
341 potentially relevant publications according to the PRISMA statement, a guideline for reporting systematic
342 reviews. The complete repeat of our data gathering procedure confirmed that our data actually covers model
343 candidates accessible by our search till the end date in July 2018. Limitations of this study are that we may not

have identified all potentially relevant publications e.g. by limiting to English language. However, this would only be a problem if the models we missed would present completely novel approaches for the development of decision-support cattle disease models. Additionally, models that tackle vector-borne diseases, often are developed for a large spatial scale and animals are represented by location instead age (Reiner et al., 2013). This could be the reason why models of vector-borne diseases are underrepresented in this review due to our minimum requirement of an age-structured representation.

Our review protocol focussed studies published until end of July 2018. During the peer-review process the authors were said that eight other papers also eligible according to our criteria were published after the end of our study and could be mentioned. Therefore, we additionally list the following eight studies: Calsamiglia et al. (2018), Camanes et al. (2018), Gussmann et al. (2018), Iotti et al. (2019), Kirkeby et al. (2019), Qi et al. (2019), Rossi et al. (2019) and Widgren et al. (2018). The authors were said that for example Camanes et al. (2018) is a new IBM MAP model at herd scale, Iotti et al. (2019) is a new BVDV model with an original way of accounting for herd specificities and Qi et al. (2019) is a new BVDV model at regional scale.

The lessons learnt from this study were two-fold. First, we achieved our intended goal to assemble a structured overview of technicalities and principles of existing age-structured cattle disease models that assist with animal health decision making. Secondly, we identified a self-evident logic for structuring the ingredients of cattle disease models into biological, farming-related and pathogen-related processes. Even if this logic seems obvious it was not yet explored in literature.

4.1. Good modelling practice

Our initial objective, to provide an overview of world´s cattle disease models, was motivated by our impression of the variety of existing models. This intention was supported by the 52 different models that we encountered in this study, using a range of approaches in terms of mechanisms and processes to explicitly address diseases in cattle. The large number of different models caused us to question why there are so many different models and what makes them different from each other, while all addressing disease spread in cattle. Why didn´t we find one more or less unchanged model adapted for alternative diseases and infection scenarios? An answer to this question is included within our analysis and depicts the validity of several well acknowledged paradigms of good modelling practice.

The degree of detail with which a model describes a system is determined by the peculiarities of the system itself. For instance, we recognised differences related to pathogen-specific modelling, meaning that only those

processes were taken into account which were considered important for the disease under investigation and the questions posed. A comparison of the proportional consideration of biological processes in models of BVDV and bTB revealed differences in the inclusion of the reproductive processes (fertility and pregnancy) of a cow. Whereas bTB models typically neglected these processes, nearly all BVDV models included the relevant processes. The apparent differences can be explained by the epidemiology of the diseases (see Ezanno, Fourichon, & Seegers (2008). For BVDV, prenatal infections are the main determinant for disease spread (Lanyon, Hill, Reichel, & Brownlie, 2014). For a certain window of pregnancy, *in utero* infection of the foetus results in the birth of persistently infected calves which are recognised as being the major source of BVDV spread. Thus, simulating reproductive processes in models of BVDV is fundamental to represent the disease adequately. In contrast, a representation of reproductive processes for bTB models is unnecessary and would add useless complexity as the disease is not transmitted vertically.

A number of modelling studies state that IBMs were chosen due to their ability to represent complicated patterns and emergent phenomena. In this study, we wanted to determine whether authors of the models made use of the capabilities of IBMs and actually represented processes with a greater level of detail. Indeed this was the case, cattle disease modellers used the capabilities of IBMs and represented e.g. reproductive with a higher degree of complexity than compartmental models (Fig. 5).

