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# Model or meal? Farm animal populations as models for infectious diseases of humans

Cristina Lanzas\*, Patrick Ayscue\*, Renata Ivanek<sup>†</sup> and Yrjö T. Gröhn\*

**Abstract** | In recent decades, theory addressing the processes that underlie the dynamics of infectious diseases has progressed considerably. Unfortunately, the availability of empirical data to evaluate these theories has not grown at the same pace. Although laboratory animals have been widely used as models at the organism level, they have been less appropriate for addressing issues at the population level. However, farm animal populations can provide empirical models to study infectious diseases at the population level.

## Infectious period

The time period during which an infectious individual is able to transmit the pathogen to a susceptible host. The duration of the infectious period is exponentially distributed in deterministic models, in which the rate of infected individuals leaving the infectious class is constant, and in stochastic models, in which each infectious individual has a fixed duration of infectiousness drawn from an exponential distribution at random.

Worldwide, infectious diseases account for more than a quarter of human deaths annually<sup>1</sup>. The emergence and re-emergence of infectious pathogens and the continuing struggle to manage other diseases emphasize the challenges facing public health professionals. The optimism that marked an era when scientists were confident in the success of eradication efforts and declared victory in the fight against infectious agents has long since passed. The complex interactions among processes acting at different organizational levels that underlie the dynamics of infectious diseases are now becoming evident. Mathematical models are central in providing insight into such complex interactions and in understanding why interventions that have a benefit for an individual may not ultimately be optimal for the population (for example, the use of antimicrobials). Mathematical models based on ecological and evolutionary theory have been used to study pathogen invasion, persistence and evolution in human populations<sup>2</sup>. The predictions generated by these models have been pivotal tools in the process of public health decision making, forecasting the long-term epidemiological and economical consequences of intervention strategies. For example, mathematical models that examined strategies to mitigate the impact of an influenza pandemic have shaped the guidelines for preparedness and response to such an event<sup>3</sup>. In the absence of long-term follow-up clinical studies, mathematical models have also helped to evaluate the efficacy and delivery strategies of vaccines against human infections by pathogens such as human papilloma virus<sup>4</sup>, HIV<sup>5</sup> and mycobacteria<sup>6</sup>. BOX 1 outlines the steps in the development of a mathematical model.

Mathematical modellers provide hypotheses with a rigorous test, but the models that they use often rely on untested assumptions. Empirical data are crucial for

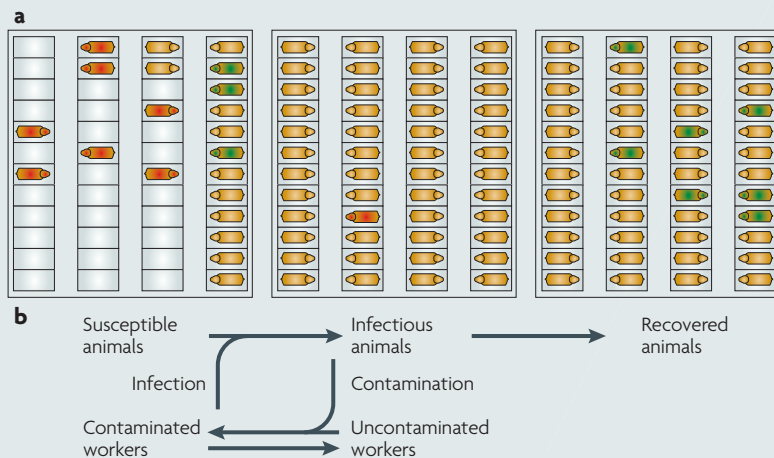
assessing whether these assumptions hold true and for determining the conditions under which model predictions are valid. For example, a common assumption of infectious disease models is that the infectious period is exponentially distributed, and theoretical studies have shown that changing this assumption has a profound impact on the predicted infection dynamics<sup>7,8</sup>. Furthermore, assuming that the infectious period is exponentially distributed is not realistic for some diseases<sup>9</sup>. Nevertheless, data on how infectious periods vary with factors such as pathogen strain, route of excretion or initial infective dose are very limited, thus the exponentially distributed infectious period remains a routine assumption of models. Similarly, the transmission–virulence trade-off hypothesis has been the basis for most of the theory that has been developed through mathematical modelling of evolutionary epidemiology for the past three decades<sup>10</sup>, but this hypothesis has been increasingly challenged owing to the lack of empirical evidence<sup>11</sup>. Both examples underscore the importance of combining mathematical models and empirical data. The fields of experimental and mathematical epidemiology have been linked from their beginnings. In 1936, Greenwood *et al.*<sup>12</sup> published the first quantitative transmission experiments, which were analysed the same year by Kermack and McKendrick in their highly influential series on the mathematical theory of epidemics<sup>13,14</sup>.

