

Original citation:

Brooks-Pollock, E., de Jong, M. C. M., Keeling, Matthew James, Klinkenberg, D. and Wood, J. L. N.. (2015) Eight challenges in modelling infectious livestock diseases. *Epidemics*, Volume 10 . pp. 1-5. ISSN 1755-4365

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Eight challenges in modelling infectious livestock diseases



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ARTICLE INFO

Article history:

Received 21 February 2014

Received in revised form 14 August 2014

Accepted 18 August 2014

Available online 26 August 2014

Keywords:

Challenges

Livestock diseases

Mathematical modelling

Data-driven modelling

Modelling for policy

ABSTRACT

The transmission of infectious diseases of livestock does not differ in principle from disease transmission in any other animals, apart from that the aim of control is ultimately economic, with the influence of social, political and welfare constraints often poorly defined. Modelling of livestock diseases suffers simultaneously from a wealth and a lack of data. On the one hand, the ability to conduct transmission experiments, detailed within-host studies and track individual animals between geocoded locations make livestock diseases a particularly rich potential source of realistic data for illuminating biological mechanisms of transmission and conducting explicit analyses of contact networks. On the other hand, scarcity of funding, as compared to human diseases, often results in incomplete and partial data for many livestock diseases and regions of the world. In this overview of challenges in livestock disease modelling, we highlight eight areas unique to livestock that, if addressed, would mark major progress in the area.

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Introduction

The global livestock population is growing rapidly in order to meet the increasing demand for meat and dairy products from the expanding human population. The Food and Agricultural Organization (FAO) estimate that there are currently upwards of 1.5 billion cattle, 1.1 billion sheep, 0.97 billion pigs and goats and 60 million horses in an industry that employs at least 1.3 billion people. Infectious diseases pose a persistent challenge for the livestock industry. The World Organisation for Animal Health's list of notifiable diseases includes 65 diseases that affect livestock and 12 diseases of poultry and fowl, including well-known infections such as Foot-and-Mouth Disease (FMD), Classical Swine Fever (CSF) and Highly Pathogenic Avian Influenza (HPAI). A major motivation for countries reporting and controlling infectious threats is international trade as losing a "disease-free" status can have major economic consequences.

In this paper we define eight challenges related to modelling diseases of livestock. They are broadly ordered by scale: challenges 1 and 2 deal with transmission within farms and herds; challenges

3 and 4 deal with the need for data and methodological challenges involved in repurposing veterinary databases; challenges 5, 6 and 7 place livestock modelling within a wider context with the need for improved spatial models, unifying multiple scales of transmission and links with other species. Finally, challenge 8 deals with the politics and economics of modelling livestock diseases.

1. Linking models to transmission experiments

To draw reliable conclusions from data analyses, it is essential that there is a clear relationship between models and data, whether obtained by experiments or field observations. Much attention is given to host and microbe heterogeneity (see challenges 2 and 6), but a third issue is at least as relevant: the type and frequency of transmissible contacts between infected and recipient hosts, and how this depends on circumstances. Density of the host is often used as a proxy to scale contact rates, but this is dependent on knowledge of transmission pathways. Observational data on endemic diseases could be used to address such questions in the field (Carslake et al., 2011). Transmission experiments are also valid tools to address these questions; for instance, it has been shown experimentally that, for some diseases at least, if the relevant density is constant, contact rates should not scale with population size (De Jong et al., 1995).

Recent experimental results have shown that simple extrapolations are not valid if transmission is indirect, via the environment.

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In the case of faecal-oral transmission, when starting with a few infected individuals in a clean environment, the transmission rate will initially increase, then reach a plateau (Velkers et al., 2012), and continue but decrease after the last infected individual has been removed. If indirect transmission occurs when individuals are spatially separated, when starting with a clean environment, the transmission rate remains zero for some time, and then gradually increases (Dekker et al., 2013; Van Bunnik et al., 2014). These results show that a proper way to scale indirect transmission with population size and density is needed: an important new challenge to be addressed by transmission experiments and, wherever possible, field observations to ground experimental data.

Experiments are also very useful to make the link between epidemiology and within-host dynamics, as they allow intensive testing during the course of an infection. This allows quantification of heterogeneity between animals based on underlying (immunological) processes and thus helps to explain and predict infectivity (Chase-Topping et al., 2013).

2. Disease control by selective breeding

The increasing use of genetic data on infectious diseases is one of the current major developments in infectious disease modelling. By far most of this work is related to genetics of the pathogen, either to reconstruct transmission pathways or to study the evolutionary process itself, for example with respect to escape from vaccine control or virulence (Hoa et al., 2011). In veterinary applications, the genetics of the host is relevant as well, not only to identify carriers of genes or SNPs related to increased susceptibility, but also in breeding programmes.

