Review of the use of models in informing disease control policy development and adjustment.

A report for DEFRA

by

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1. Executive summary

After a brief preface (chapter 2), chapter 3 of this document presents a background to the techniques of modelling. Chapter 4 discusses specific roles which models may play in animal health decision making. The different types of model, their scope, basic principles and constraints, are discussed. Chapter 5 provides examples of the use of modelling in animal disease control planning and evaluation. In particular earlier models of foot-and-mouth disease (FMD) and modelling of the 1997/98 classical swine fever (CSF) epidemic in the Netherlands are discussed. Chapter 6 specifically examines the influence of modelling during the FMD epidemic in the UK in 2001. Chapter 7 provides recommendations for the future research and development required to support decisions involved in control of FMD. Chapter 8 presents guidelines to be followed when using models to support decision making.

1.1 Modelling basics

Principally, models are used as a substitute for, or adjunct to, real life study. They mimic real life and are most often used to explore how a situation may develop in response to different interventions.

However, models can also be used as an aid to understanding how a real system works. In this case the veracity of the end result of the model (i.e. the accuracy of any predictions) may be secondary to the process of modelling itself.

Models can also be an important aid to communication. They can help in explaining complex and often difficult aspects of system behaviour to ‘non-experts’, especially if the models can produce graphical visual, even animated, outputs. However, the very fact that such graphical outputs can be persuasive may also be a danger if the limitations of a model are not appreciated, or, indeed, if a model is fundamentally flawed. The output, by its very nature of consisting of numbers and charts can appear deceptively certain.

1.1.1 Importance of data in making models

Any model ultimately depends for its validity on the accuracy and completeness of the data underpinning it. Close collaboration between the model builders and subject matter experts is important in ensuring that a model is based in reality. With respect to modelling of FMD, there is still some way to go before all the data required for comprehensive models are available. The UK epidemic of 2001 represents a potential source of data. Careful analysis of the epidemic will help to identify important epidemiological determinants of that particular epidemic. However, there are still data gaps, on detailed virology (e.g. survival of virus in different conditions, infectious doses by different routes to different species etc.) and on disease spread within populations (e.g. the probabilities of different types of contacts between animals, and what factors govern these probabilities) which make the production of models with truly predictive capacity difficult, if not impossible.

1.1.2 Validation of models

There are no simple rules to follow when validating models. Several key issues are identified in chapter 3 and again repeated in chapter 8. These are:

* Valid models should make biological sense;
* Valid models should mimic real life;
* Valid models should be fit for the use they are designed for;

* Sensitivity analysis should be carried out to assess the influence of uncertain parameters on the model outcome.

1.2 Examples of use of models in animal health

1.2.1 Before 2001

FMD

Several models are described in chapter 5. Those of Miller (1976), Haydon and others (1997) and Howard and Donnelly (2000) were all state-transition models in which the population of farms was assumed to be homogeneous, i.e. all equally susceptible and equally infectious following infection. The models did not attempt to represent the spatial arrangement of the population or any heterogeneity in the contact structure of the population. These models were used to evaluate different control strategies as an aid to contingency planning for epidemics.

InterSpread (Sanson and others, 1994) is a model that attempts to simulate the spread of disease in a quasi-realistic way. This was developed as a component of an epidemic management system, that would be used as a tool during combat of an unfolding epidemic.

Specialised models of the airborne spread of FMD and risk assessments are also discussed.

CSF

The Dutch made quite extensive use of disease modelling and in particular demonstrated the flexibility of the InterSpread model as a basis to model CSF and other diseases. Modelling was used exclusively in the retrospective evaluation of the 1997/98 epidemic and the control measures used. Lessons were learned which contributed to contingency planning for the future. The use of a financial model along with the disease model was key in the use of modelling to influence policy. Arguments for different choices could be made on financial grounds. Also the costs of disease and control were split into public and private categories, and this informed the debate about who should bear the cost of measures aimed at preventing and/or limiting future epidemics.

Regarding the use of such models to support tactical decisions during epidemics, the view of those closely involved in this process is that such complicated simulation models should not be used during an epidemic, but in fact between epidemics to be better prepared and study ‘what-if’ situations. This means that models may be used to study a range of hypothetical situations, in order to provide guidelines for contingency planning, but then tactical decisions during epidemics are better based on field data which may rapidly indicate which modelled situation is actually being faced.

1.2.2 During the FMD epidemic in UK in 2001

The FMD epidemic in UK in 2001 was the first situation in which models were developed in the ‘heat’ of an epidemic and used to guide control policy. The engagement of modelling with the control of the FMD epidemic was not part of the pre-arranged contingency plan, but came about in an *ad hoc* way. The models are discussed in detail in chapter 6 and, with the benefit of hindsight, an assessment of their validity and the appropriateness of their use in tactical decision making is made.

A key tactical decision made with the strong support of models was the introduction of the contiguous culling policy. Evidence from later analyses, by one of the groups who produced the model key to this decision (the Imperial College group), and other analyses of the field data, suggest that the contiguous culling policy may not have been necessary to control the epidemic, as was suggested by the models produced within the first month of the epidemic. If

this is indeed the case then it must be concluded that the models supporting this decision were inherently invalid and/or used in an inappropriate way.

This conclusion was also implied by other reviewers of the models. Kao (2002) questioned the value of making detailed quantitative predictions for alternative policies, and Green and Medley (2002) suggested that the use of models to provide specific tactical advice early in the epidemic was not an ideal use of modelling.

It is suggested that incorrect assumptions used in building the models were responsible for the recommendation that contiguous culling was necessary to stop the epidemic. If an epidemic is modelled with parameters which describe disease spread as being predominantly over very short distance then such models will demonstrate a beneficial effect of local culling. In addition, if the model has the majority of disease spread from IPs occurring before reporting of disease, then such models will inevitably conclude that pre-emptive culling (culling premises before disease is reported) is ***essential*** to control the epidemic. To be effective, the pre-emptive culling would be targeted at the premises most likely to have been infected, i.e. local or neighbouring premises. The Imperial College and Cambridge/Edinburgh models were parameterised in just such a way that favoured the use of contiguous pre-emptive culling. However, the field data on which these parameters were based was deficient, and subsequent analyses are suggesting that the model parameterisation in these crucial areas was incorrect – i.e. short distance spread was not as predominant as modelled and the infectivity of infected farms was not maximal until after disease reporting.

Two main problems within the process of decision-making on FMD control during 2001 are identified:

1. The existing contingency plan for FMD control was overwhelmed and had no ‘ready made’ fall back position.
2. Field data were not being adequately collected and analysed early in the epidemic – in other words there was a lack of ‘veterinary intelligence’. The best decisions are made on the basis of good information. Had more accurate and timely field data been available in 2001, a better analysis of the developing situation may have led decisions in different directions. In 2001, the quality of information was compromised and model-based analysis was used as a substitute for poor information. What was perhaps not taken into account was that models themselves are equally dependent on good information for their validity. In truth, models were simply the tool used to analyse the data, but the novelty of this analytical tool to decision makers at the time and the nature of model outputs to appear more certain than perhaps they are, meant that the distinction between data and assumption was lost.

It will be important in the future to establish better bases for making tactical disease control decisions.

1.3 Recommendations for the future

Chapter 7 presents recommendations for further research and the role of modelling in the future, with particular reference to FMD control.

1.3.1 Potential roles of models with respect to FMD control

Modelling can contribute in all of the following areas:

* retrospective analysis of epidemics and evaluation of different control strategies;

- contingency planning – exploration of the effect of different strategies in hypothetical epidemics;
- resource planning – exploration of the resource requirements of different strategies in hypothetical epidemics;
- training – the use of models to provide 'virtual' experience of epidemic combat;
- surveillance targeting – in particular the use of risk assessments to identify priority areas;
- tactical decision support – limited use of models during epidemics.

The most appropriate use of models is as tools in 'peacetime' to aid retrospective analysis of real epidemics to gain insights into behaviour of epidemics. Hypothetical scenarios can then be modelled to develop insights into the relative merits of different strategies in different situations. In this way decision makers can be provided with *a priori* supporting guidelines.

The use of models during 'wartime' should then be restricted to monitoring the epidemic and aiding short term fine adjustments to strategies. 'Wartime' models should be one of several tools available to the epidemiologists to aid them in analysing and understanding the behaviour of the epidemic. Comparing real behaviour to 'expected' (model-generated) behaviour could alert epidemiologists to unexpected circumstances in the field which could then be targeted for action. 'Wartime' models could also be used to carry out limited 'what-if' simulations, to assess risks associated with various developments of the epidemic, so that appropriate contingencies could be made in resource planning. During epidemics, models can be usefully used to support the requisition of resources needed by well-tried control measures by graphically demonstrating the possible development of an epidemic.

1.3.2 Specific needs of DEFRA with respect to FMD control

There is a need to have more detailed contingency plans ahead of time; plans which cover several scenarios, including worst case scenarios, and anticipate the criteria on which decisions to adjust strategies and/or bring in different strategies will be made.

Contingency planning should be based on the wide range of available knowledge about disease epidemiology, disease control, the logistics of control and the economic consequences of disease and control. Modelling can play an important part in combining all this knowledge together to produce useful output for decision support.

The conclusion of this report is that the use of predictive models to support tactical decisions is not to be recommended. Tactical decision making should be based more on real veterinary intelligence than on predictive modelling. However, models can also play a role in interpretation of veterinary intelligence.

The establishment of a dedicated modelling section at DEFRA headquarters level is **not** recommended. Modelling is a highly specialised area of work, in which techniques are various, constantly developing and becoming ever more sophisticated. Attempting to establish, within DEFRA, a group who's modelling work might be considered 'definitive', and given priority over the work of other groups outside DEFRA, is unrealistic and would also lead to an over-reliance on model-generated solutions.

Rather, DEFRA needs to make sure that it has staff with adequate skills, in particular quantitative epidemiology, of which modelling is just a part, so that they can better integrate scientific advice with policy making. DEFRA should establish a core group with broad expertise in epidemiology, including quantitative epidemiology, which includes an understanding of statistical analysis and modelling. This group could consist of both

headquarters and field based staff. The remit of this 'epidemiology group' would be to collate, analyse, and interpret all information on animal health issues about which decisions are to be made. The group, would, of course, call on outside specialist expertise, for example in modelling, where necessary. The group would also be responsible for evaluation of all research which may have implications for animal health policy. The models developed during 2001 are still being used to explore aspects of FMD epidemiology and control. Modelling methodology is also being developed and opportunities to use novel approaches to explore old issues may arise. Researchers whose work may be relevant to DEFRA policy should be invited to discuss their work in a forum including DEFRA and independent scientists. One suggestion would be to maintain a standing committee to regularly review FMD epidemiological research, including modelling, being carried out in the wider scientific community, so that, where possible the results of good research may be incorporated into policy. The suggested DEFRA epidemiology group could play a key role in coordinating and contributing to this activity.

With particular reference to FMD, establishment of such a group would ensure that all possible lessons are learned from the 2001 epidemic.

In any future epidemic, such a group would be responsible for the rapid provision of real veterinary intelligence, based on targeted monitoring of key parameters of the unfolding epidemic.

1.3.3 The main areas for epidemiological (including modelling) research

The following are suggested as specific issues for DEFRA to address:

- quantitative analyses of real FMD epidemics;
- 'basic' epidemiology of FMD – experimental studies.
- commissioning of work to address specific policy questions as an ongoing, reviewing and updating, contingency planning process, this to include economic and practical logistic considerations;
- development of an 'in-house' simulation model for use as part of an epidemic management system and for training exercises;
- development of other tools for 'wartime' epidemic management – e.g. logistics models, risk assessments, airborne spread models;

1.4 Practical guidelines for the use of models

Chapter 8 provides a brief summary of the practical lessons to be learned from this report. This chapter should be read in full, but some of the most important points are also reproduced below.

From the outset it must be understood that models are rarely universal, or reproductions of reality in miniature. Models are most often produced to serve a specific purpose or to answer a specific question, and therefore include only what is relevant to their purpose. When commissioning research, the desired output is what should be specified, with the methodology left open to the researchers, unless of course, a working model forms part of the desired output. The problem to be solved, or the decision to be supported must be defined and the detail of information required must be specified.

It is extremely important that any interpretation of model output is made with reference to the assumptions and simplifications inherent in the model. Sensitivity analysis must be carried out to assess the influence of assumptions and simplifications on the final model outcome.

Sensitivity analysis is used particularly when the values assigned to model parameters are uncertain due to lack of good quality data. A model which is highly sensitive to parameters on which there is little reliable data is of limited use, perhaps even dangerous, in decision making.

Since the process of model building can itself be a learning process there is much to be said for decision makers and their advisers themselves being involved with or interacting with the process. This would ensure that the simplifications, assumptions and limitations of the model are fully appreciated by all involved in the decision.

When presented with model results, it is especially important that decision makers understand that the range of outcomes predicted by a stochastic model, or the confidence intervals associated with the results of a deterministic model, may result from any of three sources:

* natural variability in the real world (reflected in the model);
* the effect of chance events in the real world (reflected in the model), or;
* data uncertainty (insufficient precision in knowledge).

The fact that a stochastic model predicts a range of possible ‘futures’, reflecting the unpredictability of real life, means that it must be used with care as a decision support tool. Decision makers must not rely on the model to make a decision for them but be prepared to use it as part of a process in which other factors, such as the ‘riskiness’ of a policy, are weighed. This means that models cannot provide complete and unequivocal answers to a decision making problem. Models should therefore be seen as tools for exploring some of the issues involved, but the criteria on which the decision will be based will include other issues not addressed by the model.

Decision makers require some sort of framework within which model results can be combined with other quantitative and qualitative criteria to guide decisions. Development of such a framework may be a useful topic for future research.

2. Preface

The development of quantitative epidemiology has shifted the purpose of epidemiology from that of simply providing technical information on the life cycle of diseases and methods to control them to that of providing up to date ‘disease situation analyses’, complete with estimates of the economic effects of disease and consequences of alternative control strategies. There is an expectation that the availability of improved data about animal disease and its epidemiological analysis will lead to the development of better policies on disease control. With the role in policy development in mind it has become common to view epidemiology as an important component of a ‘decision support system’.

The decision support ‘toolbox’ has been gradually developed and filled with tools. These include statistical methods related to disease surveillance and analytical epidemiology, information technology used in data management and communication, mathematics and computer programming used in disease modelling and economic methods.

Of these new tools, disease modelling has proved to be a particularly important development. Since decision making involves an assessment of the future course of events following the choice of a particular action, the ability to represent reality using a model is seen as an invaluable decision support tool, especially if the model can be used to somehow predict the future.

3. Background to modelling: basic techniques

3.1 What is a model?

A model is a representation of reality, almost always simplified in some way. In technical language, a model is a representation of a 'system'. A system is defined as a collection of components which work together to produce some kind of output. In real life the system reacts to various external influences through its components so that the output is modified. With simple systems it is often possible to predict the effect of external influences on the output without the need for a model, e.g. vaccination on an individual animal will produce the effect of protection from a given disease. But as systems become more complex it is no longer possible to guess exactly how the system will behave in different circumstances, e.g. what would be the effect on disease incidence of vaccination of only certain classes of livestock within a large population? The boundaries of the system have been cast wider so that more interacting components have to be considered simultaneously in order to predict the effect of vaccination – in this case these components include the structure of the population and its dynamics. Models of complex systems are made in order to understand the effect of external influences on output through representation of the interactions between the component parts of the system, i.e. to answer the questions, "*what might happen if…?*", and sometimes also, "*why or how does the effect come about?*".

3.2 Why make models?

The prediction of the outcome of a particular action on a system is not the only use to which models may be put. Models can have several uses. In addition to using models:

* to predict the effects of changing or modifying different components in the system;

models may also be used:

* to test (verify) and improve our understanding of a system;
* to analyse and explain behaviour of a complex system, and;
* to determine the relative importance of different components of the system.

Models can therefore be used as an aid to understanding, rather than being an end in themselves.

> Teclaw (1979) says: "*Models not only mimic real systems in a more comprehensible way, but may go beyond description and lead to conclusions contrary to intuition. Additional benefits of models include the ability to experiment with a complex system without actually tampering with the real system. Models aid in hypothesis formulation and testing. Important variables operating within the system may be identified. The time scale may be expanded or contracted through the use of models. Certain well-constructed models may be used for forecasting, but the outcomes should be expressed as probabilities*."

A further common benefit of model building is that during the modelling process areas where our knowledge of the system is fundamentally lacking are often identified, so that field research can be directed more effectively.

> Dent and Blackie (1979) say: model building "*forces those concerned with building the simulation model to examine the system objectively and consequently undertake a thorough and critical review of knowledge concerning the system. The enlightenment that this process provides is often surprising*."

Models can be an important aid to communication. They can help in explaining complex and often difficult aspects of system behaviour to 'non-experts', especially if the models can produce graphical visual, even animated, outputs. However, the very fact that such graphical outputs can be persuasive may also be a danger if the limitations of a model are not appreciated, or, indeed, if a model is fundamentally flawed. The output, by its very nature of consisting of numbers and charts can appear deceptively 'correct'.

3.3 Basic considerations and modelling problems

3.3.1 Beginning

The first decision to be taken in model building relates to the overall extent and scope of the model. The boundaries of the system to be modelled need to be set. In fact there are two sets of boundaries to consider – in a model of FMD the 'inner boundary' might be the farm or the individual animal and the outer boundary might be the national population.

The level of detail to be included within these boundaries also needs to be considered, e.g. are different farm types to be represented differently in the model? It is important to realise that it is not always necessary to include every detail of the system in a model to arrive at a satisfactory answer to the question asked of the model. Haywood and Haywood (2002) comment that including too much detail can confuse the output of a model.

The scope of the model is another kind of boundary issue relating to the level to which the outcomes of the system are to be modelled, e.g. are numbers of infected farms sufficient as the model output or is it required to model the economic effects of disease on the national economy? A common approach to these issues is to split the modelling effort into a series of sub-models, which can be fitted together.

Having decided on the important parameters to be included in a model, if the model is to be quantitative rather than conceptual (e.g. a simple diagram), the parameters must be given values. Some values are easily knowable, e.g. the number of farms in a given county, but other values may be difficult or impossible to measure in real life, e.g. the probability of contact between two specific farms on a given day. It is inevitable that in model building simplifications and assumptions will have to be made to overcome this issue. This does not invalidate modelling but it is extremely important that any interpretation of model output is made with reference to the assumptions and simplifications inherent in the model. Specific areas where assumptions and simplifications are made are discussed below.

3.3.2 Real life is variable

For example, milk yield of cows varies, prices of products vary, incubation periods of disease vary etc.. Some models deal with this variability by assigning average values to parameters (simplification). Other models aim to be more realistic by assigning parameter values which are individually chosen from a distribution. In the latter method, different individuals in the model can have different values for the same parameter, e.g. if a disease model has 10 animals infected with virus the incubation periods may be different for each animal. The incubation periods may be chosen from a normal distribution with, say, mean 5 days and standard

deviation 1 day. The computational processes or programming of the model are set up such that, although incubation periods are randomly assigned to individuals, the end result will be that the mean incubation period in the modelled population will be 5 days (with standard deviation 1 day) – i.e. the model is realistic. However, the model is still based on an assumption that the mean and standard deviation of incubation period in the modelled population will be the same as measured in a different population.

3.3.3 Real life is subject to chance

Systems, in particular those containing living things, do not respond to stimuli exactly the same way every time. Many events in real life appear to occur by chance. Chance is quantified using the concept of probability. For example, given exposure to a source of infection an animal may or may not become infected. Models may deal with chance by representing what happens on average (simplification), e.g. when a group of animals are exposed the model assumes that a fixed proportion of them will become infected – this proportion is equal to the probability of infection. Other models explicitly model the chance element by randomly infecting, or not, each individual animal. This is done by generating a random number for each animal between zero and one – if the random number is less than or equal to the probability of infection then the animal is infected. This is known as the 'Monte Carlo' method. Given several groups of 10 animals exposed and a probability of infection of 0.2, the resulting number of animals infected in each group will tend to be around two (the expected or average outcome) but it is possible that in some groups no animals are infected and in other groups more than two are infected. The mathematical distribution of numbers infected is binomial. An alternative modelling technique is to treat the exposed animals as a group and assign the number infected by programming the model to choose a number directly from a binomial distribution.

3.3.4 Real life contains uncertainty (lack of precise knowledge)

Modelling is a rigorous discipline. Building a quantitative model requires that the parameters in the system are quantified. For example, it is not sufficient to know that "*sometimes sheep stray from one farm to another, potentially spreading infection*", if this event is to be modelled then it is necessary to assign a probability to sheep straying. It is frequently encountered when building models that values of parameters or probabilities have to be assigned when there is no objective evidence, such as estimates from large scale surveys, of what the true value or probability might be. The problem of uncertainty in a system which modellers wish to model is circumvented by assigning values based on a best guess (assumption), perhaps resulting from consultation with several experts (expert opinion). In some models a single value is used but in other models a degree of uncertainty in the guestimate may be represented in the model by assigning an uncertain value as a distribution, e.g. most likely value with minimum and maximum. This is similar to the inclusion of variability in models but it is important to realise that there is a qualitative difference – in this case the distribution reflects uncertainty, resulting from a lack of precise knowledge, not measured real life variation. The result is more variability in the model output, but rather than representing natural (realistic) variability, the variability due to the uncertain parameters reflects lack of precision in the model, which is a result of lack of data and/or knowledge about the real life system.