Empirical data can be obtained from field or experimental settings using biological models of animal diseases. Although these animal models have been widely used to explore pathology and pathogen dynamics at the cell and individual animal levels, their use to describe population-scale disease dynamics and their feedback interactions has been limited. Appropriately designed

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Box 1 | Developing a mathematical model



Mathematical modelling facilitates inference from biological model systems. There are four steps in the modelling of an infectious disease, illustrated by the following outline of the steps used for the modelling of a multidrug-resistant *Salmonella enterica* subsp. *enterica* serovar Newport (*S. Newport*) outbreak in a calf-raising facility (see the figure; part **a** shows the prevalence and location of the affected animals in the outbreak, with green indicating clinical cases and red indicating deaths, and part **b** shows a flow diagram representation of the model)<sup>23</sup>.

**Formulate the research question**

The most important step in modelling is the formulation of the research questions. These questions provide criteria to help researchers decide which elements of the system under study must be included in the model. In the case of the *S. Newport* outbreak, these include questions such as: what factors contribute to the transmission and persistence of the outbreak, and what are the best control strategies to stop outbreaks?

**Develop the mathematical model**

To develop a mathematical model, the variables and assumptions to be included in the model need to be defined. Then a flow diagram is drawn to describe the changes to these variables over time. The modeller must then decide whether a deterministic or stochastic model is appropriate and write the mathematical equations. The animals in the calf-raising facility are individually penned animals (see the figure, part **a**), and therefore transmission of the pathogen is through contaminated fomites and mechanical vectors. In this situation, an indirect SIR transmission model (which classifies individuals as susceptible, infectious or recovered) is appropriate, in which the host population is divided according to their epidemiological status.

**Analyse the mathematical model**

Based on simulations, a model analysis is chosen that best addresses the problem. Threshold values and conditions for invasion and persistence of the pathogen are evaluated and scenarios simulating control strategies are run.

**Validate the mathematical model**

The results of the simulations are checked against data or known cases. Alternatives to the model and to the assumptions are considered.

**Relate the model back to the research question**

The results from the previous step are interpreted to assess whether the results answer the research question. During the outbreak of *S. Newport*, environmental reservoirs, the high turnover rate of individuals and the continual admission of susceptible individuals favour persistence. Immunization of a high proportion of admitted individuals (>75%) and completely closing off facilities to reduce the effective contact rate by allocating personnel and equipment to subgroups were effective strategies to control outbreaks.

studies involving animal models should also be used to improve our understanding of the impact of treatments and control strategies and the evolutionary dynamics of pathogens that take place at the population level. In addition, attempting to predict or control the evolution

of drug resistance and virulence or to inform vaccine design requires animal models in which the interactions between processes acting at different organizational levels (for example, within a host and between hosts) can be quantified<sup>15</sup>.

The search for appropriate biological models to study infectious disease dynamics has often overlooked promising systems that are available in animal agriculture. Mathematical models in farm animal populations have been largely limited to offering guidance to veterinary decision making for pressing food protection, animal welfare and economic issues, such as those presented in outbreaks of bovine spongiform encephalopathy<sup>16</sup> or foot-and-mouth disease<sup>17</sup>. We propose that farm animal populations, coupled with mathematical models, are well-suited model systems to study infectious-disease population dynamics and problems that span several levels of organization and that are relevant to the control of human infectious diseases. We discuss the features, advantages and disadvantages of these systems and highlight research areas that might benefit from the knowledge generated by studying infectious disease dynamics in farm animal populations.

**Farm animals as natural infection model systems**

In this section, we discuss the key features of the farm animal systems that are relevant to infectious disease dynamics, with emphasis on the similarities and differences between farm animals and humans at the population level (BOX 2). Pathogen–host systems in which the pathogen is studied in its natural host are necessary to investigate infectious disease dynamics at the population level. In surrogate models, the pathogen does not naturally infect the host animal outside a laboratory setting, and high doses of the pathogen administered through artificial transmission routes are often necessary to induce infection<sup>18</sup>. These issues complicate the study of pathogen transmission in the surrogate model, because it may not take place at all or it may result in invalid measures of pathogen life history traits such as the duration of the infectious period. Laboratory animals, especially mice, have been the main animal models for studying specific aspects of human pathogenesis and immunity. However, mice are more often surrogate models than natural models for the pathogen under study. At the individual level, farm animals are being used as natural models for a wide range of human infectious diseases (TABLE 1). In many cases, humans and farm animals share pathogens. More than half of human infectious diseases are caused by multihost pathogens<sup>19</sup>, for which farm animals are often natural hosts and serve as an important infection reservoir for humans<sup>20</sup>. Farm animals are therefore good candidates for studying infectious disease dynamics at the population level.

