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Modelling control of avian influenza in poultry: the link with data

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Summary

In this paper the authors discuss the use of modelling in the evaluation of strategies designed to control epidemics of highly pathogenic avian influenza (HPAI) in poultry. Referring to a number of published models for HPAI transmission in poultry, the authors describe the different ways that modellers use quantitative information. Quantitative information can be used for model building, parameter estimation, and model validation. The authors emphasise that in the case of HPAI transmission in poultry there are important gaps in our understanding. Due to these gaps the models for the effects of certain control strategies, especially those involving vaccination of poultry, need to be based on provisional assumptions. Hence, it is necessary to validate these models and to do research to improve our understanding of the underlying processes in order to better parameterise the models and better estimate the parameters.

Keywords

Avian influenza – Epidemiology – Mathematical modelling – Model validation.

Introduction

Ideally, the design of strategies for the control of an infectious disease in a host population, in this case highly pathogenic avian influenza (HPAI) in poultry, is based on quantitative information of the transmission dynamics under different conditions. In principle, such knowledge can only be obtained by analysing the data from natural outbreaks and animal experiments; but modelling is also needed, particularly when the conditions under which control measures are applied are different from the conditions under which the effects were observed in outbreaks and/or experiments. These different conditions include scenarios in which new combinations of previously adopted control measures are used, as the combined effect of two measures can in general not be derived simply from the separate effects of each of the measures. Thus, modelling is used whenever there is a need to extrapolate from current or previous conditions.

Modelling is important for infectious disease control because it helps with the interpretation of data, the design of experiments, and the choice of control strategy (by calculating various options). The mathematical models may be very simple, e.g. comparing only incidence with control measures to incidence without control measures. However, more complex models are required to account for other differences that may exist between groups of hosts that are subject to control measures and groups that are not. These more complex models can lead to more reliable extrapolation of the control effect to new conditions.

There are two approaches to predicting, on the basis of existing knowledge, the outcome of applying new scenarios: one approach is based on randomisation using statistical models, and the other on mimicking the mechanics of the relevant (demographic and transmission) processes using mathematical modelling. Randomisation is the basis of prediction used in statistical inference: the effect of a control measure can be estimated because all

relevant conditions that could influence the outcome are chosen at random from the relevant target population. Hence, any new situation in the future will also be a random draw from this same distribution and the new control effect will, to a certain degree of confidence, fall within the corresponding confidence interval and thus prediction is possible (Fig. 1). In contrast, mechanistic prediction or extrapolation is based on the assertion that the appropriate model is fitted to the observations and, provided that sufficient knowledge exists regarding the future conditions, the correct outcome for these future conditions can be calculated (Fig. 1). The adequacy of the mechanistic extrapolation depends on applying the valid model and knowing the future conditions. If, in Figure 1, model B is valid and model A is not, it is clear that using the correct model for the future condition (as given by the arrow on the x-axis) is very important.

In the modelling approaches to be discussed below, statistical and mechanistic (or 'structural') elements are combined. Statistical prediction is always valid provided that observations are available for the relevant set of conditions. However, predictions made using the statistical approach may not be as accurate as those extrapolated using a valid mechanistic model. The mechanistic model can give better predictions because uncertainty is reduced by using the additional mechanistic information. Moreover, for extrapolation to conditions outside the reach

