How mechanistic modelling supports decision making for the control of enzootic infectious diseases

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ABSTRACT

Controlling enzootic diseases, which generate a large cumulative burden and are often unregulated, is needed for sustainable farming, competitive agri-food chains, and veterinary public health. We discuss the benefits and challenges of mechanistic epidemiological modelling for livestock enzootics, with particular emphasis on the need for interdisciplinary approaches. We focus on issues arising when modelling pathogen spread at various scales (from farm to the region) to better assess disease control and propose targeted options. We discuss in particular the inclusion of farmers' strategic decision-making, the integration of within-host scale to refine intervention targeting, and the need to ground models on data.

1. Introduction

The control of animal diseases is a major challenge not only for sustainable livestock farming and competitive agri-food supply chains, but also for veterinary and public health (Tomley and Shirley, 2009). Disease risks increases due to globalization, especially international human travel and trade of animals and animal products. Although very few comprehensive studies are available at a global level, it is estimated that diseases cause an average loss of 20 % of livestock production (OIE, 2015), with detrimental impact on food security (Tomley and Shirley, 2009). To produce a given amount of animal proteins, more animals are needed, which enhances the negative environmental externalities associated with animal productions (e.g., increasing greenhouse gas, nitrate, land and water use, etc.; Thornton, 2010). Medicine usage also generates detrimental externalities (residues in food, transfer of antimicrobial resistance to humans; Perry et al., 2013). Furthermore, many pathogens have a zoonotic potential (Lefrançois and Pineau, 2014) and can spread at the interface between livestock and humans. They pose a significant threat to public health as illustrated by recent human outbreaks of salmonellosis and Q fever. Reducing the burden of animal diseases is thus a priority to feed the human population while limiting the environmental and sanitary risks (Perry et al., 2013).

Enzootic (also called endemic) infectious diseases in livestock have a substantial impact on farming as they persist over long time periods (Fig. 1), potentially generating a large cumulative incidence, and leading to poor animal welfare, increased use of antibiotics and production losses for farmers (Tomley and Shirley, 2009). They involve various pathogens, with different survival and transmission characteristics, and circulate in a wide range of biological and managerial systems (Radostits et al., 2006). The costliest enzootics for farmers and society are mastitis, lameness, bovine viral diarrhoea (BVD), and tuberculosis in cattle; enzootic abortions in sheep; influenza in pigs; and salmonellosis in poultry (Bennett and Ijpelaar, 2005). Specific data collection is often required to assess the field impact of these diseases as case reports are not mandatory. Indirect evaluation of their impact can however be supported by production data, sometimes routinely collected in livestock.

Predicting the spread and control of enzootics needs to account for

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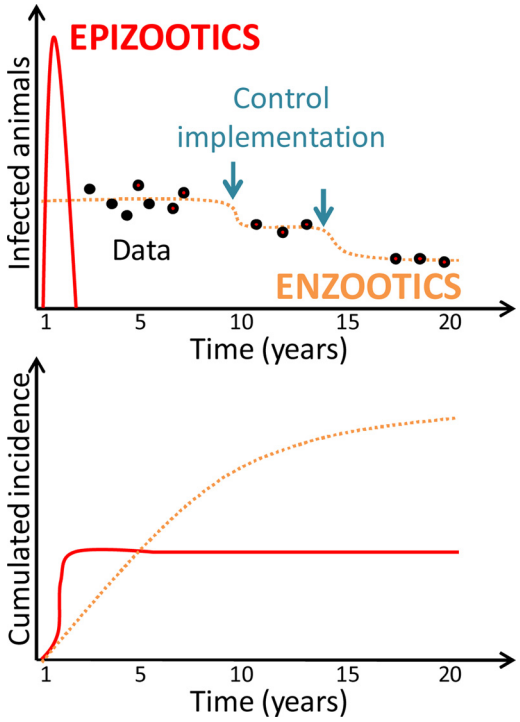

Fig. 1. Epizootic infectious diseases (red) cause major losses over short time periods, while enzootic infectious diseases (dotted orange) persist and can lead to a large cumulative incidence. Data collection is required to assess the field impact of enzootics and assess the efficacy of control strategies. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).

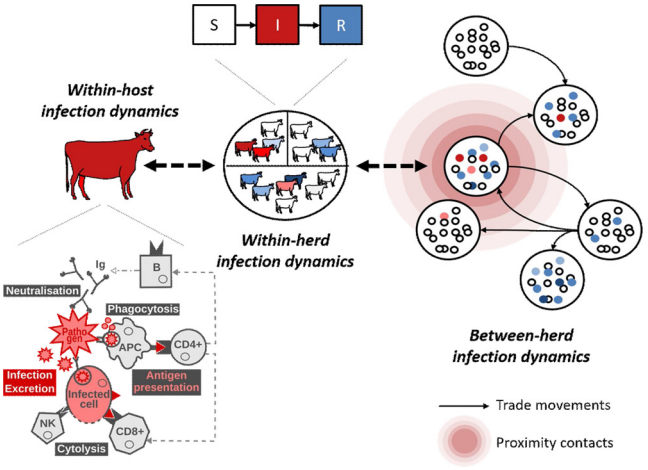

Fig. 2. To better target control measures and decrease the spread of enzootics, multiple scales should be considered: within the host (left) to modulate transmission features, within the herd (middle) accounting for host heterogeneity, managed demography and contacts, and between herds (right) accounting for relevant transmission pathways (trade movements, proximity contacts, …).