There are many similarities in the underlying principles that govern infection transmission in human and farm animal populations, which allows us to use the animal system as a model. At the population level, livestock production systems include a range of population settings and contact structures, including backyard poultry flocks, highly extensive herds and highly controlled production

**Box 2 | Features of farm animal populations that are relevant to their potential use as models**

- The disease mechanisms and immune systems are sufficiently similar between some farm animals and humans.
- The populations are outbred.
- Natural transmission takes place, and quantification of life history traits, including infectious period and transmission rate, is feasible.
- The populations are highly stratified with multiple sources of heterogeneity (for example, spatial, genetic and management factors and age) that can be readily manipulated.
- We have extensive knowledge of the host–pathogen systems.
- Diverse interventions are logistically and ethically feasible.
- Long-term interventions such as mass vaccination programmes are applied.

management systems. Factors that contribute to animal disease outbreaks (for example, crowding, close contact, poor hygiene and contaminated fomites) are common to human settings such as hospitals, army camps, schools, daycare facilities and dense urban areas<sup>21,22</sup>. From a population dynamics point of view, both calf-rearing units and health care settings are small, transient populations; a high turnover rate of individuals in the facility, the presence of environmental reservoirs of infection and continuous antimicrobial selective pressure prolong the transmission of multidrug-resistant clonal pathogens in both situations<sup>23,24</sup>. Furthermore, heterogeneities that lead to differences in infectiousness and transmission dynamics are often similar across different combinations of hosts and pathogens<sup>25</sup>. Factors that influence the infection process and transmission dynamics in both animals and humans include age, nutritional health, vaccination history, physiological state and genetic heterogeneity of the host, as well as environmental factors such as hygiene and the type of social interactions and contacts that occur in the population. It should be noted, however, that at certain spatial scales transmission dynamics between farm animals and human populations may not be comparable. For example, transmission at large spatial scales can be dissimilar, as networks of livestock and human movements can differ substantially<sup>26</sup>. In addition, the progress made in our understanding of those farm animal diseases that have wildlife reservoirs (for example, bovine tuberculosis) has been slowed owing to the difficulties in characterizing transmission between domestic and wild animals.

In agricultural systems, decisions regarding the use of intervention strategies are based on individual and population health (of both the animals and their human carers), animal welfare, food safety and economic considerations. Because of the need to balance these considerations, infectious disease management makes use of diverse control options; for example, vaccines that do not prevent transmission but do reduce clinical disease are used to reduce the economic burden of diseases<sup>27</sup>. Vaccines with diverse modes of action (for example, inhibition of pathogen growth rate or toxicity, or blocking transmission) and a range of vaccination strategies (for example, cohort or continuous vaccination) are used for farm animals. Other control strategies used for animal diseases include surveillance, environmental hygiene, ‘all-in, all-out’ management (in which animals are managed in groups, and cleaning and sanitation of

facilities is carried out before introducing a new group) and targeting of specific groups (for example, the detection and treatment (‘test and treat’) or culling (‘test and cull’) of infected animals)<sup>28</sup>. The wide range of available control strategies for farm animal diseases has contributed to the unravelling of infectious disease dynamics. For instance, endemic stability is an epidemiological concept that is well described in veterinary medicine, especially in tick-borne diseases, and that may also be relevant to the control of a wider range of diseases, including malaria or dengue in humans. At endemic stability, the clinical disease prevalence is low despite high levels of infection in the population, because immunity is acquired at a young age, when the disease is milder<sup>29</sup>. Decreasing transmission increases the age at which animals become infected, thus increasing the percentage of infections that result in clinical disease. Not controlling infection transmission is considered a more sustainable option than partial control in this case, because higher transmission rates result in lower clinical disease levels. It was hypothesized that endemic stability could be observed in all human and animal diseases for which the probability or severity of clinical disease increases with age and the probability of disease is reduced after two or more infections<sup>29</sup>. This is illustrated by the results of the control measures that were taken for dengue. Dengue is a mosquito-borne viral disease that can cause symptoms ranging from mild fever to life-threatening haemorrhagic fever. For decades, several Asian countries, including Thailand and Singapore, have applied vector control programmes to control dengue. Despite these measures, the incidence of dengue cases has not declined. The stagnant incidence was initially attributed to the failure of the vector control programmes to decrease transmission, but analysis of the epidemiological data revealed that virus transmission has decreased, and the increase in dengue cases at lower transmission rates may result from the loss of endemic stability<sup>30,31</sup>.

**Infectious disease dynamics in farm animals**

To study the complex processes underlying infectious disease dynamics, approaches that integrate different fields and methods are required. By gathering scientific evidence about the host–pathogen systems through experimental, field, model and historical investigations at different organizational levels, a complete picture of the causal mechanisms shaping the infection dynamics can be uncovered<sup>32</sup>. Using challenge and transmission experiments carried out in animal agriculture systems,

**Transmission–virulence trade-off hypothesis**

The proposal that increased host survival and, therefore, pathogen transmission represent a trade-off for the parasite: high parasite reproduction in the host and high levels of virulence can cause host death, reducing the chances of the parasite being transmitted to another host.

**Stochastic model**

A mathematical model that incorporates elements of chance. Stochastic models are necessary when small populations, such as those in a transmission experiment, are being modelled.