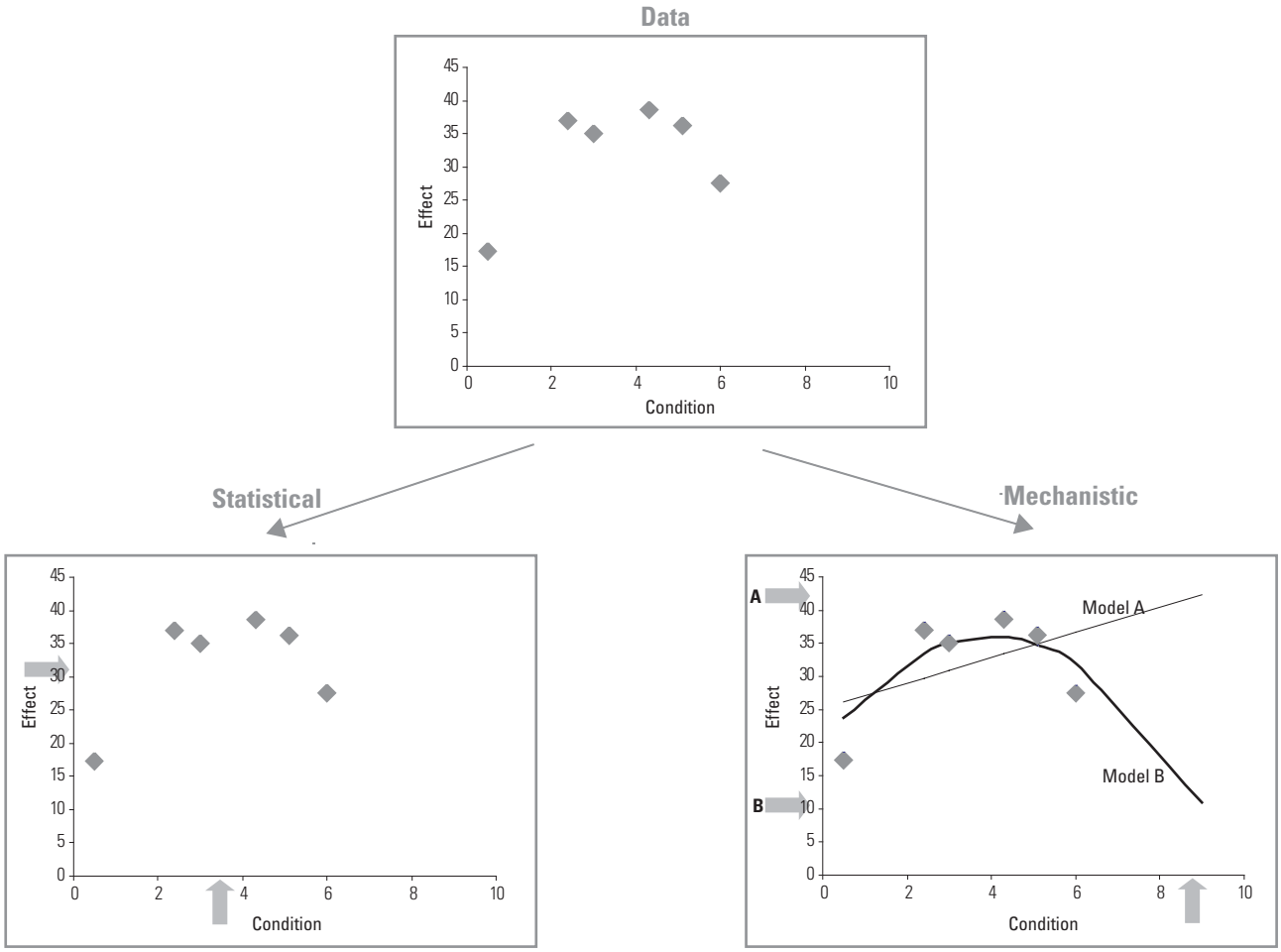

Fig. 1
An illustration of extrapolation by statistical methods or by modelling
Top panel: a data set with observed outcome (y-axis) and observed conditions (x-axis)
Left lower panel: a new outcome can be predicted statistically, where each new outcome is just a new realisation of the process given a random draw from the distribution of conditions (arrow x-axis), and thus a random draw from the outcome distribution gives the right prediction (arrow y-axis)
Right lower panel: on the other hand mechanistic modelling can show how the outcome depends on the underlying conditions (two lines) and how knowledge of the new condition (arrow x-axis) can give a better prediction of future outcome, given that the model is correct. Here model B applies and model A does not apply

of the existing observations on which the statistical analysis was based, mechanistic model elements are essential. For example, an estimate of the effect of culling of neighbourhood farms made in an unvaccinated region cannot directly be used for predicting what will happen in a vaccinated region.