specifics of livestock populations. Enzootics frequently display variable levels of prevalence over time within an infected herd, and among infected herds at a given time since pathogen introduction (e.g., in VTEC: Widgren et al., 2015). Hence, herd infection statuses and transitions between statuses cannot be easily determined. They depend on managerial processes (e.g., herd renewal, contact structure, detection and control; Künzler et al., 2014) and on host heterogeneity in susceptibility and infectiousness (Beldomenico and Begon, 2010). Interactions with other herds, evolving over time, also play a significant role (trade, neighbourhood contacts, etc.; Salines et al., 2018). In addition, managing enzootics relates to various control options available for farmers, who are the key decision makers as many enzootics are left to regional or individual regulation (Carslake et al., 2011). Control results from a balance between disease losses and control costs, but also requires a good understanding of the infection process, resource allocation to control actions, and farmers' compliance. However, field observations with regards to these processes are scarce or missing (Brooks-Pollock et al., 2015). In contrast, for epizootics (i.e. epidemics in animals) such as foot-and-mouth disease, African swine fever, and avian influenza, that can easily spread in naive livestock, mitigation strategies are regulated at national or transnational levels (Wentholt et al., 2012).

Since the dynamics of such managed epidemiological systems result from the complex interplay between various phenomena, multiple data sources, scales, and disciplines need to be integrated (Fig. 2). Mechanistic modelling provides a useful framework: it can rigorously describe the multiscale interactions between the elements involved in pathogen spread in a wide range of contexts (Keeling and Rohani, 2008). It also enables assessing *ex ante* control actions. Modelling is complementary to observational approaches which cannot always be implemented on commercial livestock farms for obvious ethical, logistic, and financial reasons. By providing an integrated view of epidemiological systems, it also complements experimental approaches that aim at generating new knowledge on specific biological processes (e.g., in diseases of oysters: Lupo et al., 2019). Through computationally intensive simulations, mechanistic epidemiological models can explore the effectiveness of control strategies at various scales (animal, farm, region, supply chain). For example, targeted vaccination, test at purchase for traded animals, or trade regulations according to source herd statuses can be assessed. Accounting for farmers' decisions in such models, while enabling to account for an adaptive control, remains a challenge.

In this paper, we discuss the benefits and challenges of mechanistic epidemiological modelling for livestock enzootic diseases, with particular emphasis on the need to adopt interdisciplinary and integrative approaches. In the first two sections, we focus on issues related to modelling pathogen spread at the farm and region scales, aiming at better assessing disease control and proposing targeted options. We emphasize the importance of accounting for farmers' decisions in models for enzootics. In the third section, we focus on the within-host dynamics and heterogeneities among animals. We highlight the importance of their inclusion in within-farm models to refine intervention targeting. The fourth section is devoted to the need of grounding models on data to render model outputs et predictions more relevant and meaningful.

2. Spread of enzootic pathogens within a farm

Understanding pathogen spread in animal populations better starts at the local (herd) scale, which has so far been the most studied scale (e.g., for cattle Brock et al., 2020). As with most other hosts, farm animals are heterogeneous in susceptibility and infectiousness. To account for such a heterogeneity without explicitly representing within-host infection, appropriate health statuses and transmission functions need to be considered (Courcoul et al., 2011b). In addition, in many areas, animal herds can be small, in which case stochastic events play a large role and should be accounted for (Lambert et al., 2018).

Three issues have been particularly investigated in livestock enzootics: (1) the interplay between demographic and infection processes, (2) the role of the within-herd contact structure, and (3) the impact of external infectious risks in open populations. First, enzootics usually spread over a much longer time scale compared to epizootics (which can spread rapidly, especially for pathogens introduced in a naïve population). Demographic processes (birth, death, culling, herd renewal, physiological evolution) and related management practices thus occur at comparable time scales as pathogen spread, and should be

considered (Brock et al., 2020). This is even more crucial if vertical transmission is possible, demography and transmission being closely intertwined. For instance, a seasonal breeding during the pasture period, when contacts and transmission are modified, may lead to an increased exposure of gestating females. Second, herds are structured populations, contacts occurring more within than between groups, which possibly impacts pathogen spread (Ezanno et al., 2008; Marcé et al., 2011b). As a typical example, batch management in pig herds largely constrains pathogen carriage (Lurette et al., 2008). However, herd structure has in other cases barely any impact, e.g., when group composition changes over the year (Damman et al., 2015). Third, herds are not isolated entities; they interact with other herds and possibly with wildlife outdoor, inducing an external risk of pathogen introduction through purchases (Ezanno et al., 2006; Frössling et al., 2014) or through proximity contacts (with the same or with other species; Brooks-Pollock and Wood, 2015).

If interactions between pathogens, hosts, and the farm environment are generally well represented, farmer's management decisions are barely accounted for. The farmer manages herd demography (breeding and culling), contact structure (age groups, building usage), and contacts with other herds (trade movements, equipment sharing, pasture usage). Such decisions, which are in most situations not specific to a particular disease, influence pathogen spread. They could be more disease-specific to reduce the disease impact on production (e.g. for bovine tuberculosis in New Zealand, Hidano et al. 2019). In particular, the farmer could decide to improve the internal biosecurity by reducing contacts between groups or enhancing hygiene.

3. Control of enzootics in a farm, prioritisation of options

A key challenge to control enzootics is to make the best use of the various control measures available, which requires to identify the most effective combinations of measures according to the (possibly time varying) sanitary context. To assess the effectiveness of a measure, long term effects should be analysed. Control measures not effective for rapidly spreading epidemics, such as within-herd biosecurity, are worth being considered for enzootics (e.g., in *Salmonella* carriage, Lurette et al., 2011b). In addition, some measures are disease-specific (vaccination as in Q fever, Courcoul et al., 2011a; test-and-cull as in paratuberculosis, More et al., 2015), but others are not (e.g., herd management) whose effectiveness would be better assessed considering the multiple diseases they affect. Finally, it may be impossible to control a disease using a single measure, and measure combinations could be more effective (Camanes et al., 2018). Modelling can be of great help to design effective control schemes.