**Organizational level**

Living entities are organized in hierarchical levels (for example, cell, individual, population and ecosystem). Each level of organization builds on the level below it but often has emergent properties (that is, properties that result from the interactions between the parts of the level below).

Table 1 | **Farm animal models for human pathogens or diseases**

Animal pathogen	Farm animal hosts	Human disease or pathogen	Examples of studied disease processes	Refs
Bovine papilloma viruses	Cattle	Human papilloma viruses	Latency mechanisms of papilloma viruses and vaccine development	98
Bovine respiratory syncytial virus	Cattle (calves)	Human respiratory syncytial virus	Vaccine development	99
Caprine arthritis encephalitis virus and Visna/maedi virus	Goats and sheep	HIV	Genetic susceptibility and lentivirus–host adaptation	100
<i>Cryptosporidium parvum</i>	Cattle (calves) and swine (piglets)	<i>Cryptosporidium parvum</i>	Therapeutic treatment testing and clinical responses to diverse strains	101
Hepatitis E virus	Swine and chickens	Hepatitis E	Mechanisms of pathogenesis and vaccine development	102
Marek's disease virus	Chickens	Virus-induced lymphoma	The role of immune control and evasion in neoplasma formation and mechanisms of virus-induced lymphoma	48
<i>Mycobacterium bovis</i>	Cattle, goats and swine	Human tuberculosis	Mechanisms of pathogenesis, host defences and vaccine development	103,104
<i>Salmonella enterica</i>	Cattle (calves)	Human enteritis	The role of virulence factors on infection and <i>S. enterica</i> pathogenesis	105

large-scale and long-term field data can be gathered on the same host–pathogen system, and thus model systems that span several organizational levels can be obtained.

Understanding infectious disease dynamics often requires gathering data to estimate virulence, infectiousness and transmission, and such data can be obtained from farm animal populations. Pathogen excretion has been more readily quantified in farm animals than in humans. *Listeria monocytogenes* infection in cattle has been used as a biological model to develop a mathematical approach to quantify the duration and frequency of shedding episodes for pathogens that have an oral–faecal mode of transmission<sup>33</sup>; this is a route of transmission for many important human infectious agents, including *Salmonella* and hepatitis A virus. Transmission information can be obtained from experiments or field studies, which are often used to test interventions such as vaccination. Experimental studies testing vaccines have characterized their effects at both the individual and population levels<sup>34</sup> using group or one-to-one transmission experiments (FIG. 1). Statistical methods based on stochastic transmission models have been developed to quantify transmission parameters and pathogen life history traits<sup>35</sup>. In controlled conditions, the contribution of specific aspects affecting transmission can also be studied<sup>35</sup>. The effect of expressing an F4 receptor for intestinal adhesion of the F4 fimbrial antigen of *Escherichia coli* on the susceptibility and infectivity of piglets to *E. coli* infections was quantified by testing all possible combinations in one-to-one experiments, in which one infectious animal (either positive or negative for the F4 receptor) was housed with one susceptible animal (either positive or negative for the F4 receptor)<sup>36</sup>. F4 receptor-positive piglets were more susceptible, and the maximum proportion of F4 receptor-positive piglets that can be present in a population without outbreaks occurring was estimated to be 0.14.

Quantitative experiments in veterinary medicine using farm animals have linked transmission measurements to within-animal dynamics (for example, the pathogen load and the immune response)<sup>37–39</sup>, and thus detailed information such as time-dependent infectiousness can be quantified<sup>40</sup>. Combined quantitative information about within-host dynamics and transmission is crucial to parameterize and validate mathematical models that seek to understand pathogen evolution.

Using field and historical data, the long-term effects of control strategies can be investigated. In field studies, animal productivity and health databases are often available and can provide extensive information on health, management and disease control. It is not unusual for a typical farm to know at any given time exactly how many animals are present, the density at which they have been held, what they are eating and drinking, their deep geographic and genetic pedigrees, their clinical disease states and histories, their ages and how these age-structured classes have been stratified, and measures of their performance and production in detail. In human and wild-animal systems, information regarding movements, density, contacts and even population size are often unknown, even to an order of magnitude. In farm animals, information at lower hierarchical levels (such as at the organ or tissue level) can be gathered by biological and post-mortem sampling. Biological sampling can be performed on a regular basis and can be accomplished easily, with minimal disturbance to the animals; necropsies are commonly performed on either culled or dead animals, and carcasses are inspected at the abattoir. Owing to legal requirements, data describing the network of animal movements between farms are available in some countries. Combined, these data provide far richer information about infectious diseases dynamics across scales than is typically available in wildlife or human systems.



