Epidemiological models to assist the management of highly pathogenic avian influenza

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Summary
In recent decades, epidemiological models have been used more and more frequently as a tool for the design of programmes for the management of infectious diseases such as highly pathogenic avian influenza. Predictive models are used to simulate the effects of various control measures on the spread of the infection; analytical models are used to analyse data from outbreaks and experiments. A key parameter in these models is the reproduction ratio, which indicates to what degree the virus can be transmitted in the population. Parameters obtained from real data using the analytical models can be used subsequently in predictive models to evaluate control strategies or surveillance programmes. Examples of the use of these models are described in the current paper.

Keywords
Avian influenza – Control – Mathematical model – Poultry.

Introduction

The control measures implemented during past epidemics of infectious diseases in livestock populations have been based on experience gained during previous epidemics and on extrapolation of scientific data from epidemics and experimental infection. It is, of course, well known that extrapolation of results from previous studies, either from field observations or from laboratory studies, may not be straightforward. In general, the transmission of pathogens in a population is a complex phenomenon, and inherently non-linear, and extrapolation from observations in individuals to processes in populations is not easy. Populations are heterogeneous; they consist of various types of individuals, the proportion of which may vary between populations. Individuals in a group interact with each other, which implies that the infection rate of individuals depends on the presence of other individuals in the population (1, 14, 17).

It is, therefore, difficult, if not impossible, to determine the efficacy of control measures or surveillance programmes from the results of challenge experiments or observational studies alone. Epidemiological models have become an indispensable tool in the design of programmes for the control of infectious diseases. The aim of this paper is to describe various models, their advantages and disadvantages and the suitability of such models for the analysis of epidemics of highly pathogenic avian influenza (HPAI) and the measures used to manage them.

Epidemiological models

The use of statistical and mathematical modelling approaches may clarify some of the essential factors that determine the rate and scale of transmission of an infectious disease (1). Several epidemiological models have been developed that use scientific data to simulate various control strategies and to evaluate the efficacy of these strategies. These models have been used in scenario studies for the control of classical swine fever (5, 25, 26, 29), bovine herpes virus infections (21), foot and mouth disease (40) and Aujeszky's disease (11, 48). These models have also been applied to avian influenza (AI) in poultry populations (4, 16, 18, 23, 28, 36, 41), and to model influenza A infections in humans (2, 12, 13, 22, 24, 34).

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These so-called predictive or simulation models are a convenient way to assist the control of infectious disease explicitly, and are helpful for policy-makers. The advantages are that they can demonstrate the effect of changes in parameter values on the outcome of the model, and they can be used without carrying out experiments or collecting field data, or in situations that cannot be examined experimentally or in the field if the pathogen is absent. These advantages may, however, be misleading, because these models need to be based on solid data. If these data are not available, additional experiments or analyses of outbreak data are essential (15).

Models may also differ in the number of parameters included. Simulation models often contain a large number of parameters, and therefore take into account many of the factors that can affect the spread of the infection in the population of interest. This may seem appropriate, because transmission is complex. As mentioned before, however, the difficulty with these models can be that the majority of these parameters have not been quantified, and the models do, therefore, contain several (implicit) assumptions.

Analytical models are often simple models with few parameters. Of course, these models are a simplification of reality and do not describe the transmission mechanism in much detail, but these models contain parameters that can be estimated, and may be sufficient to 'explain' the infection processes. These analytical models are used to describe epidemics, and to unravel the complex behaviour of pathogens in the population.

From a scientific point of view, the analytical use of epidemiological models is more interesting, because it provides a tool to unravel, describe and quantify the mechanisms behind the spread of infections between animals or between farms. Moreover, this step is essential to derive the parameters necessary to run predictive models.

Analytical models

The SEIR model

A model used frequently in the case of AI is the so-called SEIR model, which assumes that a population of birds consists of susceptible (S), latently infected (E), infectious (I) and removed (R) birds (e.g. 17, 42, 49). The rate at which susceptible birds (S) become infected is expressed by the transmission rate parameter β (defined as the average number of new infections caused by one infectious individual per unit of time). Recovery is the event that causes the infectious bird (I) not to be infectious any

longer, either owing to an immune response or because the bird died of AI. It is assumed that recovery occurs at a constant rate, α, which has an expected value equal to the inverse of the duration of the infectious period, T.