3.3.5 Events are connected

Typically, the output of a system is the result of chains of events. Sometimes the probability of an event depends on previous events in the chain, e.g. a farmer who has received an animal as a result of an illegal movement may well be less likely to report suspected disease promptly

than farmers in general. To take account of dependencies of probabilities through chains of events models have to be more complex. Whether an increase in complexity to achieve greater realism is justified is usually left to the discretion of the modeller.

3.3.6 Real life can be truly chaotic

Events which are subject to chance may yet be somewhat predictable when something is known about the probabilities involved with those events, because they will follow some sort of pattern.

However, if the probabilities of certain events happening are themselves variable, and therefore essentially unknowable, these events will not follow a pattern. They will be chaotic and therefore unpredictable. Chaotic events can be modelled, but here the purpose is to better understand how the events come about, rather than to attempt to predict when the next event might be. For an example see section 6.2.5, where a risk model of the introduction of FMD to UK livestock is described.

3.3.7 Behaviour can change over time

When modelling a process which takes place over a considerable period of time, such as a disease epidemic, it must be recognised that behaviour may change over time. For example, as an epidemic of FMD progresses farmers may pay increasing attention to reduction of contacts between their livestock and livestock of other farms. If an epidemic is very prolonged farmers may 'fatigue' and lessen the attention they pay to restricting contacts. Thus, the contact parameters in a model, if the model is to be as realistic as possible, should also change over time. However, it is very difficult to predict how such behaviour might change in the future which means that predictive models of epidemics can only be based on assumptions about future changes in independent parameters. Commonly predictions are based on the assumption that things remain as they are, unchanged.

3.3.8 In conclusion

The modelling problems described above are inherent to any attempt to describe concisely the real world. Simplification is inevitable.

> Graat and Frankena (1997) say "*As a model is made to be used for a specific goal … only key elements of a system or process are included… therefore, a model is by definition a simplification of the real system or process*."

The art of modelling lies in knowing which components to include in the model: the goal of the modeller is to include only those components which have a significant influence on the output of the system. It is important to realise that the accuracy of model predictions depends on which components are included or excluded, the validity of any assumptions made about them and the accuracy of modelling of the interactions between them. Modelling is indeed a mixture of science and art, but because modelling is a quantitative discipline it can appear entirely scientific and 'real'.

> Haywood and Haywood (2002) comment that "*modelling, although seemingly objective, should be seen as being a subjective activity in which the world-view of the modeller is an integral part of the process*".

Dent and Blackie (1979) also say, "*It will never be possible to prove a model 'true', yet the use of the computer can lead the unwary to accord the results a greater degree of precision than is justified. The model may contain undetected flaws, poor data transformations and intentional and unintentional biases included by the model-builder. All of these can seriously affect the validity of information provided by the model*."

Decision makers and their advisers must be aware that "*if the model is to be used as an additional tool in decision making, the goal and limits of the model should be fully understood by the decision maker*" (Den Ouden quoted by Graat and Frankena, 1997).

Since the process of model building can itself be a learning process there is much to be said for the idea that the decision makers and their advisers themselves should be involved with or interact with the process. This would ensure that the simplifications, assumptions and limitations of the model are fully appreciated by all involved in the decision.

3.4 Data and knowledge with respect to modelling

Graat and Frankena (1997) point out that data and knowledge are central to modelling. For example, if a model of a disease epidemic is to be built then quantitative data would be needed from real epidemics on which to base parameter values within the model. Knowledge of the disease epidemiology is important so that the components of the model can be put together correctly, with the correct interactions. Teclaw (1979) noted that one of the most important factors limiting the application of models is the lack of adequate epidemiological data. The aspiring modeller may be in one of four situations, as illustrated by the following table (modified from Holling, 1978):

Table 1: Data and knowledge with respect to modelling

		quantity/quality of data	
		poor	good
epidemiological knowledge	poor	(a) Exploratory – hypothesis development.	(c) Empirical / analytical – hypothesis testing.
	good	(b) Simplified representation of past events with data assumptions. Guarded predictive use ('what if?') BUT with uncertainty limits.	(d) Good representation ('simulation') of past events. Can be used predictively (what if?) IF the future is predictable.

Situation (d) is the best one. With good data and knowledge it should be possible to produce high quality models, e.g. flight simulators, models to track the trajectory of missiles. Note that these examples of the best models are of systems which operate under the influence of a few physical laws. This allows the confident use of such models as predictive tools, e.g. inherent in the use of flight simulators to train pilots is the understanding that an aeroplane in 'real life' would respond to the pilot's controls in exactly the same way as the simulator responds. Biological systems are inherently more difficult to model because their governing principles

are more complex and variable. It is therefore extremely difficult to attain the situation approaching perfect data and knowledge about a biological system. While it may be possible to produce a good simulation of a recorded epidemic it may still be difficult to use this model predictively. Especially if there are important factors which determine spread of an epidemic which involve human behaviour it becomes difficult to be sure that a real life epidemic would always respond to changing controls in exactly the same way as a simulated epidemic does. Whether this difficulty of predicting biological events is put down to simple lack of data (represented by situation (b)) or an inherent unpredictability of some aspects of behaviour, meaning that prediction is difficult even with good data, is a rather philosophical point akin to the question of whether the future of the universe could, in theory, be predicted if all physical laws were understood. What is important is to realise that even a model which mimics past events perfectly should be used with caution as a predictor of the behaviour of a system under changing conditions.

Situation (c) is interesting. When good data are available, but epidemiological knowledge is lacking, statistical techniques can be used to see how closely observed data fit hypothesised relationships. This process can be seen as analytical modelling (McLeod, 1993), e.g. regression of various types. In epidemiology these analytical models increase epidemiological knowledge by identifying and quantifying disease risk factors, which can then be included in models. This highlights the importance of data and data analysis as a pre-requisite for good modelling. Analysis of data allows progression from situation (c) to (d) but situation (d) is only attainable from situations (a) or (b) through an improvement in data availability. However, modelling can still be useful in the absence of good data (situation (b)), but such models should be used with great care. These models would contain much uncertainty because input data would be largely based on expert opinion and poor quality field data. An important use of such models would be to indicate which data are more important in the system, so that data collection activities can be focused more efficiently.

Currently, FMD modelling perhaps best fits in cell (b). The UK epidemic of 2001 represents a potential source of data. Based on this, empirical models of the epidemic may be constructed which will help to identify important epidemiological determinants of that particular epidemic. However, there are still data gaps, on detailed virology (e.g. survival of virus in different conditions, infectious doses by different routes to different species etc.) and on disease spread within populations (e.g. the probabilities of different types of contacts between animals, and what factors govern these probabilities) which make the production of models with truly predictive capacity difficult, if not impossible.

3.5 Types of model

There is no agreed classification system for models. Different authors have focused on different aspects of models which may distinguish them from each other (see McLeod, 1993). For the purposes of this report it is important to recognise that models may differ in three important aspects.

3.5.1 Treatment of variability, chance and uncertain data – stochastic models and deterministic models

Models which assign average, or most likely, values to all parameters and model the average or most likely outcome of chance events are termed ‘deterministic’ models. They produce a single output or result for each set of input values (scenario).

Models which include variability and the effect of chance in the method are termed ‘stochastic’. Because parameter values within the model are allowed to vary and because the

occurrence of chance events is randomised, stochastic models must be run repeatedly and produce a range of outcomes from the same input scenario.

Stochastic models, by explicitly including variability and chance, appear to be more realistic than deterministic models. This does not mean that deterministic models are unrealistic. The important realistic feature of stochastic models is that, given a single intervention in a disease epidemic model for example, a range of possible results is produced, reflecting the influence of chance events and the variability of nature on the final outcome. This provides decision makers with more information than a deterministic model. Figure 1, below, presents a stylised example. Imagine a stochastic disease model has been made. The model simulates an epidemic which is controlled by stamping-out and one of the outputs recorded is the total number of farms culled to achieve eradication. Two different culling policies are simulated as policies 1 and 2 – perhaps involving different levels of pre-emptive slaughter. The model produces a range of output for each policy because of the element of chance in the infection process and variability in model parameters. Figure 1 presents frequency distribution histograms for the total number of farms culled in each policy. Say the model had been run 100 times for each policy, then in scenario 1, 14 runs resulted in 301-400 farms culled, while in policy 2, 20 runs resulted in 601-700 farms culled. Results in these two ranges were the most frequent in each case and might be the ‘expected’ or ‘most likely’ results calculated by a deterministic model. While the ‘most likely’ result for policy 1 may be a better one than policy 2, the stochastic model suggests that in some cases a less favourable result is possible with policy 1. The cumulative frequencies of stochastic model results can be interpreted as predicted probabilities of particular outcomes. Thus, since 33/100 runs of policy 1 produce 500 or less farms culled, the probability of this outcome is predicted as 0.33. By the same token, the probability of 500 or less farms being culled under policy 2 is only 0.25, suggesting that policy 1 is better. However, under policy 1, there is a predicted probability of 0.25 that over 1,000 farms will be culled (25/100 runs produced this result), while in policy 2 the predicted probability of the same outcome is only 0.08. This suggests that policy 1, while potentially better than policy 2, is also more risky, i.e. there appears to be a higher chance that things could go badly wrong.

The fact that a stochastic model predicts a range of possible ‘futures’, reflecting the unpredictability of real life, means that it must be used with care as a decision support tool. Decision makers must not rely on the model to make a decision for them but be prepared to use it as part of a process in which other factors, such as the ‘riskiness’ of a policy, are weighed.

It is especially important that decision makers understand that the range of outcomes predicted by a stochastic model may also be, at least in part, a reflection of data uncertainty. This again means that models cannot always be expected to provide definitive guidance in decision making. In the past decisions have often been made in the face of imperfect data, and the skills involved in this process must not be forgotten – models must not be seen as a tool to produce knowledge without data.

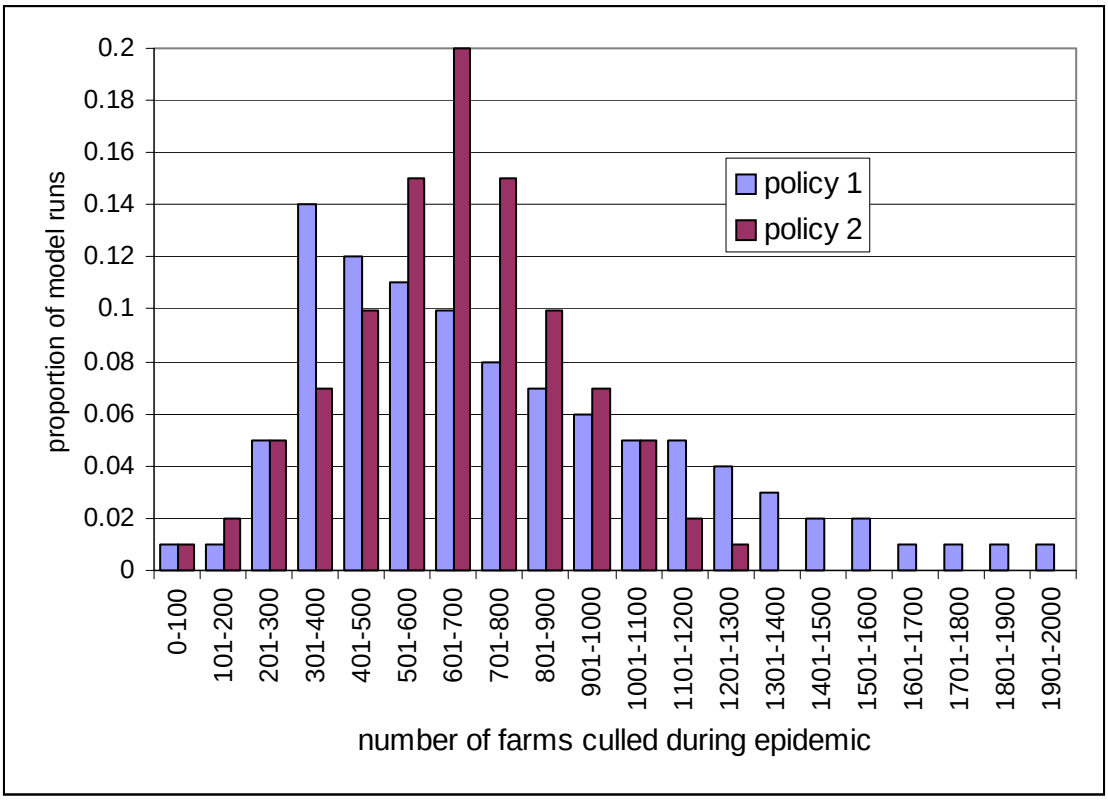

Figure 1: Stylised example output of a stochastic model

In some cases stochastic models can produce a huge range of possible outcomes, particularly where the model contains uncertain factors which may be given wide estimates by experts. This limits the value of the models in decision making. Medley (2001), commenting on model-based predictions of the course of variant Creutzfeldt Jacob Disease (vCJD) says that predictions that vary by two or three orders of magnitude are meaningless. That is, the results are not helpful as a basis for decision making. In fact, what this situation indicates is that the model contains either too much uncertainty, because data are lacking, or the system in reality contains so much variability as to be truly unpredictable.

Another advantage of stochastic models results from the method used to simulate chance events. A deterministic model of infection with disease, for example, uses the probability of infection to calculate that a proportion of exposed animals will be infected. As the model runs over several infection periods a proportion of the remaining susceptible animals will be infected in each period. Given that the infection probability is greater than zero there will always be some spread of infection in each subsequent period but an ever decreasing part of the population will always remain uninfected – i.e. the model cannot mimic an end to the process. However, a stochastic model simulates integer numbers of infections and may allow zero infections in a period, thus bringing the spread of infection to an end, e.g. if 10 susceptible animals remain in a population and the infection probability is 0.2 there is a good chance that zero would be infected and the infection therefore eradicated.

3.5.2 Treatment of time

Models may treat time as continuous or progressing in discrete intervals, e.g. days, weeks, etc.. This leads to quite distinct methods by which the model result is calculated.

Continuous time models use differential equations representing the rate of change of parameters within the model with respect to time. Such models are computationally elegant,

in that the behaviour of a complex system is crystallised into a few equations which can be calculated fairly quickly and produce a graphical representation of the changes in the system over time. A set of equations is organised in such a way that the state of the system at any future time can be calculated based on the input values of all parameters, but a possible weakness of models based on differential equations is the common assumption that parameters do not change over time (Thrusfield and Gettinby, 1984). An important consideration is that these models also tend to be more difficult for the non-mathematician to understand.

Discrete interval models break time into convenient units. The changes taking place in the modelled system from one time unit to the next are then simulated repeatedly over as many intervals as necessary. This requires the carrying out of many calculations, e.g. to simulate an epidemic over 200 days (where the time unit is one day) requires 200 sets of calculations to be done. If the set of calculations for each day is large this can lead to the model being cumbersome to run, even with modern day computers. One advantage of this type of model is that it is relatively simple to allow parameters to change over time, e.g. complex seasonal effects can be modelled. A further great advantage of this type of model is that by breaking the simulation down into a series of small steps, the logical framework of the model is usually transparent and easier for the non-mathematician to understand. This is particularly relevant when models are to be used to support decision making.

3.5.3 Treatment of space

Disease models represent the behaviour of disease in populations of animals. In real life those animals exist in space. Models may or may not attempt to represent the spatial relationships of animals in the modelled population. The first disease models modelled disease in populations under the assumption that members of the population were homogeneously mixed, so that only the size of the population was important and not the spatial relationships between animals. More recently the spatial dimension has been incorporated into models. This requires refinements particularly in models of contagious disease such as FMD, when data describing the ‘contact structure’ of the population are required. The term, ‘contact structure’, refers to the fact that contacts between animals are no longer completely random, but are determined by their relative positions in space.

3.6 Stages in model development

The following description of model building is largely adapted from Martin and others (1987) and Dent and Blackie (1979).

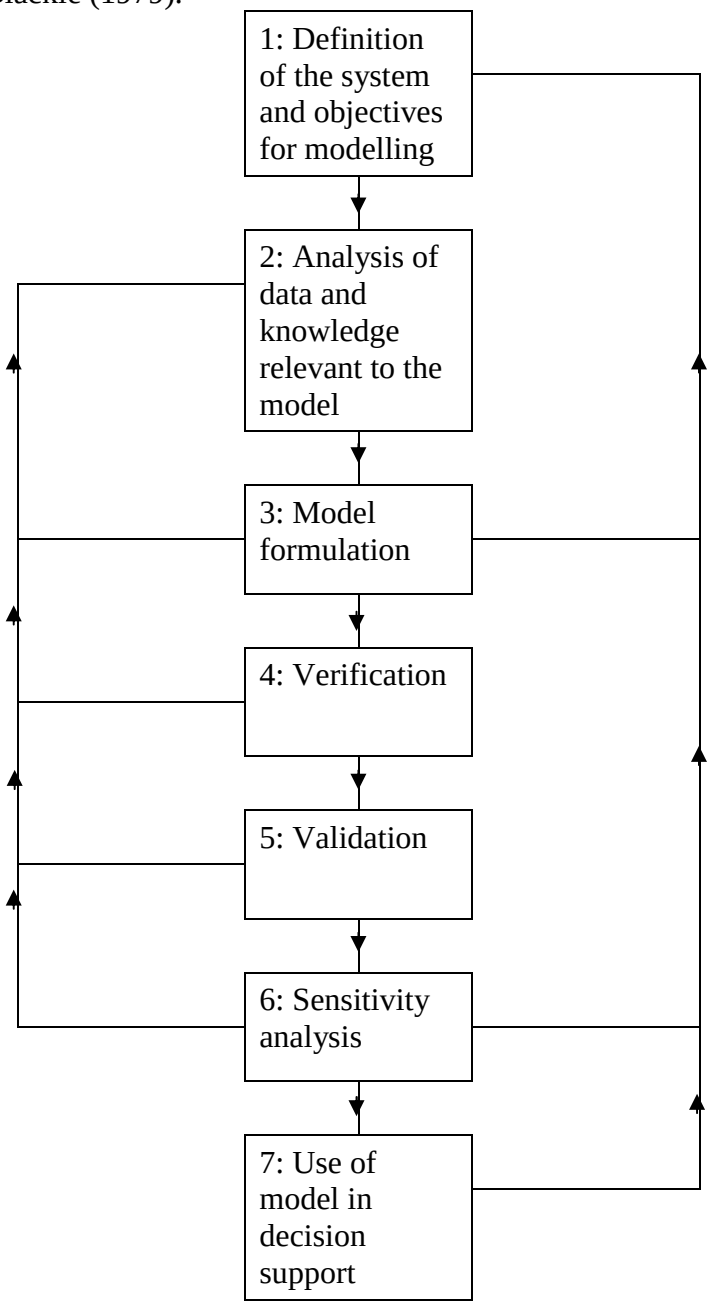

Figure 2: Stages in model building

3.6.1 Definition of the system and objectives for modelling.

There must be a clear statement of objectives. Models developed as ends in themselves may be of limited use in decision support. **The problem to be solved, or the decision to be supported by the model must be defined and the detail of information required from the model must be specified**. The initial specifications with regard to detail may have to be modified later on the basis of sensitivity testing or as a result of experience using the model to support decisions, i.e. it may turn out that the decision critically depends on a particular detail of the system, which must then be modelled in more detail.

3.6.2 Analysis of data and knowledge relevant to the model.

This consists of determining the principal components of the system under consideration and their interrelationships. These components and interrelationships are translated into a logical model framework on which quantitative data can be pinned. This step represents a learning stage which is vital, as it establishes the model structure. **Close collaboration between the model builders and subject matter experts is important here**.

3.6.3 Model formulation.

The model framework established in step 2 has to be implemented on a computer. There are various techniques available which are described in more detail elsewhere in this report. Constraints in model implementation may dictate modification of the basic framework.

3.6.4 Verification

Model verification consists of checking that the model is doing what the modeller intended it to do. It is the process of checking that the formulae and programming correctly reproduce the logical framework conceived by the modeller. This is usually achieved by carrying out internal checks within the model.

3.6.5 Validation

Whereas model verification checks that a model is 'true to the modeller', model validation is concerned with checking that models are 'true to life'. Unfortunately there are no objective and universal tests of model validity. However, some common themes are evident in the general literature on models, as follows:

1) Valid models make biological sense:

Disease modelling should not be carried out in isolation from other branches of epidemiology and 'reality checking' is an important aspect of modelling. According to Thrusfield (1986) a valid model should make biological 'common sense'. The model should be examined to ensure that all the known determinants that influence outbreaks of the disease have been included, i.e. does the model include all current epidemiological knowledge about the disease? It is also important to determine whether the value of these determinants can be assessed with accuracy, i.e. is there sufficient data of sufficient quality to fuel the model? This last question is related closely to which situation of the four detailed in table 1 the model has been constructed in. If important determinants are missing, or cannot be accurately parameterised within the model, then the model's validity is compromised.

Similarly, Miller (1976) stated that a model's mechanisms should be intuitively acceptable. It should behave in a biologically and mathematically reasonable way (e.g. it should be 'sensitive' to appropriate variables).