### Host–pathogen model systems in farm animals

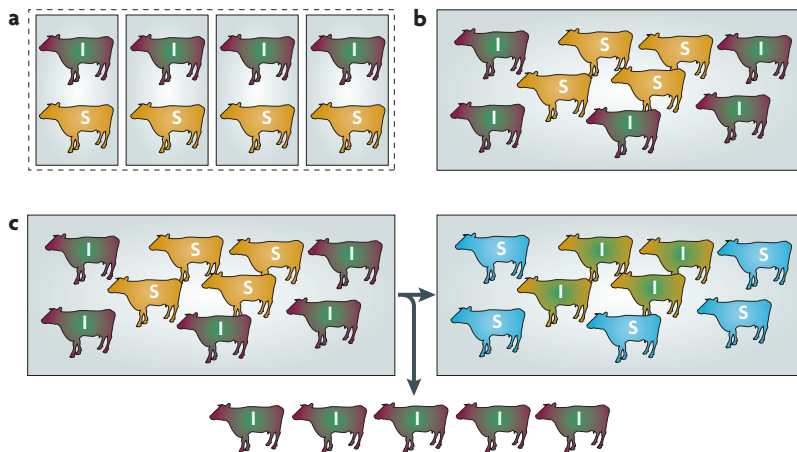
An outline of some areas of fruitful work using animal agricultural models is presented in TABLE 2, with emphasis on those models that are relevant to human health, and we briefly discuss some examples of these research areas below.

**Vaccine research.** Vaccination has been a very successful control strategy for several diseases, including yellow fever, hepatitis A and childhood diseases, providing life-long immunity. However, vaccines are now being developed for human and animal pathogens that have fast antigen variability (for example, the influenza virus) or short natural immunity (for example, malaria parasites) or that induce a cell-mediated immune response (for example, HIV and *Mycobacterium tuberculosis*). For these pathogens, the available vaccines are imperfect, as they do not stop individuals from becoming infected on exposure to the pathogen. Imperfect vaccines can alter the selective pressures imposed on pathogens and, thus, potentially alter the evolution and composition of pathogen communities<sup>41</sup>. Mathematical models investigating the evolutionary consequences of the use of imperfect vaccines have been developed in recent years<sup>42–44</sup>. These models have investigated the short-term and long-term evolution of a pathogen under vaccine pressure and have suggested that vaccines reducing the fitness cost of virulence (for instance, by reducing host death) may favour the spread of more virulent strains in the vaccinated population. It was concluded that vaccines that are designed to reduce pathogen growth rate or toxicity could lead to increased pathogen virulence<sup>42</sup>, which could cause

more severe disease in unvaccinated individuals. To predict the direction and speed of evolution, measures of the life history traits (including the transmission rate, the infectious period and virulence) in both vaccinated and naive hosts are necessary<sup>44</sup>. Tracking virulence changes in humans is difficult, as exposing humans to virulent strains is unethical, and historical data is confounded by changes in factors such as medical treatments<sup>45</sup>.

Except for laboratory experiments with rodent malaria<sup>46</sup>, the only reported cases of increased virulence for a pathogen under vaccine selective pressure have been in domestic animals. In commercial chickens, two generations of vaccines against Marek's disease virus have been abandoned (reviewed in REF. 47). Marek's disease, caused by an alphaherpesvirus, is a lymphoproliferative disease that has caused major economic losses to the poultry industry owing to its high morbidity and mortality<sup>47</sup>. The first vaccine against Marek's disease virus was introduced in 1969, but in the late 1970s a more virulent pathotype emerged and prompted the deployment of a new vaccine. In the early 1990s another virulence shift took place, followed by the development of a new vaccine<sup>47</sup>. The evolved mutants have the same epitopes as strains from the pre-vaccine era but have shown greater viral replication and higher immunosuppressive capabilities<sup>47</sup>. Marek's disease is a unique empirical model to study virulence evolution in vaccinated populations. Marek's disease in chickens is already used as an animal model to study vaccine immunity to cancer and viral-induced oncogenic transformations<sup>48</sup>. New knowledge in evolutionary epidemiology may lead to the inclusion of evolutionary considerations in vaccine design and development.

**Antimicrobial resistance.** The increase in the prevalence of infections that are caused by antimicrobial-resistant organisms is linked to the intensity of the selection that is imposed by the use of antimicrobials, and therefore infections with antimicrobial-resistant bacteria are especially common in health care facilities and on farms, where antimicrobial use is intensive. Transmission of clones of resistant bacteria between individuals is key for the dissemination and persistence of antimicrobial-resistant pathogens, both in health care facilities<sup>49,50</sup> and on farms<sup>51</sup>. The decrease in antimicrobial pressure has not always resulted in a decrease in antimicrobial-resistant bacteria at the population scale, however<sup>52</sup>. The mechanisms and determinants responsible for the persistence of antimicrobial resistance remain largely unknown, although several mechanisms have been postulated, including compensatory mutations that reduce or revert fitness costs<sup>53</sup>, co-selection with heavy metals and biocide resistant genes<sup>54</sup>, and increased horizontal gene transfer under stress responses<sup>55</sup>. The determinants leading to the persistence of antimicrobial resistance can be studied systematically in farm settings, because the suspected determinants can be manipulated at the population level. For example, the determinants responsible for the persistence of commensal *E. coli* that is resistant to streptomycin, sulphonamide and tetracycline in dairy calves were investigated in a series of studies<sup>56–59</sup>. Three