Breeding for production traits and health characteristics is generally done by use of quantitative genetic methods. Breeding for infectious disease resistance is generally not very successful for several reasons. Firstly, heritability estimates from observational data on disease development are generally low (Bishop and Woolliams, 2010). Secondly, selection of animals is ineffective because it takes time until symptoms of disease develop and development of disease depends on the level of exposure. Thirdly, by selecting animals that do not develop the disease, one might select for lower susceptibility or higher tolerance, but not necessarily for reduced infectivity. For control of infectious diseases, the latter is at least as relevant to reduce transmission and thus incidence in the population (Lipschutz-Powell et al., 2012). Moreover, modern transgenic techniques may allow introduction and rapid selection through breeding pyramids of animals with substantial resistance to infection and less infectivity (Lyal et al., 2011).

With the advancement of sequencing techniques, selective breeding may become more relevant as a method for disease control in the future as selection can be based on genetic information instead of phenotype. A first challenge in this respect is the further development of statistical techniques to relate measured (genetic) variation to observable traits in animals related to infectious diseases, and to predict the effectiveness of selection. Breeding for infectious disease resistance is still relatively new, as heritability of resistance measured by classic methods has been low and breeding ineffective (Van Hulzen et al., 2014). When favourable genetic traits are identified, a second challenge is the incorporation of infectivity measures in breeding programmes. Quantification of variation in infectivity, in relation to more easily observable traits for selection, can only be done indirectly and may be done experimentally or by use of transmission models with observational data.

3. Applying models to data/resource-poor settings

The global burden of livestock diseases disproportionately affects the world's poorest countries, however many of the

state-of-the-art livestock models are heavily based on large-scale databases which are not available in resource-poor settings. Epidemic data are often patchy or not available for less-common endemic diseases. There are multiple challenges involved in data collection, including maintaining anonymity and controlling access to sensitive information, consistent recording and database maintenance, and sharing of (raw) data when publishing analyses of these data. Our challenge here is to model diseases in a global context, share expertise and data, develop methods for repurposing existing models for limited data and to develop efficient and targeted data capture systems.

Only a small proportion of diseases that affect livestock have compulsory reporting and are of high political priority, therefore often little is known about their epidemiology (Carslake et al., 2011). Furthermore, modelling livestock epidemics at a national level often involves spatial models that can capture local heterogeneity and predict the impact of localised control measures (Keeling et al., 2001). Essential information for developing spatial models includes locations, sizes and types of farms and livestock holdings. Livestock tracing systems have been used to refine spatial models (see challenge 4) and the FAO help implement national agricultural censuses. However, as of 2014, nearly 50% of countries, mainly in Africa, South-East Asia and Latin America, had yet to conduct a census. This is reflected further in the use of models for contingency planning: only 28% of countries in Africa and the Middle East use models due to either a lack of data, expertise, resources or perceived need (Dube et al., 2007).

Developing models for livestock epidemics in the absence of population or epidemic data is challenging and relies on many inbuilt assumptions. Even when data are available, adapting existing models to new countries can be problematic and at least require a re-estimation of parameters (Tildesley and Keeling, 2008). Some novel methods for overcoming a lack of spatial population data include using land-use cover to infer farm locations (Tildesley and Ryan, 2012), predicting disease spread based on environmental data (Purse et al., 2007) and reconstructing transmission trees based on spatial case data alone (Metras et al., 2013). International collaborations are key, and in data-poor settings there are opportunities for developing model-guided surveillance methods.

4. How best to exploit rich livestock data?

In contrast to the previous challenge, there is a need to develop models and techniques for capturing the rich detail of livestock data. Livestock are closely managed populations that can yield both targeted data on infection and transmission in small groups of animals and detailed population-wide statistics, that would be regarded as impractical or invasive in other species. The many dimensions of livestock data can be collapsed in a multitude of ways to address a wide variety of different problems. This particularly rich potential source of realistic data provides crucial information for modelling disease transmission and can be used to investigate the role of population structure in models of other species and systems.

