Rev. sci. tech. Off. int. Epiz., 2011, **30** (2), 467-481

Estimation of foot and mouth disease transmission parameters, using outbreak data and transmission experiments

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Summary
Mathematical models for the spread of foot and mouth disease (FMD) have been developed and used for a number of purposes in the recent literature. One important purpose is predicting the effect of strategies to combat between-farm epidemic spread, in support of decision-making on epidemic control. The authors briefly review the various modelling approaches, discussing the parameters used and how estimates may be obtained for these parameters. They emphasise that, in addition to the estimation of FMD transmission parameters, the choice of model structure (including the number and type of parameters used) is also crucial. Two gaps in the knowledge of FMD transmission, related to model construction and parameter quantification, are identified: transmission between different species and the way in which vaccination affects such transmission, and route-specific FMD transmission properties. In particular, the authors pay attention to the role that small-scale transmission experiments can play in bridging these gaps.

Keywords
Foot and mouth disease – Mathematical modelling – Modelling – Parameter estimation – Transmission experiment.

Introduction

Mathematical models for foot and mouth disease (FMD) transmission have been used to interpret observational data on outbreaks or epidemics, and to make extrapolations to new situations. Extrapolation is necessary to inform policy-making on disease control, both for contingency planning before an epidemic, and for 'real-time' evaluation of the control strategies applied during an epidemic. For successful extrapolation, it is not sufficient to fit the model to the observational data. In addition, the model's representation of the transmission mechanisms underlying the extrapolation must be sound (18). Therefore, experimental studies combined with modelling are often required to guide model construction or to improve on previous, provisional model assumptions.

Historically, the first modelling of FMD transmission focused on airborne transmission between farms. This was mainly due to the fact that, in the 1966 FMD epidemic in the United Kingdom (UK), it was suggested that airborne transmission played a key role (59). In the more recent 2001 UK epidemic, airborne transmission is thought to have played a minor role in comparison to other transmission routes, involving human- or animal-mediated contacts between farms (30, 32). This latest epidemic stimulated the creation of a significant body of modelling work that used the epidemic data to estimate (either all or a subset of) parameters (36), and was directed towards analysing patterns of spread and/or predicting the effect of alternative sets of control measures. A third purpose for FMD modelling, found in the literature, is to interpret the results of small-scale transmission experiments that study transmission within groups of animals and how that transmission is influenced by vaccination (24, 51, 52, 53, 54, 55, 56). The authors will show that the results of both the work quantifying airborne transmission and of the transmission experiments can inform future FMD modelling work necessary for assessing new candidate control strategies.

The authors will first briefly review the different purposes and approaches of the three FMD modelling activities described above. They will then discuss the parameters in FMD transmission models. First, they explore a few very simple models to illustrate their views on which parameters should be included in a model and which should not. Secondly, the authors review the present status of model parameterisation and parameter quantification for FMD, in both within-farm and between-farm transmission models. Finally, they examine the role that small-scale transmission experiments could play in the near future to obtain estimates for (as yet) ill-quantified parameters of interest.

Foot and mouth disease transmission modelling: purposes and approaches

Predicting airborne transmission

Historically, the airborne route of between-farm FMD transmission has been studied in more detail than other possible routes. Airborne transmission models for FMD were developed after the 1966 FMD epidemic in the UK. This was because the major cause of spread during this epidemic was thought by many to be airborne transmission. These models were developed with the aim of predicting FMD airborne transmission between farms, using information on wind speed and direction, as well as other meteorological data (48). For instance, in 2001 they were used at the beginning of the UK epidemic to map farms at risk of becoming infected by airborne spread. The approach followed is a mechanistic description of airborne spread, with explicit consideration of:

– the emission of viral particles in the air from infected farms

– the transport by wind across a certain distance to a farm at risk

– the dose inhaled by animals on the farm at risk

– the associated dose-response relationship (59).

Transportation of the airborne virus is described using plume models for atmospheric dispersion (33, 58). The resulting models for FMD virus (FMDV) transmission by air try to incorporate the differences between the different species in terms of the infectious dose and the amount of virus excreted after infection. Cattle are highly susceptible to infection with FMDV and, in some publications, are considered to require as few as 10 to 20 median tissue culture infective doses ($TCID_{50}$) of virus by the respiratory route to become affected (20, 21), whereas pigs are relatively resistant to aerosol infection (1, 2). However, full analysis of the published airborne infection experiments involving cattle shows that the probability of infection with such a low dose is very small (28). An additional difficulty in this respect is the existence of seven serotypes and multiple subtypes, which may differ in excretion properties (1).

Calculating the effect of strategies to control between-farm epidemic spread

The large 2001 epidemic in the UK has stimulated much FMD modelling work, which began during the epidemic to support policy-making on control strategies (36). After the epidemic, modelling was required to uncover more epidemiological information from the epidemic data, including the actual effect of the control measures taken (27, 67). The policy options available and used at that time included movement bans, culling of animals on infected premises and preventive ring culling. Owing to the local character of many of these control measures, a spatial modelling approach was required. As discussed and reviewed by Kao (36) and Keeling (39), three technically different spatial modelling approaches have been used, one employing a deterministic model (26), and two making use of stochastic models: the Keeling model (43) and the Morris model (50).

In this paper, the authors classify between-farm transmission modelling approaches into (only) two categories: models that attempt to explicitly model different between-farm transmission routes/mechanisms (49, 50), and more parsimonious models that describe the combined effect of all possible routes and gather them together into one mathematical quantity (9, 26, 27, 37, 38, 40, 42, 43, 62, 63, 64). In the remainder of this paper, the authors will denote the first type of models as 'stratified' and the second as 'non-stratified' (for a schematic overview of the parameters needed in both models, see Fig. 1).