4.2. Structuring Cattle Disease Models

The 52 models may have been more readily comparable if the authors of the cattle disease models had taken a more modular view in terms of the included processes. This leads us back to the second achievement of this study, the proposed structure. In this review, we structured the key characteristics of cattle disease models by these three main features: **[1] biological processes**, **[2] farming-related processes** and **[3] pathogen-related processes**. Biological processes comprise all natural biological processes of a bovine in the absence of human interaction (e.g. ageing, fertility). In contrast, farming-related processes reflect the farmers´ actions. These include all processes whereby the farmer impacts the natural life history of bovines (e.g. culling, grouping). The last category includes processes related to pathogens (e.g. pathogen transmission and disease course). During the review, we found a total of 18 elements/processes (7 biological + 8 farming-related + 3 pathogen-related) that were accounted for while simulating the spread of infectious diseases in cattle (Figure 6). This proposed logic helped us to structure the mess that we observed, and facilitated the comparison of the models. We believe the added value of our structure is threefold as it may [1] improve transparent model reporting, [2] enhance conceptual model development and [3] simplify model implementation. Therefore, we propose that the elements of a cattle disease model are structured according to three main features: biological processes, farming-related processes and pathogen-related processes. We acknowledge that the listing in Figure 6 is only

temporary and may extend in future together with more complex problems addressed with cattle disease models.

4.2.1 Model documentation

In the reviewed cattle disease modelling publications, the emphasis has been on the interpretation and communication of model outcomes, while transparent and comprehensive model documentation was of secondary importance. Also the models that we have classified as fully documented were sometimes difficult to replicate from the published description and do not therefore fulfil the requirements of good modelling practice proposed by Schmolke, Thorbek, DeAngelis, & Grimm (2010). We corroborate the paradigm that standardizing model documentation would be a valuable starting point to implement good modelling practice. Therefore, we suggest structuring the documentation of cattle disease models according to our proposed classification of the included processes. We believe that such a harmonized model description would be accurate in a way that it raises readers' expectations about what information should be expected and where it can be found.

The structure proposed by us can be easily integrated into Grimm´s et al. (2006) ODD protocol. The ODD protocol is a standardized scheme designed to produce a transparent and comprehensive model description following a generic structure. It consists of seven elements: Purpose, State variables and scales, Process overview and scheduling, Design concepts, Initialization, Input, and Sub-models. In the sub-model section all implemented processes are presented and explained in detail. Here it is advisable to structure this section according to the key characteristics (biological, farming- and pathogen-related processes) of cattle disease models.

4.2.2. Model implementation

Most beneficially, we see the possible impact of our proposed structure on conceptual and participatory model development which is a hot topic in current project debates. The development of a decision-support model is always a participatory project in which the goal is for participants to co-develop the model (Voinov & Bousquet, 2010). Often, the diversity of participants is high and includes those with high levels of technical and mathematical expertise and those with other relevant experience e.g. in farming practices, disease control, or other fields. Nevertheless, all participants (including those with less numerical and technical skills) should be engaged in the development of the model, which presupposes high transparency and accessibility of the

included processes. We are convinced that high transparency will be achieved by deconstructing the system to be modelled into its basic elements, ergo into its biological, farming-related and pathogen-related processes. For the models we reviewed it seems that authors have not consequently broken down the system into its individual processes. A comparison of the proportional inclusion of farming-related processes between models of BVDV and MAP revealed differences in terms of the farmer-induced reproductive processes (Figure 4D). It is well recognized that both pathogens can be transmitted vertically, but in contrast to MAP the age of the foetus at time of infection is playing a vital role for BVDV transmission (Lanyon et al., 2014). Instead of considering these different system behaviours solely by a more detailed representation of the breeding-related biological processes (e.g. fertility and pregnancy) a considerable number of BVDV models have also represented farmer-induced reproductive processes with a high level of detail. Such an implementation implies that the farmer him/herself can influence the biology of the disease, which is not true in reality. A farmer will breed animals irrespective of the presence of a pathogen. The apparent mixing of processes in models of BVDV is not wrong per se, but it neglects the logical separation of system processes and thereby, hampers the transparency of a model.