Over the past 20 years, individual animal tracing has become a routine component of livestock management in many industrialised countries and is being implemented in new regions and for new species. The United States of America is a notable exception, where the implementation of a national system has been limited by privacy concerns. Birth, death and movement records provide a daily census of the current population that can be used to estimate seasonal forcing and timing of epidemics (Kao et al., 2006), the impact of diseases in subpopulations (Brooks-Pollock et al., 2013) and the role of farm management in disease risk (Gates et al., 2013), to name just a few applications. An approach

being developed for human diseases is evidence synthesis, in which diverse data sources are combined in a single framework (Presanis et al., 2011). The wealth of information available for livestock has led to a temptation for incorporating as much detail as possible into simulation models. However, parameter inference, model selection and understanding fundamental mechanisms from such models is a challenge in itself (Brooks-Pollock et al., 2014). Network models provide an abstraction that has been used to investigate vulnerabilities of the system such as highly connected premises (Woolhouse et al., 2005) and times of year (Kao et al., 2006). However, linking the highly detailed demographic data with epidemiological data can be challenging due to mismatches in the scale and extent of recording and many network model predictions are made in the absence of disease data. Livestock databases still contain much unexploited potential in disease modelling; the challenge is to develop tractable models that can be linked with disease data from surveillance programmes and field studies.

5. Improving spatial models

Unlike human populations where people move freely and potentially make many epidemiologically relevant connections each day, livestock are generally characterised by their tendency to remain on a farm for extended periods of time. This means that livestock epidemics affecting multiple farms have a strong spatial component and require models that can capture the spatial transmission routes between farms. Two main routes have been investigated, direct transmission through the movement of livestock (e.g. Kao et al., 2006) and indirect transmission considered to be a function of the separation between farms (e.g. Keeling et al., 2001). Both of these require improvements.

The network of livestock movements is often seen as key to the long-range dispersal of infection. In many countries these network data are being routinely collected and greatly aid predictive modelling. Theoretically, there are challenges in interpreting this dynamic network; understanding how the wealth of tools and intuition developed for static networks translates to a network formed by discrete movements (Keeling et al., 2010). Practically, we would wish to understand what this network means for the early spread of novel infections and for position of sentinel farms or surveillance operations. Finally, the movement data is always historic so models are necessarily retrospective; being able to predict future movement patterns and how these would respond to changes in economics or legislation would have substantial policy implications.

Distance-based transmission is used to capture a multitude of transmission routes, from local movements of vehicles, to wind-borne infection, to transmission by livestock movements and insect vectors. Modelling each of these routes could be separated and refined, allowing a better assessment of differing control policies. Traditionally, modellers seek to capture distanced-based transmission with a single isotropic and homogeneous kernel (e.g. Boender et al., 2007) – but in practice transmission is likely to depend on local conditions including topology, meteorology, farm density and many other factors (Ypma et al., 2013). Understanding the dependencies and functional forms of such transmission kernels is key to their statistical estimation and their ability to be used for predictive modelling. Combined, these challenges call for a deeper mechanistic understanding of livestock movements and infection dynamics that can only come from a detailed statistical analysis of multiple examples of high-quality epidemic data. The ultimate goal would be to extrapolate the understanding gained from past outbreaks to policy-relevant predictions in new scenarios.

6. Unifying multiple scales of transmission

Generally, specific experiments are designed to address individual questions where the scale is most appropriate for that question. Examples are discussed above regarding parameterisation of between-host transmission experiments; typically, these relate most closely to within epidemiological group, or within farm models, as exist for different diseases in different species, e.g. (Dekker et al., 2013). There are many other examples, including foot and mouth disease (Keeling et al., 2001) or classical swine fever (Jalvingh et al., 1999), where experiments would be impractical and epidemiological data have been used to develop models of between farm transmission, as an aid to exploring different controls. There are rather fewer examples of where models combine within and between farm or epidemiological unit scales, especially where there is statistical parameterisation of models from data (Baguelin et al., 2010). There also are a multiplicity of experiments conducted in individual animals to explore disease pathogenesis and the impact of vaccination which provide exquisite individual or within host data. These have sometimes been used to develop within-host models, such as for influenza (Saenz et al., 2010), but are often rather overlooked; their utility may lie in linking immune dynamics and understanding novel vaccination approaches in the development of improved prevention and control.

Similar to epidemiological modelling approaches, pathogen evolution in rapidly mutating pathogens such as influenza virus is typically only studied at the epidemiological, or global phylogenetic scale. However, the use of deep sequencing techniques in livestock experiments also allows study of within host evolution and between host transmission of variants (Murcia et al., 2011), but such detailed experiments are typically not currently linked by models to larger scale data. In fact, how this should be done remains unclear. Pathogen sequencing during epidemics can, in contrast, be used to infer epidemiological links (e.g. HPAI in Netherlands Ypma et al., 2013) and can also be used to provide estimates of transmission rates at different scales, although some of the techniques used to do this may be rather sensitive to missing data.

There are huge opportunities to gain simultaneous understanding of pathogen transmission and control, including addressing of important aspects of pathogen evolution in livestock, because of the opportunity to make detailed observations and experiments, but the methods needed to link these different scales are currently poorly developed or absent. Filling this gap could facilitate major progress in disease control.