When using the non-stratified models to make extrapolations to scenarios that differed in the radius and/or speed of ring culling, all model parameters could be estimated from the observational data of the 2001 epidemic. More recent between-farm transmission modelling work also looked at the expected effects of control strategies, including vaccination, e.g. emergency ring vaccination (7, 64) and even large-scale preventive vaccination (42), and explored the use of risk maps to define high-risk areas for FMD spread and evaluate the effects of different control strategies in such areas (9). Clearly, when including vaccination as a control measure, the model for the effect of vaccination on between-farm transmission cannot be informed by the data from the UK 2001 epidemic. Therefore, the modelling of vaccination effects is inevitably based on provisional model

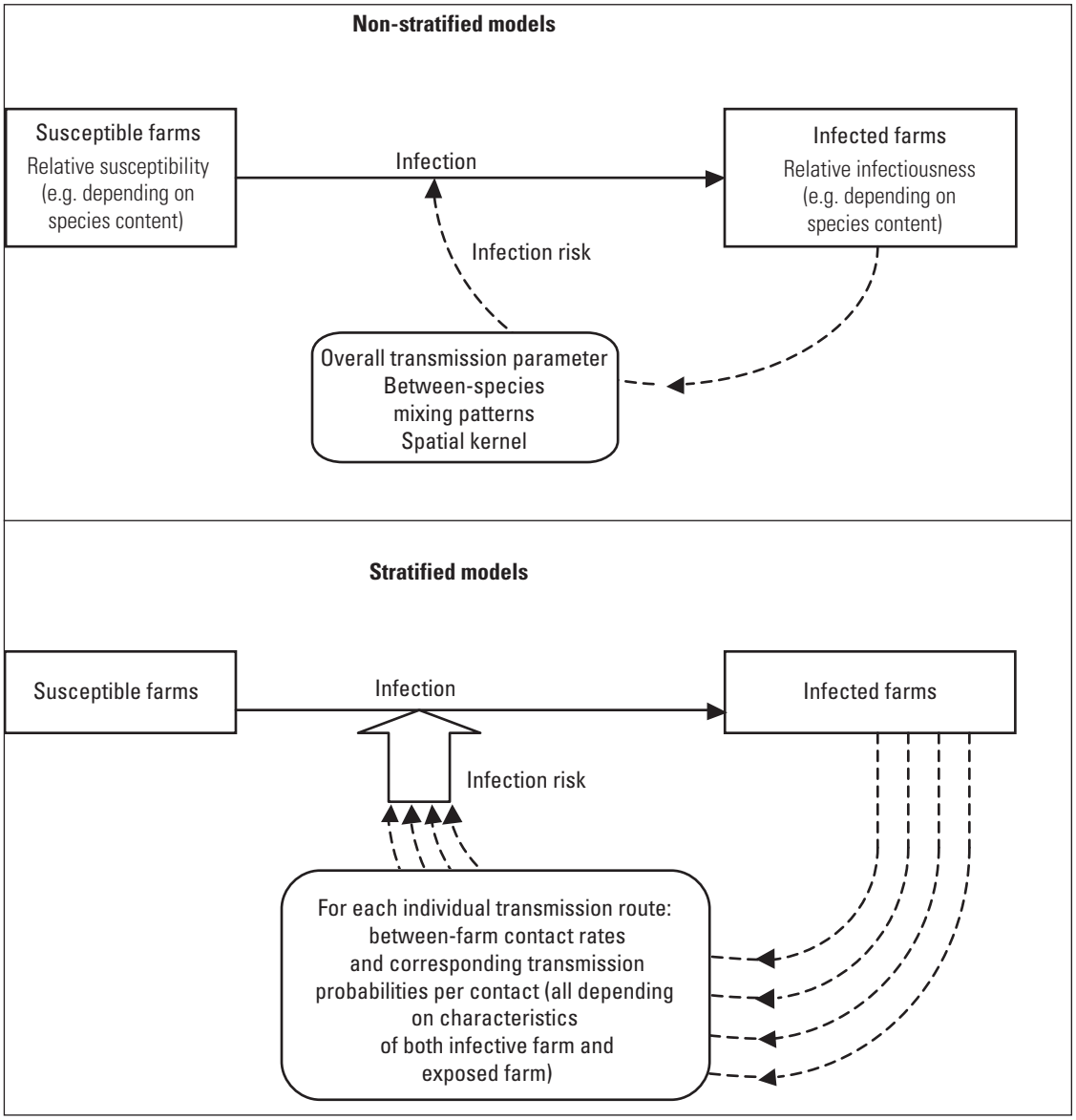


Fig. 1.
A schematic representation of models of foot and mouth disease transmission between farms, non-stratified versus stratified (by transmission route)

assumptions. Thus, confidence in the correctness of these model extrapolations is weaker than in the analyses extrapolating to scenarios that differ only in terms of culling parameters from the actual control strategy used in 2001. One particularly difficult issue is the effect that replacing preventive culling with emergency vaccination can have on the number of people and materials moving between farms. This may lead to changes in the transmission risks between unvaccinated farms, in comparison to the risks estimated from the 2001 epidemic.

Apart from the models of Morris and colleagues (49, 50), further work using stratified FMD models can be found in various publications (12, 19, 29, 35).