In other words, it should be possible to explain the outcomes of models according to current biological knowledge. This is not the same as saying that a valid model must produce a result that was expected beforehand. Model results may appear counter-intuitive at first sight, but as Dent and Blackie (1979) point out, model building "*forces those concerned with building the simulation model to examine the system objectively and consequently undertake a thorough and critical review of knowledge concerning the system.*" One of the benefits of modelling can be that it prompts the development of better understanding of the basic biology underlying the system being modelled.

2) Valid models mimic real life:

Spedding (1988) describes model validation as simply establishing whether a model behaves sufficiently similarly to the real system being modelled. This involves demonstrating that the model gives the same output as the real system over a range of variables. Spedding (1988) gives two conditions to be satisfied with respect to this method of model validation:

1. the model is tested against data not used in its construction, and;
2. that what is meant by 'the same output' is specified in advance. In other words the precision and accuracy required of the model must be specified in advance, recognising that the real system performance may vary considerably.

This latter condition is particularly relevant to models of FMD epidemics, which are highly variable and rare (in UK). There has to be a decision as to how close to the real epidemic of 2001 a model has to be, given that 2001 may itself have been an extreme event. The first condition is also difficult with respect to modelling FMD, because there is so little data on real epidemics that this is usually used in model building and therefore should not be used in validation.

A major problem with validating models against real life is that a model is often constructed to simulate scenarios with which there are no real life data to compare.

According to Dent and Blackie (1979) model validation is an elusive issue. Although the agreement between model output and real life behaviour may be tested using statistical significance tests, such agreement does not necessarily indicate model validity. Model building is an iterative process where refinements are made such that outputs approach agreement with measured reality and the simple fact of agreement may result from invalid or unjustifiable refinements. As with any scientific hypothesis, it is necessary that the hypothesis fits with reality, but this alone is not sufficient to prove the hypothesis because there may be alternative hypotheses which also fit reality. This is the issue of 'identifiability' mentioned by Green and Medley (2002). The key question here is, could the same model output result from more than one set of parameters? Although a model may make biological common sense or produce a true result when given unrelated data, de Jong (1995) points out that "*It is not sufficient to show that a model with a particular set of assumptions gives correct predictions. Other models, based on very different assumptions may give equally good predictions. A careful comparative approach to evaluate the main factors, both implicitly and explicitly included in the model, is necessary*."

Martin and others (1987) suggest that subsections of a model should be validated separately prior to validation of the model as a whole, because errors in one section may be compensated for by errors in another section.

3) Valid models should be fit for the use they are designed for:

Rather than attempting to decide whether models are 'valid' or 'invalid' it may be better to ask whether a model is 'useful'. Green and Medley (2002) reproduce the quotation, attributed to George Box, "*all models are wrong, but some models are useful*", and raise the question, "*how wrong does a model have to be before it is useless?*". It may be better to phrase the question, "*how valid must a model be to be useful?*". Dent and Blackie (1979) closely link confidence in a model with its validity and point out that "*the process of gaining confidence in the model is a slowly emerging one over the period of model construction, through formal validation, to application of the model.*" This implies that for the decision makers to have maximum confidence in the model they, and their close advisers, should be involved in all of

these steps. Given that a model is built to perform a specific purpose, for example to inform a decision, Dent and Blackie (1979) suggest two sets of judgements to be made:

1. that the model is not different from the real system to a degree that will detract from the value of the model for the purposes for which it was designed;
2. that the decisions made with the assistance of the model will not be measurably less correct than those made without the benefit of the model.

The second of these judgements, which must be made *ex ante*, must be subjective and is difficult, but Dent and Blackie note that this may be the most relevant aspect of validation.

3.6.6 Sensitivity analysis

Sensitivity analysis has two purposes:

a) to check the sensitivity of the model's output to poor quality data – i.e. data about which there is uncertainty;

b) to check the sensitivity of the model's output to known variability in system parameters.

Sensitivity analysis is used particularly when the values assigned to model parameters are uncertain due to lack of good quality data (situation 'a' or 'b' in table 1). The values of uncertain parameters are varied to see the effect on the final output of the model, i.e. the sensitivity of the model to the value of the parameter is assessed. A model which is highly sensitive to parameters on which there is little reliable data is of limited use, perhaps even dangerous, in decision making. Those values to which the model is sensitive should be the focus of data collection efforts if the validity and utility of the model is to be improved. On the other hand, if varying a parameter has little material influence on the key outputs of the model, uncertainty about the value of that parameter does not detract from the value of the model in decision support.

Finding parameters which are known to vary in real life and to which the output is sensitive is useful in a different way, providing direct guidelines for management (Dent and Blackie, 1979). If these are parameters which could be influenced by disease control activities they become 'critical control points' which should be monitored and controlled in an outbreak.

Sensitivity analysis may reveal that a model is more sensitive to a particular parameter than is the case in real life, suggesting the model is not valid. This would lead to reformulation of the model and revalidation such that the model becomes a more balanced representation of real life.

3.6.7 Use of model in decision support

The results of the model are combined with other knowledge by the decision maker. New knowledge from other sources and also perhaps unexpected results from the model may prompt modifications to the model or even a redefinition of the objectives for modelling.

4. Modelling and animal health

4.1 Roles of models in animal health

Possible reasons for model building have already been discussed in general in section 3.2. More specifically, in the field of animal health, models may be useful in the following ways:

∗ retrospective analysis,

where good data are available from past epidemics models can be constructed as an aid to understanding the dynamics of the epidemic (requires model to mimic a specific real-life epidemic) – this understanding can then be utilised in … ;

∗ contingency planning,

based on the lessons learned from modelling past epidemics, models can be used to answer questions of the type, "*what if this had been done differently?*" – the answers to these questions may justify adjustment of the contingency plans for tackling future epidemics (a model which reproduces a range of imaginary epidemics can be used);

∗ resource planning,

models of epidemics and their control can be used to estimate the development of resource requirements so that these may be planned for – resource planning should be part of contingency planning but models may also be useful in the short term during 'live' epidemics to predict the scale of increase in resource requirements in specific situations (a model which reproduces a range of imaginary epidemics can be used);

∗ training,

models can be used as 'virtual epidemic simulators' for training purposes (a model which reproduces a range of imaginary epidemics can be used);

∗ surveillance targeting,

a specific type of model which attempts to quantify the risk of disease arising in different circumstances (risk model) can be used to indicate where it is most crucial to target surveillance efforts;

∗ 'real time' decision support,

during the 2001 FMD epidemic in UK, models were used to support decisions on control policies in real time (requires model to mimic a specific real-life epidemic).

In the rest of this report the appropriateness of using models in such situations will be examined through review of specific examples.

4.2 Types of models in animal health

As noted above, models may serve different purposes and this means that different models are often made to suit a particular purpose. Different models may also be developed which concentrate on certain details of animal health. The following list contains examples of types of model relating to animal health:

∗ risk models which describe qualitatively and may also quantify the risk of introduction of disease into a population through particular routes (risk pathways);

∗ analytical models which seek to establish associations between occurrence of disease and risk factors;

- disease models which model the spread of disease in a population;
- population models which model the dynamics of a population;
- economic models which model the production and use of resources and add on economic values;
- specialised models for particular details, such as climatic and air flow models to model the airborne spread of disease agents.

The basic principles involved in these types of model will be discussed briefly below. Most emphasis is placed on disease modelling.

4.3 Modelling principles

4.3.1 Risk models

Risk modelling firstly identifies and clearly defines a hazard, e.g. the infection of livestock in UK with FMD virus. The next step is to elaborate various risk pathways (chains of events) through which that hazard may be released. Qualitative risk models stop at this point, or may attempt a qualitative assessment of the risk as 'high', 'medium' or 'low'. Quantitative risk modelling requires the quantification of the probability that the hazard release route will be taken at each step of the risk pathway. The overall risk that a hazard is released is then calculated by multiplying the probabilities through the steps of each pathway and adding together the overall probabilities for all pathways.

HACCP (hazard and critical control point) is a separate technique which is used to identify points in a risk pathway where risk can be controlled by external interventions, and then to set up management systems to control risk.

4.3.2 Analytical models

These models, which may also be called empirical models (Thrusfield 1986), use statistical analyses to quantify associations between disease morbidity and other variables. Their purpose is to identify risk factors for disease and they are the usual output of epidemiological field studies.

4.3.3 Disease models

The models to be discussed here are models of infectious disease. In modelling, distinction is made between macroparasitic disease and microparasitic disease (Graat and Frankena, 1997). Macroparasites, such as helminths, have significant stages of their life cycle outside the mammalian host, and it is often this part of the life cycle which is important in determining the dynamics of disease and which must be modelled in most detail. Microparasites such as bacteria and viruses multiply within the host and the dynamics of disease depends critically on the transfer of microparasites from host to host. Since this report is concerned with the modelling of FMD, the basic techniques of modelling microparasitic diseases will be discussed.

Units and population:

In models of animal disease the smallest unit of concern may be the individual animal or groups of animals (herds or farms). Therefore a model may consider disease spreading through a population of individual animals, or disease spreading through a population of herds. In the following discussion 'unit' refers to the smallest unit of concern, whatever it may be.

States:

As a starting point for modelling infectious disease, members (units) of the host population are considered to exist in one of a number of defined states. At the most simple these states are susceptible, infected and recovered or removed, leading to the acronym, SIR model. The model describes the movement of units from one state to another. Models can be increased in complexity and realism by the definition of further states, such as: infected but not infectious (latent); infected and infectious; infected and clinically sick; recovered but carrying infection, etc. etc..

Transition between states:

Once an unit has become infected, the transition through to the recovered or removed state is mostly governed by time factors, which can theoretically be measured in field or experimental epidemiological studies. The model may also consider additions to the susceptible state based on birth rates and waning of immunity, and removals from the population based on mortality rates or culling. The key transition in disease modelling is that between susceptible and infected. This transition depends on the modelling of disease transmission.

Disease transmission:

Transmission of a contagious disease, such as FMD, is, by definition, through the medium of contact.

In order to model transmission of a contagious disease it is therefore necessary to quantify the following key factors:

- the duration of the latent and infectious periods
- how many contacts will a diseased unit make per unit of time and hence during the whole infectious period?
- how many of those contacts could potentially lead to infection of a susceptible unit, i.e. how many 'effective contacts' will there be?

If the number of effective contacts made by each infected unit was known this could be used to quantify the transition of susceptible individuals into infected individuals. This is an important concept in contagious disease modelling. The average number of effective contacts made by each infected unit would be the number of secondary infections to be expected when a single primary case of infection is introduced into a fully susceptible population. This number is called the basic reproductive ratio (otherwise known as basic reproductive rate or number), R_0 (Anderson and May, 1991).

The concept of effective contacts can be used to calculate the risk of infection among susceptible units in a model, which is proportional to the number of infectious units. Models must take account of the fact that as epidemics progress, and the proportion of units remaining susceptible falls, contacts are wasted on already infected units. This results in the natural waning of epidemics in undisturbed populations. Thus, as an epidemic progresses the number of secondary infections arising from each infected unit falls. This number is called the effective (or case) reproduction ratio, R (Anderson and May, 1991).

A well known epidemic model based on the concept of effective contacts is the Reed-Frost model (Abbey, 1952; Frost, 1976). This basic model has been adapted widely since its inception.

Estimates of the number of effective contacts made by individuals, or R_0, are needed in order to reproduce disease epidemics in models. Modellers may use field data on infection rates and epidemiological tracing data, which link primary and secondary cases, in order to produce

these estimates (Haydon and others,. 2003). However, this method requires detailed field data which are seldom available and it is common for R_0, or similar measures of disease tranmission, such as transmission rate or 'force of infection', to be derived by fitting a model to an observed epidemic (e.g. Haydon and others, 1997; Matthews and others, 2002).

The basic Reed-Frost model and similar models contain two important simplifying assumptions:

1. that contacts within the population are made randomly, or that the population is homogeneously mixing, and;
2. that infectiousness and susceptibility do not vary between individuals.

The first assumption may be reasonable for relatively small populations of individual animals kept in a group, but even on a single farm animals may be split into management groups between which there may be little contact. When a model is concerned with the spread of disease between farms the assumption of homogeneous mixing and random contact is harder to justify and the limitations such an assumption brings must be borne in mind when interpreting the results of such a model.

The second assumption may also be reasonable for relatively small populations of similar units, e.g. only adult dairy cows or only sheep farms, but if output of such a model is to be used to extrapolate to bigger, more diverse, populations, again, the limitations such an assumption brings must be borne in mind.

In general, models carrying these two assumptions would tend to reproduce epidemics where disease spread is more rapid, more widespread and more random than in real life. In real life animals, or farms, do not contact others randomly and in large populations all units cannot have access to all other units. There are likely to be more contacts with units closer by than those further away and other factors such as marketing channels further modify contact patterns. This could lead to local waning ('burn out') of epidemics in real life whereas a model might predict continuing spread and a large epidemic.

The second assumption basically implies that there is only one kind of contact between infected and susceptible units and that a fixed proportion of these will be effective and lead to infection. In real life some types of contact are riskier than others and also some infected units may be more infectious than others (e.g. bigger farms containing more infected animals) and susceptibility of units may also vary (e.g. farms containing different species or breeds of animals). In real life this results in heterogeneous spatial distribution of infection, taking the 'line of least resistance' through high risk contacts between highly infectious/susceptible contact pairs.

Increasing the detail of models:

In order to avoid the assumptions in the simple epidemic model, modellers have constructed models which, to a greater or lesser extent, include additional parameters relating to infectiousness and susceptibility and/or reproduce the contact pattern within the modelled population. It is important to recognise that this increases the requirement for data and knowledge to fuel the models and the feasibility of providing detailed data must be seen as a constraint to producing models with ever increasing detail and realism.

The inclusion of variability in infectiousness and susceptibility in models depends on knowledge or assumptions about such variability. This knowledge will most likely come from epidemiological field studies and analysis which would identify risk factors for infectiousness and susceptibility. The modeller then has to further subdivide the modelled population into

different risk groups. Contacts may then be modelled randomly between these risk groups or detail may be further increased by modelling different contact rates between different groups.

When considering the spread of disease within a population of farms, which cannot move about, distance between farms is an important determinant of the rate of contact between farms. In order to include this aspect, models have to represent the spatial relationships between units of the population in some way. Some models make use of geometry or other mathematical methods to model simplified neighbourhoods around individual farms while others make use of geo-referenced data to reconstruct real populations within a model. Contact rates between farms which vary according to distance between them can then be modelled.

A feature of the models which reproduce real populations is that the transitions between disease states can be modelled for each unit in the population separately and individually, as opposed to a modelling process which considers groups and transition rates between groups. This move to modelling at the individual level can make the logic and mathematics of the model simpler and more transparent but at the same time the computational load of the model is increased.

Constraints to disease modelling:

The preceding discussion highlights that in order produce a model of the behaviour of disease in a population there are key requirements to be able to quantify the contact patterns within populations and also to be able to quantify the factors which make contacts effective contacts, leading to disease transmission. The latter of these requirements can be addressed by epidemiological studies to identify risk factors for disease spread, but it is unrealistic to expect that all risk factors for a disease will ever be fully quantified. The former requirement is a more serious constraint. The contact pattern in a population is often unknown and difficult to study and record in real life. Furthermore contact patterns can be unpredictable, depending to a large extent on human behaviour. Contact patterns can also change in response to an epidemic. All of this makes reliable predictive disease modelling difficult.

4.3.4 Population model

Population models may be used alone to explore the effects of management and other factors on animal production, or to provide disease models a realistic population within which to simulate disease. Population models simulate the changes within a population due to births, deaths, sales and purchases. The techniques of population modelling are similar to disease modelling in that the population is split into groups on the basis of age, sex, type, pregnancy status etc.. Transitions between groups and additions to or removals from groups are easier to model as these depend on factors such as birth rate, mortality rate, conception rate, sale rate etc., which are easier to measure or estimate from field data.

Disease models where the farm is the unit of interest (rather than individual animals) do not require a population model because the population of farms is virtually static.

4.3.5 Economic models

Economic models may be added on to disease or population models so that resource costs and economic values can be assigned to the output of these models. For example the resources required to deal with the number of cases in a modelled epidemic and the economic value of disease losses may be calculated.

In addition economic models may attempt to model wider economic effects, such as the effect of changing supply of animal products due to an epidemic on domestic price.

4.3.6 Specialised models

Technical aspects will be discussed along with specific examples.

5. Some examples of use of models in animal disease control planning and evaluation

In this chapter some disease and other models will be briefly reviewed. The theoretical modelling of disease began at least 50 years ago (Abbey, 1952) and modelling of FMD was explored as an aid to disease control planning as early as 1976 (Miller, 1976). In the last 10 to 15 years, models of various types have been promoted as components of decision support systems with the potential to answer 'what-if' questions related to disease control strategy.

Recently the animal diseases Bovine Spongiform Encephalopathy (BSE), Classical Swine Fever (CSF) and Foot and Mouth Disease (FMD) have caused serious problems in Europe and modelling has been a prominent tool used to aid understanding and policy formulation in the fight against these diseases. Various models have been developed for different purposes with regard to these diseases, for example, to explore hypotheses on how epidemics developed, to attempt to predict the future course of epidemics and to predict the likely effect of different control measures. Modelling of these three diseases will be covered in more detail. Especially, the modelling of the UK 2001 FMD epidemic, and the influence of modelling on disease control policy will be covered in detail in chapter 6.

5.1 Some examples of early models

The table covering the next few pages contains examples of disease models developed over the recent and not so recent past. The purpose of this is to illustrate the scope of modelling and its development. Particular attention is paid to how models have been used in decision support for animal health planning. This table represents a small selection of the disease models reported in the literature, the list is illustrative rather than exhaustive. It should be noted that some entries refer to papers describing individual models whilst others are review papers describing several models of other authors.

Table 2: Examples of disease models and their use in animal health planning

Disease	Authors	Comments	Particular use made of model in animal health planning / decision support
Fascioliasis	Gibson, 1978; Ollerenshaw, 1966; Ollerenshaw and Rowlands, 1959	These are all empirical (analytical) models which quantify associations between disease morbidity and associated variables; namely rainfall and temperature, which are easily measurable. There is no attempt to simulate the life-cycles of the parasite and intermediate hosts, nor is there any need to model disease processes in the final host. The utility of the models stems from their requirement for easily measurable data to produce results. The predictions tend to be accurate because the life cycle of the parasite responds in a fairly uniform (i.e. predictable) way to climatic factors.	Forecasting when disease risk may be increased so that prophylactic measures can be applied tactically (i.e. in response to short term changes in disease risk).
Ovine ostertagiasis	Thomas and Starr, 1978	These are also empirical (analytical) models in which sunshine and rainfall are the key parameters affecting the parasite life cycle.	Predicting when peak pasture contamination with infective larvae may occur so that prophylactic measures can be applied tactically (i.e. in response to short term changes in disease risk).
Nematodiriasis	Gibson and Smith, 1978a,b; Thomas 1978	These are also empirical (analytical) models in which soil temperature is the key parameter affecting the parasite life cycle.	Predicting larval hatching date so that prophylactic measures can be applied tactically (i.e. to target timing of preventive measures). Predicting pasture larval counts and from that predicting national incidence (UK).
Bovine ostertagiasis	Gettinby and others 1979	This is a simulation which models steps in the parasite life cycle, both outside and within the bovine host, separately and through several cycles. Empirical data are needed to ‘parameterise’ the model, e.g. the relationship between adult worm burden and faecal egg output, the herbage intake of cattle, establishment rates of larvae etc..	Predicting levels of infective larvae on herbage and so to facilitate optimum anthelminthic use or disease prevention by pasture spelling.

Table 2, cont.: Examples of disease models and their use in animal health planning

Disease	Authors	Comments	Particular use made of model in animal health planning / decision support
Bovine ostertagiasis	Grenfell and others (1987) Smith and others (1987)	A differential equation model of the parasite's population dynamics. Ten differential equations, some non-linear and some containing step functions, represent the influence of host and microclimate factors on the parasite life cycle.	To investigate possible therapeutic and prophylactic strategies against the disease.
Vector borne diseases transmitted by *Culicoides imicola*	Wittmann and others (2001).	This is an empirical model making use of statistically demonstrated links between climatic variables and variables derived from satellite imaging with abundance of the vector, *C. imicola*. There is potential to use the model for prediction of outbreaks of AHS or blue tongue where these viruses are known to occur.	To identify geographic areas in Europe where the climate is suitable for the insect vector, which are therefore at potential risk of the diseases transmitted by this vector. Therefore of potential use in targeting disease surveillance.
Rabies in wild fox population.	Macdonald and Bacon, 1980	The model was a deterministic differential calculus model with several components: - fox population dynamics – assumptions were made about regular seasonal fluctuations; - disease component of model – assumption had to made of contact rate (related to R_0); a range of figures were used in the model that reproduced disease patterns and fluctuations similar to those observed; - control strategies component (slaughter, temporary sterilization, bait vaccination of foxes). The model identified that vaccination of foxes offered the best control solution compared with slaughter of foxes. Note that knowledge of (or assumptions about) the real life population and disease patterns was needed. The model contained the assumption of homogeneity of mixing within the population. This assumption was probably reasonable. However, homogeneous mixing is probably more likely in a wild living population which responds to natural 'laws' than in a farm population subject to human manipulation which increases heterogeneity and unpredictability.	To compare different control and eradication strategies.