7. Linking livestock populations to other species

Many livestock infections are not confined to domesticated species. Three different cases can be studied: those diseases that also infect humans (zoonotic infections); those diseases that can persist in wildlife reservoirs; and those diseases that are spread by insect vectors. For all of these cases the key challenge is to infer the level of transmission between species. Often this is made more complicated by the majority of data only being available on infection in livestock, with infection in wildlife or vectors difficult to measure and zoonotic infections in humans being comparatively rare. The controversy around bovine TB in the Great Britain and Ireland illustrates this point; while the prevalence of infection is relatively well recorded for cattle, the role-played by badgers as a vector or reservoir of infection is still disputed despite years of research (Godfray et al., 2013). Some of this relates to historic veterinary dogma about specific diseases having wildlife reservoirs, where there is a binary categorization of the role of different species, rather than a more nuanced ecological, quantitative approach. Similar questions arise for bTB in other countries,

where the precise role of deer in North America and possums in New Zealand is still debated.

For vector-borne infections, many of the challenges relate to modelling the spatial spread of infection. When we are faced with cases in the livestock population, how do we infer the types of spatial movement of vectors that govern the transmission process (Turner et al., 2012). This is made particularly challenging by the range of meteorological and environmental factors that can influence the behaviour of insect vectors. Once the question is framed in this way, most of the issues are statistical. Given data on infection in one species, how do we infer the role of other species, the impact of control targeted at a single species (Matthews et al., 2013), and most importantly, how can we determine if they act as a reservoir which could confound effects to eliminate the infection?

8. Livestock modelling with political and economic constraints

The FMD epidemic in the UK in 2001 provides a recent example of when modelling played an integral part in forming control policy (Keeling et al., 2001; Ferguson et al., 2001). Modelling identified that depopulation of ‘dangerous contacts’ would be essential for bringing the disease under control, but this became one of the most controversial areas of government policy (Haydon et al., 2004). The motivation for controlling livestock diseases is often a complex (and potentially poorly defined) mix that includes economic constraints bound by trade agreements and regulations, animal health and welfare issues, political positioning, often based on historic norms, practicalities of control and public opinion, even if control is epidemiologically well defined (Carslake et al., 2011; Brooks-Pollock et al., 2014). Central questions to be addressed are what defines cost effectiveness for livestock diseases and how are economic costs balanced against animal health, public opinion and other constraints. This will require increased communication between interested parties, including modellers, policy makers, veterinarians and farmers. Modellers can contribute with transparent modelling work, open access data and publicly available code.

For livestock diseases, there is no single quantity by which control interventions are judged, such as the cost per quality-adjusted life year (QALY) gained used to assess interventions against human diseases. In economic terms, the impact can be broken down into three components: (a) economic impact on the individual farmer including loss of capital, reduction in productivity or quality and greater use of inputs; (b) wider economic impacts such as costs of surveillance, international trade restrictions and any human health costs; and (c) economic impact on rural economies and tourism (Bennett, 2012). However, few data-driven models have included economic analyses as well as a dynamic transmission component due to a lack of data. Future models will also have to consider the public acceptability of controls interventions, which is recognised as an important factor in political decision making. Acceptability depends on many factors including perceived risk, cultural acceptability, and convenience and varies by region and country (MacRitchie et al., 2014).

To address this challenge, we need universally agreed measures of cost effectiveness for livestock infections, more data on the full economic and social impact of livestock infections and improved collaboration and communication with veterinarians, policy makers and animal health economists. Models that are used as decision-support tools in real-time need to be developed in advance, preferably by multiple modelling groups, so that models are held to the highest standards and subject to rigorous checks and cross validation, as has been achieved for Foot-and-Mouth (Sansom et al., 2011) and HIV (Pretorius et al., 2014). Such collaborative modelling efforts increase the impact and utility of models by increasing

trust and being explicit about the strengths and weaknesses of models.

Conclusions

Livestock diseases have often not received the attention from the modelling community given to other aspects of disease modelling. Yet, the highly detailed data, the potential to identify fundamental aspects of transmission and the ability to explore a wide range of control options mean that livestock modelling is a fruitful area of research with plenty of scope for expansion and influence in other areas.

Acknowledgments

EBP is funded by EPSRC fellowship EP/H027270/1. MJK was supported by the ERA-NET anihwa call funded by Defra. JLNW is supported by the Alborada Trust, the RAPIDD program of the Science & Technology Directorate, U.S. Department of Homeland Security, the Fogarty International Center, U.S. National Institutes of Health, the European Union FP7 project ANTIGONE (contract number 278976) and by BBSRC grant BB/1012192/1.

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