Calculating the effect of vaccination on between-animal transmission

Vaccination against FMD is a well-established prophylactic tool, and is currently still used in many countries all over the world. Large-scale vaccination strategies have been successful in realising the FMD-free status of the European Union (EU). Vaccination on a large scale started in large parts of Europe in the 1960s and the incidence of outbreaks declined to almost zero in about 20 years. In 1992, the EU Member States adopted a non-prophylactic vaccination policy. Emergency vaccination was still allowed in the case of an epidemic but was unlikely to be used, due to its economic consequences, especially for countries producing large numbers of livestock for export.

During the 2001 epidemic in the Netherlands, emergency vaccination was used. As a result of economic constraints, the vaccinated animals were killed afterwards in order to regain FMD-free status as soon as possible. Modern marker tests now allow differentiation between vaccinated and infected animals (11) and, in 2003, EU legislation was amended to lay down more specific trade regulations for animals and animal products after controlling an outbreak with emergency vaccination. As a result, in western European countries, FMD emergency vaccination has recently gained renewed interest and a vaccination-to-live policy is considered in several countries as an alternative to preventive culling, not only because of its effectiveness but also because it is an intervention strategy that is more acceptable to the public (8).

To compare different vaccination strategies, we must model the effect of vaccination on between-farm transmission. It is therefore important to extrapolate small-scale experimental results that test the effectiveness of a vaccine to a bigger (i.e. farm) population. For this purpose, the stochastic susceptible-infected-removed (SIR) model framework (5) is most frequently used. The authors note that the effectiveness of a vaccine within a farm may not be the sole criterion for its usefulness in control: a vaccine that fails to fully control within-farm transmission may still be effective in controlling virus spread from one farm to another (24). When analysing the final screening strategies for declaring freedom from disease after emergency vaccination (7, 8) (J.A. Backer *et al.*, work in preparation), both within- and between-farm transmission must be included, as the intra-herd seroprevalence is important. For within-farm modelling, parameters estimated from small-scale transmission experiments with vaccination are directly relevant.

Foot and mouth disease transmission parameters: which ones are necessary for the model's purpose?

Owing to differences in purpose and approach, the various FMD models briefly discussed above differ in the number and type of parameters used. For a given purpose, as discussed in more detail in the book by Keeling and Rohani (40), modelling infectious diseases always involves a 'trade-off' between model realism and model tractability; FMD modelling is no exception. The tractability aspect is closely linked with the issue of data availability for parameter estimation. The optimal level of model complexity depends on the specific research question that the model analysis is aiming to answer, and on the quantitative information available (or obtainable by future studies) to calibrate the model. The authors have already noted that, to model local control measures, such as preventive ring culling, as in the 2001 UK epidemic, the model must be spatial. That is, it must incorporate the geographical locations of farms, or at least some measure of the distances between farms. As a result, the model must specify how transmission probabilities change with between-farm distance.

To illustrate how to tailor the complexity of the model to the type of calibration data that can be obtained, the authors use two very basic examples of within-farm transmission modelling. These examples also allow them to introduce three basic transmission parameters for later reference.

Example 1

Consider an SIR model (5, 41), as shown in Figure 2a, describing the transmission of FMD on a single-species (e.g. cattle) farm of size N (41).

Here, β is the transmission rate parameter, representing the average number of new infections caused by one infectious animal per unit of time in a large susceptible population, and γ is the inverse of another important parameter, the mean infectious period. A third relevant parameter is the basic reproduction number, R_0, defined as the expected number of secondary infections caused by a single primary infected animal in a totally susceptible population. R_0 has a threshold property (5, 41): as long as $R_0 > 1$, an infection can spread on a large scale (major outbreaks are possible), but as soon as $R_0 < 1$, an ongoing epidemic will start to fade out, and new introductions of the infection can only lead to minor outbreaks.

In this model (2a), the basic reproduction number can be calculated as:

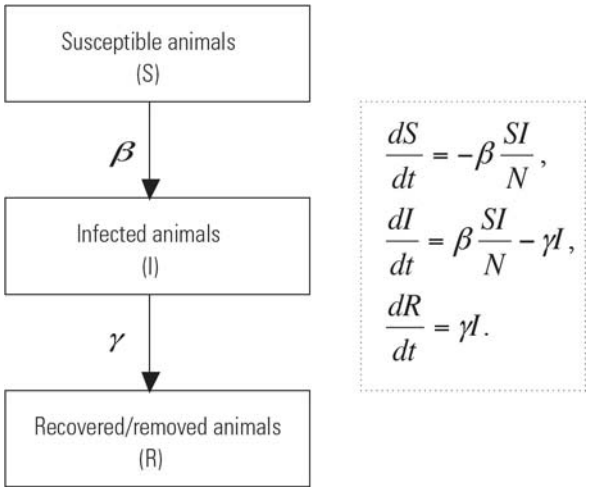
$$R_0 = \frac{\beta}{\gamma}$$

The parameter β can be considered as a product of the between-animal contact rate c, i.e. the average number of contacts between animals per unit of time, and the transmission probability for each contact, p:

$$\beta = pc.$$

Therefore, an alternative, more complex model could be obtained by replacing β in model 2a by the product of p and c, as depicted in Figure 2b. This alternative model is, although perhaps more intuitive biologically, mathematically more complex because it has an additional parameter. A crucial point to note is that it would be harder to obtain useful calibration data for the second model than