Table 2, cont.: Examples of disease models and their use in animal health planning

Disease	Authors	Comments	Particular use made of model in animal health planning / decision support
Mass vaccination against childhood diseases (e.g. measles, rubella)	Nokes and Anderson (1988)	This review describes the modelling of childhood diseases using the state transition idea with mathematical rate equations to quantify transitions between states. Homogeneity of population mixing was usually assumed. The authors note that "*much of the theory developed to date describes the transmission of directly transmitted viral and bacterial infections that induce lasting immunity to reinfection … and have relatively short duration*". The animal disease rinderpest is directly transmitted, by animal to animal contact only, making it directly analogous to measles in humans. FMD can be transmitted by many kinds of indirect contact, which introduces another level of complexity into its transmission dynamics.	Describe the calculation of R_0 for different childhood diseases and the phenomenon of 'herd immunity' and critical vaccination coverage to achieve disease eradication.
Veterinary vaccination programme design	Woolhouse and others (1997)	Describes generally applicable mathematical relationship between R_0 and critical vaccination proportion. This, and similar models are useful in designing criteria for successful vaccination, but they critically rely on knowledge of R_0, which is not constant for any disease, depending on many factors associated with population and livestock management characteristics.	To provide general guidance on levels of vaccination coverage required to control or eradicate disease in populations.
Rabies	Brochier and others (1991)	The authors applied the basic disease transmission theories as discussed by Nokes and Anderson (1988) to set a target for vaccination coverage of 80%. A post vaccination survey showed 81% of foxes had taken the vaccine and no cases of rabies were found.	Used a model to calculate proportion of foxes that had to be immunised in bait vaccination programme to achieve eradication.
Brucellosis	Hugh-Jones and others 1976	This is a stochastic multi-state model. Many parameters had to be based on expert opinion, notably infection risks. The model would have been parameterised such that it produced infection rates consistent with observed reality. The model demonstrated that the optimum frequency for testing was every four to six months. The model showed no advantage in testing more than every four months. It should be noted that this model was not developed in response to policy development needs, rather it was an academic exercise which was then used to illustrate the potential value of modelling in policy development.	Model was used to examine brucellosis eradication strategies and potentially to guide policy on test and slaughter and to explore effects of management based control policies – e.g. segregated calving.

Table 2, cont.: Examples of disease models and their use in animal health planning

Disease	Authors	Comments	Particular use made of model in animal health planning / decision support
Brucellosis	England and others 2002	A stochastic within herd model and simple deterministic mathematical model for between herd spread. The model was used to evaluate the risk of brucellosis spreading from an insertion in a single herd to other herds, under different frequencies of testing. The modelling used is simple; i.e. a detailed simulation of real life is not attempted. The model contains many simplifications and relies on expert estimation of key disease parameters. The aim is to provide a tool to examine the consequences of varying testing frequency, not necessarily to pinpoint the exact optimum.	To examine frequency of testing for surveillance in a disease-free country.
Rinderpest	James and Rossiter (1989) Rossiter and James (1989)	This was a stochastic simulation model of spread of disease within a population of animals. Normal population turnover is included in the model. Spread of disease between individuals is modelled in a similar way to the Reed-Frost approach, assuming perfect mixing in a homogeneous group of animals. Because of this assumption the authors caution against extending the model to multi-herd populations. The model demonstrated the dependence on population size of the ability of the virus to persist in a population. The model also suggested that mild strains of the virus could become established in populations with low levels of immunity (e.g. resulting from inefficient vaccination). Note that rinderpest is spread only by direct, reasonably close, contact between animals. There is no spread by carriage of virus on fomites, as with FMD. This makes this a simpler disease to model because assumptions about perfect mixing of the population are more easily justified.	To examine the effects of different vaccination policies on the behaviour of the disease in populations.

Many of the earliest models of specific animal diseases (as opposed to 'general' epidemic models) were of macro parasitic diseases such as fascioliasis and ostertagiasis. Reasons why these diseases may have attracted modelling attention may include:

* the existence of good data and knowledge about the lifecycles of the parasites involved;
* the existence of demonstrable and predictable associations between measurable determinants (often climatic factors) and the parasite life cycle;
* the lack of need to simulate the contact pattern within the host population; the models usually deal with disease in a single population of co-grazing animals; infection is picked up from the pasture and contamination is passed back to the pasture in a predictable way to act as the source of infection for other animals; transmission of disease is via the pasture, all members of the population have equal access to the pasture, so there is in effect perfect mixing of the population.

Similar considerations apply to microparasitic diseases which are vector transmitted, where the life cycle of the vector is sensitive to climate/environment and transmission of disease is via a large vector population.

Earlier models of microparasitic diseases tended not to attempt to model heterogeneous contact patterns. They mostly modelled the spread of disease within populations where perfect mixing was assumed. These models are useful in learning general lessons about the 'natural behaviour' of epidemics. The vast amount of work on modelling of childhood diseases led to the important concepts of herd immunity and critical vaccination thresholds to prevent epidemic spread of disease. These concepts were easily applied to animal diseases, for example the rinderpest model of James and Rossiter (1989).

A major challenge in the way of development of disease modelling was to include heterogeneity of the population and to simulate the 'contact structure' within the population; i.e. to take account of the fact that the population is made up of different individuals and contacts between some individuals are more likely than others. In the human field this was particularly important in modelling, for example, sexually transmitted diseases and in the animal health field this challenge is faced by any model which attempts to simulate spread of disease between farms, rather than between animals within a defined, homogeneously mixing population.

5.2 Modelling of FMD before 2001

Teclaw (1979) drew attention to particular difficulties associated with modelling applied to FMD. He noted that, "*the fact that not all spread is due to direct contact but may be due to a common source (e.g. garbage, feed) and fomites compromises models based on assumptions of homogeneous mixing.*"

The ability to predict the course of an epidemic, by whatever means, also depends on the extent to which random chance plays a role in the disease epidemiology.

> Teclaw (1979) also noted, "*the 'chancy' nature of any epidemic spread, especially in the early stages when the number of infected animals is relatively small, detracts from the usefulness of a deterministic model. It is the early part of an epidemic when generalising from data based on large numbers to a small number of initial infectives has the least validity, and this is also the time of greatest interest to those attempting to control the epidemic. Once the epidemic becomes large enough to allow the use of parameters based on averages, it may be too late to use the model in decision making strategies*."

Teclaw uses this as an argument for use of stochastic models, which take account of the chance element. But there is still the problem that early in an epidemic a model would have to be run with parameters based mainly on data from previous epidemics, and therefore the outputs of such a stochastic model would include a wide range of uncertainty.

It could also be argued that models of disease other than FMD are easier to validate and therefore can be used with more confidence. This is because validation relies heavily on checking that a model behaves like real life in all conditions (e.g. under different treatment regimes). With parasitic diseases it is easy to test models with controlled experiments and there is also plenty of field data on the disease in different conditions. Field data are also abundant for childhood diseases such as measles. But it is not possible to test control measures against FMD in controlled conditions. At best, comparisons can be made between often very different real life scenarios. Field data are available from only a small number of FMD epidemics in non-vaccinated populations. All of these epidemics are different and unique, making the data of less value in model validation.

Previous to 2001, the UK suffered a large FMD epidemic in 1967-68. This event, and the data resulting from it, stimulated efforts to model epidemic FMD (e.g. Tinline, 1972), and to use these models in contingency planning.

An early example of FMD modelling is given by work carried out by Miller (1976). The aim of that model was to simulate a 'worst case' scenario of spread of FMD across the USA, assuming that disease entered the marketing system and became rapidly established in a majority of states, and then to assess the effect of different additional control policies. The model was a deterministic, non-spatial state transition model. The spread of FMD through large populations of herds or premises was modelled. The modelling of disease spread used a parameter termed 'dissemination rate', which represents the average number of herds to which virus is delivered by an infectious herd during each time step of the model. Dissemination rate is similar to the 'effective contact rate' used by Reed-Frost type models, and the model was similarly formulated to account for the possibility of a susceptible herd receiving multiple contacts. The dissemination rate itself had to be estimated based on data from the 1967-68 UK outbreak. Dissemination rate was not constant during the 1967-68 epidemic, but decayed exponentially. Miller attributes this decay to the effects of traditional control measures, farmers changing their behaviour and the depletion of 'easy' targets, i.e. farms which are somehow more vulnerable to infection. He used a decreasing dissemination rate in his model, but chose a starting dissemination rate higher than calculated for the UK 1967-68 epidemic so that a 'run away' epidemic ensued.

In the model it was relatively easy to include control measures such as slaughter of affected herds, contact (pre-emptive) slaughter and vaccination because the effects of these policies can be represented by moving herds between the states already defined in the model. Vaccination was represented by moving herds from 'susceptible' to 'immune' states. Pre-

emptive slaughter was represented by moving a chosen percentage of infected herds directly to the 'removed' state without passing them through the 'infectious' state. The method by which infected herds could be identified for pre-emptive slaughter in real life, and the degree of 'overkill' of falsely identified contacts was not considered by the model, rather its purpose was to demonstrate the overall effect of contact slaughter which somehow achieved pre-emptive removal of a certain percentage of infected herds. Miller notes that while it is also theoretically possible to represent market closures, quarantine etc. in the model as a reduction in the dissemination rate, it is difficult to quantify the relationship between such measures and the dissemination rate, and so these were not modelled.

Using the model, Miller concluded that a 'runaway' epidemic could occur in the USA, given dissemination rates slightly greater than those recorded in the UK 1967-68 epidemic. Such an epidemic could affect at least 60% of susceptible herds within 30 weeks and if traditional control measures were abandoned (i.e. no slaughter of affected herds) and vaccination was not used, further epidemic cycles would begin after another 60 weeks. The model illustrated the beneficial effects of contact (pre-emptive) slaughter and suggested that pre-emptive removal of 19% of potentially infectious herds could reduce an epidemic similar to that in the UK in 1967-68 by half. It is worth noting that a degree of contact slaughter was carried out in the FMD epidemic in the UK in 1967-68 and slaughter of so-called 'dangerous contacts' was part of the control policy from the beginning of the epidemic in UK in 2001.

More recently, Haydon and others (1997) used a discrete time, state-transition model to generate a set of estimates of the transmission rate of FMD between herds in the 1967-68 UK epidemic. The basic reproduction number, R_0, could be directly derived from transmission rate. The estimated transmission rate had high values over the first few days, corresponding to an R_0 of 38.4, but the value rapidly declined, corresponding to a value of R_0 of 2.0. The early high values are consistent with the view that unusual meteorological conditions produced exceptionally good conditions for wind-borne spread of the virus over the first few days. The authors concluded that prophylactic control measures, such as vaccination, would have to be extremely effective to prevent epidemics with the higher R_0 value.

Howard and Donnelly (2000) used a stochastic, discrete time, mechanistic model, based on the method of Haydon and others (1997) to similarly estimate the 'force of infection' (= 'rate of transmission between infectious and susceptible farms') during the 1967-68 UK epidemic and an epidemic in Taiwan during 1999. The resulting models were then used to quantify the effects of delays in slaughter of infected farms. This was achieved by expressing 'force of infection' in units per day of the infectious period of an infected farm. Thus, the transmission of disease could be modelled for different scenarios in which infected farms were slaughtered at different times after infection. The modelling demonstrated the importance of reducing slaughter delays in FMD epidemics. It was estimated that same-day-as-diagnosis slaughter could have resulted in a 60% reduction in the scale of the Taiwan epidemic.

The models of Miller (1976), Haydon and others (1997) and Howard and Donnelly (2000) were all state-transition models in which the population of farms was assumed to be homogeneous, i.e. all equally susceptible and equally infectious following infection. The models did not attempt to represent the spatial arrangement of the population or any heterogeneity in the contact structure of the population.

Sanson and others (1994) introduced an explicitly spatial model (InterSpread) which had been developed over a period of time as a component of a comprehensive decision support system (EpiMAN – Sanson, 1993). The system is described concisely by Sanson and others (1999). This decision support system had been developed for New Zealand to assist national disease control authorities to contain and eradicate outbreaks of animal diseases as efficiently and

cost-effectively as possible. It was designed primarily to be used during real epidemics. The specific objectives, when designing the system, included provision of facilities to:

* provide up to date status reports that facilitate decision making (i.e. a variety of reports which directly addressed the information needs of decision makers);
* achieve optimisation of manpower, and other, resource allocation;
* evaluate the relative merits of technical decisions (i.e. predictive modelling to assist in choices of control strategy).

The whole system is a combination of databases, expert systems, various simulation models and statistical analyses to monitor the state of the epidemic. Some of the components of EpiMAN are as follows:

* Simulation of virus spread off an IP. This component uses field data gathered from individual IPs during an epidemic, such as: on farm prevalence of affected animals; age of lesions; reported contacts, etc.. These data are linked with models which predict possible airborne spread (using meteorological data) and non-airborne 'local' spread. Farms at risk of infection can then be identified so that surveillance visits, or other action, can be organised and prioritised.
* Expert systems. Essentially a series of logical rules to prioritise the most urgent tracings to be done so that manpower allocation can be optimised.
* Dissemination rate model. The estimated dissemination rate (EDR) is defined as the number of cases in a week divided by the number of cases in the previous week (Miller 1979). If the weekly EDR is falling the model can extrapolate forwards to predict the cases expected in future weeks and the end of the epidemic by log transforming EDR and fitting a linear least squares regression line. This method was validated against data from the 1967-68 UK epidemic.
* Epidemiological reports. Designed to provide insights into the epidemic and the effectiveness of control measures. Reports could summarise such things as: sources of infection for each IP to build up a picture of methods of transmission; analysis of relative risk of different types of contacts which may help to identify those dangerous contacts to be subject to pre-emptive slaughter.
* The InterSpread (inter farm spread) model. The main reason for including this model in the whole package was so that the likely consequences of major policy options could be explored in advance. The model is used to predict the progress of an epidemic under the influence of different control policies, by running so-called 'what if' simulations. For example, pre-emptive slaughter options or vaccination options could be explored.

Sanson (1993) describes the specific roles of the different modelling tools within EpiMAN thus: "*the simulation of virus spread off farms addresses the core purpose of EpiMAN to identify farms that are likely to have been exposed to infection, so that resources can be focused on these farms; in contrast the InterSpread model does not attempt to identify which actual farms will be infected but is used to indicate the pattern of outbreaks that are likely to occur. InterSpread is therefore a medium to long term planning tool, aimed at providing decision support for major control strategy decisions.*" Sanson highlights the importance of integrating the model with the database containing the real-time data of the epidemic so that it can pick up the state of the epidemic at any time and simulate forwards.

In contrast to models already discussed, the InterSpread model is an explicitly spatial model. This means that the 'real life' farm population is represented 'in microcosm' inside the model.

This requires data on the farm population which includes location data (as geo-referenced points or polygons). Like in a state-transition model, farms may be in one of several states with respect to disease. The model is initialised by setting the states of farms known to be infected or depopulated to represent the real status at anytime during a real epidemic. InterSpread has to predict a number of farms which are infected but as yet unknown (incubating or undiscovered disease) at the time of initialisation. The model can then be run to simulate the continued progress of the epidemic.

The model treats time as a series of discrete steps, typically days. On each day the model runs through the list of infected farms and simulates disease spread off each infected farm. The effects of control measures on the status of farms are also simulated. The simulation is repeated for as many days as required.

InterSpread attempts to simulate the spread of disease in a quasi-realistic way. Rather than using data from real epidemics to estimate overall dissemination or transmission rates, InterSpread separately deals with known routes of disease transmission according to epidemiological knowledge. This makes the model more reliant on detailed data, much of which has to be estimated on the basis of limited true measurements combined with expert opinion. However, this approach means that parameterisation of the model is less reliant on 'fitting', using limited data from an unfolding epidemic. 'Fitting' can tend to produce models which 'self-fulfil', i.e. they are fitted to the real data so their output, of course, matches reality, which can give the models a false illusion of validity. By explicitly reproducing the known epidemiological mechanisms, according to current knowledge, InterSpread can be used to test that knowledge by comparing the model output with real life. Any divergences may then show where current knowledge is flawed. The model typically deals with the following methods of disease spread:

* animal movement;
* vehicle movement, specifically milk tanker movement between dairy farms;
* 'local spread' – i.e. non-specified spread within a short range (excluding airborne);
* airborne;
* recrudescence of infection on emptied farms after restocking.

Disease spread by the different routes is modelled using probabilities. These probabilities are difficult to ascertain but default spread parameters have been derived from analyses of past epidemics, particularly the 1967-68 UK epidemic. The model uses a Monte Carlo process to produce stochastic output, i.e. each time the model is run, different farms will be infected, according to chance.

Control policies which affect the different methods of disease spread can be explicitly simulated in the model. Movement controls affect spread by movement, stamping-out of infected farms cuts short the period during which infected farms act as a source of infection and pre-emptive slaughter or vaccination protects farms from becoming infected (they move to depopulated or protected states – both non-susceptible).

Since the early 1990's, the InterSpread model has been adapted as a tool to explore control policies for other diseases, including Classical Swine Fever (CSF), Infectious Bovine Rhinotracheitis (IBR) and paratuberculosis (Johne's disease) – see below for further discussion. InterSpread was also modified to incorporate EU control strategies (Donaldson, 1996).

5.2.1 Airborne spread models

The importance played by airborne spread of FMD virus during the FMD epidemic in the UK in 1967-68 (Northumberland, 1969) led to the development of models which aim to forecast airborne spread of FMD virus from infected farms. These models can be used to identify farms at risk of infection by airborne virus during real epidemics. An aerosol dispersion model was used to predict the Isle of Wight outbreak in 1981. When FMD occurred in pig farms in Brittany, the model correctly identified the risk of virus transport across the English channel. A dairy herd was infected, and following clinical diagnosis was slaughtered (Gloster and others, 1981; Gloster and others, 1982; Donaldson and others, 1982).

Several model systems have been developed over the years. Donaldson and Alexanderson (2002) review models developed in England, Denmark, France and Spain and discuss the operational use of such models and the field data required to run them. Models have been developed to predict spread over short distances (<10km) or distances of several hundred kilometres.

A Danish model (Sorensen and others, 2000) was used to retrospectively examine the possibility of airborne transmission of disease from France to UK in 1981 and Germany to Denmark in 1982. The model uses a combination of a virus production model (VPM) and atmospheric dispersion model (Rimpuff), model of spread of airborne particles over several hundred kilometres.

During the FMD epidemic in UK in 2001 the UK Met Office used a short distance model which was virtually unchanged from that developed in the 1980's. The model was calibrated and compared with the Danish model and gave similar predictions.

The UK Met Office have also developed a long range atmospheric dispersion model, called NAME (Ryall and Maryon, 1998). This model was also used in the 2001 epidemic to identify farms potentially at risk from airborne infection (Donaldson, 2002; Gloster and others, 2003). The NAME model has the advantage that it can easily make use of many sources of meteorological data, both real and projected (forecast model derived). It is a general purpose model which is maintained and continuously developed by the Met Office to handle work on forecasting the dispersion of any pollutant in the atmosphere, e.g. ash from volcanic eruptions, leakages resulting from chemical or nuclear accidents. Given the location coordinates of FMD infected animals the NAME model can calculate the likely dispersion of airborne virus from that location over any distance. This model now supercedes the short range model, which will not be developed further (Gloster, pers. comm.).

All these systems rely on several components in order to identify farms at risk of infection by airborne virus:

1. a virus production model, which quantifies the amount of airborne virus produced by the infected farm and requires data on virus production by different species and the period of excretion;
2. a meteorological component which models the movement of air in the locality, based on available meteorological data and possibly also topographical information;
3. parameters describing the survival of viable virus in the air;
4. parameters describing the minimum infectious airborne dose for different species of livestock;
5. demographic data describing the locations of surrounding farms and the species of livestock present.

Also, for operational use, it is clear that good field epidemiological data are needed from the infected farm (prevalence of infected animals of different species, lesion ages etc.) in addition to good meteorological data.

Components 1 and 4 rely on virological research for data. Component 2 is provided by the general purpose dispersion models developed by meteorologists.

The survival of virus in the air, component 3, depends on measurable air parameters. Decay of virus viability over time is not modelled in detail. Since airborne carriage of virus happens over a short time scale, e.g. 12 hours for the virus plume from Brittany to cross the English Channel, the models simply 'decide' whether virus in the air would survive or not. The critical factors are temperature (virus survives well at less than 27^{o}C) and relative humidity (virus survives at over 60%) but there may be other relevant factors such as pH and pollution factors, collectively termed the 'outside air factor'.

Donaldson and Alexanderson (2002) note that further research is still needed to provide data on amounts of the different strains of FMD virus produced by different species. This, and other areas of research needed to refine airborne spread models are discussed later (section 7.3.4).

5.2.2 Risk assessment models

As an example of risk assessment work on FMD, Gallagher and others (2002) carried out an estimation of the risk of importation of foot-and-mouth disease into Europe. The assessment was made using expert opinion through a formal workshop technique, during a meeting of the Standing Technical Committee of the EUFMD in 2000. The researchers felt that gathering information based on expert opinion through the workshop method used provided useful information in a cost-effective way when hard data were not available, or would be expensive and logistically difficult to collect.

The experts considered that the Balkan group of countries was most at risk among the European group, and of the non-European source groups (i.e. countries acting as a potential source of infection to Europe), Turkey was considered the most likely source of infection. Although the Islands group of countries (including UK) was considered least at risk of having a primary outbreak, the experts were 90% certain that the number of outbreaks in this group would be between zero and two between 2000 and 2005, and that the most likely source would be illegal import of animal product (Gallagher and others, 2002).