An additional issue is that a farmer individually decides to control or not an unregulated disease (and his effort level) based on his economic rationality. Individual decisions may be distant from public health objectives, implying possible non-compliance, as well as vary among farmers and over time. This highly contrasts with regulated diseases whose control is decided by the competent authorities leading to almost uniformly complied on-farm measures. However, to assess on-farm disease control, epidemiological models usually compare *a priori* defined strategies (*ex-ante* assessment). Although various strategies can be compared, this assumes that the farmer continuously applies the strategies as defined in the model.

To better account for such a heterogeneity in the decision-making, economic modelling could be helpful to explicitly represent farmers' behaviour with regards to disease control decisions. Economic models first focused on the farmer's trade-off between disease losses and resources allocated to disease control (McInerney et al., 1992), and then on the trade-off between preventive and curative expenses (Chi et al., 2002). Health management has been considered jointly with the various choices to be made on a farm (e.g., breeding, renewal; Santarossa et al., 2005). However, such models only account for the on-farm epidemiological situation, which is only influenced by the farmer's decisions, while the farm infection risk often depends on the regional prevalence. Therefore, microeconomic models should account both for the individual farm epidemiological status and its environment. Because individual decisions also impact the regional prevalence, epidemiological and economic models should be combined to consider the global problem. Such an approach has emerged in human health economics (Brito et al., 1991; Gersovitz and Hammer, 2003, 2004), and was transposed to the control of animal diseases (Gramig and Horan, 2011; Rat-Aspert and Fourichon, 2010). Risk behaviours and temporal preferences (Horan et al., 2010; Enright and Kao, 2015), as well as information bias (Gilbert and Rushton, 2018; Hennessy and Wolf, 2018) start to be accounted for.

4. Spread of enzootic pathogens in a production area or a supply chain

For many enzootics, local infection dynamics must be accounted for to predict infection dynamics at a larger scale. First, herds may have encountered the pathogen before or be exposed to multiple pathogen introductions, which impacts herd immunity. Second, the prevalence highly varies among infected herds due to farm intrinsic characteristics (e.g., size, structure, management) and local control decisions made by farmers. As a result, the contribution to the spatial propagation of pathogens is heterogeneous across farms and varies over time for a given farm. In contrast, for epizootics, most herds are naïve when facing a new pathogen spreading. The variability among farms is expected to be smaller, and models often neglect or highly simplify the within-herd infection dynamics. For enzootics, the contribution of each farm to the upper scale infection dynamics cannot be summarised through simple herd statuses. The evolution of the within-herd prevalence and the frequency of contacts between farms occurring at similar time scales, both spatial scales should be considered to prevent bias in the mutual influence of farms concerning the epidemiological risk.

A key issue at large scales is to identify the transmission pathways playing a pivotal role in pathogen spread and persistence (Keeling and Rohani, 2008). Endemicity could be due to pathogens persisting locally once introduced with no need for further introductions. This is for example the case for chronic diseases or if the pathogen shows a long survival in the environment. However, in most cases, disease endemicity is due to a rescue effect (Jesse et al., 2008) which induces successive colonization / fade-out / recolonization events (Fig. 3A). In any case, contacts between animal populations increase the risk of pathogen (re)introduction. Two main types of contacts occur, with different consequences on the local and regional pathogen spread and persistence: neighbourhood contacts and animal movements.

Neighbourhood contacts generally occur in a continuous manner over rather long time periods. They can be due to direct contacts in a shared local environment (e.g., in bovine tuberculosis, Brooks-Pollock and Wood, 2015) or over fences during pasture season (e.g., in BVD, Qi et al., 2019). They can also consist in indirect contacts, e.g., airborne (e.g., in avian influenza, Ssematimba et al., 2012), water-borne (Lupo et al., 2019), or vector-borne pathogen transmission (e.g., in bluetongue, Gubbins et al., 2008). Seasonal occurrence of new cases is frequent in these cases, potentially impacted by host and vector distribution (Charron et al., 2013). To represent such contacts, various between-group transmission functions have been proposed (Hoch et al., 2018). Neighbourhood contacts in animal populations, often similarly influencing enzootics and epizootics, contrast with human situations where proximity contacts vary over a day (working time, school time) or a few weeks (holidays vs. school time). An interesting exception is represented by markets, where animals from multiple herds are gathered for a day, especially impacting the dynamics of directly transmitted pathogens (Vidondo and Voelkl, 2018).

Animal movements between populations (trade movements and transhumance for livestock; migration for wildlife) can introduce new infected individuals in remoted areas. Contact networks most often are