a) The standard susceptible-infected-removed (SIR) model



b) A slight variation on the standard SIR model

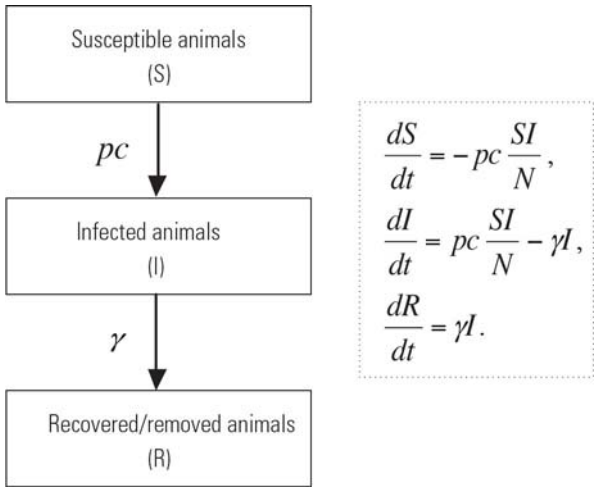


Fig. 2
Schematic and mathematical representations of example models of foot and mouth disease transmission
In the mathematical representations, the authors use the deterministic ordinary differential equations format to describe the models, although, for parameter estimation, the stochastic equivalent model is applicable

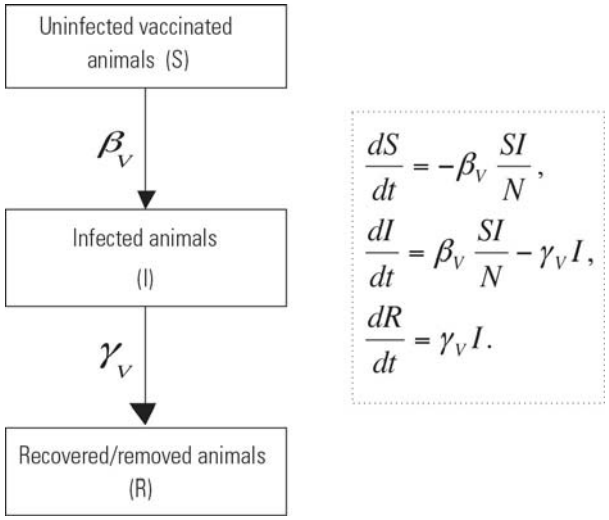
for the first. For example, whereas available epidemiological data from the field or from transmission experiments would possibly be detailed enough to allow estimation of the two parameters β and γ estimating the three parameters p, c and γ of the model 2b would, in addition, require a study defining and quantifying numbers of between-animal contact events (e.g. per day). In the absence of such a study, it is thus preferable to use the simpler model (2a), with only two parameters to estimate.

In contrast, for the example of transmission by (artificial) insemination with infected sperm, the model formulation 2b (extended to distinguish between bulls and cows) would be more natural than 2a, as the parameter c is then simply known (from the insemination records), and the probability p remains an estimable parameter.

Example 2

Now consider an SIR model describing the transmission of FMD on a single-species farm with (only) vaccinated animals, with two model parameters β_V and γ_V, for which the subscript V denotes that animals were vaccinated before the introduction of FMDV onto the farm. This model is depicted in Figure 3a. Estimation of the model

a) A susceptible-infected-removed (SIR) model for a vaccinated population



b) A slight variation on the SIR model in 3a

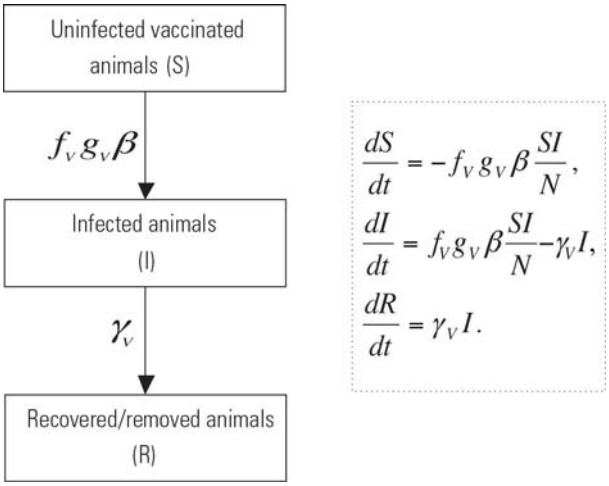


Fig. 3
Further schematic and mathematical representations of example models of foot and mouth disease transmission
In the mathematical representations, the authors use the deterministic ordinary differential equations format to describe the models, although, for parameter estimation, the stochastic equivalent model is applicable

parameters β_v and γ_v could be achieved by, for example, using the results of a transmission experiment in a group of vaccinated animals (16, 25). An alternative model describes the (possible) reduction of β in vaccinated animals, perhaps more intuitively, as arising from a combined effect of a reduction in susceptibility, g_v, and an infectiousness reduction, f_v, (with $0 \leq f_v \leq 1$ and $0 \leq g_v \leq 1$). This model is depicted in Figure 3b.

Even when assuming that an estimate of β is already available, the estimation of the remaining three parameters, f_v, g_v and γ_v of model 3b, requires more information than that of the two parameters β_v and γ_v of model 3a. If the results of a transmission experiment in a group of vaccinated animals were available, one would still need another set of carefully designed experiments – ideally, transmission experiments in which infectious non-vaccinated animals were brought into contact with vaccinated versus non-vaccinated animals (56) – to estimate (8) both f_v and g_v.