A report of the work was circulated to all Chief Veterinary Officers in the EU and led to the adjustment of contingency planning in some countries (Marion Wooldridge, pers. comm.).

It is suggested that, even though hard data may be lacking, the regular assessment of risk by this kind of activity can help to focus surveillance and protection activities and prevent complacency, i.e. countries can be alerted to emerging potential risks and maintain and update contingency planning accordingly.

5.3 Modelling Classical Swine Fever in The Netherlands

In 1997, the Netherlands suffered a huge epidemic of classical swine fever (CSF), with estimated total financial losses of US$ 2.5 billion. The epidemic was tackled using traditional stamping-out slaughter of infected herds (429 herds) and movement controls. Pre-emptive slaughter (of 1286 herds) was also used. In addition to the 1.8 million pigs slaughtered by stamping-out and pre-emptive slaughter, 9.2 million were slaughtered for welfare reasons (pigs unable to be marketed due to movement restrictions). Dijkhuisen (1999) describes how, shortly after the epidemic, the Dutch disease control authorities as well as the parliament

asked for an evaluation of the efficacy of control strategies, including those actually used and possible alternatives. Models were used extensively in this evaluation.

5.3.1 A simple model

Stegeman and others (1999) used a simple SIR modelling approach (similar to that used by Haydon and others, 1997, for FMD) to produce estimates of the infection rate parameter, β (average number of herds infected by one infectious herd during one week) and the herd reproduction ratio, R_h (average number of herds infected by one infectious herd during its whole infectious period – i.e. β multiplied by infectious period in weeks). Essentially, the real field data of weekly infection incidence were substituted in the simple SIR model equation to derive the value of β for each week of the epidemic. As the analysis specifically modelled the transition from the susceptible to infected state, data on infection dates were needed from the real epidemic and assumptions were required regarding the timing of the start of the infectious period. Definite infection dates, associated with known dates of a single infectious contact, were available for only 82 cases. For most (328) of the remaining cases serological data were available and dates of infection were derived from that.

The values of β and R_h decreased over the course of the epidemic. The effect of the gradual introduction of different control measures was assessed by estimating β and R_h for five phases of the epidemic, the first of which was the period after infection of the first herd and before detection of disease in the country. The conclusions of this analysis included:

* the basic EU control strategy of culling infected herds, movement controls and contact tracing appeared insufficient to eradicate CSF from regions with high pig-farm density;
* pre-emptive slaughter of contact herds, increased hygiene measures and reduction of transport movements associated with welfare slaughter, introduced later in the epidemic, were necessary for the control of the epidemic.

5.3.2 Use of an adaptation of the InterSpread model

The model used by Stegeman and others was a deterministic, non-spatial model, which included the assumption of random mixing. At the same time a spatial and stochastic simulation model, named InterCSF, which was based on the InterSpread model developed in New Zealand (Sanson, 1993) was also used. InterSpread was adapted for CSF in Dutch conditions by Jalvingh and others (1999). The spread of CSF between pig farms was modelled using three types of contact spread, plus a 'black box' of transmission mechanisms in a locality, i.e. 'local' spread:

1. animals;
2. vehicles;
3. persons;
4. 'local' spread up to a specified distance (local spread to farms 0-500m and 500-1000m from an IP was considered very important in the real epidemic).

The control measures to be included in the model were:

1. IP diagnosis and culling;
2. movement control areas;
3. tracing;
4. pre-emptive slaughter (basically neighbourhood culls of premises around IPs).

Welfare slaughter was also included in the model.

InterCSF was calibrated to mimic the real epidemic of 1997, i.e. the probabilities of disease transmission by the different routes, which are difficult to quantify from direct measurements, were adjusted in the model by 'trial and error' iteration such that the median size and duration of epidemic from many runs of the model matched the actual epidemic.

The model was re-run using different control strategy parameters to examine the potential outcomes had control been carried out differently. Because this was a stochastic model it was run several times (100) for each scenario (taking about 8 hours) and the key outputs were summarised as median and 5% and 95% percentiles. The disease model was linked to a financial model (EpiLoss) so that the financial consequences of the real outbreak and of any adjustments to policy could be evaluated (Meuwissen and others, 1999).

Immediately following the 1997 epidemic the model was used to evaluate the possible effects of various control strategy variations (Nielen and others, 1999). The use of vaccination was not investigated at first because this option was ruled out due to the overwhelming negative consequences of vaccination on exports. Using the model the Dutch researchers concluded:

1. That the length of time between introduction of infection and detection of the first case, leading to full operation of control strategies, is a critical determinant of the eventual size of an epidemic. Reduction of this time delay from the real situation (6 weeks from first infection in the country to first detection of disease) to 2 weeks earlier (i.e. 4 weeks from first infection in the country to first detection of disease) reduced costs by 20%. The use of the financial model to quantify in money terms the potential value of shortening this period gives an indication of the funds which could justifiably be used to improve disease surveillance.
2. That consistent use of pre-emptive slaughter from the beginning of the epidemic could have significantly reduced the size and duration of the epidemic, leading to an almost halving of the total cost. This conclusion, based on modelling, led to the proposal by the Minister of Agriculture that pre-emptive slaughter be a standard strategy in future epidemics in the Netherlands.
3. Dutch Parliament was considering reduction of pig herd sizes by 20% and clustering of pig farms to leave pig-free corridors (to slow down 'local spread'). These measures were controversial and challenged in courts. Modelling suggested that a notional maximum hygiene option ('biosecurity'), which effectively reduced the risk of local spread to zero while keeping other measures as they were in 1997, reduced the cost of the epidemic by two thirds. They argued that improvements in hygiene, perhaps stimulated with money incentives, would make these industry adjustments unnecessary.

The use of a financial model along with the disease model was key in the use of modelling to influence policy. Arguments for different choices could be made on financial grounds. Also the costs of disease and control were split into public and private categories, and this informed the debate about who should bear the cost of measures aimed at preventing and/or limiting future epidemics.

Although Nielen and others (1999) found that pre-emptive slaughter of herds within 1,000m would have reduced the economic cost of the epidemic considerably, it is important to understand the economic importance of welfare slaughter in the Dutch epidemic (and of diseases involving pigs in general). The contribution of welfare slaughter to the total number of pigs slaughtered during the epidemic and presumably to the total cost of the epidemic was huge. This means that any measure which the model predicts would reduce the duration of the epidemic significantly would produce a big cost saving, even if the measure itself entails

widespread slaughter of pigs. Also, including wide reaching pre-emptive slaughter measures in the model would not tend to lead to higher total numbers of pigs culled because in the scenarios without pre-emptive slaughter the same farms would eventually be welfare slaughtered anyway. Therefore, inclusion or not of pre-emptive slaughter tended not to affect ***how many*** farms were culled, but only ***when*** they were culled. In a different situation, perhaps involving different species where welfare culling was not so necessary, the economic effect of pre-emptive slaughter may be less favourable.

Nielen and others (1999) also caution that, "*it should be realised that the effectiveness of pre-emptive slaughter in InterCSF is dependent on the underlying disease spread mechanisms (e.g. local spread and contacts)*". The analyses of the CSF epidemic suggested that short distance, 'local', spread was a very important feature and this was reflected in the modelling. In the average results of the basic scenario, 85% of the simulated infections was caused by local spread (541/626). Local spread was modelled to a radius of 1,000m because the simulated (and real) epidemic took place in one of the most pig-dense areas in the EU most infected farms had several neighbours located within 1,000m.

Comments on parameterisation and utility of the InterCSF model

The Dutch researchers made some comments on model parameterisation which have general implications:

* They note that validation of the total model with data from the real epidemic (as opposed to validation of the underlying parameters and mechanisms) leads to problems with using the model to explore other scenarios.

> "*Because the simulated epidemic was 'calibrated' on the size of the real 1997/98 epidemic, the current outcomes of InterCSF can not be used to predict the absolute expected size of a next epidemic in The Netherlands*." (Jalvingh and others, 1999).

* This kind of calibration against a real outbreak also means that the effects of control measures in place are implicitly included in the model and it is difficult to get the model to simulate the situation had no control taken place.

* They make the case that the underlying mechanisms and effects of control mechanisms need to be translated into quantified parameters.

> "*We strongly believe that a model such as InterCSF should be validated as much as possible on the underlying parameters and mechanisms, and not mainly on the final outcome of a real epidemic. However, although a wealth of data seems available, a large epidemic such as occurred in The Netherlands is still only one epidemic from a range of possible epidemics. Particularly if a model will be used to compare various control strategies, it is very important that the underlying mechanisms are modelled as correctly as possible based on available knowledge. The comparison of various control strategies will always be very dependent on parameter settings of the underlying disease spread mechanisms, which in turn are influenced by the control strategies*." (Jalvingh and others, 1999).

* The model output is very sensitive to estimates of spread parameters in particular and the results should be interpreted with great care.

The following comments were made on the construction and use of the model in general:

- The full complexity of the 'contact structure' between pig farms was difficult to model.
- The model could be improved by making the time delay to detection more realistic (rather than a random effect from a distribution) and by modelling a varying level of infectivity of a farm (i.e. in real life the infectivity of a farm builds up over time as the on-farm epidemic progresses). This modification has been implemented in InterSpread for IBR (Jalvingh and others, 1998; Vonk Noordergraaf and others, 1999).

It is interesting to note that the InterCSF model included limits on pig rendering capacity, so that slaughtering delays will be modelled if too many farms were to be culled and slaughter capacity would run out.

5.3.3 Use of the models by decision makers

Van Klink and others (1999) describe the evaluation of the outbreak from the point of view of the Dutch Ministry of Agriculture, Nature Management and Fisheries. One aspect of this was the engagement of the Wageningen University research group to construct a simulation model of the outbreak as a tool to evaluate the control of the outbreak. An essential component was also the use of a field epidemiology team to gather the data needed to feed the model. The Ministry also had teams looking at decision making during the epidemic. These teams found that information needed for the planning and execution of control measures and management of the control exercise was not always directly at hand and too much time was needed to find it. Problems were encountered because databases were not linked up where necessary. Policy-makers complained about the adequacy of the information provided on which to base policy decisions at the central Ministry level.

Van Klink and others (1999) concluded that, in principle, the InterCSF model, used in the present outbreak as an evaluation tool, could be linked to the information system, and developed further into an online decision support system.

Contrary to this latter point, the Dutch have not chosen to develop InterCSF, InterFMD and other InterSpread-based models as part of an online system, which may be used to support tactical decisions during epidemics.

Somewhat bizarrely the EU used the evidence of the InterCSF model, that consistent use of pre-emptive slaughter from the beginning of the epidemic could have significantly reduced the size and duration of the epidemic, to reduce the amount of recompense provided to the Dutch government from EU funds, on the grounds that control measures had not been optimally implemented. This despite the fact that pre-emptive 'zonal' culling was not a specified EU control measure at the time (Ed Van Klink, pers. comm.; Mirjam Nielen, pers. comm.). This was seen as a negative effect of using the model in evaluation.

Since the 1997 CSF outbreak the livestock industry, in cooperation with the government, has funded model work on IBR and paratuberculosis and this work has guided control policy for IBR and paratuberculosos (Mirjam Nielen, pers. comm.). In addition, model work on FMD has been used in advice to the Government. For example, Mourits and others (2002) adapted InterFMD and used it to examine the control of epidemics arising in areas with different livestock densities. In the introduction to this analysis the authors note that during an epidemic decisions have to be taken under intense time pressure. Therefore the use of the model is seen as a method of providing decision makers with *a priori* supporting guidelines, in this case 'area specific rules of thumb' for control measures to be considered in different density livestock areas. Mourits and others (2002) concluded that different control measures would be justified in different density livestock areas and this idea has been adopted within the Dutch contingency plans for CSF and FMD (Mirjam Nielen, pers. comm.).

The Dutch have therefore made quite extensive use of disease modelling and in particular have demonstrated the flexibility of the InterSpread model as a basis to model other diseases. However, regarding the use of such models to support tactical decisions during epidemics, the view of those closely involved in this process is that "*such complicated simulation models should not be used during an epidemic, but in fact between epidemics to be better prepared and study 'what-if' situations*" (Mirjam Nielen, pers. comm.). This means that models may be used to study a range of hypothetical situations, in order to provide guidelines for contingency planning, but then tactical decisions during epidemics are better based on field data which may rapidly indicate which modelled situation is actually being faced.

5.4 BSE

When BSE appeared in UK as a novel disease, modelling was used as an adjunct to traditional epidemiological investigation, to explore hypotheses about the new disease. A simulation model was constructed on a spreadsheet platform to examine the time of onset and duration of exposure to the causal agent, the incubation period and the age classes of animals exposed (Wilesmith and others, 1988). The fact that it was assumed that no, or very little, animal to animal transmission of infection occurred made the disease conceptually simpler to model. The model consisted basically of an age-banded population turnover model. Values for the unknown parameters (time and duration of exposure and incubation period) could then be imposed on the model with the goal of reproducing the observed age and time distribution of actual cases. Once fitted to reproduce the case profile to date, the model could be used to tentatively predict expected case incidence in coming years, though this was not the original intention. Modelling was thus used as an aid to investigation and understanding of the disease. Later, another model was used to predict numbers of expected cases for financial resource planning (Richards and others, 1993). Modelling the disease process was preferred over an empirical curve fitting approach. A simple model predicted incidence of clinical cases each month in a simulated cattle population using calculations relying on three input parameters: rate of inclusion of infectious agent in the cattle feed; a factor reflecting differential infection probabilities in different age groups (e.g. calves assumed to face a higher level of exposure), and; the incubation period (represented in the model as a distribution). This relatively simple model produced predictions which proved to be remarkably accurate (J. Wilesmith, pers. comm.).

When it became necessary to consider pre-emptive culling policies as an attempt to precipitate a quicker end to the epidemic, simple calculation methods based on the known case data could be used to identify the most cost efficient method of targeting a cull (MAFF/DEFRA, 1996).

Due to the national importance of BSE and its subsequent public health significance following linkage with the disease, variant Creutzfeldt Jacob Disease (vCJD), in humans, several research groups modelled various aspects of the disease, such as the possible implications of maternal transmission, and its possible control by culling strategies (e.g. Donnelly and others, 1997; Ferguson and others 1997; Ferguson and others 1999; Medley and Short, 1996; Anderson and others, 1996). These models do not appear to have directly influenced national control policy, rather they form part of the process of scientific exploration to be expected when a novel disease emerges.

A current question to be addressed regarding BSE control is the possibility of adjustment of the 'over thirty month' rule, by which cattle over 30 months old are excluded from the food chain. Modelling will be used to contribute to the debate over this question (DEFRA, 2003).

6. Use of models during the FMD epidemic in UK, 2001

6.1 Key impact of modelling on disease control policy formulation in 2001

Although mathematical modelling had been used as a tool in veterinary epidemiology for many years before 2001, the FMD epidemic in UK that year was the first situation in which models were developed in the 'heat' of an epidemic and used to guide control policy. Several reviews that have already been published describe various aspects of the use of models during the epidemic (Green and Medley, 2002; Haywood and Haywood, 2001; Kao, 2002; Lusmore, 2002). Some of the inquiries conducted after the epidemic also discuss the role played by epidemiology in general and modelling in particular (Anderson, 2002; Follet, 2002). The role of modelling during the epidemic was also discussed during a workshop hosted by DEFRA in May 2002 (DEFRA, 2002).

The engagement of modelling with the control of the FMD epidemic was not part of the pre-arranged contingency plan, but came about in an *ad hoc* way. The 'Lessons to be Learned' inquiry report (Anderson, 2002) describes how Sir John Krebs, Chairman of the Food Standards Agency began speaking to a number of experts in mathematical modelling in late February 2001, soon after the epidemic began. An *ad hoc* meeting, in which the modellers discussed the data requirements for modelling of the epidemic, then took place on March 6. DEFRA (then MAFF) supplied the data requested on March 13 and four groups of modellers began their analysis.

One of these four groups was led by John Wilesmith, of the DEFRA Veterinary Laboratories Agency (VLA), who was working closely with the epidemiology group in DEFRA headquarters, Page St., London. This group, assisted by Roger Morris of Massey University, New Zealand, was using an adaptation of the InterSpread model. The other three groups were: a group led by Mark Woolhouse at Edinburgh University, a group led by Neil Ferguson at Imperial College, London; and a group led by Matt Keeling, then at Cambridge University. The Edinburgh group also collaborated with the Cambridge group.

The 'Lessons to be Learned' inquiry report (Anderson, 2002) states that the Imperial group were furthest advanced at that stage and reported initial findings to MAFF on March 16. According to the report, the main advice at that point was that the delay between report of disease on a premises and slaughter must be reduced. This advice simply reinforced current knowledge and practice (Northumberland, 1968). A meeting between the mathematical modellers, the Government's Chief Scientific Adviser, the Chief Veterinary Officer and experts from the Institute of Animal Health and Veterinary Laboratories Agency occurred at the Food Standards Agency on March 21 (MAFF, News Release March 23). The MAFF News Release of March 23 indicates that model forecasts produced by the VLA, Imperial and Edinburgh groups were presented at this meeting. Model outputs, which supported conclusions that the epidemic was out of control and that current control measures were insufficient to establish control, were presented. The text of the News Release contains: "*Speedier slaughter of infected animals will help to reduce transmission. But this needs to be accompanied by immediate slaughter of all susceptible species around infected farms…*". The source of this specific advice, however, is not fully apparent from the summary of models and the expert opinion attached to the News Release. The findings of the Imperial group presented at the March 21 meeting are not given in the News Release, but, judging by later publications, it was this group that specifically advocated slaughter of all susceptible species around infected farms (Ferguson and others, 2001a). According to the News Release, the options to enhance control given by the Edinburgh group were: early diagnosis and early slaughter of affected holdings; and by the VLA group: reduction of tracing time and increased patrols

around infected premises, with the optional addition of pre-emptive slaughter of pigs and sheep within a 1.5km radius of each IP.

The bleak predictions of models presented at the meeting of March 21 precipitated a change in the management of the disease control efforts. The Government's Chief Scientific Adviser took over the lead role in policy advice and he created the FMD Science Group, comprising of representatives of the modelling groups and other FMD specialists. At the same time the Government activated the Cabinet Office Briefing Room (COBR) mechanism through which the Government responds to civil emergencies. Initially, twice daily meetings of COBR would involve 10 Government Departments and representatives of the Scottish Executive and the National Assembly for Wales.

Meanwhile, Professor Roy Anderson of the Imperial group made public statements on the *Newsnight* television programme (BBC 2, March 21) that the epidemic was "*out of control*". He also referred to "*preventative culling*" of livestock, saying, "*the epidemic would not peak for many weeks and it would be five months before foot-and-mouth was eliminated – and only then if the government brought forward its preventative cull of livestock*".

Before the meeting on March 21, referred to above, an extended cull of sheep and pigs within 3km of infected premises in Cumbria and Dumfries & Galloway had already been announced (MAFF News Release, March 15; *Hansard*, March 15, 2001, column 1200). Clearly, extended culling of livestock was being considered as a measure that would be necessary to control the epidemic, although details were unclear at that point. Between March 21 and March 26, when the first meeting of the FMD Science Group was held, the modellers were asked to look at the potential effects of various pre-emptive culling policies. The 'Lessons to be Learned' inquiry reports that the Government's Chief Scientific Adviser specifically asked the Imperial group to model culling within different radii of infected premises (Anderson, 2002).

Following the first meeting of the FMD Science Group, on March 26, a clear statement of an extended culling policy was made in the House of Commons on March 27 (MAFF News Release, March 27). In addition to the already announced 3km cull, culling of all animals on farms contiguous to (neighbouring) infected premises were to be culled (the 'contiguous culling policy'). The Minister of Agriculture said, "*All animals (cattle, sheep and pigs) on infected farms are to be culled within 24 hours of the infection report. All animals (cattle, sheep and pigs) on contiguous farms are then to be culled within 48 hours*." This became known as the '24/48 hour policy'.

In the same statement the Minister said, "*The key task is to reduce the time between the first report of the disease and the slaughter of the herd or flock. Our target remains that this should not exceed 24 hours. The epidemiological studies published last week confirmed that this is the single most important intervention in controlling the disease. We are achieving this in large parts of the country, including Devon in recent days; in Cumbria the high density of infection and sheer number of cases has meant that we are not yet achieving that target.*" (MAFF News Release, March 27). This indicates that the policy-makers were working under the impression that culling on infected premises was not yet being carried out with optimum speed in Cumbria, where a large proportion of the cases currently were occurring. The implication is that model forecasts that achieving this target alone would be insufficient to control the epidemic, were important in influencing the decision to adopt the 'contiguous culling policy' rather than simply continuing to strive for more rapid culling on infected farms.

According to a statement by the Government's Chief Scientific Adviser made on April 4 (MAFF, April 4, 2001) the necessity of the contiguous culling policy, in addition to bringing

down report to slaughter times, was based on the modelling work. In particular, the briefing of April 4 and subsequent briefings refer to the modelled scenarios produced by the Imperial group.

The FMD Science Group continued to meet regularly until November 1, and models were refined and further results presented and discussed. In addition to examining refinements to the culling policies, models were also used to examine the potential effects of different interventions using vaccination.

The influence of mathematical modelling on disease control policy, in general, and tactical decisions, in particular, during 2001 was therefore both substantial and unprecedented.