Deconstructing the ingredients of a cattle disease model at the stage of conceptual model development will also help with model implementation, especially if a modular programme structure is chosen. Such modules enforce logical boundaries between the components of a model and thereby improve maintainability (Bugliesi, Lamma, & Mello, 1994). Besides a higher flexibility in design, modularity offers other benefits such as augmentation (adding new solutions by merely plugging in a new module) and exclusion. For the development of decision-support models, modularity is of high importance to overcome changing stakeholder demands (new control strategies etc.) and to make the implementation process more adaptive to change. This will become more easier by using our proposed structure.

5 Conclusion

Our review provided a comprehensive overview of the state of the art of age-structured cattle disease modelling. Although cattle disease models are gaining importance in decision support, no specific guideline exists for their development and documentation. The literature review supports structuring cattle (and likely other livestock) disease models by their key components: [1] biological processes, [2] farming-related processes and [3] pathogen-related processes. Approaching the complexity of a cattle disease model according to this structure is valuable for conceptual design, model implementation and transparent reporting. We are

convinced that these results can serve as a guide for future model development, reinforcing good scientific modelling practice conducted at the interface with decision support.

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Conflict of interest

No conflict of interest.

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Figures & Tables (all figures are intended for colour reproduction in web and print, tables can be printed without colors)

Table 1 Search strategy applied on 26th of July 2018

Set	Search string	Resulting
#1	TS=(cattle) OR TS=(beef herd*) OR TS=(dairy herd*)	161,045
#2	TS=(model*)	6,966,517
#3	TS=(control* program*) OR TS=(control* strategy*) OR TS=(contact structure*) OR TS=(transmis*) OR TS=(outbreak*)	1,658,039
#4	#3 AND #2 AND #1	2,630
#5	TS=(decision* support*) OR TS=(evaluat* efficacy) OR TS=(hypothesis test*) OR TS=(herd dynamic*) OR TS=(herd management) OR TS=(scenario*) OR TS=(strategy*) OR TS=(decision* make*)	2,672,635
#6	#5 AND #4	1,290