However, as model 3b applies to a fully vaccinated population, for all practical purposes of calculation with this model, only the value of the composite parameter $f_v g_v \beta$ is needed (equivalent to β_v in model 3a), and not the values of f_v and/or g_v separately. It is therefore unnecessary to consider the vaccine effects on susceptibility and infectiousness separately; i.e. the simpler model (3a) is the correct choice. Note that separating out f_v, g_v and β could become useful when modelling transmission between different species as it allows incorporation of the results mentioned above, which identify cattle as the most susceptible species and pigs as the most infectious.

Foot and mouth disease transmission parameter quantifications: present status

In this section, the authors briefly discuss the most relevant FMD transmission parameters and the present status of the quantification of these parameters. They first consider the parameters for within-farm transmission before moving onto the parameters for between-farm transmission modelling.

Within-farm transmission

Relevant within-farm FMD transmission parameters include the latent versus infectious period distribution, the transmission parameter β and the within-farm basic reproduction number R_0. One important difference between the last two parameters is that β contains a time dimension, which is needed in epidemic models to analyse the temporal course of an epidemic. If modelling the detection of clinical disease on a farm, which is important if, for instance, we want to estimate when animals will be detected/culled during an outbreak, the incubation period distribution is also relevant.

The infectious period is usually identified with the period in which virus can be detected in certain excreta or blood. This involves the assumption that infectiousness coincides with the measurable presence of the virus. The authors note, however, that it has been shown that different strains, differing in virus excretion, may nevertheless not necessarily differ in transmission (12). The following are examples of studies from which the latent and infectious period distribution can be estimated for:

– cattle (54)

– pigs (23, 53)

– sheep and goats (4, 47).

The infectiousness of 'carriers' (cattle with a long infectious period and low virus excretion) has been reviewed by Tenzin *et al.* (61).

For pigs and sheep, estimates for the basic reproduction number in a group of animals in one pen have been obtained in a number of transmission experiments (24, 56).

Estimates of the incubation period distribution for FMD (47), and its dependence on challenge dose and virus strain, can be obtained from a number of experiments in the literature (17, 44, 45, 46, 56).

For models describing mixed farms, it is also necessary to estimate transmission parameters β_{ab} between all relevant combinations of different species a and b. A recent quantification activity is estimating transmission parameters in the presence of vaccination. Such estimates are particularly important for modelling studies commissioned by policy-makers who are considering emergency vaccination as a possible alternative to large-scale preventive culling (64) (J.A. Backer *et al.*, work in preparation). The relevant parameters are those given in model 2a, that is:

– β_v, a (reduced) transmission rate parameter in a vaccinated population

– γ_v, a reduced infectious period.

However, due to a time lag between vaccination and the onset of vaccine protection, these parameters are dependent on the time between vaccination and challenge/exposure.

Other important subtleties associated with vaccination are also worth mentioning here. Studies by Eblé *et al.* (23)

show that, although vaccinated pigs can be protected from FMD if exposed for only a short period, disappointingly, they will not be protected against longer exposure to infectious pigs within the same pen. Further experiments provide evidence that vaccinating pigs, however, can provide protection against *between-pen* transmission (21, 64).

More complete and accurate parameter quantification in the presence of vaccination is desirable, particularly if the aim is to use these parameter values for model extrapolation to between-farm transmission in a partially vaccinated population and/or for farms comprising different species. This type of model extrapolation is relevant when assessing the effects of emergency vaccination as a control strategy during an FMD epidemic. The transmission between different species, and how vaccination affects this, therefore defines the first broad parameter quantification gap.

Between-farm transmission

As a result of its magnitude, the 2001 UK FMD epidemic generated a statistically powerful data set for estimating parameters in models that aim to describe between-farm transmission of this O/UKG/2001 strain, or a similar FMD virus, and the effects of the types of control measures applied in 2001. This has enabled useful parameter estimation for between-farm transmission models that are non-stratified with respect to transmission route. As a result, in the UK context, models have parameter estimates of sufficient accuracy to enable researchers to make useful extrapolations to certain combinations of control measures that differ from those actually used in 2001 (37, 42, 64). In essence, the parameters are:

– an overall average between-farm transmission rate parameter

– parameters that describe how this rate is modulated by:

i) the species of the source farm ('relative infectiousness')

ii) the species of the receiving farm ('relative susceptibility')

iii) the species combination of the source and receiving farms ('between-species mixing pattern')

iv) the distance between the source and receiving farms ('spatial kernel').

In addition, the size of both source and receiving farms modulates the transmission (13, 27, 43). This aspect of the model becomes important when extrapolating to areas outside those where the epidemic occurred and in which the average farm size could be different. The authors note that the value of the overall transmission rate may change in time over the course of an epidemic, as was the case in the 2001 UK epidemic, as shown by Ferguson *et al.* (13, 27). This is an example of the way in which modelling can help to interpret epidemic data, by revealing patterns in the transmission dynamics underlying the data.

Pigs played a very minor role during the 2001 epidemic, in terms of the total number of farms on which they became infected, in comparison to cattle and sheep (30). As a result, when considering the parameters describing the species effects, the uncertainty in the parameter estimates for sheep farms and cattle farms is small, whereas the uncertainty for pig-related parameters is very large. In fact, in the analysis by Keeling *et al.* (43), only cattle and sheep farms were modelled. Although a pig farm category was included in the analysis by Ferguson *et al.* (27), this category was based on the relative abundance of pigs on farms (in general, on mixed farms) and not on whether these pigs were actually infected. For this reason, the corresponding relative infectiousness and susceptibility cannot be interpreted as a true species effect. Whereas earlier analyses assumed homogeneous mixing between farms with regard to species content, Chis Ster *et al.* (13) found evidence for 'assortative mixing', i.e. sheep farms having more contact with other sheep farms than with cattle farms and *vice versa*. In a further statistical analysis of the UK 2001 epidemic data set, Chis Ster *et al.* (14) also estimated parameter values for a farm infectivity profile that varied over time, as well as for the degree to which farm susceptibility and infectiousness depended on farm size.