**Figure 1 | Designs of transmission experiments.** **a** | One-to-one experiments. One infectious animal (I) is housed with one susceptible animal (S)<sup>96</sup>. A transmission chain can be obtained by using the infected animals to infect the next generation of susceptible animals. **b** | Group experiments. A number of infectious and susceptible animals are housed together<sup>97</sup>. **c** | Extended transmission experiments. Artificially inoculated animals are mixed with susceptible animals. Artificially inoculated animals are removed, and the newly infectious animals (yellow and green), infected by contact with the inoculated animals, are used to start the transmission experiment by mixing them with new susceptible animals (blue)<sup>39</sup>. This design is useful when the artificial inoculation creates highly infectious animals; however, the initial infection process is less controlled. Aspects that need to be considered in the design of the experiment are the infection route, inoculation dose, mathematical model and statistics used to infer transmission parameters.

Table 2 | The use of farm animal populations to study infectious-disease dynamics

Research area	Animal pathogen or disease	Animal model or system	Refs
<b>Vaccine research</b>			
Evolution of pathogen virulence and antigenic escape	Marek's disease	Poultry	47
	Infectious bursal disease	Poultry	106
	Avian influenza	Poultry	107
	Foot-and-mouth virus	Ruminants	108
Vaccine design for multistrain or multihost pathogen systems	<i>Salmonella enterica</i>	Swine, dairy cows and poultry	109
<b>Antimicrobial resistance</b>			
Emergence and persistence of resistance	Multidrug-resistant <i>Salmonella</i> spp. strains	Dairy cows	110
	Methicillin-resistant <i>Staphylococcus aureus</i>	Swine	N/A
	<i>Escherichia coli</i>	Swine and dairy cows	63
<b>Transmission dynamics</b>			
Feedback between the within-host pathogen dynamics and transmission	Foot-and-mouth virus	Ruminants and swine	69
Empirical testing of transmission rate formulations and contact patterns	Multiple pathogens	Closed herds	35
Effect of infection imports on occurrence, frequency and persistence of disease outbreaks	Multiple pathogens	Connected open herds	111
<b>Host heterogeneity</b>			
Genetic determinants of vaccine responses	Foot-and-mouth virus	Ruminants	112
	Marek's disease	Poultry	47
Genetic determinants of disease susceptibility	Marek's disease	Poultry	48
	Nematode parasites	Sheep	75
	<i>Trypanosoma congolense</i> and <i>Trypanosoma vivax</i>	Cattle	113
	<i>E. coli</i>	Swine	36
<b>Dynamics of polymicrobial diseases</b>			
Dynamics of multiple colonizations and transmission dynamics	Bovine respiratory disease complex	Cattle	114
	Porcine gastroenteritis	Swine	115
<b>Emergence of new strains and cross-species infections</b>			
Mechanisms of emergence of new strains and cross-species transmission	Avian influenza	Live-bird markets	94
	Hepatitis E	Swine	102
	Influenza	Swine	82
<b>Dynamics of chronic infections</b>			
Dynamics of host–pathogen interactions and the determinants of persistence at the population level	Johne's disease	Dairy cows	28
	Mastitis	Dairy cows	116

N/A, not applicable.

hypotheses were tested: that the direct antimicrobial selection pressure maintains the high prevalence of the resistant strain; that the resistant strain provides a secondary advantage; and that a milk supplement (skimmed milk with vitamins D and A) provides a selective advantage. The persistence of the resistant *E. coli* in calves was found to be linked to the consumption of the vitamin D that was present in the milk supplements<sup>56–58</sup>. These studies showed that there can be a causal link between factors other than antimicrobial presence and the persistence of the antimicrobial resistance.

Field studies have been used to monitor the persistence of antimicrobials after the reduction of their use in farms. Antimicrobial pressure on farms ranges from non-existent (in antimicrobial-free farming systems) to high levels, as antimicrobials are used at different doses depending on the purpose (for example, therapeutic versus growth promoter uses). Studies comparing conventional and organic farms have shown that the level of antimicrobial resistance of enteric bacteria was lower on organic farms than on conventional farms, but that the difference in levels varied depending on the

antimicrobial<sup>60–62</sup>. The influence of antimicrobial selection on the genetic composition of *E. coli* populations was studied by comparing *E. coli* isolates from both organic and conventional farms<sup>63</sup>. Organic farm isolates had lower ampicillin resistance than conventional farm isolates, which showed clonal resistance, but tetracycline resistance persisted in organic farms, probably owing to genetic hitchhiking. Such studies can aid in predicting when antimicrobial reduction policies might be successful in human populations, as well as helping to determine the time that is necessary for antibiotic resistances to revert. In this regard, longitudinal studies of herds undergoing the transition to organic farming, in which antimicrobial resistance and the genotypes of the pathogens found in the farm are characterized, would be especially helpful.