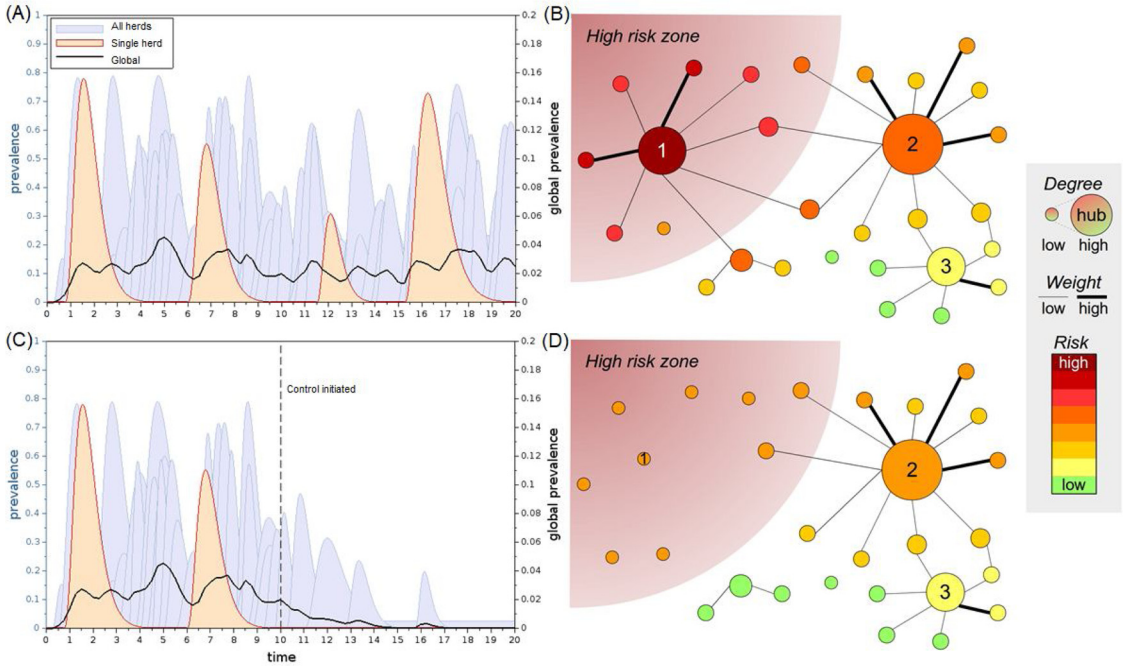

Fig. 3. Local and global prevalence are affected by contact network and the associated rescue effect. (A-B) Local epizootics lead to global enzootics. Despite local disease extinctions in most herds (A), it persists at regional level due to local contacts and movements among herds (B). The global prevalence (mean prevalence over all herds) remains low but infection does not fade-out due to re-colonization events (e.g., in a single herd in orange). (C-D) Control at herd level can impact the global enzootics. Reducing direct and indirect contacts with other herds in few but well-chosen herds may lead to a drastic drop of the regional prevalence (C). Restricting movements, i.e. connections among herds, modifies herd risk levels (D), especially if targeting the most connected and infected herd (herd 1).

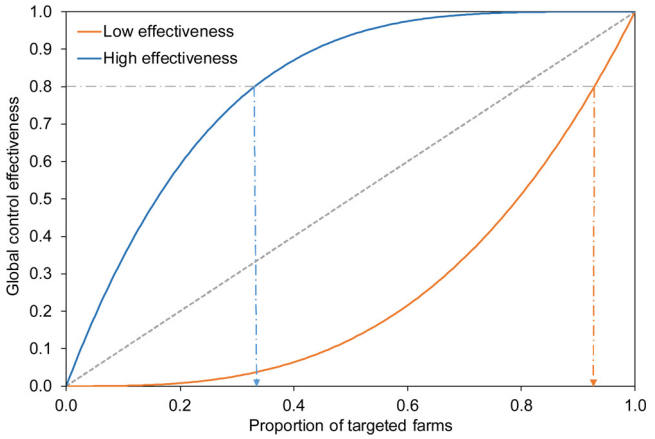

Fig. 4. Proportion of farms to be targeted by a given control strategy to reach an acceptable global control effectiveness according to the local control effectiveness (low vs. high).

dynamic (relationships vary over time), directed (movements are not symmetric), and weighted (several animals can move simultaneously) (Woolhouse et al., 2005; Dutta et al., 2014). Again, such networks both influence enzootics and epizootics. However, they differ from human movement networks, characterised by back-and-forth persistent links between cities (inter-cities flights, commuters; Keeling and Rohani, 2008; Arino and Portet, 2015). In animal populations, the moving individual leaves its source population, at least for a period (e.g., in transhumance; Pomeroy et al., 2019). This also impacts the prevalence in the source population, especially if low. In a network, the node infection risk depends on its connectivity (Fig. 3B), i.e. the number of connections with other herds (degree in the network) and the connection weight (frequency of contacts and number of traded animals). It also depends on its position in the transmission chain, nodes with a high betweenness (i.e. located on a large number of network paths) being at a higher risk to spread pathogens. Farms contributing the most to pathogen spread on such networks are not necessarily those selling many animals, but those selling and purchasing many animals (e.g., for bovine paratuberculosis: Beaunée et al., 2015). Furthermore, animals are transported in trucks or bought during markets or in assembling centres, inducing a risk of contamination during the between-herd transfer (Ferrer Savall et al., 2016; Vidondo and Voelkl, 2018).

5. Control of enzootics in a production area or a supply chain

5.1. To assess and prioritise collective static control strategies

As at the farm scale, models at a larger scale usually consider a unique set of control strategies for the whole metapopulation. The most studied measures are test-and-cull and vaccination. Either uniformly distributed actions (Noordegraaf et al., 2000; Charron et al., 2011) or strategies targeting a fraction of the farms (Brooks-Pollock and Wood, 2015; Beaunée et al., 2017; Widgren et al., 2018) are tested. Using targeted strategies, the aim is to act on as few farms/animals as possible, for practical and economic reasons, while ensuring the highest effect. This requires targeting the most relevant farms (Fig. 4), i.e. the ones that contribute significantly to pathogen spread at large scale. First, control can be targeted based on epidemiological criteria, such as within-herd prevalence, herd location in a high-risk area, and between-herd intensity of contacts (Fig. 3C-D). Second, control can be targeted based on economic reasons, such as stocks (within-population) or flows (between-population), with potentially highly contrasted impacts when resources are limited (Moslonka-Lefebvre et al., 2016). The control of animal movements has also been used to minimise the risk of introducing a pathogen in a free population, e.g., through tests at purchase (Beaunée et al., 2017). An accurate evaluation of the health status of purchased animals is required before their introduction in the new herd. Alternatively, a modification of trade partnerships, and of the number and type of traded animals, can be used to protect disease-free and low prevalence herds from pathogen introduction (Lurette et al.,

2011a; Gates and Woolhouse, 2015; Hidano et al., 2016).