The authors note that, apart from parameter values, the between-farm transmission models also need input values for the spatial locations, size and species content of all farms that could potentially be infected within the area of study. Usually, this information can be obtained from identification and registration databases with links to geographic information for the country or region of interest. Clearly, the information in such databases will never be 100% accurate or complete. Whereas inaccuracies in the individual farm data (such as their location) are likely to average out in the model calculations, the absence of a subset of farms from the database can lead to underestimation of expected transmission rates, thus compromising the quality of the model's extrapolation results.

In countries that have not experienced an epidemic, and so for which country-specific estimation of transmission parameters is not possible, the values estimated from the 2001 UK epidemic data are probably the best starting point for devising plausible model scenarios. Clearly, some parameter values are likely to be country-dependent. In particular, the overall transmission parameter might differ between countries because it depends on (compliance with) biosecurity measures and movement restrictions. In addition, both this parameter and the species-dependent parameters might differ because of differences in farm management and typical farm size. Furthermore, some

countries of interest, such as Denmark (62), contain areas with high densities of pig farms. Such densities are not encountered in Britain, and the parameter uncertainty in the British species-related parameters for pig farms already leads to a great deal of uncertainty in the outcome, even when one ignores the uncertainties due to country-dependent factors.

The Dutch epidemic of 2001 was much smaller than the UK outbreak (which was the source of virus introduction), and mainly affected cattle farms: 26 in total. The epidemic data set enabled Boender *et al*. (9) to estimate an overall transmission parameter as well as two additional parameters defining the spatial kernel. As a result of the relatively small size of the Dutch epidemic, there is greater uncertainty in these parameters than in their British counterparts. Moreover, due to a lack of outbreaks on sheep and pig farms, it is not feasible to estimate species modulation parameters. Instead, Boender *et al*. provisionally assume that the relative infectiousness and susceptibility equal 1 for all three types of farms.

For most of the transmission events in 2001 in the Netherlands or in the UK, the route was not traced and, as a result, the data do not allow useful estimations of the parameters for specific routes. Therefore, models that explicitly consider different routes, such as dairy tanker movements, animal movements, windborne spread and 'local spread', cannot use the data from the 2001 outbreaks to estimate the large number of parameters required in these models. As a result, many of these parameters are currently being guessed, or obtained by seeking expert opinion (as, for example, in 12). Although expert opinion can be important to inform certain model simplifications, the authors do not consider it a good basis for estimating (highly) uncertain parameters (see also de Jong and Hagenaars [18], in the context of avian influenza transmission). Rather, if estimating such a parameter is not possible from the quantitative data, we should consider whether a more parsimonious model, lacking the parameter in question but still enabling the desired model extrapolations, could be developed. If there is no alternative to including the highly uncertain parameter, the model should be evaluated for different scenarios, in which the parameter is varied across a credible range of values. Parameters that are very difficult to estimate, particularly in models which distinguish different routes of transmission, are the probabilities of transmission, given that a contact occurs through such a route (compare parameter p in model 2b). The contact rates themselves (compare parameter c in model 2b) can often be estimated from detailed data, such as records of animal transports and dairy tanker movements.

When deciding between the use of models that explicitly consider different transmission routes and models that do not, the guiding principle is the same as for the model examples in Figures 2 and 3. If the purpose of the more complex (parameter-rich) model is the same as that of the less complex one, the simpler model should be preferred (36). In fact, the authors believe that models that explicitly consider different routes are only needed when trying to evaluate intervention strategies that have different impacts on different routes. This need has not arisen in past analyses of disease control, since the control strategies considered so far concentrate on (ring) culling and vaccination, and the transmission-reducing effect of these is not expected to differ between possible individual transmission routes. However, if we want to study the effect of specific biosecurity measures targeted against individual routes, it would clearly be necessary to explicitly include these individual routes in the model. This brings us to a second broad parameter quantification gap: route-specific transmission probabilities. Transmission experiments can play a role in bridging this gap, as the authors discuss in the next section.

Future role of transmission experiments to quantify model parameters

Parameters for transmission within and between different species

Most small-scale FMD transmission experiments carried out until now were designed to quantify the within-herd transmission in one species. Reproduction numbers and transmission rates for within-pen transmission of FMD between cattle (54, 55), sheep (56) and pigs have been quantified (24, 53). The effect of vaccination has also been quantified in similar types of studies. These studies already enable a substantial improvement in the provisional model assumptions made in earlier models (64) about the time lag between vaccination and protection and the effect of vaccination on farm-level susceptibility and infectiousness.

The authors note, however, that, due to the small number of studies thus far, further quantification is desirable, e.g. of the differences in transmission between serotypes of FMD; of the differences in transmission between age categories within one species; of differences in transmission between species, and of the influence of husbandry conditions. Similarly, the effect of vaccination on transmission has been quantified either 14 days or seven days post vaccination, but for no longer. In addition, the influence of a possible lack of homology between vaccine and challenge strains needs more attention. The results of these types of experiments can inform both the model structure (the number and type of parameters needed) and parameter estimation.