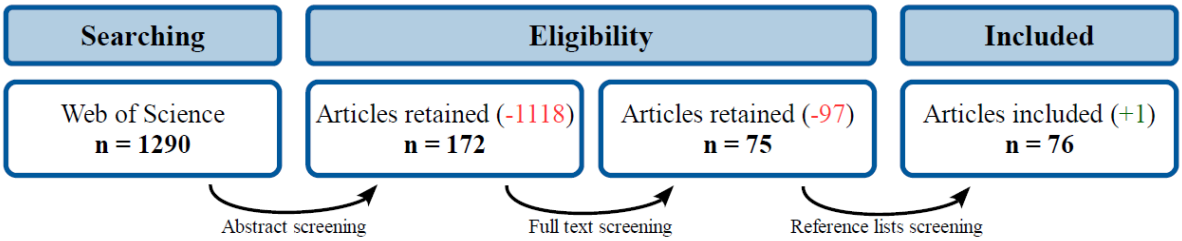


Figure 1 Adapted PRISMA flow diagram representing the selection process

Table 2 Included models

Author	Pathogen	Year	Study area	Cattle system	Effect of chance	Model paradigm	Spatial scale
Al-Mamun et al. (2016)	MAP	2016	USA	Dairy	Stochastic	Individual based	Herd based
Barbudo et al. (2008)	BVDV	2008	UK	Beef	Stochastic	Compartmental	Herd based
Beaunée et al. (2015)	MAP	2015	France	Dairy	Stochastic	Compartmental	Pseudo-regional
Bekara et al. (2014)	bTB	2014	France	Mixed	Stochastic	Compartmental	Herd based
Bennett et al. (2010)	MAP	2010	UK	Beef	Deterministic	Compartmental	Herd based
Brooks-Pollock et al. (2013)	bTB	2013	UK	Mixed	Deterministic	Compartmental	Herd based
Charron et al. (2011)	VEC.-BORNE	2011	France	Mixed	Deterministic	Compartmental	Herd based
Cho et al. (2012)	MAP	2012	USA	Dairy	Deterministic	Compartmental	Herd based
Collins & Morgan (1991)	MAP	1991	USA	Dairy	Deterministic	Compartmental	Herd based
Courcoul & Ezanno (2010)	BVDV	2010	France	Dairy	Stochastic	Compartmental	Pseudo-regional
Damman et al. (2015)	BVDV	2015	France	Beef	Stochastic	Hybrid	Herd based
Dorshorst et al. (2006)	MAP	2006	USA	Dairy	Deterministic	Compartmental	Herd based
Ezanno et al. (2007)	BVDV	2007	France	Dairy	Stochastic	Compartmental	Herd based
Fischer et al. (2005)	bTB	2005	Netherlands	Dairy	Stochastic	Individual based	Pseudo-regional
Gates et al. (2014)	BVDV	2014	UK	Mixed	Stochastic	Individual based	Pseudo-regional
Gaucel et al. (2009)	BVDV	2009	France	Mixed	Deterministic	Compartmental	Herd based
Groenendaal et al. (2002)	MAP	2002	Netherlands, USA	Dairy	Stochastic	Compartmental	Herd based
Gunn et al. (2004)	BVDV	2004	UK	Beef	Stochastic	Compartmental	Herd based
Humphry et al. (2006)	MAP	2006	UK	Beef	Stochastic	Compartmental	Herd based
Innocent et al. (1997)	BVDV	1997	UK	Dairy	Stochastic	Compartmental	Herd based

Kirkeby et al. (2016)	MAP	2016	Denmark	Dairy	Stochastic	Individual based	Herd based
Kirkeby et al. (2017)	MAP	2017	Denmark	Dairy	Stochastic	Individual based	Herd based
Kudahl et al. (2007)	MAP	2007	Denmark	Dairy	Stochastic	Individual based	Herd based
Lu et al. (2013)	MAP	2013	USA	Dairy	Deterministic	Compartmental	Herd based
Marcé et al. (2011)	MAP	2011	France	Dairy	Stochastic	Hybrid	Herd based