The main difficulty in mechanistic modelling, and thus in obtaining correct extrapolations, is that it is often difficult to determine the actual transmission mechanism(s) underlying the observed infection dynamics. In other words, models can be made to mimic the real world as it is observed, but that is no proof that the models give the correct outcome for the correct reasons. Finding out whether the transmission processes are modelled correctly requires specifically designed experiments, well planned field studies, and accompanying data analysis to elucidate the true underlying mechanisms. The need for studying underlying mechanisms is often left unaddressed in modelling papers. Instead, emphasis is often placed on the need for measuring the underlying conditions better. For example, with respect to questions regarding the factors that exacerbate the risks of spread and the factors that help determine the most effective control strategies, Sharkey *et al.* state that 'Such questions can only be addressed through detailed consideration of specific features of the population at risk ..' (8). Truscott *et al.* consider that there are uncertainties regarding disease transmission in poultry, but that 'these uncertainties could be reduced only with considerably more data on the structure and movements …' (11). Although sufficiently detailed knowledge of underlying conditions can be important, it first remains to be determined which parameters are required (and how detailed they must be) to understand the relevant transmission mechanism. Below, the authors try to explain and illustrate that not yet all the questions regarding the quantitatively important aspects of these transmission mechanisms of HPAI in poultry have been answered.

Classification of modelling approaches

All the models for the control of HPAI in poultry that are discussed here use a combination of mechanistic structural elements and statistical or parameter-fitting elements. Here the authors look at modelling analyses of HPAI in poultry that aim to evaluate the effect of control measures and discuss to what extent we know that these models are valid and how we can improve them. The only limitations to improving the models further reside in the creativity of the researchers and in the availability of data. Although no model will be perfect, we need to have more critical discussions about the models and their assumptions and more quantitative investigation to either falsify or corroborate the assumptions. In this paper the authors focus on modelling papers exemplifying different approaches (Table I) with respect to using data for predicting future scenarios.

The differences discussed here relate to the ways in which these models are linked to data. There are three different

Table I
The different modelling approaches discussed in this paper

Article	Date and location of epidemic data analysis	Type of model		Prediction
		Statistical	Mechanistic	
(Stegeman *et al.*, 2004)	Netherlands, 2003	Transmission rates and the effect of control measures	SIR	Statistical
(Mannelli *et al.*, 2007)	Italy, 1999/2000	Transmission rates and the effect of control measures	SIR	Statistical
(Boender *et al.*, 2007)	Netherlands, 2003	Transmission kernels	Spatial SIR	Statistical
(Garske *et al.*, 2007)	Italy, 1999/2000 Netherlands, 2003 Canada*, 2004	Reproduction ratio based on observed trees	Branching process	Statistical
(Le Menach *et al.*, 2006)	Netherlands, 2003	Transmission rates w/wo control measures and dependent on distances	Spatial SIR	Simulations with the fitted model
(Truscott *et al.*, 2007)	None	Not applicable	Spatial SIR	Simulation with mechanistic modelling
(Sharkey *et al.*, 2008)	None	Not applicable	Stochastic SIR with contact structure	Simulation with mechanistic modelling
(Dent *et al.*, 2008)	None	Not applicable	Contact structure analysis	Simulation with mechanistic modelling

* In the province of British Columbia
SIR: susceptible–infectious–recovered model
w/wo: with and without

approaches. On one side of the spectrum are studies that use a relatively simple model structure that requires only fairly limited assumptions and apply statistical inference. Examples are the models by Stegeman *et al.* (9), Mannelli *et al.* (7), Boender *et al.* (1), and Garske *et al.* (5). In these models the structure is modelled with few parameters, which perhaps cannot be mechanistically interpreted but which can be estimated statistically from an observed epidemic. The models are used to learn from observed outbreaks of HPAI and estimate the impact of particular control measures.

On the other side of the spectrum are the models by Truscott *et al.* (11), Sharkey *et al.* (8) and Dent *et al.* (3), which use mechanistically founded parameters that are estimated from the literature or from available data sets; the final forms of these models, however, are not validated against data. For these three papers the lack of validation was unavoidable as the modelling was done for the United Kingdom (UK), where no outbreak data were available. The aim of these modelling efforts was to study features specific to the situation in the UK, either with respect to the risk for transmission or with respect to the possibilities for controlling the epidemic.