It is clear that more information can be gained by performing additional transmission experiments. However, such experiments are very costly and, from the point of view of animal welfare, it is not acceptable to conduct more experiments than strictly needed. Therefore, new experiments must be carefully designed and carried out only when it is expected that the results will provide new information that cannot be obtained from existing data sources.

Sometimes it is possible to estimate transmission parameters from previous animal experiments that were not originally conducted for that purpose, even when the design of these experiments was different from the design most commonly used for estimating transmission. For example, transmission parameters from pigs to cattle can be quantified from challenge experiments in which donor pigs were used as a means of naturally challenging (vaccinated) cattle. Another example of a 'non-standard' design is when additional (groups of) animals were added to the pool of contact animals after some time had passed in the experiment. Examples of both types have been encountered recently in collaborative efforts in the European Network of Excellence, 'EPIZONE', to (re-) analyse past experiments. These analyses have produced estimates for transmission parameters for several serotypes within various species (34) (S.J. Cox *et al.*, work in preparation). Preliminary results indicate that transmission parameters do not differ substantially between the different serotypes. In addition, a number of transmission parameters have been estimated between different species (34) (S.J. Cox *et al.*, work in preparation). Ideally, for modelling purposes, the whole 'matrix' of between-species transmission parameters should be estimated, for both vaccinated and non-vaccinated populations. A relevant 'model structure' question to address here is how many independent parameters are needed to construct this matrix.

Another priority is to obtain transmission parameters between vaccinated and non-vaccinated groups of animals. Spread from the vaccinated to the non-vaccinated area (or *vice versa*) should be taken into account, particularly in the context of emergency vaccination. The inclusion of these parameters would not only be useful to estimate the spread of FMDV during an outbreak in which emergency vaccination was used, but would also be essential to estimate the number of samples needed for final screening, to detect subclinically infected herds.

Yet another issue for study is to quantify possible temporal changes of the infectiousness of an animal infected with FMDV. In the models for FMD transmission between animals in the literature, infectiousness has been assumed to be constant throughout the infectious period, which is a basic assumption in the standard SIR model. In general, however, due to time-dependencies in virus excretion, infectiousness might be expected to also be time dependent. After infection with FMDV, and after the latent period, virus is excreted in all secretions and excreta (3). Virus excretion may, after the latent period, rise to a peak and then gradually decrease. Also, the infectiousness of excreta with a given viral load need not be constant, due to co-excreted immunologically active components. Time-dependent infectiousness might give rise to time-dependent transmission rates, as has been found for porcine circovirus type 2 (6). The inclusion of time-dependent infectiousness in model calculations might be especially important for sheep, since infections can remain unnoticed in sheep for relatively long periods.

Route-specific transmission parameters

Foot and mouth disease virus spreads predominantly by direct contact between infected and not-yet-infected animals. Thus, an immediate standstill of transport of FMDV-susceptible animals when an outbreak is detected would be expected to strongly reduce risks of transmission to other farms. However, recent outbreaks have shown that there can still be considerable spread of the disease even when movement of animals is prohibited, most probably by indirect transmission routes. This indirect transmission is caused by transporting secretions and excreta from infectious animals and can occur via several routes, such as transport vehicles, humans, contaminated feed, etc.

As mentioned above, in the stratified FMD transmission models, detailed information is included on some contact events, both direct and indirect, between different herds. Although good-quality contact rate information may be available for some transmission routes, such as animal transport, many other possible contact events between farms are highly complex and very difficult to analyse. Moreover, the contact structures during an outbreak probably differ from those during periods without outbreaks. Apart from pinning down the normal contact structures as precisely as possible during periods without outbreaks, logging all contacts on farms during outbreaks should also be considered, to uncover actual contacts, and to overcome recollection bias, present in conventional interviews. Interviews and (full-length) sequence information from detected new outbreaks might also be used to deduce transmission routes causing outbreaks. For instance, full-length sequencing was used in the recent 2007 FMDV outbreak as a means of inferring transmission patterns (15).

As well as detailed knowledge about the contact rates associated with certain specific transmission routes, the amount of infectious material transferred per event by these routes also needs quantification. This is, in fact, the study of the underlying mechanisms of FMDV transmission and their contribution to overall

transmission. Such a study could be designed in the following way. First, quantitative data are needed on viral loads in secretions and excretions. Tailored transmission experiments can then be used to link the observed viral loads with infectivity. Based on this, and on data for the survival of the virus in secretions and excretions, a transmission model could be developed to clarify the quantitative importance of the various secretions and excretions in transmission. This type of approach was recently explored for classical swine fever virus (66). Such a model, if its structure has been informed by appropriate experiments and its parameters are quantified sufficiently, could form a basis for improving disinfection protocols, or guidelines for the use of material possibly containing FMDV.

One particular transmission route for FMDV, at which much experimental work has been directed, is airborne transmission (1, 3). These studies provide important data for the estimation of biological parameters in the plume models (33). However, airborne FMD transmission in itself is not yet fully understood. Historically, the maximum amount of virus that animals, especially pigs, can excrete was often used to set excretion parameters in the models. Later, it was found that the initial high excretion for pigs, found by Sellers *et al.* (60), could not be reproduced, either by using the same virus strain or by using other strains (3). In fact, the quantity of excretion found was 100 to 1,000 times lower. Moreover, the susceptibility of pigs to airborne FMD infection was found to be much lower than previously assumed (1). In many cases, it is not possible to explain observed between-farm transmission events as being caused by airborne transmission when using average instead of maximum excretion estimates in the plume model (31). The susceptibility of cattle was also originally overestimated. Later studies showed that the probability of infection in cattle inhaling 10 $TCID_{50}$, which was used in the airborne spread model developed after the 1966 outbreak, is extremely low (28).