From these two events it follows that the average number of new infections caused by one infectious individual in a totally susceptible population (R_0) during the total period when the bird is infectious equals β/α or $\beta \times T$ (17). R_0 is unambiguously the key parameter in an epidemiological model, because it tells us whether a highly pathogenic (HP) AI virus infection can ($R_0 > 1$) or cannot ($R_0 < 1$) spread within the population, and thus whether control measures such as vaccination are effective in eradicating the virus (17).

Whether or not the AI virus can spread in a flock depends on the infectiousness of infected birds, and the susceptibility of uninfected birds, and on their mutual contacts. A proxy measure of infectiousness is the amount of virus shed by infected birds, whereas a proxy for susceptibility is the median infective dose (ID_{50}). Although virus shedding can be measured, for example by sampling daily during challenge experiments, it is a proxy, because the link between the virus titre and level of virus transmission is unknown. Moreover, because the exact route of transmission is unknown, the measure itself may not reflect infectiousness accurately. For example, virus excretion can be measured in tracheal and cloacal swabs, but which of these routes of transmission contributes to infection is not clear. Experiments to determine ID_{50} are rarely carried out, because they require large numbers of animals, separate housing, etc., and the actual route and dose of exposure in the field is also unknown. The contact frequency and probability of infection per contact are even more difficult to determine.

Quantitative knowledge of the transmission of AI is important for the control of this disease. First, the transmission rate affects the prevalence of an infection in a population over time, which, in turn, determines the probability of detection. Second, this knowledge enables us to determine which measures can reduce transmission, and whether the magnitude of the effect is sufficient. This might result in only minor outbreaks after the introduction of infection, which will reduce a subsequent epidemic.

As mentioned before, the level of virus transmission within a group of animals cannot be determined from measurements in individual infected birds. The transmission and accompanying parameters (β and R_0) may, however, be estimated from properly designed experiments and data properly collected from field studies, as described below.

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Experiments

Experiments can be carried out under controlled conditions, and can be used to study the effect of one factor (e.g. an intervention measure) on transmission. They are sometimes the only possible way to study the effect of a control measure. They do, however, often have low power, and extrapolation is difficult. Nevertheless, experiments do provide estimates of essential parameters that can be used subsequently in, for example, simulation models.

In so-called transmission experiments birds are exposed to inoculated (infected) pen mates, and the virus transmission within the group is based on the rate at which contact birds become infected after exposure (49). The number of newly infected birds per day (or other appropriate time period), expressed as the transmission rate parameter β, can be estimated with the mathematical SEIR model mentioned previously. In combination with the duration of virus shedding (T), the reproduction ratio can be calculated. An alternative technique is to estimate the reproduction ratio R_0 from the total number of birds that became infected due to contact exposure with inoculated birds during the whole experiment. This final size method (49) can, for example, be used when sampling each day is not feasible and as a check on the interpretation of the estimates based on daily measurements. The final size method is less powerful statistically but it is less dependent on assumptions, such as the assumption about the duration of the latent period of AI.

Various studies have been carried out to quantify transmission of different AI strains in populations of different susceptible species. In a study with an H5N2 strain (44, 45), the reproduction ratio was estimated for both a high and a low pathogenic (LP) strain in groups of chickens. The R_0 of the HPAI strain was significantly higher than the R_0 of the LPAI strain. In another study (46), the transmission characteristics of the H7N7 isolate from the Dutch epidemic in 2003 were quantified. The reproduction ratio of an H5N1 virus strain from Indonesia was estimated in layer-type (7) and native-type chickens (33). Bos *et al.* (7) estimated these parameters for another H5N1 strain in turkeys. Van der Goot *et al.* (46, 47) also carried out experiments with other bird species. In Peking ducks (47), the virus spread without inducing clinical signs; in teal and pheasants (46), the virus spread as well, but induced clinical signs, in pheasants more than in teal. The transmission parameters quantified in the above-mentioned studies are summarised in Table I.