Massaro et al. (2013)	MAP	2013	USA	Dairy	Deterministic	Compartmental	Herd based
McCormick et al. (2010)	BVDV	2010	UK	Beef	Stochastic	Hybrid	Herd based
Mitchell et al. (2008) - A	MAP	2008	USA	Dairy	Deterministic	Compartmental	Herd based
Mitchell et al. (2008) - B	MAP	2008	USA	Dairy	Deterministic	Compartmental	Herd based
Mitchell et al. (2015)	MAP	2015	USA	Dairy	Deterministic	Compartmental	Herd based
Monti et al. (2007)	BLV	2007	Argentina	Dairy	Stochastic	Compartmental	Herd based
Moustakas & Evans (2015)	bTB	2015	UK	Mixed	Deterministic	Individual based	Pseudo-regional
Nielsen et al. (2012)	SALM.	2012	Denmark	Dairy	Stochastic	Individual based	Herd based
Østergaard et al. (2005)	MAST.	2005	Denmark	Dairy	Stochastic	Individual based	Herd based
Raboisson et al. (2014)	VEC.-BORNE	2014	France, UK	Beef	Deterministic	Compartmental	Pseudo-regional
Robins et al. (2015)	MAP	2015	USA	Dairy	Stochastic	Individual based	Herd based
Sekiguchi et al. (2018)	BVDV	2018	Japan	Dairy	Stochastic	Individual based	Pseudo-regional
Smith et al. (2010)	BVDV	2010	USA	Beef	Stochastic	Compartmental	Herd based
Smith et al. (2014)	bTB	2014	USA	Beef	Stochastic	Compartmental	Herd based
Smith et al. (2015)	MAP	2015	USA	Dairy	Deterministic	Compartmental	Herd based
Smith et al. (2017)	MAP	2017	USA	Dairy	Deterministic	Compartmental	Herd based
Thulke et al. (2018)	BVDV	2018	Ireland	Mixed	Stochastic	Hybrid	Regional
Turner et al. (2003)	E. COLI	2003	UK	Dairy	Deterministic	Compartmental	Herd based
Turner et al. (2006)	E. COLI	2006	UK	Dairy	Stochastic	Compartmental	Herd based
Turner et al. (2008)	E. COLI	2008	UK	Dairy	Stochastic	Compartmental	Herd based
VanderWaal et al. (2017)	bTB	2017	Uruguay	Mixed	Stochastic	Compartmental	Pseudo-regional
Verteramo-Chiu et al. (2018)	MAP	2018	USA	Dairy	Stochastic	Individual based	Herd based
Viet et al. (2004)	BVDV	2004	France	Dairy	Stochastic	Individual based	Herd based
Widgren et al. (2016)	E. COLI	2016	Sweden	Mixed	Stochastic	Individual based	Regional
Xiao et al. (2005)	SALM.	2005	UK	Dairy	Deterministic	Compartmental	Herd based
Xiao et al. (2006)	SALM.	2006	UK	Dairy	Stochastic	Compartmental	Herd based
Yamamoto et al. (2008)	BRUC.	2008	Japan	Dairy	Stochastic	Individual based	Pseudo-regional