The model by Le Menach *et al.* (6) is in between, in the sense that it uses parameters from the literature and parameter estimates from a data set to which they fit the model (calibration) and compare the model fit (validation). This paper (6) and the paper of Garske *et al.* (5) both implicitly start with the assumption that quantitative information from previous outbreaks in certain areas/countries can also be useful in the modelling of transmission risks in other areas/countries.

Model structure

All these models for the transmission of HPAI in poultry are based on explicit and implicit assumptions about the underlying mechanisms. These assumptions become visible in how the model is built up, i.e. in the model structure. In particular, as control of HPAI in poultry is based on dealing with infected farms or premises (IP), the transmission between premises has to be modelled. Failed attempts during natural outbreaks, such as the 2003 epidemic in the Netherlands, to stop the transmission between premises show that we do not completely understand how that transmission occurs. In fact, it emerged that unexplained neighbourhood transmission was predominantly responsible for the difficulties in stopping major epidemics (2, 4, 10). The modelling of transmission between premises is therefore not straightforward, however tempting it may be to assume a set of routes based on known contacts between premises.

It is important when discussing these mechanistic or structural parts of the models to clarify to what extent the mechanisms on which the extrapolations are based, are known. Transmission processes are often not well understood and, thus, even when transmission parameters are estimated as a function of the underlying conditions it is unknown whether the model structure is valid. Hence, the extrapolations obtained also need to be critically assessed.

Truscott *et al.* (11) consider transmission in a vaccinated population as part of their modelling. They model the effect of vaccination assuming reduction in susceptibility of the vaccinated premises and reduction in contact rate (infectivity) between premises. Two issues arise with this model. First of all, does the model accurately reflect the effect of vaccination? Second, is there a way to estimate the parameters used for modelling these effects from available data? The experiments of van der Goot *et al.* (12, 13, 14, 15) have shown that vaccination can reduce transmission. However, this is at the level of transmission between animals, not between premises. The experiments of van der Goot show that it is possible to stop transmission between chickens for a certain vaccine and virus combination, and thus it will most likely also be stopped between premises for that combination or a comparable combination. However, what will happen under circumstances in which the flock is not well vaccinated, for example, because of a mismatch between vaccine and circulating field strains? Then it becomes important whether, for example, the infectivity of a vaccinated farm is a function of the distance between that IP and premises at risk of infection. Also, other measures of the intensity of contact between the IP and the receiving premises can be important, for example, in the case of a professional visitor as a possible transmission vector, the kind of work they have done on the IP and how much contact they had with infectious animals and materials. Furthermore, levels of reduction in transmission due to vaccination that are insufficient to stop transmission between poultry in direct contact may still be sufficient to stop the transmission between poultry at different locations. There is thus a need for better research before extrapolation of the vaccine effect can be done with more confidence.

Another important aspect is local spread, as it underpins the use of locally defined control options, i.e. measures implemented in the neighbourhood of an IP. Examples of such measures are reactive vaccination, pre-emptive culling and increased surveillance for IPs. Local spread is defined as the spread to premises in the neighbourhood of an IP without any known specific contacts with that IP. Again, ways of modelling this aspect can differ and there is as yet not enough knowledge to identify the correct mechanisms. Boender *et al.* (1) estimate a kernel for the spatial transmission of HPAI between poultry farms from

the 2003 outbreak data from the Netherlands. A kernel is the mathematical relationship between the distance from the infected farm to the receiving farm and the infection probability of that receiving farm. The kernel describes all possible transmission events, including those that have not been assigned to specific contacts. The approach of Boender *et al.* is statistical and as explained above this means that it is applicable to the conditions under which it is observed and more has to be assumed to extrapolate these results. For example, the estimated kernel applies to the mixture of large and smaller poultry holdings as found there and then and it may not apply, for example, in regions where all farms are relatively small. Le Menach *et al.* (6) have used three different probabilities for three different distance bands and estimated these from the data. In contrast, Sharkey *et al.* (8) have only used one probability for the nearest neighbours of an IP, which they estimated from the literature.

Another interesting paper, namely Dent *et al.* (3), sets out to look at only the observable contacts and what role they can play in the transmission of HPAI in poultry. Although this goal is interesting, there is the need to better know how these contacts could lead to transmission between premises. For example, the different contact types may differ in their contribution to the risk of transmission. Also, this issue illustrates the possible interaction between control measures, as the risk transmitted by first visiting an IP and then another premise with poultry may be reduced when one or both of these premises have been vaccinated.