**Transmission dynamics.** Transmission is the key process underlying infectious disease dynamics. Infectious disease models use varying transmission formulations that convey different assumptions about the structure of contacts among individuals of the population and their scaling with population density<sup>64</sup>. The predictions of the models can vary greatly when different transmission formulations are used, but empirical studies comparing these formulations are limited<sup>65</sup>. In human populations, the scaling of transmission rates with host population size and type of mixing (that is, homogeneous or heterogeneous) has only been assessed for measles, for which there are good data records for both large and small communities<sup>66</sup>. Experimental transmission studies in farm animals have evaluated the effect of density and the scaling of contact-based transmission<sup>67,68</sup>. Understanding how pathogen transmission in a population is affected by the pathogen dynamics within the host is important for predicting outbreaks and pathogen evolution<sup>15</sup>. Quantitative data linking both scales are limited, but some studies in veterinary medicine suggest that small differences in the observed duration of latent and infectious periods for the individual host can result in large differences in pathogen transmission at the population level<sup>37</sup>. Latent and infectious periods were estimated for equine influenza viruses in animals vaccinated with a homologous (immunologically identical) strain or a heterogenous (immunologically similar but not identical) strain. Vaccine escape, occurring in animals vaccinated with the heterogeneous strain, increased the duration of the infectious period. Studies that quantify transmission and within-host dynamics have also been conducted for foot-and-mouth disease in different species<sup>69</sup>, which provided unique data on a pathogen's life history traits, including the relationship between pathogen load and transmission.

**Host heterogeneity.** Pareto's Law is pervasive in transmission dynamics; it states that 20% of infected individuals contribute 80% of the net transmission for a wide range of diseases<sup>25</sup>. Transmission is influenced by many sources of heterogeneity, including behavioural and genetic factors, age, vaccination status and nutrition<sup>70,71</sup>. Untangling the causes and providing an

accurate representation of the population heterogeneity in models are important ongoing challenges in the study of infectious disease transmission dynamics and control<sup>71</sup>. A notable implication of the presence of heterogeneity on infection transmission is that individual-specific control measures designed to target the most infectious individuals (such as isolation) or susceptible individuals (such as vaccination of high-risk individuals) are more efficient at controlling the transmission than population-wide control measures (such as vaccination at random)<sup>25,71</sup>. The distribution of helminth parasites between hosts is usually highly overdispersed<sup>72</sup>; in humans the relative roles of exposure and genetic resistance in generating the overdispersed distribution is unknown<sup>73</sup>. Arguably, gastrointestinal nematodes in livestock are one of the best understood of all host-parasite systems, and extensive research to determine the sources underlying helminth overdispersion has been conducted<sup>74,75</sup>. A detailed quantitative genetic analysis indicated that additive genetic variation was the most important source of variability in faecal egg counts in sheep<sup>76</sup>. Two loci accounted for a large portion of the additive variation: the interferon- $\gamma$  gene (*IFNG*) and the major histocompatibility complex class II DR  $\beta$ -chain locus (*DRB1*)<sup>75</sup>. Genetic approaches are now being integrated with epidemiological models in order to quantify the contributions of the non-genetic and genetic variations in host immune responses to the observed transmission patterns and the impact of these variations on parasite control<sup>77</sup>.

**Emergence of new pathogens.** The interest in the emergence of new infectious diseases has grown considerably owing to highly publicized cases such as highly pathogenic avian influenza, swine-origin H1N1 influenza A and severe acute respiratory syndrome (SARS). The emergence of infectious diseases can be seen as a four-step process<sup>78</sup>: exposure of a new host to the pathogen, infection of the new host, transmission within the new host population, and epidemic spread. Although there is agreement that both ecological and evolutionary factors contribute to this process, their specific contributions to driving the basic reproduction number above 1 and to the resulting epidemic spread in the new host is unknown. In addition, it is unclear at which step the evolutionary changes that favour crossing species barriers or transmission in the new host take place<sup>79</sup>. Monitoring the transmission dynamics and the emergence of new pathogens among animals in agricultural systems provides an opportunity to study the mechanisms underlying emergence and to identify areas and pathogens from which the next human emerging infectious disease is likely to originate. Influenza viruses in farm animal populations not only serve as multiscale models for human disease, but also are major components of the natural system driving disease evolution and emergence into the human population.

The emergence of new influenza viruses is caused by reassortment involving human, swine or avian influenza viruses or by host-switching events in which the accumulated mutations favour the emergence of new strains that are capable of crossing species barriers

#### Genetic hitchhiking

A process in which alleles increase their frequency in the gene pool because they are associated with alleles at genetically linked loci that are favoured by selection.