This experimental design can also be used to determine the efficacy of intervention measures, because this is often possible only in an experimental setting and not under field conditions (10). Up to now, the efficacy of vaccination against AI has been tested only in experiments. Experiments have been carried out with turkeys (7), Peking ducks, pheasants and teal (46, 47), layer chickens (10, 43) and native chickens (33). In most studies, vaccination significantly reduced transmission, to such a level that the reproduction ratio was below one. This indicates that, in principle, vaccination could eradicate the virus from an infected population. An exception was found for pheasants, in which vaccination did not reduce the R value to a level below one (46).

Although these studies provided essential knowledge on transmission parameters, effectiveness under experimental conditions does not necessarily mean effectiveness under field conditions. Therefore, it is important to quantify

Table I

Estimates of transmission of various avian influenza virus strains between birds of various species

Pathogenicity	Strain	Bird type	β (day^{-1})	R_0	Study type	Reference
HP	H5N1	Chickens	–	2	exp.	33
	H5N1	Chickens	1	1.6	exp.	9
	H5N1	Ducks	–	>1.5	exp.	47
	H5N1	Turkeys	1.26	7.8	exp.	8
	H5N1	Poultry	–	2.6	field	39
	H5N2	Chickens	–	>1.3	exp.	45
	H7N7	Teal	–	>1.5	exp.	46
	H7N7	Pheasants	–	>1.5	exp.	46
	H7N7	Chickens	–	10	exp.	43
	H7N7	Chickens	4.5		field	6
LP	H5N2	Chickens	–	>1.3	exp.	45

β: transmission rate (average number of new infections caused by one infectious individual per unit of time)

R: reproduction ratio (average number of new infections caused by one infectious individual in a totally susceptible population)

HP: highly pathogenic

exp.: experiment

– : not available

LP: low pathogenicity

transmission under field conditions as well. Moreover, experiments are usually carried out to measure spread between birds. Transmission between flocks can be quantified only in field studies.

Field studies

Studies within flocks were carried out by Tiensin *et al.* (39) and Bos (6, 8). Tiensin *et al.* (39) used data from Thailand to estimate the reproduction ratio for H5N1 between birds. Bos *et al.* (6, 8) estimated the within-flock transmission that occurred during the H7N7 epidemic in the Netherlands in 2003. These estimates give an indication of the within-flock spread of AI viruses of different H and N types, and allow comparison of transmission parameters estimated in experiments and in the field. Moreover, these estimates can be used in simulation models to develop a surveillance programme, because they may indicate when, after introduction of the virus, an infected flock can be detected (*cf.* 21). Moreover, these data can be helpful in determining the number of infected birds over time after virus introduction and the level of infectiousness to other flocks in the neighbourhood.

Transmission between flocks can, most likely, only be studied under field conditions. Stegeman *et al.* (37) estimated the reproduction ratio between farms (R_h) in two affected areas before notification and after implementation of control measures (32). Manelli *et al.* (30, 31) quantified the R_h for the H7N1 epidemic in Italy in 1999/2000. Ward *et al.* (51) did a comparable study in Romania and quantified the reproduction ratio on a village level. They suggested that the environment and landscape played a critical role in the introduction and initial spread of HPAI H5N1 during the autumn and winter of 2005, and that the movement of poultry might have introduced the infection into central Romania during the spring and summer of 2006. Parameters estimated for AI virus strains between flocks are summarised in Table II.

Table II
Estimates of transmission of different avian influenza virus strains between poultry flocks, based on field studies

Pathogenicity	Strain	β (week^{-1})	R_0	Reference
HP	H5N1	–	2-2.6	51
	H7N7	2	6.5	37
	HxNx[a]	–	1.1-2.4	19
LP	H7N1	0.04-0.07	0.6-0.8	30

β: transmission rate (average number of new infections caused by one infectious individual per unit of time)

R: reproduction ratio (average number of new infections caused by one infectious individual in a totally susceptible population)

HP: highly pathogenic

LP: low pathogenicity

a) H7N1: Italy 1999/2000; H7N7: Netherlands 2003; H7N3: Canada 2004; H5N1: Asia 2003

These studies provided estimates in the so-called high-risk period (without control measures), but the studies also determined the effectiveness of control measures such as stamping out and pre-emptive culling. Stegeman *et al.* (37) showed that during the Dutch H7N7 epidemic, after implementation of the regular European Union (EU) control measures, in combination with pre-emptive culling, R_h was reduced significantly, but this was not sufficient to eradicate the virus from the affected areas. Manelli *et al.* (30, 31) also showed that the control measures reduced transmission of virus in Italy.