Model predictions

As a result of the differences in how the different modelling approaches are based on quantitative data, different weight has to be attached to the conclusions drawn from the analyses. Conclusions based on statistical inference are typically robust, although they only apply to the specific situation studied. For example, it is obvious that major HPAI outbreaks can occur in areas with high densities of poultry farms even with control measures in place (1, 5, 8).

Better understanding of underlying mechanisms would be necessary to try and understand how the local spread between premises is actually occurring and what one could do to control it. Perhaps by changing certain conditions the farm density at which an epidemic cannot really be stopped would change. This includes increased biosecurity, encompassing better protocols for visitors going from farm to farm and for teams culling poultry at IPs.

Firm conclusions about the effect of vaccination can only be drawn when better mechanistic models are available, because vaccination has never been carefully studied in the field. One approach could be to make provisions to follow the first applications of vaccination, preferably during an outbreak, with appropriate field observations. Finally, modelling-based conclusions can be trusted more when they are specific about the applicability to poultry species, vaccines, and field viruses. For example, what is true for chickens might not apply to other species.

Conclusions

For deciding on HPAI control strategies an element of predicting the future is desirable, i.e. predicting the effect of the control measures. The basis for such prediction is formed by past experiences analysed using statistical methods, and fundamental knowledge of the behaviour of the virus in the host population obtained by analysis of experiments and field observations. Modelling plays an important role in the analysis and the design of experiments and field observations, and also in interpolating and extrapolating between these measurements. To make useful predictions, a sufficient understanding of the mechanisms underlying transmission is needed. Hence, for a model to be used when deciding upon which control measures to implement, this understanding must be demonstrated by validation and by discussing the validity of underlying assumptions, although sometimes validation will have to be done during the first application of the measures.

La modélisation de la lutte contre l'influenza aviaire chez les volailles : comment utiliser les données

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Résumé
Les auteurs examinent les modèles utilisés pour évaluer les stratégies de lutte contre les épizooties d'influenza aviaire hautement pathogène (IAHP) chez les volailles. À partir de plusieurs modèles publiés relatifs à la transmission de l'IAHP chez les volailles, les auteurs décrivent les différentes manières d'utiliser les données quantitatives dans les modèles. L'information quantitative peut être utilisée pour construire un modèle, pour en évaluer les paramètres, et pour le valider. Il est important de souligner que d'importantes lacunes subsistent encore au sujet de la transmission de l'IAHP chez les volailles. De ce fait, les modèles utilisés pour déterminer les effets de certaines stratégies de lutte (notamment la vaccination des volailles) reposent sur des hypothèses provisoires. Il est donc impératif de valider ces modèles et de continuer à élucider les processus de transmission à l'œuvre afin de mieux paramétrer les modèles et d'évaluer plus précisément ces paramètres.

Mots-clés
Épidémiologie – Influenza aviaire – Modélisation mathématique – Validation du modèle.

El nexo con los datos en la modelización de la lucha contra la influenza aviar en las aves de corral

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Resumen
Los autores examinan el uso de modelos para evaluar estrategias de control de epidemias de influenza aviar altamente patógena (IAAP) en las aves de corral. Refiriéndose a varios modelos de transmisión de la IAAP en las aves que han aparecido en publicaciones, describen las distintas formas en que los creadores de modelos utilizan los datos cuantitativos. La información cuantitativa puede usarse para elaborar y validar modelos y para estimar parámetros. Los autores recalcan que todavía hay muchas cosas que no entendemos en la transmisión de la IAAP en las aves de corral. Debido a estas lagunas, los modelos que describen los efectos de ciertas estrategias de lucha, en especial las que entrañan vacunaciones, están necesariamente basados en premisas provisionales. De ahí la necesidad de validar esos modelos e investigar más a fondo para entender los procesos subyacentes, a fin de introducir en los modelos parámetros más fiables y de poder estimarlos con más exactitud.

Palabras clave
Epidemiología – Influenza aviar – Modelos matemáticos – Validación de modelos.

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