Designing effective control strategies on a large scale is not straightforward and usually involves the use of several measures, possibly varying over time and among herds or areas. Computational approaches based on intensive simulations and extensive exploration of combined control strategies offer a useful tool to optimally target herds in space and time. The duration of measure implementation also must be optimised in relation with time-varying epidemiological and economic criteria. However, such a complexity increases the risk of farmers' non-compliance. Therefore, the combination of large scale epidemiological models and collective decision models needs further developments. The main challenge is to integrate interactions between space-varying and time-varying components, which are first the on-farm epidemiological risk and farmers' decision, second the regional epidemiological risk and collective decision-maker's strategy (social planner).

5.2. To analyse individual decision-making and their interactions at large scale

Integrating farmers' control decisions in a between-herd epidemiological model enables specifying the epidemiological and economic criteria for implementing measures. Such an approach comes from *behavioural epidemiology* (Manfredi and d'Onofrio, 2013) and *economic epidemiology* (Tassier, 2013; Perrings et al., 2014) fields, and has rarely been applied to veterinary epidemiology (Horan et al., 2010). Defined at the farm level, criteria depend on farmers' characteristics (e.g., risk aversion, trust). They can vary over time, allowing the representation of dynamic decisional processes. When decisions are decentralised (as for most unregulated diseases), private interests are the core of individual decision-making (Fig. 5).

A simple way to formalise farmers' behaviours is to consider that farmers decide independently. Decisions can be identical (e.g., control of the porcine reproductive and respiratory syndrome (PRRS): Rat-Aspert and Krebs, 2012) or variable among farmers (e.g., control of BVD virus spread in a context of risk aversion, Rat-Aspert and Fourichon, 2010). However, as farms are connected, information on regional prevalence plays a key role in decisions also at large scale (Gramig, 2008). Besides, decisions are not independent among farmers who may adopt strategic behaviours (Murray, 2014; Bauch et al., 2003; Laguzet and Turinici, 2015). Finally, farms are spatially distributed, and farmers belong to professional and regional networks, possibly leading to clusters of farmers sharing information. To represent the complex interplay between biological, technical, and economic processes, agent-based models can be useful. They have already been used in ecology (coupling of human and natural systems: Heckbert et al., 2010; An, 2012) and in agricultural economics (Wilen, 2007). Applications to animal health economics remain rare (Rich et al., 2005).

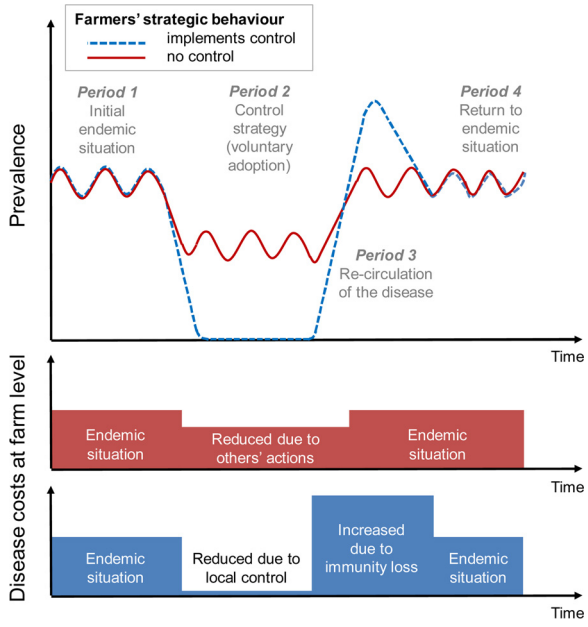

Fig. 5. Effect of the unequal adoption of a voluntary control strategy on disease dynamics. Two schematic behaviours coexist. Farmers can choose to implement disease control in their farm (blue), which reduces the within-farm prevalence and further the risk for farms they are connected to but may decrease their herd immunity once control is stopped. Or, they can choose to do nothing (brown), but still benefit from others' actions. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).

5.3. To account for a social planner

When decisions are decentralised (*laissez-faire* situation), individual efforts are likely to be suboptimal from a social point of view (Rat-Aspert and Fourichon, 2010; Murray, 2014; Bauch et al., 2003; Laguzet and Turinici, 2015). To improve the social outcome while accounting for individual constrains and objectives, there is a need to consider situations where farmers' decisions are coordinated at an upper level by a social planner (Gersovitz and Hammer, 2004), e.g. using incentives. Farmers' associations, such as Animal Health Services, play such a role of social planner. They aim at assessing animal- and farm-level prevalence at a regional scale. They also propose collective control schemes to improve the sanitary situation at the collective level. Sometimes, pathogen eradication is not targeted, because a low level of prevalence can be acceptable for farmers and society.

A first approach is to determine how to direct coordination efforts over time to optimise the social welfare (Manfredi et al., 2009). However, the added value of coordination is often overestimated because the diversity of individual decision-making is not considered. This approach is barely used in animal health (Enright and Kao, 2015; Viet et al., 2018; Mohr et al., 2020). It also raises the issue of evaluating farmers' response to coordination measures, which could be addressed thanks to data obtained through experimental behavioural studies (Chapman et al., 2012) or using coordination data for other diseases (Nöremark et al., 2009).