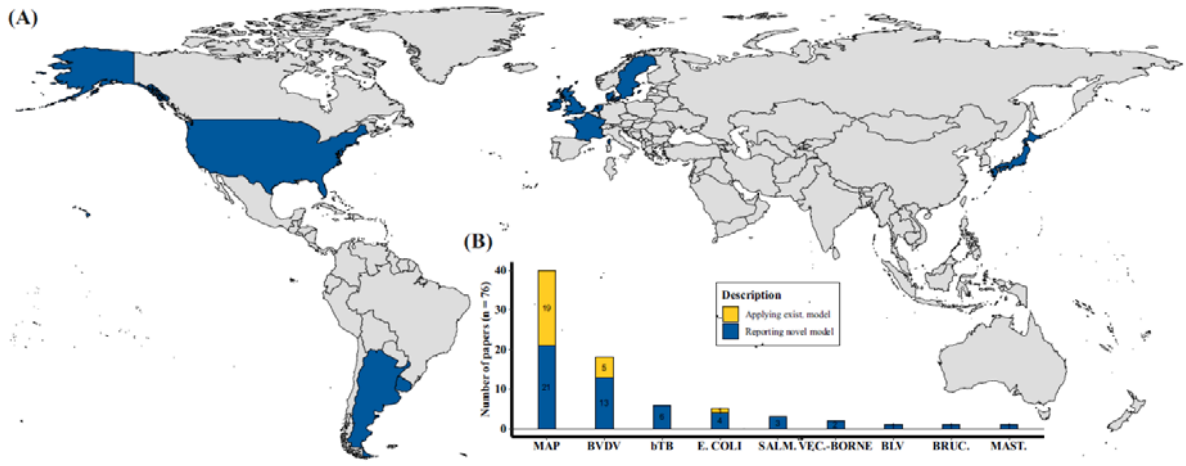


Figure 2 General model characteristics. (A) Countries where cattle disease models have been developed (blue). (B) Number of papers (n = 76) and models (n = 52) per pathogen/disease. *Mycobacterium avium* subspecies *paratuberculosis* (MAP), bovine viral diarrhoea virus (BVDV), *Escherichia coli* (*E. coli*), *Mycobacterium bovis* (bTB), Salmonella (SALM.), Vector-borne diseases (VEC.-BORNE), Bovine Leukaemia Virus (BLV), Brucellosis (BRUC.), Mastitis (MAST.).