These studies demonstrated the effectiveness of the whole set of control measures implemented, but the contribution of each measure separately could not be determined (as for example described by Stegeman *et al.* [38]). An attempt was made to investigate the effectiveness of vaccination in an endemically affected area in Indonesia, but it was not feasible to carry out a clinical trial with sufficient power (10). This study showed that it is very difficult to design field studies comparable to experimental studies to evaluate the efficacy of control measures.

The focus of the above-mentioned analyses was on transmission among commercial farms. In various areas facing an outbreak, backyard poultry are also present. Backyard poultry are often considered to be a reservoir of HPAI, but they are sometimes considered to be only 'victims' of exposure to virus shed by commercial flocks. Bavinck *et al.* (3) carried out a study to quantify the epidemiological contribution of backyard flocks using data from the H7N7 HPAI epidemic in the Netherlands in 2003. They also used a SEIR model, but with flocks as the unit of analysis. The analyses aimed to estimate the susceptibility and infectiousness of backyard flocks relative to commercial farms. The results showed that backyard flocks were considerably less susceptible to infection than commercial farms, but estimates of the relative infectiousness of backyard flocks could not be determined owing to the small data set. These results indicated that backyard flocks played a marginal role in the outbreak of HPAI in the Netherlands in 2003. Similarly, in Thailand (39), the probability of infection was lower in backyard poultry than in commercial poultry. However, owing to the high number of backyard flocks, their contribution to the epidemic was still considered important.

Spatial aspects

The models described above contributed substantially to gaining more knowledge about the spread of AI within and between flocks. These models did not, however, take into account the spatial distribution of flocks. Boender *et al.* (4) used a mathematical model to identify high-risk areas for the propagation of AI. A central concept in their study was the transmission kernel, which determines the probability

of virus transmission from infected to uninfected farms as a function of inter-farm distance. This method provided estimates of the critical farm density and local reproduction ratio, which allowed evaluation of the effectiveness of control strategies. In the Netherlands there are two poultry-dense areas where epidemic spread is possible, and in which local control measures are unlikely to be able to halt an unfolding epidemic. In these regions an epidemic can only be brought to an end by the depletion of susceptible farms by infection or massive culling. The analyses provided an estimate of the spatial range over which HPAI viruses spread between farms, and emphasised that measures aimed at controlling such outbreaks need to take into account the local density of farms.

This kind of spatial analysis can be helpful in the development of more differentiated control strategies, as for example in the Netherlands (31). Le Menach *et al.* (27) presented a mathematical model based on stochastic farm-to-farm transmission that incorporated flock size and spatial contacts to evaluate the impact of control strategies and to link control measures to reduction of human exposure. They identified high-risk areas of spread by mapping the farm-level reproduction ratio and suggested that immediate depopulation of infected flocks, following accurate and rapid diagnosis, would have a greater impact than simply depopulating surrounding flocks.

Simulation models

Predictive simulation models are often used to demonstrate the effect of various control strategies and surveillance programmes on the course of an epidemic, and they can also be used for situations that cannot be examined experimentally or in the field. The values of the infection rate parameter β, infectious period and R_0 obtained can be used as inputs in predictive models, together with information on the poultry sector, with respect to, for example, the various types of contacts and the frequency of contact between flocks. Using more complex models, the results from simulations can be extrapolated to situations or geographical areas other than the ones they were derived from (15).