In addition to mathematical models of disease dynamics and control, other models were utilised during the 2001 epidemic: notably the Met Office's models to predict potential airborne spread of virus from infected farms and risk analysis was used by the VLA to provide risk assessments as decision support tools throughout the epidemic.

6.2 A closer look at the models

6.2.1 The Edinburgh model

As the daily number of cases reported continued to increase during the first five or six weeks of the epidemic, there was some argument about whether the epidemic was 'under control' or not. For example, in an editorial article in the March 22 edition of *Nature* (Adam, 2001) a spokesman for MAFF is reported as denying that the epidemic was out of control, pointing out that new cases could still be traced back to animals infected during the initial stage of the epidemic (before initial detection of disease). The article highlights the disagreement on this matter among other experts. It quotes Professor Roy Anderson as stating that the situation "*is quite clearly not under control*". The reason behind this conclusion was that each infected farm was leading to more than one other susceptible farm being infected. Essentially, Anderson was referring to the case reproduction ratio, *R*, and equating a situation of 'control' with an *R* value below 1, as explicitly stated by Woolhouse and Donaldson (2001) in a commentary in the March 29 edition of *Nature*. The Edinburgh team worked on direct estimation of *R* from the available epidemic data (Woolhouse and others, 2001). They used data provided them by MAFF headquarters epidemiologists. These data included estimated infection dates and contact tracing information. Based on these data, the pattern of infectious contacts throughout the progress of the epidemic was reproduced. From this, the average number of secondary cases infected by each primary case during weekly periods of the epidemic could be induced. Their results suggested that the epidemic was brought under control (*R* less than 1) during the two weeks 17-30 March. Though not explicitly stated in the text of the brief communication, the fact that this coincided with the introduction of the extended culling policies was seen as supportive, though not proof, of the interpretation that control of the epidemic was a consequence of the 24/48 hour culling policy (Woolhouse, 2002a).

The Edinburgh team are continuing to look at the culling question (e.g. Matthews and others, 2002) and also continue to work with Keeling and others on a spatial model of the epidemic (Keeling and others, 2002; Keeling and others, 2003).

6.2.2 The Imperial model

The Imperial group produced a deterministic, state-transition type model based on differential equations. Results of an analysis of the first two months of the epidemic were published in May 2001 (Ferguson and others, 2001a). In the model, farms within the population could be

in one of several states: susceptible; infected but not infectious; infectious but not reported; reported; slaughtered (assumed uninfectious). The model did not explicitly represent the spatial relationships within the UK farm population. Complex mathematical techniques were used to represent local spread of disease (see Kao, 2002, for a technical commentary). The mathematical complexity of this model makes it especially difficult for the non-mathematician to grasp.

As with the Edinburgh model, the Imperial model was based on the data provided by MAFF headquarters epidemiologists. Again, estimates of infection dates and contact tracing information were key to allowing the modellers to derive the transmission rates, through local and more distant contacts, needed to run the model. Proximity to infectious farms was an important risk factor included in the model: "*Contact tracing for all FMD-affected farms has produced unique data on the spatial scale of disease transmission, clearly demonstrating that farms closest to index cases of FMD are at greatest risk of infection. We estimate that farms 0.5, 1 and 1.5km away from a single infectious farm would have probabilities of 0.26, 0.06, and 0.02 of becoming infected*." (Ferguson and others, 2001a). This distance-related gradient of infection risk was known as the 'spatial kernel', and was a key feature of this and also the other, explicitly spatial models.

The model did not take account of different farm types, but used 'average' parameters for all farms. Infection to report time was allowed to vary within the model according to the actual variation over time estimated from the data. In this first model produced by this group, the transmission coefficient, the parameter quantifying the daily rate of spread of infection between infectious and susceptible farms, was assumed to be constant except for a drop when movement restrictions were imposed on February 23 (Ferguson and others, 2001b).

The Imperial model was the model most extensively referred to in support of the 24/48 hour culling policy (MAFF, April 4, 2001). The results presented in the paper published in May 2001 (Ferguson and others, 2001a) are indicative of what was presented during the meeting of the FMD Science Group on March 26.

The model predicted a very large epidemic if the key control parameters (report to slaughter interval and amount of pre-emptive culling) remained as they appeared to be on March 28. The 95% confidence interval for the final size of the epidemic was estimated as 44% to 64% of population at risk, assumed to be the approximately 45,000 farms in currently infected areas in Great Britain. That prediction implied an epidemic involving from 20,000 to 29,000 infected premises. The group also fitted the model to data from the Cumbria, Dumfries & Galloway area only. Here they found that transmission intensity was higher, giving an estimate for the final size of the epidemic in this area of 79% of 5,000 farms, again assuming the model parameters remained unchanged from the status quo on March 28. This prediction implied an epidemic in the Cumbria, Dumfries & Galloway area involving 4,000 infected premises.

The model suggested that meeting a target of report to slaughter interval of 24 hours on all farms would slow down the spread of disease, but the researchers say, "*more drastic action, such as "ring" culling or vaccination around infection foci, is necessary for more rapid control. Culling is predicted to be more effective than vaccination. … The current policy, based in part on these analyses, is to cull IP's (infected premises) within 24hrs of report and CP's (contiguous premises) within 48hrs*." (Ferguson and others, 2001a).

The model used important assumptions about the infectivity of infected farms. Constant infectiousness was assumed from three days after infection until slaughter (for an average of eight infectious days). It is not clear how this infectious period coincides with the onset of clinical disease on a farm, but the onset of infectivity was assumed to occur before reporting

of disease. The model used a parameter, r_I, which was the ratio of infectiousness after disease reporting to infectiousness before disease reporting. The researchers explored the possible consequences of the assumption of constant infectiousness (r_I = 1) by running their model with r_I = 5 (infectiousness after reporting is five times greater than before reporting).

With r_I = 1, the model predicted that achieving the target of culling infected premises within 24 hours of report from March 31 would result in an epidemic in which 30% of the 45,000 farms at risk in Great Britain would be culled (i.e. 13,500). In the Cumbria, Dumfries & Galloway area only, the same scenario was predicted to result in an epidemic in which 70% of the 5,000 farms at risk would be culled (i.e. 3,500).

If r_I was set to 5, then the model predicted that achieving the target of culling infected premises within 24 hours of report from March 31 would lead to rapid control, resulting in an epidemic in which 5% of the 45,000 farms at risk in Great Britain would be culled (i.e. 2,250).

In the final analysis the researchers chose to keep the assumption of constant infectiousness and therefore concluded that control measures in addition to rapid culling on infected premises were necessary. Quoting from the paper: "*Our analysis shows that achieving the goal of slaughtering on all farms within 24 hours of case reporting ….. can significantly slow the epidemic. However, such improvements in slaughter times fail to reduce R_0 below 1 under the assumption that the infectivity of farms after disease reporting is at the same level as that before (r_I = 1), and only results in rapid control if we assume that infectivity increases throughout the time from infection to slaughter and hence peaks after the disease is diagnosed on a farm (r_I = 5). … because data do not exist with which to estimate the infectiousness of a farm as a function of time since infection, prudence dictates that … it is necessary to consider other interventions. … In this context ring culling or vaccination strategies target infection hotspots by reducing the density of susceptible farms in the vicinity of diagnosed farms, thereby removing the 'fuel' essential to maintaining the epidemic*." (Ferguson and others, 2001a).

As indicated in the above quotation, both ring vaccination and ring culling were explored using the model. Although vaccination was shown to be effective, it was not considered as a viable policy at the time because of the perceived necessity to cull vaccinated animals at a later date in order to quickly regain export markets after the epidemic. The model could not specifically represent culling on premises contiguous to infected premises but the model structure allowed evaluation of pre-emptive culling in areas local to the infected premises. Various culling radii were explored, but a 1.5km radius was considered to most closely represent a cull of contiguous premises.

The predicted effects of pre-emptive culling on the epidemic curve were similar for radii of 1km, 1.5km and 3km, bringing the epidemic rapidly under control with peak incidence of around 50 cases per day for the whole of Great Britain and around 30 cases per day in the Cumbria, Dumfries & Galloway area only (Ferguson and others, 2001a).

In the May paper, the researchers drew attention to the possible negative effects of ring culling, in terms of total farms culled. They noted that: "*Policies can be overaggressive, however: a 3km ring cull is predicted to result in more farms being culled to eliminate the disease than a 1.5km cull*." (Ferguson and others, 2001a). In the context of ring culling, the possible influence of the assumption of constant infectiousness was again referred to. The value of r_I was seen to effect the 'trade off' between infected premises prevented and premises preventively culled: "*This trade off is more acute if r_I >1, where ring culling still accelerates the decline of the epidemic but at the cost of a larger cull than rapid index case* (infected premises) *slaughtering alone*." (Ferguson and others, 2001a). The authors point out

the need for research to quantify how farm infectiousness depends on time from initial FMD infection. It is interesting that in an appended note to the paper the authors report that: "*The rapid decline in case incidence seen after completion of the analysis presented in this paper has given new estimates of r_I significantly above 1, though more precise estimation awaits availability of detailed data on all slaughter schemes in operation since 30 March 2001*." (Ferguson and others, 2001a).

The same group of researchers carried out a retrospective analysis based on data up to July 16, 2001 (Ferguson and others, 2001b). The purpose of this analysis was to identify the risk factors determining the spatio-temporal evolution of the epidemic and to explore the impact of control policies on FMD incidence.

Three key parameters describing disease spread were targeted for estimation. These are:

* intervention-adjusted R_0 (i.e. R_0 varied during the course of the epidemic in response to speed of IP culling, biosecurity and movement control);
* effective R (R depends on R_0 but can be lower, being further reduced by depletion of the population at risk as a result of infection and non-IP culling);
* the average daily transmission coefficient per infectious farm, β (this is a component of R_0 but, because it is daily rate parameter, the authors state that it is not affected by speed of IP culling).

These parameters were estimated directly, using field data on IPs, estimated infection dates and contact tracing data. In estimating R, and hence, R_0 and β, it was necessary to identify the source of infection for all IPs. Source of infection was identified with any degree of certainty for only a few of the IPs, therefore the researchers attributed sources to IPs using a probabilistic method.

Important risk factors determining these three parameters were identified by the analysis as:

* proximity between IPs and susceptible farms, as described by the spatial transmission kernel;
* species present on farms, which affected infectiousness and susceptibility;
* farmland fragmentation (number of separate land parcels in a farm), which affected susceptibility.

These three factors were used to explain the spatial variation in transmission intensity observed during the epidemic. Based on the analysis and census data providing information on farm density, species farmed and farm fragmentation, coloured maps were produced showing the relative risk of FMD spread across England and Wales. These maps identified areas unaffected by the epidemic at the time, but which would be at high risk of disease spread if disease was introduced.

The analytical framework used allowed direct estimation of the spatial transmission kernel (defined as the "*multiplicative relative risk of transmission as a function of distance from an IP*"). The researchers report that this directly-estimated kernel "*differed significantly from that previously derived from the infectious contacts identified by DEFRA, with considerably more long-distance transmission events being predicted … suggesting that most transmission probably occurred through the movement of animals, personnel or vehicles, rather than through animal contact or wind-borne spread*." (Ferguson and others, 2001b).

R, R_0 and β, also varied over time. R and R_0 fell from initial values of around 4 at the start of the epidemic to below on from the week ending April 2. During May, June and July or R and

R_0 rose slightly to fluctuate generally between 1 and 1.5. β varied in parallel with R and R_0. The observation of steeply falling transmission parameters during the first month of the epidemic mirrors observations of falling dissemination rate or R_0 in the early days of the 1967-68 UK epidemic (Miller, 1976; Haydon and others, 1997).

As already mentioned, variations in these parameters over time are attributed to changes in speed of IP culling, biosecurity and movement control, with R being further reduced by depletion of the population at risk. The authors suggest that β is not affected by speed of IP culling, but this would only be true under the assumption that the level of infectivity of IPs is constant over the whole infectious period. If the level of infectivity increased over the duration of the infectious period, then earlier IP culling would reduce the average daily transmission coefficient per infectious farm (i.e. β). Despite having noted previously that farm infectivity may increase over time (Ferguson and others, 2001a), the analyses and further modelling are still carried out with the stated assumption that "*infectiousness does not vary from the day after infection until the date on which the farm was culled.*" (Ferguson and others, 2001b). It is noteworthy that, in addition to maintaining the assumption of constant infectiousness, the assumed time of onset of infectivity was shifted from three days after infection to only one day after infection, which would tend to increase the apparent necessity of a pre-emptive cull of incubating farms.

The analysis allowed the effect of culling policies on the spread of disease to be assessed. The researchers conclude that changes in culling policies and their implementation explain less than 50% of observed variation in transmission rates, which in turn indicates that effective movement restrictions and rigorously maintained biosecurity were equally vital in reducing disease spread. This would seem to suggest that the role of the contiguous cull in controlling the epidemic was less vital than suggested by the earlier model which led to its adoption.

This aspect was explored by re-running the original model, which had carried the assumption that β was constant, using the time-varying β derived for all Great Britain, Cumbria alone and Devon alone. The original model was thus used to explore 'what-if' scenarios in which different culling policies were applied. Charts illustrating the results suggest that scenarios involving IP culling alone, with slaughter delays modelled according to the recorded data and with no non-IP culling, would have resulted in reasonably well-controlled epidemics, although the model suggests that without non-IP culling the tail of the epidemic would not have been controlled and case incidence is shown as increasing dramatically in July. Given this IP culling-alone scenario, the adjusted model predicts epidemics affecting about 10% of farms in all Great Britain and 30% of farms in Cumbria. These are much smaller epidemics than previously predicted (critically at the time when decisions to change policy were being taken) using a constant β, for scenarios involving IP culling alone, as already reported above, i.e. 30% of farms in Great Britain culled and 70% of the farms in Cumbria, Dumfries & Galloway culled (Ferguson and others, 2001a).

Although the model suggests that without non-IP culling the tail of the epidemic would not have been controlled, predictions concerning the tail of the epidemic must be viewed with caution. The authors themselves comment that, "*stochastic low-probability long-range transmission events causing significant outbreaks in new areas are likely to be a central factor determining the duration of the epidemic tail … The unpredictability of these factors, together with the stochasticity intrinsic to the tails of epidemics, lead us to avoid making predictions of the extinction date of this epidemic here.*" (Ferguson and others, 2001b).

Nevertheless, the results of the analyses are presented as continuing to show that "*extended culling programmes were essential for controlling the epidemic.*" (Ferguson and others, 2001b). In particular, the region-specific modelling is presented as showing that "*non-IP*

culling was much more critical to controlling the epidemic in Cumbria than in Devon, owing to the more intense transmission there". (Ferguson and others, 2001b).

6.2.3 InterSpread

During the epidemic, InterSpread was being used to monitor the unfolding epidemic (John Wilesmith, pers. comm.; Roger Morris, pers. comm.; Morris and others, 2002). The full EpiMAN system had been introduced to the UK previously but its adaptation to the UK situation and population of the model with UK farm data had not been carried out due to diversion of resources to deal with BSE. However, with an experienced team, the model was set up and in use within a week of the start of the epidemic (Morris and others, 2001). From the beginning, InterSpread was used to estimate the number, and approximate location, of undisclosed IPs at any time – i.e. infected but not yet reported. This could have helped to estimate the short term changes in resource requirements as the epidemic grew, but in reality, resources at that time were already stretched, so information that more resources were needed was not surprising.

Later in the epidemic, specifically in late March and early April, InterSpread was used to examine control policy options. Morris and others (2001) describe the use of the InterSpread model in this respect.

In the model, four methods of disease spread from infected farms were modelled:

- animal movement (in order to represent longer distance spread by fomites, which was apparent from the field data, the model allowed a low level of illegal movements to take place);
- local spread to nearby farms on fomites and personnel;
- windborne spread;
- spread by dairy-tanker movement.

As with the other models, assumptions about the start of infectious period are needed. Morris and others (2001) mention that, within InterSpread as used in 2001, infectivity starts on or just before clinical signs appear and stops when control measures are completed (i.e. the end of slaughter), and varies according to both the stage of disease and control measures. Both of these characteristics (onset of infectivity and variability of infectivity over time) are therefore different from the other models, where infectivity is assumed to begin soon after infection and several days before reporting of disease, and infectivity is assumed to be constant during the whole infectious period (Ferguson and others, 2001a; Ferguson and others, 2001b; Keeling and others, 2001).

InterSpread is a very detailed simulation model which attempts to represent transmission of disease by specific contact routes and also include the effects on transmission of differences between species and other farm level factors. The model therefore includes many epidemiological parameters. Morris and others (2001) list 54 epidemiological parameters and 19 control strategy definitions. It should be noted that, although this may seem a large number of epidemiological parameters, this number (54) actually includes many variations of the same parameter used for different farm types (Roger Morris, pers. comm.). Parameterisation of the model can be simplified by aggregating some of the farm types. Many of these parameters were assigned values based on data from the 1967-68 epidemic and a review of the literature, although the parameter governing the tendency for airborne spread was reduced to reflect knowledge about the behaviour of the 2001 epidemic. In addition to the demographic data required to populate the model, data on the infected premises up to the start

date of the simulation was required. As with other models, InterSpread requires infection dates of IPs, and these had to be estimated in many cases, based on average incubation periods.

The work reported by Morris and others (2001) consisted of examinations and comparisons of different control policy options. The model was used to predict the temporal and spatial evolution of the epidemic for 200 days beginning from the *status quo* on April 10, 2001.

The different control strategies modelled were:

- culling IPs within 24 hours of report and different intensities of pre-emptive culling on premises surrounding IPs within 72 hours (within the model, pre-emptive culling was conducted radially from each IP to achieve different pre-defined levels);
- culling IPs within 48 hours of report and different intensities of pre-emptive culling on premises surrounding IPs within 72 hours;
- vaccination alone, which entailed stopping IP culling and establishing, vaccination bands across the country to 'fence in' the affected areas which are left to burn out;
- combination of slaughter and 'damping down' vaccination in heavily infected areas (Cumbria +/- Devon +/- Gloucestershire).

The effectiveness of different strategies was assessed in terms of:

- number of farms infected;
- mean time to eradication (if achieved within 200 days);
- proportion out of five simulations in which eradication was achieved within 200 days.

In comparison with the analyses carried out by Keeling and others (2001), the conclusions reported here were based on relatively few (only five) separate runs of the stochastic model (Keeling and others used 50 to 100 runs per scenario). However, this was considered satisfactory in the circumstances because the model's behaviour was reported as being relatively stable and the outcomes of the model were judged by expert opinion to be representative of likely real-life behaviour (John Wilesmith, pers. comm.). It was felt that using more runs would have reduced confidence intervals but not materially changed the conclusions. When used as a policy evaluation in 'peacetime' (not during an epidemic) many more runs would be done, as when used by the Dutch to evaluate the CSF epidemic of 1997-98.

The conclusions (Morris and others, 2001) were that a vaccination alone strategy was untenable and that adding vaccination to a slaughter policy made only a slight (positive) difference to control of the epidemic and would be risky in view of uncertain trading consequences and high cost. The model demonstrated the necessity of culling infected livestock quickly, with one simulation in which slaughter on IP's was delayed for 48 hours and negligible pre-emptive slaughter was carried out (as happened early in epidemic) producing 'run away' epidemics. The model predicted optimal control of the epidemic if slaughter on IP's was achieved within 24 hours and an average of between 1.1 and 1.4 premises were pre-emptively culled per IP. Increasing the ratio of pre-emptive to IP culling further produced only slight reductions in the number of farms infected. Total farms culled during the simulated epidemics is not reported, but presumably increasing the ratio of pre-emptive to IP culling would lead to an increase in this total if only a slight reduction in the number of farms infected results.

Throughout the epidemic, InterSpread was used on a daily basis to monitor the progress of the epidemic (Morris and others, 2002). The model was run to give regularly updated predictions of the overall size, duration and spatial extent (in the form of graphic contour map output) of the epidemic. InterSpread was also used to provide short term (0-14 day, 14-28 day) predictions of spatial spread of disease. These predictions were specific, in that if the model suggested disease would move to a certain place, it generally did, but not very sensitive, in that the model could not predict all location s to where disease spread (Morris and others, 2002). The model was therefore partially useful as an early warning system. InterSpread was used as a tool to explore 'what-if' scenarios so that the risk associated with emerging situations could be assessed and illustrated using the model. Being a spatially explicit model, InterSpread could be used to examine developments in specific geographic areas, such as the potential for disease spread from the Settle cluster and to pig-dense areas south of Thirsk. InterSpread modelling conclusions also coincided with field observations that the continued spread of disease south of Penrith was largely being mediated by movement of people or animals (represented in the model by increasing the level of mid-range illegal animal movements). This provided support for the introduction of improved biosecurity measures in the area (so-called 'blue boxes' in which movement of farm traffic was intensively targeted by the authorities), which finally brought the epidemic to a close. This latter scenario is an illustration of how InterSpread is an interactive tool which assists in understanding the field situation. At the time, in mid-May, InterSpread was predicting rapid extinction of the epidemic, and yet cases continued at a regular rate (3.5 per day) (Morris and others, 2002). This indicated that there had been a change in the real environment, and adjusting parameters in the model to achieve a fit could suggest what those changes were.

Since 2001 InterSpread has been used to simulate the FMD epidemic in South Korea in 2002. As InterSpread plus, the model is being upgraded with a more friendly user interface and the ability to be easily adapted to different diseases, with different epidemiological characteristics. There is currently a large project to establish InterSpread plus, fully integrated with the EpiMAN disease data management system, in Switzerland.