We may conclude that, on the basis of current plume model results, the airborne route is less important than previously thought. This illustrates how plume modelling, in combination with parameter estimation and outbreak data, can help to improve our quantitative understanding of the (airborne) transmission of FMD. As a result, plume modelling also helps in formulating stratified FMD transmission models.

Conclusion

The authors have reviewed FMD transmission modelling and the estimation of model parameters involved. In discussing the model parameters that appear in different modelling approaches, the authors emphasise one key element of good modelling practice: to choose carefully the complexity of the model (and thus the number of parameters involved), avoiding the inclusion of uncertain parameters that are not strictly necessary for the model's purpose. The authors also note that, where the model is extrapolating from observations on past control measures to new control measures (such as emergency vaccination), due attention must be paid to devising a biologically sound model representation of the effects of the new measures. Particularly relevant to inform careful model construction are studies that focus on specific aspects of FMDV transmission, using a combination of experimental quantification and modelling.

Two types of these studies can be identified in this review:

– plume modelling of the airborne spread of FMDV between farms

– measuring the effect of vaccination on between-animal transmission.

In discussing the role of small-scale transmission experiments in the current state of FMD parameter quantification, the authors have highlighted a number of specific FMD transmission aspects for further study. They are aware that, apart from such transmission aspects, many further aspects of the biology of FMDV remain to be investigated, e.g. the early course of infection within an animal still requires quantification. In a recent study, Pacheco *et al.* (57) conducted a detailed study of early events in FMDV-infected cattle. Such studies not only provide insights into the pathogenesis of the disease but also help to unravel the precise mechanisms of host infectiousness that give rise to between-animal transmission.

In addition, the authors have focused on the part that models can play in describing outbreaks/epidemics in areas that are normally free of FMDV. In areas where the disease is endemic, other factors are involved, such as: infected wildlife, the presence of carriers of FMDV, and, when prophylactic vaccination is used, young animals with maternally derived antibodies that interfere with vaccination, as well as the decline of vaccination titres over time. As a result, to model the spread of FMDV in endemic areas, the inclusion of a number of other parameters is of significant interest.

Acknowledgements

The authors would like to thank Jantien Backer for participating in discussions. This work was funded by the Dutch Ministry of Agriculture, Nature and Food Quality (WOT-01-003-011) and by the EU Network of Excellence, EPIZONE (Contract No. FOOD-CT 2006-016236).

Estimation des paramètres de transmission de la fièvre aphteuse à partir des données relatives aux foyers et d'essais de transmission expérimentale

T.J. Hagenaars, A. Dekker, M.C.M. de Jong & P.L. Eblé

Résumé
Plusieurs modèles mathématiques décrivant la propagation de la fièvre aphteuse ont été conçus et utilisés à diverses fins, comme en témoignent des articles scientifiques récents. L'un de leurs objectifs consiste à prédire les effets des stratégies mises en œuvre pour empêcher la maladie de se propager d'une ferme à l'autre, afin d'appuyer les prises de décision en matière de lutte contre l'épidémie. Après avoir brièvement exposé les différents principes de la modélisation, les auteurs examinent les paramètres utilisés ainsi que les manières d'obtenir des estimations à partir de ces paramètres. Ils mettent aussi l'accent sur l'importance de la structure du modèle choisi, en particulier le nombre et la nature des paramètres pris en compte. S'agissant de la transmission de la fièvre aphteuse, les auteurs identifient deux lacunes qui concernent la construction du modèle et la quantification des paramètres, et qui portent, d'une part, sur la transmission entre espèces et les effets de la vaccination sur cette transmission et, d'autre part, sur les propriétés que détermine la voie de transmission de la fièvre aphteuse. Les auteurs envisagent la possibilité de combler ces lacunes en procédant à des essais de transmission expérimentale à petite échelle.

Mots-clés
Estimation de paramètres – Fièvre aphteuse – Modélisation – Modélisation mathématique – Transmission expérimentale.

Estimación de los parámetros de transmisión de la fiebre aftosa a partir de datos de brotes y de experimentos de transmisión

T.J. Hagenaars, A. Dekker, M.C.M. de Jong & P.L. Eblé

Resumen
En recientes artículos especializados se han descrito modelos matemáticos de la propagación de la fiebre aftosa, concebidos y utilizados con diversos fines. Uno de los objetivos importantes estriba en predecir los resultados de estrategias para atajar la propagación epidémica de la enfermedad entre las explotaciones como elemento de apoyo a la adopción de decisiones de control de epidemias. Los autores pasan revista brevemente a los distintos métodos de elaboración de modelos, examinando los parámetros empleados y la forma de obtener estimaciones de esos parámetros. Insisten en que además de la estimación de los parámetros de transmisión de la fiebre aftosa, también es crucial la elección de la estructura del modelo (lo que incluye el número y tipo de parámetros utilizados). Los autores observan que en los conocimientos actuales sobre la transmisión de la fiebre aftosa hay dos lagunas que inciden en la construcción del modelo y la cuantificación de los parámetros: la transmisión entre distintas especies y el modo en que la vacunación influye en ella; y las

propiedades específicas de cada vía de transmisión de la fiebre aftosa. Los autores prestan especial atención a la posible utilidad de los experimentos de transmisión a pequeña escala para colmar esas lagunas.

Palabras clave
Elaboración de modelos – Elaboración de modelos matemáticos – Estimación de parámetros – Experimento de transmisión – Fiebre aftosa.

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