A second approach consists in mechanistically modelling the individual decision-making. Incentives are defined *a priori* as coordination scenarios, and their impact on farmers' decision-making and the associated epidemiological dynamics is studied. However, the optimal scenario might not belong to the set of explored scenarios, making it difficult to quantify the gap between modelled and optimal situations. In contrast, the comparison with the *laissez-faire* scenario (generally less favourable from a social point of view) makes it possible to quantify the effectiveness of an incentive scheme (e.g., for BVD: Rat-Aspert and Fourichon, 2010; for PRRS: Rat-Aspert and Krebs, 2012).

6. Animal response to infection and host heterogeneity at population scale in enzootics

Usually, within- and between-herd scales are sufficient to consider fundamental mechanisms of pathogen spread. However, sometimes within-host dynamics need to be incorporated to modulate transmission features. Indeed, hosts are heterogeneous and respond differently to infection according to their intrinsic characteristics. This complicates the way herd immunity governs the within-herd infection dynamics.

6.1. To assess host immunity and its impact on pathogen dynamics

Understanding the within-host mechanisms involved in infection dynamics is of paramount importance to better control infectious diseases (McKinley and Wood, 2007). If pathogen spread and evolution in a (meta)population are strongly conditioned by characteristics of

populations, they are also influenced by intrinsic host attributes, especially their susceptibility, immune response to infection, and shedding pattern. Such characteristics vary with age, genetics (Anacleto et al., 2015; Lough et al., 2017), immune status (Alizon and van Baalen, 2008; Luo et al., 2012). How hosts and pathogens interact at the microscopic scale should be analysed to better understand what drives the inter-individual variability. For example, super-shedder individuals, if they exist, have to be identified as they are most probably super-spreaders (Lloyd-Smith et al., 2005).

Immunity development most often leads to self-resolving infections with long-lasting effects and immune memory, enhancing the response in case of secondary infections. Here appears the primary objective of vaccination: protecting the host by developing a specific response. This leads to the concept of herd immunity: by immunizing a sufficient proportion of the population (mainly related to the basic reproduction number, R_0), disease should theoretically not spread (Keeling and Rohani, 2008). This is rarely obtained in practice, most vaccines being imperfect, i.e. providing only partial protection (Bitsouni et al., 2019).

A particular issue concerns the protection conferred by maternally derived antibodies (MDA) to very young animals. On the one hand, MDA confer partial protection against infection (e.g., in swine influenza A: Cador et al., 2016). On the other hand, MDA also interfere with several vaccines in newborn animals, thus impairing the development of vaccine-induced immune response (Renson et al., 2019). Both situations lead to heterogeneous infection statuses which may have significant epidemiological consequences.

6.2. To model within-host infection dynamics

Within-host models are commonly developed for human infectious diseases, but remain sparse in a veterinary perspective. The simplest model describes viral load evolution and the target-cell infection process, driven by a limited number of parameters favouring model fitting to viral kinetics (Perelson et al., 1996; Neumann et al., 1998). One of the possible extensions accounts for the impact of the immune response on viral dynamics and the differentiation of infectious and non-infectious viral particles (Beauchemin and Handel, 2011). Such models were also used to analyse within-host infection dynamics in animals. For example, the persistence of a resistant strain of equine infectious anaemia virus was analysed considering both cell-to-cell infection and cell infection by free virions (Allen and Schwartz, 2015). This provided guidance on treatments targeting infected cells to avoid the emergence and persistence of resistant strains.

Recently, an immunological model described immune mechanisms at the between-cell level (Go et al., 2014). This model was applied to PRRS, a worldwide enzootic disease responsible for huge economic consequences for the swine industry. Although PRRS immuno-suppressive effect is well recognised, the interplay between the virus, the target cells and different cytokines remains puzzling. It was explicitly modelled to identify the immune mechanisms governing infection duration. The model produced counter-intuitive outcomes preventing the viral load decline. It suggests that viremia rebounds observed in data, and thus possible prolonged virus transmission in a herd, could be prevented by altering the immune response through vaccines (Go et al., 2019).

Knowledge on immunity duration, which conditions the probability of (re)infection, is also essential to understand pathogen spread. The long-term duration of vaccine-induced or MDA was evaluated by fitting mathematical models to field data for different pig endemic pathogens (Andraud et al., 2014, 2018). Such analyses reinforce the need to account for host heterogeneity and immune history within modelling frameworks to develop innovative vaccination schedules.

6.3. To model host-pathogen interactions at population scale

The multiscale modelling of the interplay between immunity, viral replication and host-to-host transmission appears as useful to better understand underlying mechanisms and their consequences on pathogen transmission and control at the population scale (Doeschl-Wilson, 2011). However, this integrative view faces numerous challenges (Gog et al., 2015), in particular in the case of multi-strain pathogens (Gog and Grenfell, 2002; Wikramaratna et al., 2015). Also, modelling explicitly within-host processes should be done only if appropriate evidence is available. In the absence of accurate information, it is better suited not to consider detailed within-host dynamics, to avoid degrading the predictive model accuracy.

Immuno-epidemiological approaches have been developed first for macroparasitic infections and malaria (Hellriegel, 2001). Numerous models for human diseases (e.g., for Influenza: Handel et al., 2013; e.g., for HIV: Lythgoe et al., 2013) include assumptions about acquired immunity to study infection spread (Heffernan and Keeling, 2009; Steinmeyer et al., 2010) and host-pathogen co-evolution (Gilchrist and Sasaki, 2002; Mideo et al., 2008). The nested approach (Gilchrist and Sasaki, 2002) links immunological and epidemiological models: it embeds a mechanistic host-pathogen dynamic model into a time-since-infection epidemiological model by linking epidemiological parameters, such as transmission rate and infectiousness duration (Mideo et al., 2008; Gandolfi et al., 2014). However, such models do not always represent the host immune status upon recovery, while some diseases induce a waning or partial immunity (Steinmeyer et al., 2010).