A simulation model has been used to determine the effect of an incursion of HPAI H5N1 into British poultry flocks (36). In this study it was found that, although the majority of randomly seeded incursions did not spread beyond the initial infected premises, there was significant potential for widespread infection. The efficacy of the EU strategy for disease control was evaluated and the simulations emphasised the pivotal role of duck farms in spreading H5N1. Garske *et al.* (19) used a simulation model to show that the farm-to-farm reproduction ratio prior to

implementation of control measures ranged from 1.1 to 2.4, and that enhanced biosecurity, movement restrictions and prompt isolation of the infected farms in all four outbreaks substantially reduced the reproduction number, but it remained close to the threshold value of 1. Boender *et al.* described the effect of different control strategies for areas with different poultry densities (4).

Guberti *et al.* investigated the role of dabbling ducks in the spread of LPAI strains in Europe (23). Their model showed peaks of viral prevalence after nesting and during the moulting period, and also showed that local extinction was highly probable in the winter. Another study (20) was carried out for Southeast Asia, where H5N1 is still circulating. One of the aims was to understand the factors favouring the continuing reoccurrence of the virus. The researchers analysed the statistical association between the recorded presence of HPAI H5N1 virus and five environmental variables for three synchronous epidemic waves in Thailand and Vietnam.

Savill *et al.* (35) used a dynamic individual-based mathematical model to determine how quickly the effects of HPAI infection can be detected in poultry flocks. They demonstrated that the time to detection depended non-linearly on R_0, and logarithmically on flock size and the number of birds per cage. This model makes use of the dynamic aspects of an infection in a flock and is, therefore, more valuable than statistical models that do not take these aspects into account. Verdugo *et al.* (50) examined the use of sentinel birds for early warning systems.

It remains, of course, important to evaluate how these conclusions depend on the underlying estimates, and whether or not more parameter estimates are necessary before conclusions can be drawn with regard to control policy (15). Nevertheless, these studies all contain valuable information for policy-makers that can be used for the optimisation of control measures in the future.

Conclusion

Infectious diseases such as AI have complex behaviour, and mathematical models can be helpful in unravelling infection processes. They also provide essential estimates of transmission parameters that can be used subsequently in simulation models. The combination of experimental and field studies for parameter estimation, with mathematical modelling, contributes to a better understanding of AI epidemics, and to the design of improved control and surveillance programmes. The collection of data from experiments and epidemics should continue, in order to test the underlying assumptions in the models and to improve the models further.

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Contribution des modèles épidémiologiques à la gestion de l'influenza aviaire hautement pathogène

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Résumé

Depuis quelques décennies, les modèles épidémiologiques sont de plus en plus utilisés en appui à la conception des programmes de gestion des maladies infectieuses telles que l'influenza aviaire hautement pathogène. Les modèles prédictifs permettent de simuler les effets des mesures de lutte envisagées sur la propagation de l'infection ; les modèles analytiques sont utilisés pour analyser les données relatives aux foyers et les données expérimentales. Le taux de reproduction de base, qui indique la capacité de propagation d'un virus au sein d'une population donnée, constitue le paramètre fondamental de ces modèles. Les paramètres obtenus lors de l'utilisation de données factuelles dans des modèles analytiques peuvent ensuite être réutilisés dans des modèles prédictifs, afin d'évaluer les stratégies de lutte ou les programmes de surveillance envisagés. Les auteurs fournissent quelques exemples d'utilisation de ces modèles.

Mots-clés

Influenza aviaire – Modèle mathématique – Prophylaxie – Volailles.

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Modelos epidemiológicos para ayudar a combatir la influenza aviar altamente patógena

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Resumen

En los últimos decenios, los modelos epidemiológicos se han erigido en una herramienta utilizada cada vez con más frecuencia para combatir enfermedades infecciosas como la influenza aviar altamente patógena. Los modelos predictivos se utilizan para simular la influencia de diversas medidas de lucha sobre la propagación de la infección, mientras que los analíticos sirven para analizar datos de brotes o experimentos. Un parámetro fundamental en estos modelos es el coeficiente de reproducción, indicativo del grado en que puede transmitirse el virus en la población. Los parámetros obtenidos a partir de datos reales con el uso de modelos analíticos pueden utilizarse después con modelos predictivos para evaluar estrategias de lucha o programas de vigilancia. Los autores presentan ejemplos del uso de estos modelos.

Palabras clave

Aves de corral – Control – Influenza aviar – Modelo matemático.

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