6.2.4 The Cambridge/Edinburgh model

Keeling and others (2001) published details of this model in early October 2001, although the model had been developed and demonstrated in meetings of the FMD Science Group earlier in the epidemic. The published article represents a retrospective analysis of the epidemic up to August 2001 in which the possible effects of different control policies on the course of the epidemic were examined. The model was also used to predict the likely end of the epidemic.

The model is a spatially explicit, stochastic, individual farm based model. The model was populated with geo-referenced real farms on the basis of the UK census data of 2000. In common with standard epidemic models, farms are classified as susceptible, exposed, infectious or culled. A susceptible farm can catch disease from any infectious source, after which it is classified as exposed. In contrast to the InterSpread model, this model did not attempt to mechanistically represent different modes of disease transmission. The model related the probability of infection passing from an infectious to a susceptible farm to the distance between them (the 'spatial infection kernel') and the species and number of animals on the two farms. The spatial infection kernel was quantified based on the contact tracing data provided by MAFF. The relationships between species and number of animals on farms and the relative susceptibility and transmissibility of farms was quantified by using statistical methods to fit the model to the observed epidemic data.

From a starting position, in which the initially infected farms are seeded in the population, the model simulates progress of the epidemic in single day steps. The probability of infection of

each susceptible farm in the population is calculated each day and a Monte Carlo procedure is used to 'decide' whether or not infection actually takes place. Culling of infected premises and pre-emptive slaughter on other premises, according to actual or modelled policies and delays, are also stochastically simulated each day, moving premises from the infectious to culled state, or from the susceptible or exposed to culled state. As with InterSpread, the model will produce different outcomes each time it is run, and so many runs (50 to 100) of each scenario were carried out and the results were averaged.

As with the other models, this model simulated the transitions of farms from the point of infection to slaughter. Assumptions about the infection dates of the initially seeded infected farms were therefore necessary. More critically, assumptions about the time intervals spent in each state following infection were also required. The model used assumed values for these intervals, as follows (Keeling and others, 2001):

- infection to onset of infectivity – mean value of 4 days used;
- infectious but not yet reported – mean value of 5 days used;
- reporting and slaughter (still infectious) – 1 to 4 days (this time decreased during the epidemic).

Infectivity was considered to be constant throughout the infectious period. The researchers acknowledged the possibility of a within-farm epidemic, which would result in an increase in an infected farm's infectivity over time. However, they felt that "*there is no evidence for such a buildup from the data - the rate at which secondary cases are generated is approximately constant throughout the infectious period.*" (Keeling and others, 2001). Therefore, this model was parameterised with constant infectivity, as were the Imperial models, but in contrast to the InterSpread model.

In addition to examining different control strategies, the model was used to estimate a value for R_0 for each farm in the population (based on the determinants of disease spread used in the model; namely, farm density, species mix and herd sizes in the locality). The average R_0values for all farms within 10km squares were colour coded and displayed on a map (Keeling and others, 2001 – supplementary material). This map highlights areas at highest risk of disease spread, should disease be introduced and is similar to the relative risk map produced by Ferguson and others (2001b), although based on different determinants. Kao (2002) points out some areas of disagreement between these two maps, which would warrant further investigation.

The model was used to examine the effect of different culling and vaccination policies. Various permutations were explored producing the following key conclusions. A scenario in which culling was carried out only on infected premises, with the observed slaughter delays, produced an epidemic of a similar order predicted by the Imperial model in a similar scenario (Ferguson and others, 2001). Results indicated that if only infected premises were culled the epidemic would have infected around twenty thousand properties. A scenario in which the observed levels of pre-emptive culling are carried out, but in which the 24 hour (IP cull) and 48 hour (pre-emptive cull) targets are met from the beginning produced epidemics about half the size of the actual in terms of both number of infected premises and total premises culled. A scenario in which high levels of pre-emptive culling, similar to those achieved later in the real epidemic, are carried out, but with the observed slaughter delays, produced epidemics about half the size of the actual in terms of number of infected premises but about three quarters the size of the actual in terms of total premises culled.

Two vaccination strategies were modelled: vaccination within a 3km ring around IPs and 'barrier' vaccination carried out in a 90^o radius to 5 –10km in the direction of the highest farm

density from an IP. The addition of vaccination to all culling policies produced a slight reduction in the size of the epidemic. The model suggested that vaccination was not an equivalent alternative to pre-emptive culling, because the predicted epidemic, when 3km ring vaccination was used in combination with the IP culling only strategy, was far greater than the actual epidemic.

When the model was used to predict the end of the epidemic, a highly variable result was obtained. This was as expected, due to the unpredictable influences of stochastic transmission events during the tail of epidemics. The results were therefore presented as probability distributions. Two scenarios were modelled: one in which pre-emptive slaughter continued at the (reduced) level current at the end of July and one in which the level of pre-emptive slaughter was raised back to the maximum level achieved in mid-April. In the first scenario the model predicted a greater than 95% probability that the epidemic would continue beyond September, and a greater than 50% probability that the epidemic would continue beyond December. In the second scenario the model predicted a greater than 50% probability that the epidemic would continue beyond September (the last IP of the real epidemic was reported on September 30).

In the supplementary material to the published paper, the researchers comment on some of the uncertainties within their model. In particular they mention the quantification of the spatial infection kernel based on the MAFF tracing data, expressing concerns similar to those of Ferguson and others (2001a; 2001b); "*The contact tracing is probably biased towards short-distance infection, which may cause a similar bias in transmission kernel*." (Keeling and others, 2001). The accuracy of quantification of the spatial infection kernel would be expected to have considerable influence on the predicted effectiveness of neighbourhood culling strategies at controlling the epidemic, as the researchers themselves note; "*it is crucial to quantify the spatial infection kernel or, at least, relative contributions of local and non-local spread.*" (Keeling and others, 2001), and in a later paper on the same model; "*in terms of the total number of farms affected by the outbreak, wide diffuse kernels would mean that CP culling is an inefficient strategy as the infection is far less localised on the neighbouring contiguous farms.*" (Keeling and others, 2003).

Also of concern was the potential influence of over-reporting of cases (i.e. false-positive confirmations); "*The over-reporting of the true number of cases was largest (up to 25%) shortly after the peak of the epidemic; this would lead us to over-estimate the reproductive ratio, R, of the disease and hence over-estimate the effectiveness of the control measures necessary to limit it.*" (Keeling and others, 2001). It should be noted that it was around and just after the peak of the epidemic when pre-emptive culling began to attain high levels, so the effectiveness of this measure in particular may have been overestimated.

Since the end of the epidemic, this model is being further developed to examine novel vaccination strategies (Keeling and others, 2003).

6.2.5 Other models

Airborne spread models

Airborne spread models were not used specifically to support major control policy decisions. They were, however, used in at least two ways during the epidemic.

Early on in the epidemic the NAME model was used to identify the direction and extent of potential airborne spread around early cases (Donaldson, 2002). This allowed early local surveillance and case searching to be correctly targeted.

The airborne spread models were also used to examine possible epidemiological links retrospectively. Essentially this allowed epidemiologists to establish whether airborne spread was a possible route of infection to be considered among any other potential epidemiological links, and furthermore, whether it might be considered the most likely route. For example, the use of an airborne spread model, with expert meteorological interpretation, has identified the possible airborne spread of infection across the Solway Firth from an early IP near Longtown to several dairy farms on the north Solway coast (Gloster and others, 2003). Piecing together the contact links in the 'epidemic tree' is an important step in understanding the dynamics and method of spread of the epidemic.

The NAME atmospheric dispersion model was also used to assess (retrospectively) the chance that disease could have been spread from open pyres used to destroy carcases of infected animals (Gloster and others, 2001; Champion and others, 2002). It was concluded that this was a very unlikely cause of infection, where IPs occurred downwind of pyres, in the cases studied.

Risk analysis

During the 2001 FMD epidemic many risk assessments were carried out to support decisions, mainly to change rules, e.g. on movement restrictions, footpath closures etc. (Scudamore and Harris, 2002). Most of the FMD risk assessment and risk modelling was carried out by the Department of Risk Research at VLA.

The VLA Department of Risk Research became involved from the first week of the epidemic. Initially they were asked to look at risks associated with movements of vehicles and people (following the national ban on movement of livestock). Throughout the epidemic the Department was asked to assess risks associated with such things as access to the countryside and country activities, infection of wildlife species, movement of animal products, different types of licensed animal movements and movement of infected carcases for disposal (for fuller list see appendix 2). Most, but not all, of these risk assessments were qualitative rather than quantitative.

The major reasons why the majority of the risk assessments were qualitative were threefold: lack of useful data, lack of time (urgency), and the fact that often identifying and explaining the risk pathways was a much more important output than numerical risk. Like disease models, quantitative risk models require detailed data, particularly on such things as the amounts of virus in different excretions/secretions of infected animals, virus survival in the environment and infectious doses. Although some data on these aspects of FMD epidemiology exist, it took time to gather it together, and sufficient detail to make a meaningful quantitative risk model was lacking.

Qualitative risk assessments provided a logical and uniform framework for decision making. Greater value was seen in describing the risk pathways than in trying to provide quantified risk estimates, which would have wide confidence limits. By carefully describing the pathway through which a hazard (e.g. spread of FMD infection) is released it was possible to identify risk reduction methods; that is, possible interventions along the pathway that might manage the risk. Qualitative risk assessments were therefore used to support decisions to allow certain activities under certain conditions, or, alternatively, to prohibit activities because no practical risk reduction measures were identified.

A small number of quantitative risk assessments were carried out. An example is work carried out retrospectively to assess the probability that animals on actual IPs downwind of specific pyres used to burn infected carcases may have been infected as a result of the pyres (Jones and others, in press). The quantitative risk estimates produced by this analysis were

interpreted qualitatively; that is, the probability of the pyres causing infection was considered 'low' and, taken together with the fact that premises nearer than the IPs to the pyre (where the risk estimate was higher) were not infected, the researchers concluded that it was unlikely that pyres were a source of infection for IPs.

Since the 2001 epidemic, the VLA Department of Risk Research has continued to work on FMD. Currently, a project, commissioned by DEFRA, is underway, the aim of which is to monitor and annually review the risks and consequences (economic and otherwise) of incursion of OIE list A, and some list B, diseases. The primary purpose of this is to provide a framework for prioritisation, so that surveillance, risk reduction measures and preparedness (contingency planning) can be more effectively targeted.

A separate piece of work has been undertaken to analyse the risk of incursion of FMD into UK livestock. The original purpose was to describe in detail the various risk pathways leading to the release of the hazard (clinical FMD in UK livestock). A quantitative approach was chosen, ***not*** because it was envisaged that a useful quantified estimate of risk could feasibly be produced, but in order to identify where critical uncertainty in data exists. As with qualitative risk analyses, the main purpose was to identify the individual steps in the risk pathways and where practical and effective risk reduction measures could be applied. Despite huge data uncertainties identified in the risk pathways, leading to estimates of risk with wide confidence limits, there has been the temptation to use the quantified estimate of incursion risk as a forecast of the frequency of future primary outbreaks. This serves as an illustration of the potential misuse of the outputs of quantitative models, where often it is the disciplined process of quantitative modelling which has most instructive value, rather than the actual numerical output.

6.3 A closer look at the validity of the models and their use to inform decision making

6.3.1 Reviews already published

Kao (2002) produced a predominantly review of the different modelling approaches and techniques used. He gives a very clear description of the methods used in the various models. With respect to the use of models to examine control policies, Kao notes that culling policies were relatively easy to incorporate in the models. However, he points out a lack of inclusion of logistical considerations and the difficulty of incorporating the effects of non-culling policies, which would affect the transmission parameters, in predictive models. Specifically, Kao says, "*The difficulties associated with estimating resource limitations and including non-culling control policies such as biosecurity changes that alter the transmission kernel lead one to question the value of making detailed quantitative predictions for alternative policies. What is more useful is the insight they give us into the important parameters, helping us to identify bottlenecks in control policy*." (Kao, 2002). The clear implication is that the quantitative predictions produced by models early in the epidemic should have been viewed with caution, because they did not take into account the effect of non-culling policies which changed over time. Evidence that the transmission kernel was changed by non-culling policies as the epidemic progressed is provided by the retrospective analysis of Ferguson and others (2001b), involving the fitting of a time-varying transmission parameter.

In conclusion, Kao (2002) reminds the reader of three established roles for modelling:

* to assist in the development and evaluation of disease control policies;
* to infer the value of parameters or behaviour (by fitting models to field data) that cannot be evaluated experimentally;

- to provide short-term prediction – e.g. immediate effects of changing policy, but, Kao warns, "*no simulation, no matter how complicated, is just like real life*".

Summing up, Kao remarks, "*In the end all theoretical models are only one aspect to providing good scientific advice, augmenting experimental investigation and the good collection and analysis of epidemiological data*." (Kao, 2002).

Lusmore (2002) made a written presentation to the Royal Society of Edinburgh inquiry into the FMD epidemic in Scotland. She severely criticised the quality of the data and the data management systems in MAFF/DEFRA and therefore calls into question the advisability of using models based on poor data in a predictive capacity. She compares the model outputs with what could be achieved by "*traditional methodology*", such as simple calculations on the field data and mapping, and suggests that these methods would have been better. She also points out that modelling could have been usefully applied to the management of logistics.

Green and Medley (2002) provide a more philosophical review of the use of mathematical modelling. Rather than examining the 2001 FMD models in detail, they deal with the types of question which models should and should not be used to answer. They suggest that models are best suited to dealing with 'generic', rather than 'specific', situations, i.e. models are made using complete epidemic data (retrospectively), and then used to explore 'what if' scenarios to provide general insights into the relative merits of different strategies. The implication is that the use of models to provide specific tactical advice early in a real epidemic, as during 2001, was not a wise use of modelling – the particular problem being that high-quality data required to produce a predictive model were not available at the time.

Haywood and Haywood (2002) present a brief evaluation of the use of the models to determine control policy in 2001. These authors held a particular view that vaccination should have been used as part of the control strategy. Although they provide a comparative account of the different models used, their main criticism is that the vaccination strategies explored by the models were not the most practical vaccination alternatives, and other strategies should have been evaluated. Similar criticism about the choice of vaccination strategies explored using the InterSpread model was expressed in letters to the *Veterinary Record* by Sumption (2001), Sutmoller (2001), Boardman and others (2001) and Wood (2001).

6.3.2 Validity of the models

As already discussed, there is no easy test of a model's validity. The critical issues to consider have been listed in section 3.6.5. as:

1. valid models make biological sense;
2. valid models mimic real life, and;
3. valid models should be fit for the use they are designed (and used) for.

The extent to which imprecisely estimated input parameters affect a model's output additionally, should be subject to sensitivity analysis.

It is not the intention here to undertake an exhaustive analysis of the validity of the various models used in 2001. However, a limited exploration of some of these issues is presented in order to establish that the validity of the models as used could be questioned.

Issue 1: Valid models make biological sense;

One of the assumptions carried in the Imperial and Cambridge/Edinburgh models was that infectivity of an infectious farm was constant from the time of onset to end of slaughter. Several experts in FMD epidemiology feel that this assumption is unrealistic. It is felt that,

contrary to what is asserted by Keeling and others (2001), a 'within farm epidemic' does occur and therefore farm infectivity will increase as the number of clinically affected animals on a farm increases. It is accepted from experimental studies that maximum virus shedding by infected animals normally occurs at the same time as clinical lesions appear, 5 to 14 days after infection (Alexandersen and others, 2002). Work on dairy farms in Saudi Arabia (Hutber and Kitching, 1996; Hutber and Kitching, 2000) and in experimental infections (Hughes and others 2002) do indicate that within farm prevalence does increase over time and so the amount of virus being shed will also increase over time in the first few days of a clinical infection on a farm. This would suggest that the infectivity of an infected farm would increase over time. It would normally be expected that disease would spread between livestock on a farm producing a distinctly non-linear profile of overall farm infectiousness over time. It was also commonly experienced in the field during the 2001 epidemic that a single animal with old lesions could be found in an infected herd, along with several animals with fresher lesions, i.e. the single animal would have been infected first and been the source of infection for the others. If not culled that day, the field veterinarians would then find several more animals with lesions on the next day; that is, development of a within farm epidemic was clearly visible. It would seem logical that the infectious challenge presented by a farm would be increasing as the number of animals with fresh lesions (i.e. shedding virus) increased, especially since the time when vesicles are rupturing, i.e. around 2 to 3 days into the clinical phase, is when the greatest amounts of virus are liberated into the environment (Alex Donaldson, pers. comm.). Alexanderson and others (2003) report on contemporary investigations of outbreaks early in the epidemic of 2001, in which estimates of airborne excretion of virus from infected farms were made. These clearly indicate that virus excretion increased over time from first infection to slaughter.

The sensitivity to this assumption of the Imperial model's conclusion that IP culling alone could not control the epidemic was tested by varying the parameter, r_I, which was the ratio of infectiousness after disease reporting to infectiousness before disease reporting (Ferguson and others, 2001a). As reported in section 6.2.2., it was found that running the model with $r_I = 5$ (i.e. approximating to a situation with a within farm epidemic) produced a result in which IP culling alone could control the epidemic.

The Imperial and Cambridge/Edinburgh models also assumed that infectivity of an infectious farm began very soon after initial infection. This was also a point of contention between the modellers and the veterinary experts in FMD epidemiology. Analyses of sensitivity to this parameter are not mentioned in the published papers so far reviewed, but the issue is touched on in the Royal Society Inquiry (Follet, 2002, sections 6.12 to 6.16). It could be expected that if any disease is modelled where infection is transmitted before clinical signs appear, and therefore before any IP culling can take place, then the model would suggest that prevention of disease spread and control of the epidemic would be impossible without pre-emptive culling. Conversely, if the model allows only limited disease transmission to occur before clinical signs appear (i.e. infectivity may begin just before clinical signs and build up gradually to high levels), then it would be expected that the model would show control of the epidemic to be possible by rapid IP culling alone.

The first-hand experience of veterinarians on the ground was that infection was not rapidly spreading off IPs to contiguous premises. Many of them disagreed with the CP culling policy that was implemented; namely on stock on all premises with a common boundary with an IP, regardless of the nature of the boundary or the distance between livestock, sometimes many days after the original IP had been culled (see submissions to the various inquiries, e.g. Wardrope, 2002).

The intention here is not to argue for any particular view, but to point out that whether the models made 'biological common sense' or not, was disputed, and that there were uncertainties about key model parameters that could be expected to substantially influence conclusions about control policy.

With reference to biological sense, Thrusfield (1986) points out that it is also important to determine whether the value of the determinants included in the model can be assessed with accuracy; that is, are there sufficient data of sufficient quality to fuel the model correctly? All the mathematical models described in section 6.2 required infection dates of IPs that had to be estimated according to assumed incubation periods. More critically, the implicitly or explicitly spatial models all required contact tracings data to quantify a spatial transmission kernel. A definite source of infection was established for relatively few of the IPs in 2001. According to Gibbens and Wilesmith (2002), out of a total of 2,026 IPs, a definite source of infection was only identified for 101 IPs (5%), and early in the epidemic the number of sources identified would have been lower. In the absence of a definite source, it was common practice to attribute the source of infection to the nearest possible candidate IP. Therefore, as the modellers themselves commented (Ferguson and others, 2001b; Keeling and others, 2001), the tracings data would be biased towards short distance transmission. Indeed, Ferguson and others (2001b) found that estimating the spatial transmission kernel by retrospectively fitting a model to the epidemic data produced a wider kernel than that derived from the tracing data provided by MAFF. The significance of this is that a model with an unrealistically narrow kernel (i.e., where most disease transmission is over short distances) would tend to overestimate the efficiency of a local pre-emptive culling policy (e.g. CP culling).

Anderson and others (2001) reported other problems with data quality in oral evidence to the Royal Society Inquiry. In particular they mention deficiencies in the demographic farm data and a four-week delay in supplying culling data.

Issue 2: Valid models mimic real life;

All modelling groups claim that their models were able to reproduce the course of the 2001 epidemic with reasonable accuracy. However, the level of proof of validity this provides is compromised by the fact that some of the models were parameterised using statistical methods designed to provide a fit to the real data (Ferguson and others, 2001b; Keeling and others, 2001).

Throughout the epidemic it was widely reported that the various models produced similar outcomes, therefore supporting their validity. However, not all models produced conclusions about control policy that were alike in every detail. The InterSpread model suggested that IP culling alone would fail to control the epidemic only when slaughter was delayed to 48 hours after reporting. Culling IPs within 24 hours did control epidemics simulated in InterSpread, though addition of non-IP culling did improve control.

The first Imperial model and the Cambridge/Edinburgh model both predicted huge epidemics, with the order of 20,000 infected premises, in case no non-IP (pre-emptive) culling was carried out. However, when the Imperial model was re-run using a time-varying transmission parameter, which had been fitted using the actual epidemic data, much smaller epidemics are predicted in IP culling only scenarios. These later predictions are taken to suggest that CP culling was less critical to controlling the epidemic than had been concluded from the earlier modelling exercise (Ferguson and others, 2001b). This would suggest that the early Imperial model and the Cambridge/Edinburgh model differ from real life in the fact that they both overestimate the necessity of CP culling to control of the epidemic.