Only few immuno-epidemiological models have been proposed yet for livestock diseases (Doeschl-Wilson, 2011; Martcheva et al., 2015). Epidemiological models classically divide hosts into classes with respect to their health status. Some also account for a heterogeneous infectiousness depending on shedding intensity (Lloyd-Smith et al., 2005; Marcé et al., 2011a). However, the underlying mechanisms generally are not represented and only few relate this heterogeneity with pathogen virulence (Islam and Walkden-Brown, 2007). Structured models can be used to assess control measures targeting specific subgroups, or selective breeding for disease resistance (Rowland et al., 2012). Nevertheless, jointly modelling within- and between-host dynamics would help identifying specific points of the system to be targeted by control measures boosting host response, which is of particular interest to design new vaccines (Metcalf et al., 2015). In addition, host immunity varies over time (Andraud et al., 2009). To account for this, epidemiological models can include a time-since-recovery structure, implicitly accounting for a time-varying loss of protective immunity. Models can also use more realistic non exponential distributions for sojourn times in health state (Lloyd, 2001; Vergu et al., 2010). Explicitly representing within-host processes, where possible, would improve model accuracy, and would make it possible to determine the distribution of individuals between health states, as well as transitions between states. It would provide a better understanding of how the time-varying immune response drives transitions (Fig. 6), whose rates are often unknown and hard to estimate.

Finally, a few genetic epidemiological models have been proposed so far. They can address pathogen spread when hosts heterogeneously express disease resistance (Nieuwhof et al., 2009; Russell et al., 2013) and scenarios where selecting for more resistant hosts improve herd resilience to infection (Berry et al., 2011; Rowland et al., 2012; Raphaka et al., 2018). The coupling of epidemiological and genetic models is of growing interest with the rapid development of genomics, these data being increasingly used in animal breeding selection (Phocas et al., 2016). However, dedicated models are required to account for specifics of genomic selection compared to genetic one. In addition, selecting resistant animals to a given disease might increase susceptibility to other diseases. A current challenge, facing many threats, is to assess selection schemes aiming to improve animal immunocompetence.

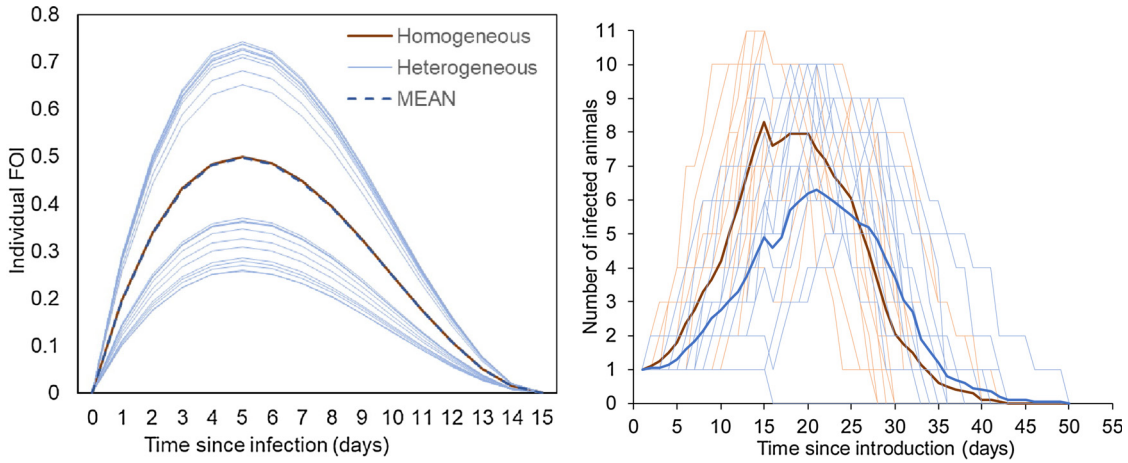

Fig. 6. Effect of heterogeneity in shedding on predicted prevalence in an SIR model (22 individuals, 1 initially infected, all others being susceptible). Assuming a homogeneous time-varying individual force of infection (FOI, left: brown curve) overestimates prevalence (right: stochastic runs in orange, mean in brown) compared to accounting for host heterogeneity (host FOI (left) and stochastic runs (right) in thin blue lines, means in dashed or thick lines). The homogeneous FOI and the mean of the heterogeneous FOI are similar. (For interpretation of the references to colour in the Figure, the reader is referred to the web version of this article).

7. Data and their added value for mechanistic models for enzootics

The relevance and practical usefulness of models presented in previous sections are acutely conditioned by data availability. Information on population characteristics and demography, epidemiological processes and economic costs is crucial (Brooks-Pollock et al., 2015). Such data are required for model calibration, estimation of key parameters, and validation, to provide reliable insights on epidemiological mechanisms and accurate predictions. In turn, models can be used to point out specific data need and hence to provide guidance for the development of data collection systems.