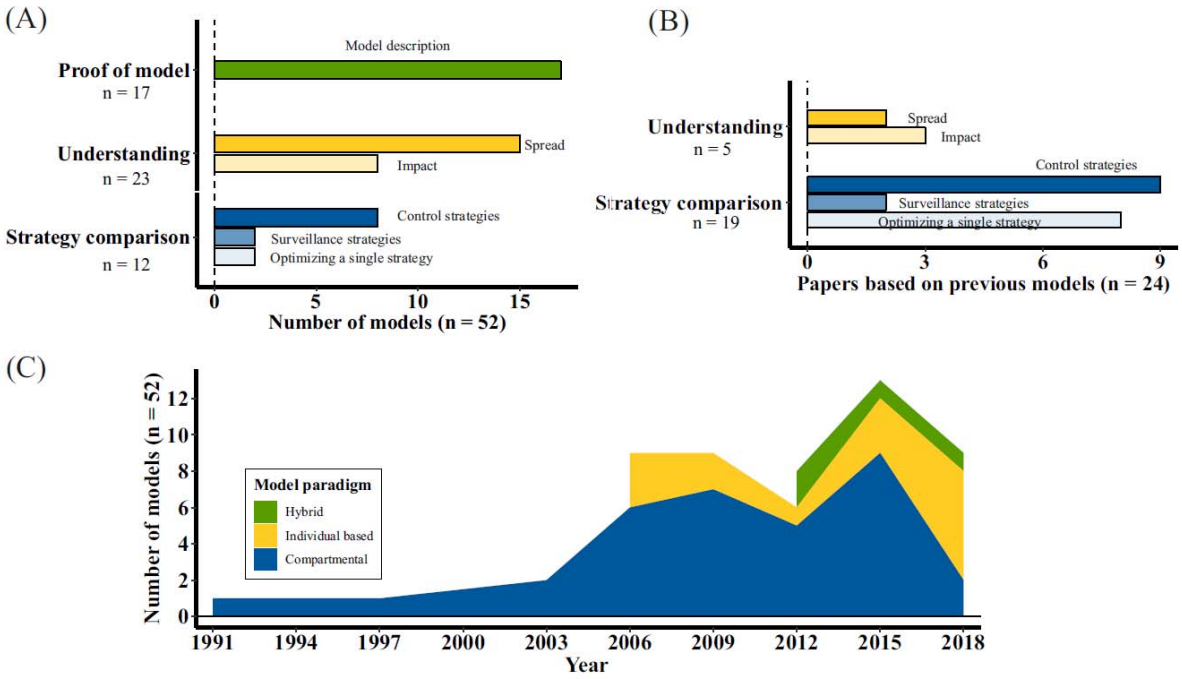
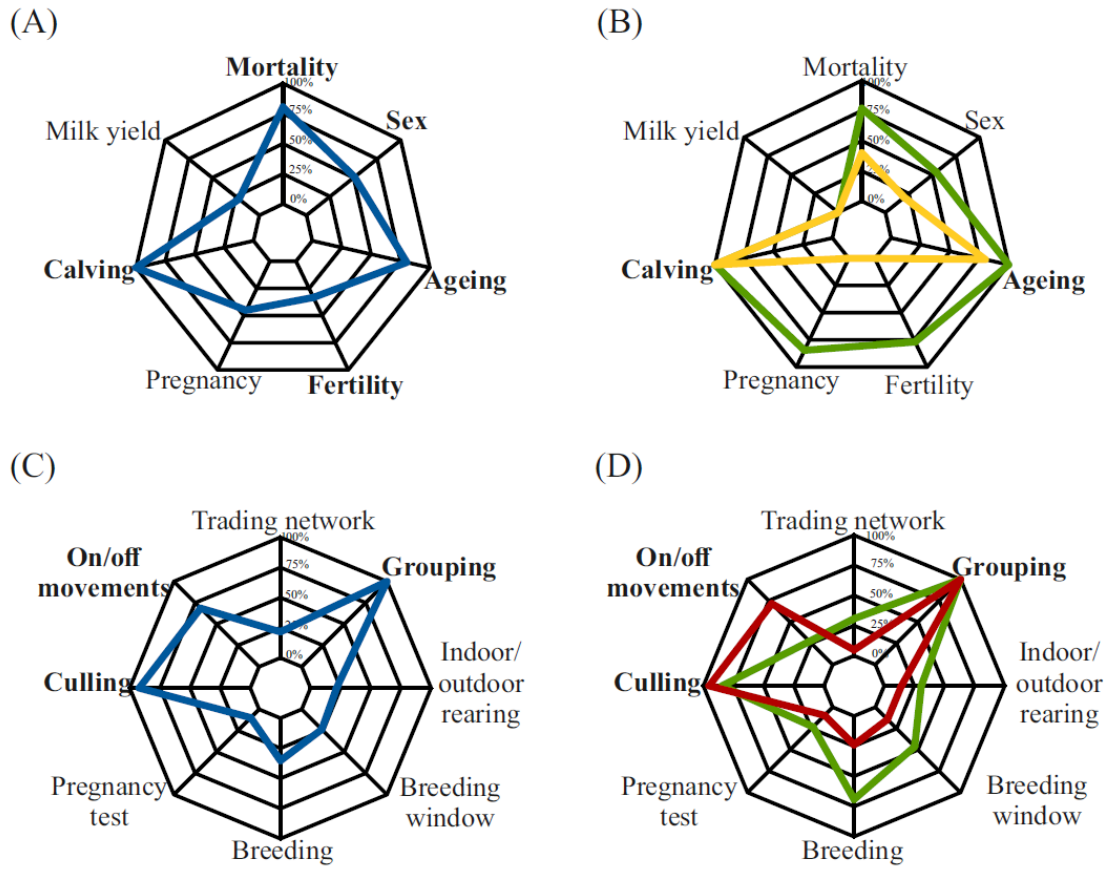