#### Overdispersed

Pertaining to a distribution with a variance that is greater than the mean. For parasites, this occurs when many hosts harbour a few parasites and a few hosts harbour a large number of parasites.

#### Basic reproduction number

The expected number of secondary cases infected by transmission from a typical infected individual during that individual's entire period of infectiousness in a completely susceptible population.

#### Reassortment

The exchange of genetic material between genetically different viruses that are infecting the same cell. It can result in the generation of a novel strain.



## Mixed vessel theory

New strains of influenza virus can emerge if an avian-origin virus and a human-origin virus simultaneously infect the same animal (for example, pigs). This dual infection can produce reassortants with pandemic potential, if the reassortant has the ability to transmit effectively through humans and if humans are immunologically naive to the new strain.

and adapting in a new host owing to the low fidelity of the viral RNA polymerase. Examples of reassorted viruses in humans include the H2N2 influenza virus that caused the 1957 outbreak of 'Asian influenza' and the H3N2 strain that caused 'Hong Kong influenza' in 1968. The deadly H1N1 influenza pandemic in 1918 was probably due to a host-switching event and the consequent adaptation of an avian virus to humans<sup>80</sup>. During this pandemic, the H1N1 strain was also introduced into the pig population and evolved into the classic H1N1 strain that remained the predominant lineage in pigs in North America until the late 1990s<sup>81</sup>. In 1997–1998, two distinct H3N2 strain genotypes were identified in the North American swine population: a double human virus–swine virus reassortment and a triple avian virus–human virus–swine virus reassortment<sup>82</sup>. The triple-reassortant H3N2 strain spread efficiently in the swine population and has continued to evolve by genetic drift and by reassortment with the classic H1N1 strain<sup>83</sup>. This H3N2 strain is one of the progenitors of the newly recognized 2009 swine-origin H1N1 influenza virus<sup>84</sup>. Other H1N1, H3N2 and H1N2 influenza virus strains circulate worldwide in swine populations, although their origins and nature varies depending on their geographical location<sup>81,85</sup>. In addition, transmission from swine to humans has been well documented and ranges from sporadic cases with no further human-to-human transmission<sup>86</sup>, to limited human-to-human transmission (for example, the Fort Dix influenza outbreak in 1976)<sup>87</sup>, to extensive human-to-human transmission (for example, the 2009 swine-origin H1N1 influenza virus)<sup>88</sup>.

This extensive accumulated knowledge about the dynamics of influenza viruses in swine populations and their potential to emerge into human pathogens makes them a suitable model to study the ecology of influenza viruses. Comparisons among the influenza viruses found in swine populations have provided insights into the molecular basis of influenza transmissibility and the role of swine in the mixed vessel theory<sup>82</sup>. Empirical evidence for the three components of the mixed vessel theory, including the findings that swine are susceptible to avian and human influenza A viruses, that reassortment between swine, avian and human viruses takes place in the pig and that pigs can transmit reassortant viruses to humans, have been documented<sup>82</sup>. Host-switching events have also

been observed in swine populations. For example, in 1979 an avian H1N1 strain crossed the species barrier and established a new lineage in swine. This lineage provided a model for studying the early evolution of influenza viruses<sup>89,90</sup>. Comparisons with the classic swine H1N1 strain, circulating since 1918, indicated that influenza viruses have weak host-specific adaptation, as no common genetic changes related to the host-switching event were identified. This suggests that we have a limited ability to predict potential emergent avian influenza viruses by identifying specific polygenic changes that are indicative of mammalian adaptation<sup>89</sup>. More recently, other host-switching events without reassortment have been described, including other avian-to-swine switches, such as the H2N3 strain in the United States<sup>91</sup>, as well as equine-to-dog switches<sup>92</sup>.

Surveillance in live-poultry markets serves as an early warning system of emerging influenza viruses and has provided another battleground for studying the ecology of this virus<sup>93</sup>. Live-poultry markets bring together a number of hosts (including humans) of multiple origins in a high-density setting. Studies on the gene pool of the influenza viruses circulating in live-poultry markets have found evidence for different propensities of reassortment among subtypes and have identified quails as another species that acts as a mixing vessel for avian and human influenza viruses<sup>94</sup>. The complex interaction between influenza ecology and evolution across hierarchical scales cannot be completely replicated in artificial laboratory settings. The study of influenza emergence requires the use of natural mixing patterns, including those observed in swine and poultry management systems.

## Conclusions

Infectious diseases in farm animals are often studied because they represent an economic cost or a zoonotic risk. Here we present yet a third important reason for such work: infectious diseases in farm animals can be used as biological models to provide empirical data that aids infectious disease modelling and to advance our understanding of infectious disease dynamics and control for human populations. As Rudolf Virchow, father of the field of pathology, said: "Between animal and human medicine there is no dividing line — nor should there be. The object is different but the experience obtained constitutes the basis of all medicine." (REF. 95.)

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### Competing interests statement

The authors declare no competing financial interests.

### FURTHER INFORMATION

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