Outside resource-poor settings (Brooks-Pollock et al., 2015), a large amount of useful data is collected for various reasons (legislation, health management, disease surveillance, research). This potentially provides critical information for performing integrative mechanistic modelling for enzootics. However, at least two challenges remain to fully exploit such datasets. First, modellers have to cope with highly heterogeneous datasets composed of demographic, trade, epidemiologic, genomic, geographic, climatic data at various temporal and spatial scales. Second, data availability does not necessarily mean permission for data usage. Many datasets cannot easily be shared since they are owned by different - and most often private – actors, partly due to the decentralised and optional management of enzootics. Data privacy also acts as an impediment to reproducibility, since model predictions based on data cannot be easily regenerated. Beyond the diversity in nature, these datasets are also different in quality. Limitations and biases in data collections should be explicitly accounted for, e.g., by appropriate weighting (De Angelis et al., 2015). This challenge stands also for epidemics. However, case reporting is not mandatory for most enzootics, decreasing even more data quality. Data are most often collected locally, affected by the long-term dynamics of enzootics. Long-term longitudinal surveys are thus required to assess enzootic pathogen spread and its impact on herds, which increases the risk of missing values, sparse spatial coverage, and high censoring. Finally, mostly indirect observations are made (e.g., past seroconversion instead of current infection), which renders difficult their use in models.

Among new available datasets, genomic data are particularly interesting since they open new ways in outbreak investigation. These are for instance related to the impact of host genetic traits affecting disease transmission and burden of enzootic diseases (Biemans et al., 2017). The inference of transmission trees also is rendered possible by recent advances in phylodynamics, a promising direction, ideally requiring deep data collection (Saulnier et al., 2017; Alamil et al., 2019). Another type of data, economic data, are not routinely collected. They are scarce and obtained at rather small scales (e.g., during a few interviews). However, they are key to address issues with regards to on-farm strategic decision-making. In contrast, some processes are very well observed in livestock, e.g., trade and demographics in European cattle populations, following individual animal tracing. Trade networks were used in many applications, e.g. to assess control strategies involving animal movements between holdings (Tinsley et al., 2012). Besides, intensive simulations to assess targeted control were used to motivate routine collection of livestock movement data in emergent economies (Chaters et al., 2019). With the rise of digital agriculture and of sensors, new data begin to be routinely collected on farms (e.g., animal performance, behaviour, body temperature). This is expected to modify the way enzootics will be predicted. Mechanistic models could be relevant tools to identify which data should be collected, and to prioritise scenarios after the alert for new cases has been given (Picault et al., 2019a).

Estimating model key parameters from data increases the accuracy of model predictions. However, appropriate inference methods are needed. It is often harder to estimate parameters with endemic diseases simply because one of the key signatures (variation over time) is usually missing. Methods have also to cope with the variety of datasets (De Angelis et al., 2015) and the partial observation of processes. More generally, methods should address the data missingness and the different sources of noise (uncomplete case reporting, imperfect diagnosis tests, measurement errors). Given the relatively high complexity of epidemiological models for enzootics, especially at large scales, and incomplete data patterns, usual likelihood-based methods are intractable. Instead, methods based on efficient particle filtering algorithms for likelihood maximization (Breto, 2019), likelihood-free methods (Sisson et al., 2018), or tailored estimation methods are highly suited. For example, those based on composite likelihoods account for main data specificities (e.g., temporal and spatial dependence of observations, over representation of the zeros).

When data are too poor to make parameter inference, experts' knowledge and literature are used to calibrate models. Model then can be used for scenario analyses (e.g., prioritisation of control options), but are not suited for quantitative predictive purposes. Experimental data are also useful to estimate specific epidemiological process (Andraud et al., 2009; Go et al., 2019). Such a knowledge is particularly relevant with regards to within-host response to infection. However, animals used in experiments are often far from similar to on-farm animals. They have never been exposed to any pathogen before the experiment. They are most often not of the same breed as on-farm animals. Finally, due to

ethical constrains, only small groups are considered compared to herd or feedlot size. All these render estimates obtained from experiments difficult to generalise at a population scale.

8. Conclusion

Mechanistic epidemiological modelling has largely contributed to better understand enzootic pathogen spread. Interdisciplinary and multiscale approaches should be further encouraged, as the few existing examples clearly demonstrated their added value. However, increasing model complexity should be carefully balanced by affordable data. Models are usually built while few data are available and many processes are incompletely and noisily observed. Although the model structure is guided by epidemiological and biological knowledge, parameterisation remains puzzling, and should benefit from experimental trials and from relevant statistical methods. As in many other fields, ensuring FAIR data (Findable, Accessible, Interoperable, Reusable) is a challenge in animal health, notably because data are largely heterogeneous and often owned by many different actors. To further develop models for enzootics, numerous and complementary skills should be mobilised in modelling, statistics, computer science, infectious diseases, immunology, epidemiology, and economics. The main challenges are: (1) to capture the complex behaviour of the biological system as well as stakeholders' decisions by integrating the necessary components and interactions in order to produce useful predictions; (2) to convert simulated outcomes into integrated knowledge that can be used by stakeholders in specific contexts for disease control; (3) to favour the spread of knowledge and the adoption of produced guidelines and recommended control options by keeping models and outcomes as realistic and practical as possible. Model transparency and flexibility should be improved to enhance relationships among disciplines, and between academics and stakeholders (Picault et al., 2019b). Research models are generally far too complex to be directly transferred to health managers. The latter are more eager nowadays to account for *in silico* outcomes in their decision making (Sutherland and Freckleton, 2012; Thulke et al., 2018). Therefore, there is also a need to develop further, together with end-users, appropriate support decision tools - based on research models - to help prioritizing alternative strategies. Epidemiological models thus should be flexible enough to represent a wide range of realistic scenarios. Territorial anchorage is needed, fed by field data, to ensure the realism and robustness of the modelling tools.

Authors' contribution

PE led project MIHMES and drafted the manuscript. All authors equally contributed to the manuscript content and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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