Figure 3 Purpose of the models (A), purpose of the excluded papers where previous models had been applied (B) and model paradigm over time (C).

Table 3 Technical elements of mechanistic cattle disease models. Most prevalent concepts (>60%) are indicated in bold.

Technical characteristics		Number of models (%)
Effect of chance	*Deterministic*	17 (31%)
	Stochastic	35 (69%)
Model paradigm	***Compartmental***	33 (63%)
	Individual-based	15 (29%)
	Hybrid	4 (8%)
Cattle system	***Dairy***	34 (67%)
	Beef	9 (18%)
	Mixed	9 (15%)
Spatial scale	***Herd-based***	41 (78%)
	Pseudo-regional	9 (17%)
	Regional	2 (5%)
Trading status	*Open herd*	26 (50%)
	Closed herd	26 (50%)
Model documentation	*Not complete*	16 (31%)
	Complete	34 (65%)
	ODD protocol	2 (4%)



781

782 **Figure 4 Biological and farming-related processes. Proportional consideration of: (A) biological cattle processes in**
783 **all 52 models; (B) biological processes in BVDV (green) and bTB (yellow) models; (C) farming-related processes in**
784 **all 52 models; (D) farming-related processes in BVD (green) and MAP (red) models.**

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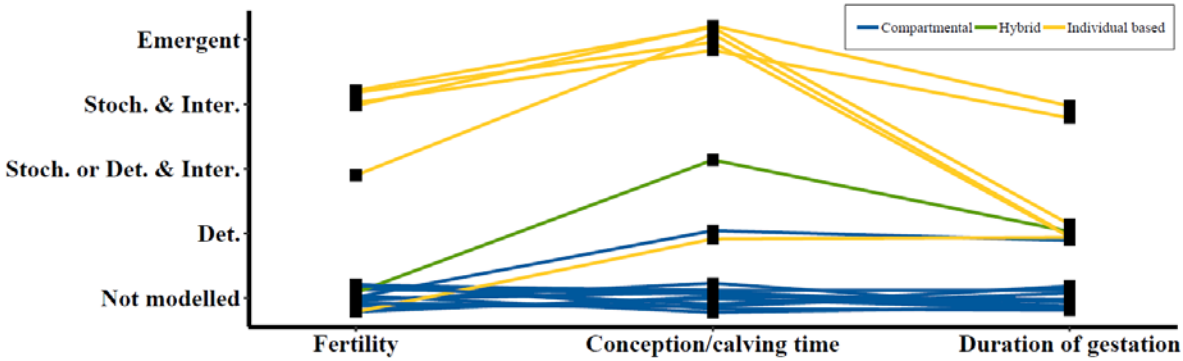

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787 **Figure 5 Parallel coordinates plot of all MAP models (n = 21). Each model is represented as a line highlighted in**
788 **blue, green or yellow, indicating compartmental, hybrid or individual-based models, respectively.**

789

790 **Table 4 Forms of the force of infection to represent direct pathogen transmission**

Transmission model	Formula	Prop. consideration
Individual probability (Frequency | Density dependent)	$P_{inf} = 1 - exp^{-\left(\beta_{I(x)} \cdot \frac{I_{(x)}}{N \mid 1}\right)}$	35% $\beta_{I(x)}$ = Transmission coefficient for infectious state x $I_{(x)}$ = Number of infected animals in state x N = Number of all animals
Individual probability (Reed-Frost)	$P_{inf} = 1 - \left(1 - \frac{k \cdot s}{N}\right)^{I_{(x)}}$	28% k = Number of effective contacts s = Susceptibility of each animal $I_{(x)}$ = Number of infected animals in state x N = Number of all animals

Cohort rate of change	$\Delta I \sim S \cdot \beta_{I(x)} \cdot \frac{I_{(x)}}{N \mid 1}$	37% S = Number of susceptible animals $\beta_{I(x)}$ = Transmission coefficient for infectious state x $I_{(x)}$ = Number of infected animals in state x N = Number of all animal

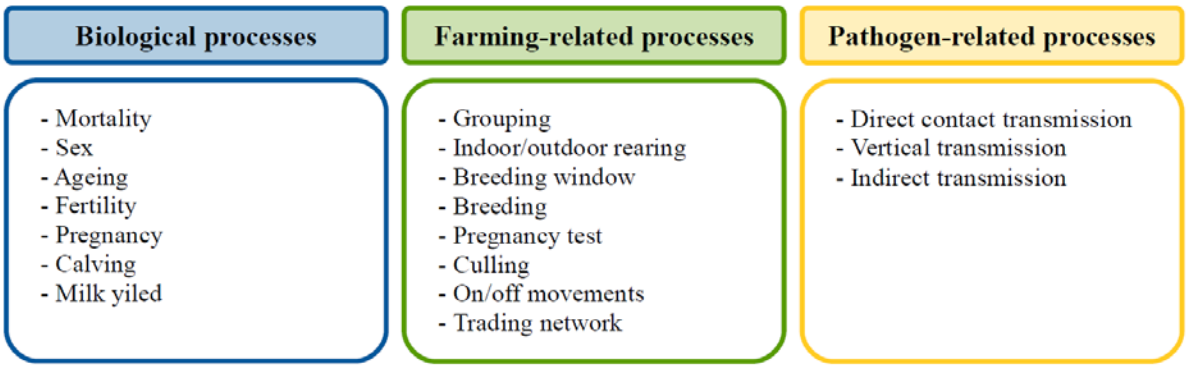

Figure 6 Processes considered in the 52 reviewed models.