There is evidence from the epidemic itself that the disease could be controlled without high levels of pre-emptive culling. Figure 3, below, suggests a temporal link between the onset of high levels of pre-emptive dangerous contact (DC) culling and the decline of the epidemic. During and after the epidemic it has been frequently said that pre-emptive culling was essential to control the epidemic (Ferguson et al., 2001a) and was responsible for doing so (King, 2001; Woolhouse, 2001).

However, figure 4, showing the epidemic and culling curves for Cumbria alone, shows that the epidemic in Cumbria had peaked before culling intensity, and in particular CP culling, increased. Indeed, compared with other affected areas, relatively little DC culling was carried out in Cumbria, where almost half the IPs in the epidemic occurred. During the period up to mid-May, in which the main part of the epidemic raged across northern Cumbria, the total number of non-IP premises depopulated was hardly greater than the number of IPs (Fig. 4), and yet the epidemic peaked and waned over a very similar time course to the epidemic in the rest of the country (Fig. 3), where culling of DCs vastly outnumbered IPs. The conclusion resulting from the modelling, that rapid and complete IP CP/DC culling was necessary for disease control and eventual elimination, appears contrary to the experience in Cumbria.

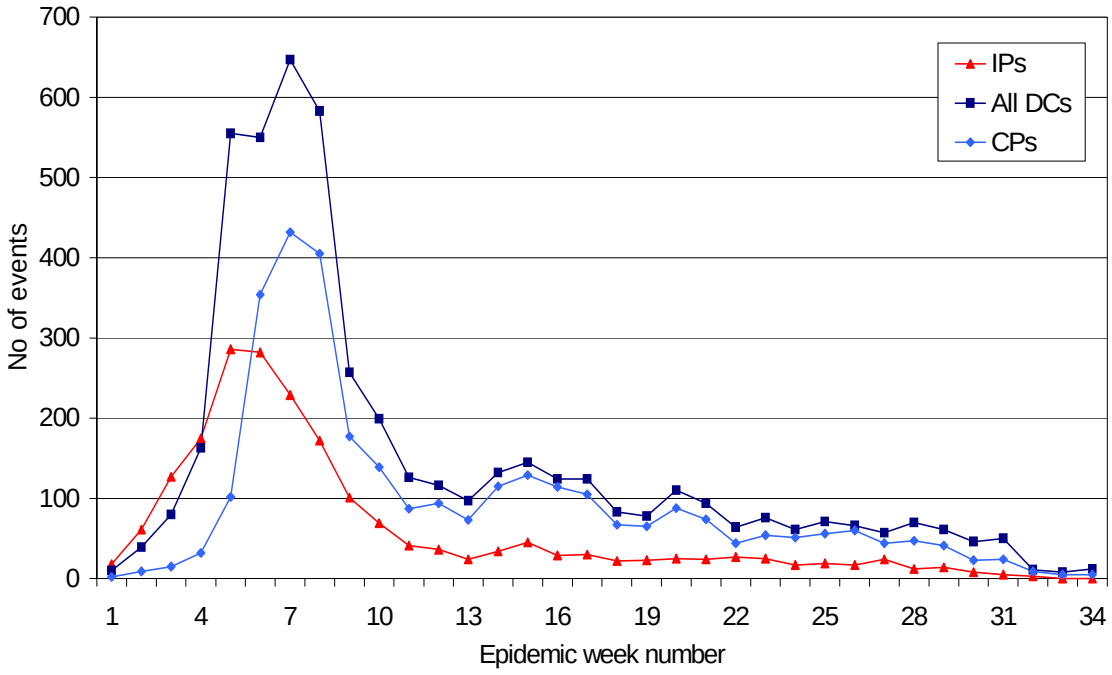

Figure 3: IP and culling data for all GB, during the 2001 FMD epidemic

Key: Numbers of infected premises (IP) are counted by date of first lesion and premises on which pre-emptive culling took place as a result of being 'dangerous contacts' (DC) are counted by slaughter date. Totals are plotted for each week of the epidemic. Note that culled contiguous premises (CP) are a subset of the total DCs.
Source: Chart supplied by Nick Honhold, DEFRA Surveillance Division.

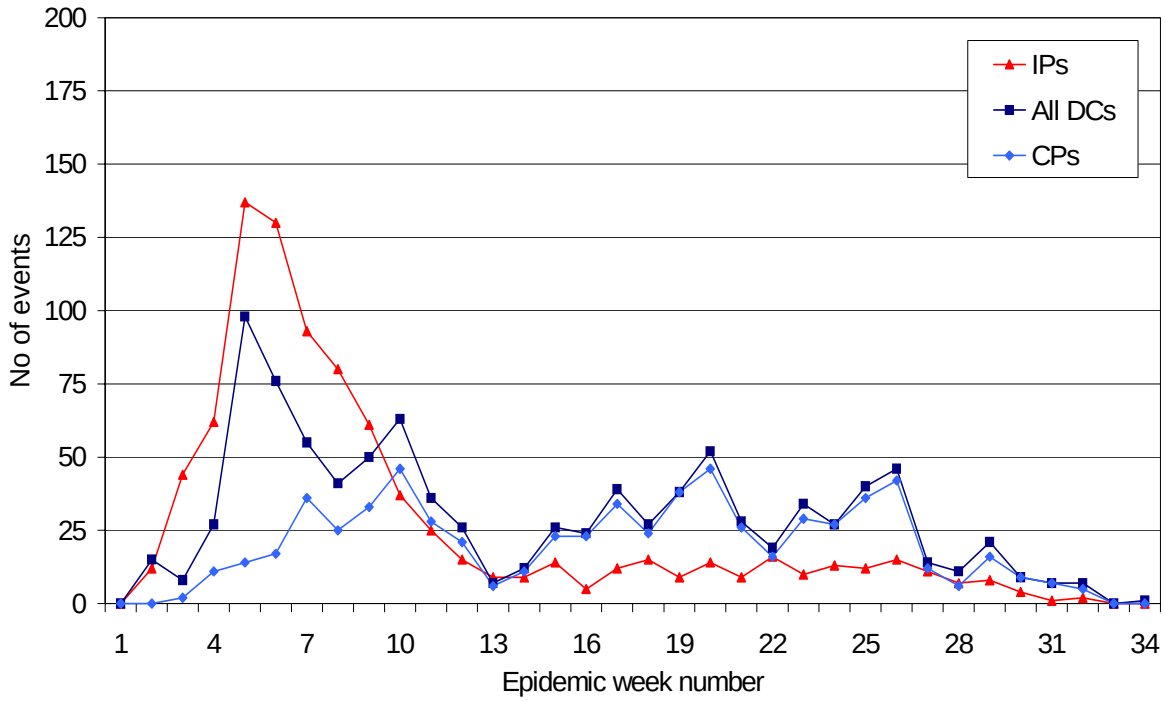

Figure 4: IP and culling data for Cumbria ONLY, during the 2001 FMD epidemic

Key: Numbers of infected premises (IP) are counted by date of first lesion and premises on which pre-emptive culling took place as a result of being 'dangerous contacts' (DC) are counted by slaughter date. Totals are plotted for each week of the epidemic. Note that culled contiguous premises (CP) are a subset of the total DCs.

Source: Chart supplied by Nick Honhold, DEFRA Surveillance Division.

In conclusion, although the models may have been able to reproduce the epidemic approximately as it occurred in 2001 (and to some extent this was achieved by 'fitting' model parameters retrospectively so that the model outcome matched the real events), the models' conclusions about the importance of pre-emptive culling may not be 'true to life'. The models suggested runaway epidemics in the absence of high levels of DC/CP culling and this did not happen in Cumbria. A possible reason for this divergence would be that the models used assumptions about infectivity and estimates of the spatial transmission kernel that would favour rapid and uncontrollable spread of disease if pre-emptive culling was not carried out (see discussion above).

In other words, the models were fitted to reproduce the actual progress of disease, with the levels of pre-emptive culling as it really occurred, but misrepresented the effect of taking away the pre-emptive culling. This highlights a problem with models, and indeed any scientific hypotheses. Although a model, or hypothesis, may fit the real world as observed, if the internal mechanisms and relationships inherent in the model or hypothesis are incorrect, then the hypothesis may not hold true when conditions in the real world change. Scientific hypotheses are tested by carrying out experiments in which conditions are changed in a controlled way. Unfortunately, such experiments are rarely possible in the case of models of epidemic diseases. It is perhaps fortuitous that the epidemic of FMD in 2001 provided at least a range of different scenarios in different affected areas of the UK. The importance of studying carefully the field data from these different areas, in order to better understand the relationships between control policies and disease dynamics cannot be overstressed. Indeed, models can never be substitutes for careful analysis of field data – onerous though it might be.

Issue 3: Valid models should be fit for the use they are designed (and used) for;

The Imperial model played a key role in the development of the 24/48 hour IP/CP culling policy (MAFF, April 4, 2001). The policy was justified on the basis of predictions of the model based on data available up to March 26. The model was therefore used as, and presumably designed to be, a predictive, or forecasting, model. A newspaper article from the time reproduces outputs from the model under the caption "*scientific predictions*" (*Daily Telegraph*, April 11, 2001), which show a large and long-lasting epidemic if IPs are slaughtered within 24 hours, but no pre-emptive slaughter is carried out.

Although the FMD models developed in 2001 have been used in other ways, for example, to better understand the risk factors influencing spread of the disease retrospectively, it was this use of models to produce predictions given different control policy scenarios, and thence to support decisions about control policy, that was unprecedented and most contentious during 2001.

With respect to the 'fitness for purpose' issue, Dent and Blackie (1979) suggested two sets of judgements to be made:

1. that the model is not different from the real system to a degree that will detract from the value of the model for the purposes for which it was designed;
2. that the decisions made with the assistance of the model will not be measurably less correct than those made without the benefit of the model.

Admittedly, with the benefit of hindsight, it seems that the predictions of the Imperial model, at the time it was used to support the development of the 24/48 hour culling policy, were pessimistic. This is apparent from the revised model outputs produced in the later work (Ferguson and others, 2001b). This means that the model did differ significantly from the real system, which must negate the value of its predictions.

If rigorous analysis of the epidemiological field data eventually suggests that CP culling, a policy which was unpopular and costly in animal life and resources, was not in fact necessary to control the epidemic, then the decision to follow that policy would have to be judged, with the benefit of hindsight, as an incorrect one. The conclusion would therefore be that the model was not fit for the use made of it. This is a view that was also implied by other reviewers. Kao (2002) questioned the value of making detailed quantitative predictions for alternative policies, and Green and Medley (2002) suggested that the use of models to provide specific tactical advice early in the epidemic was not an ideal use of modelling. However, it is impossible to know how good the policy decisions may have been in the absence of the models. **It will be important in the future to establish better bases for making tactical disease control decisions.**

This third issue with respect to model validity highlights the fact that it is not enough to consider whether models themselves are valid or invalid, more importantly it is the ***use*** of models which should be validated.

The Edinburgh *R* model was designed simply to estimate the case reproduction ratio during the epidemic to date, and therefore to judge whether the epidemic was under control. As such, the approach, use and conclusion was valid (although the much simpler rolling-mean epidemic curve fulfils the same purpose). The latest value of *R* could be used to predict the future rise in case incidence (in the MAFF press release of March 23 an estimated doubling time of 8 days is reported as an outlook of the model). Using the model to make such predictions is only valid under the assumption that *R* will remain the same, an assumption which cannot easily be made (Ferguson and others, 2001b, concluded that *R* fell from the start

of the epidemic until April). Although estimating *R* may be a valid exercise, it provides little more information than the epidemic curve itself (the slope of the epidemic curve is a reflection of *R*) and the estimated dissemination rate (EDR), which can be calculated directly from case incidence data (Miller, 1976), is an alternative indicator of the level of control over an epidemic.

The InterSpread model was used by DEFRA headquarters staff to monitor the epidemic. Its output featured less strongly in the justification for major innovations in control policy. In describing the use of InterSpread during 2001, Morris and others (2001) say, "*computer modelling assists rapid and informed decision making on relative merits of different control strategies…*". They also comment that, "*the best options suggested by InterSpread are well recognised from past decades of experience, but, the difficulty often lies in gaining approval for marshalling the required resources before the need for them is clearly demonstrable – despite the fact that this is when they will provide the largest payoff. InterSpread has a potential role in aiding early recognition of the warning signs…*". The implication is that models can be usefully used to support the requisition of resources needed by well-tried control measures by graphically demonstrating the possible development of an epidemic – perhaps in the relatively short term – but not to drive novel, untested policies that are unsupported by expert opinion, and which may have serious ethical issues, as well as personal consequences. Although the same reservations about using models to predict future events apply, if carried out with regard to epidemiological knowledge and expert interpretation, this use of models to secure resources may be valid in that it can lead to improvements in the quality of decisions made.

The models of Keeling and others (2001 and 2003) and the second model of Ferguson and others (2001b) were designed and used as analytical tools for use in retrospective analysis of the epidemic – specifically to understand the factors influencing spread of the disease (risk factors). As such they are valid and useful tools – the R_0 map and relative risk map they produced provide valid representations of the different risks of spread of FMD across the country during 2001, which would be a useful starting point when prioritising areas for surveillance and preventive measures. However, to use these models to predict how things may be in different circumstances (different control policies, different virus strain at some future time) is less valid, because in doing so it must be assumed that the models have accurately represented the internal workings of the system (e.g. farm infectivity) and that they have included all the risk factors which may be relevant in new circumstances.

6.3.3 Problems within the FMD science group and the decision making process

The 'Lessons to be Learned' inquiry (Anderson, 2002, page 91, box 10.2.2) highlights problems within the FMD science group. The group came together as a result of the Sir John Krebs, Chairman of the Food Standards Agency, consulting with a group of modellers - not as a result of the desire to bring together the necessary cadre of veterinary and associated expertise. Although experts from other scientific disciplines (including veterinarians) were brought in, the highly specialised nature of the modelling made it difficult for these other experts to engage with the detail of the models. The group was criticised as being a 'modelling sub-committee', at times there were polarised views within the group but no mechanism for handling such conflict (Anderson, 2002).

Regarding the key decision leading to the 24/48 hour policy, the 'Lessons to be Learned' inquiry admits (Anderson, 2002, page 92) to being "*unable to find a clear account of decision making around that time*." (i.e. between March 21 and March 26). The government was under increasing pressure to be seen to be doing something new, which must have ruled out any idea of continuing solely to work on reducing slaughter delays on IPs.

Those with the power in policy making had the impression that traditional methods were failing and were perhaps seduced by the illusion of truth provided by mathematics (Gupta, 2001), for example the "*scientific predictions*" of the Imperial model reported in the *Daily Telegraph* of April 11, 2001. The point has been made that modelling and decision-making are two separate activities and remained separate during the 2001 epidemic. Models were used as part of the advice given to both the Chief Veterinary Officer and the Government's Chief Scientific Adviser, who passed this advice on as they saw fit (Woolhouse, pers. comm. – see Appendix 3). Anderson and others (2001) also made the point to the Royal Society Inquiry that the scientists provided advice but did not determine policy. It is true that the FMD Science Group was not a 'decision-making' committee. However, the 'Lessons to be Learned' inquiry (Anderson, 2002, page 91, box 10.2.2) says that the "*analytical evidence … was seized upon by decision makers in a situation where hard evidence was hard to come by*". The modellers were aware of the limitations of their models and indeed these are pointed out in the papers that were published later, if one takes the time to find them. Nevertheless, modellers were forthright in expressing the unreserved opinion that the conclusions of their models and the solutions suggested by them (i.e. CP culling) were correct. A report of the Select Committee on Environment, Food and Rural Affairs quotes evidence given on November 7, 2001, at the House of Commons as follows: "*Those involved in the decision to adopt a policy of rapid contiguous culling were adamant that it had been the only way to bring the disease under control. … The Chief Scientific Adviser told us in November that 'there is a mountain of evidence to show that the cull policy we were following and pursuing … was the policy bringing it under control'. Professor Anderson said that 'it is poorly understood that the contiguous cull saved animal lives'. Professor Woolhouse was insistent that 'the contiguous cull was required to bring the epidemic under control, so to stop this exponential spread that could have taken in goodness knows how many more thousands of farms in the long run'*." (Select Committee on Environment, Food and Rural Affairs, 2002, para 26).

This alienated other FMD and disease control experts from other backgrounds and must have stifled full scientific debate within the FMD science group. That there were dissenting views within the group is evident from interviews and articles published at the time. For example, Donaldson and others (2001) argued that, in the absence of significant risk of airborne spread of disease, which could be judged by veterinarians on the site of each IP, improved biosecurity could prevent much local spread of disease without the need to slaughter vast numbers of animals. Dr. Paul Kitching, then of the FMD World Reference Laboratory, Pirbright, UK, is reported by *The Independent* newspaper as saying that, at the end of March and in early April he had told Ministers and the Science Group that the models were wrong and that the contiguous cull was unnecessary on the scale at which it occurred (*The Independent*, 24 June, 2001). The contiguous cull, as enforced rigorously until April 27, was also seen as overzealous and unjustified on veterinary grounds by many among the field staff of the state veterinary service. Among those expressing dissent with the policy (particularly temporary veterinary inspectors) were many veterinarians who had wide experience of FMD internationally and those who had worked during the FMD epidemic in UK in 1967-68. The contiguous cull diverted limited resources and created a moral (and morale) problem among field staff, which was unhelpful in the fight against the epidemic (see Wardrope, 2002). Analyses of the epidemic in Cumbria, based on field data, provide evidence that the opinion of Dr. Kitching, that the contiguous cull as enforced was unjustified, was correct, and that the cull was not of major importance in controlling the epidemic in Cumbria at least (Honhold and others, 2003; Taylor and others, 2003).

From the above discussion, two main problems within the process of decision-making on FMD control during 2001 can be identified:

3. The need to come up with novel control policies in the face of an apparently deteriorating situation is a symptom of the fact that the existing contingency plan for FMD control was overwhelmed and had no 'ready made' fall back position (e.g. see EU parliament, 2002).
4. That decision makers had to "*seize upon analytical evidence in a situation where hard evidence was hard to come by*" (Anderson, 2002, quoted above) is a symptom of the fact that field data were not being adequately collected and analysed early in the epidemic – in other words there was a lack of 'veterinary intelligence'. The best decisions are made on the basis of good information. Had more accurate and timely field data been available in 2001, a better analysis of the developing situation may have led decisions in different directions. In 2001, the quality of information was compromised and model-based analysis was used as a substitute for poor information. What was perhaps not taken into account was that models themselves are equally dependent on good information for their validity. In truth, models were simply the tool used to analyse the data, but the novelty of this analytical tool to decision makers at the time and the nature of model outputs to appear more certain than perhaps they are, meant that the distinction between data and assumption was lost.

6.4 Summary of opinion with respect to models and the contiguous cull

If an epidemic is modelled with parameters which describe disease spread as being predominantly over very short distance then such models will demonstrate a beneficial effect of local culling. In addition, if the model has the majority of disease spread from IPs occurring before reporting of disease, then such models will inevitably conclude that pre-emptive culling (culling premises before disease is reported) is ***essential*** to control the epidemic. To be effective, the pre-emptive culling would be targeted at the premises most likely to have been infected, i.e. local or neighbouring premises.

The Imperial and Cambridge/Edinburgh models are parameterised in such a way that favours the use of contiguous pre-emptive culling. However, the field data on which these parameters are based was deficient. In order to estimate the timing of disease transmission events, and the distances separating farms between which these took place, it is necessary to know the dates on which farms were infected and the identity and location of the source farm for that infection. This information was missing for most IPs in 2001, and often the nearest previous IP was assumed to be the most likely source of infection. Using this biased data, and assumptions about the very early onset of infectivity, which were contrary to expert opinion, it is not surprising that these models find pre-emptive local culling to be an efficient method of controlling the epidemic. In contrast, the InterSpread model was set up with infectivity starting on or just before clinical signs appear and varying according to the stage of disease, and this model predicted that control of the epidemic was less dependent on high levels of local pre-emptive culling.

7. The future – recommendations for future work

7.1 What needs are addressed by models and what does DEFRA need?

DEFRA is faced with the task of making decisions about FMD control. Modelling can contribute to decision support. There are two distinct situations in which policy decisions are required:

1. contingency (strategic) planning– 'standing' policy made in 'peacetime' which details the strategies to be followed in the event of future outbreaks;
2. tactical decision making during an epidemic ('wartime') – reactive decisions to adjust control measures in response to unfolding events.

One problem in 2001 was that the distinction between these two types of decision became blurred. The epidemic rapidly attained a scale unforeseen by the existing contingency plan so that new strategies had to be developed in response to the deteriorating situation. Furthermore, the lack of an adequate veterinary intelligence system meant that these new strategies were made and decided upon with the support of models based on incomplete data, using simplifying assumptions to fill in the gaps. In truth, models were simply the tool used to analyse the data, but the novelty of this analytical tool to decision makers at the time and the nature of model outputs to appear more certain than perhaps they are, meant that the boundary between data and assumption was overlooked. To avoid this in future **there is a need to have more detailed contingency plans** ahead of time; plans which cover several scenarios, including worst case scenarios, and **anticipate the criteria on which decisions to adjust strategies and/or bring in different strategies will be made**. In a discussion during the Royal Society Inquiry (Royal Society, 2002) the point was made that, "*models must be developed in advance, and used as one of the tools to assist in designing contingency disease control plans. Those plans must be subject to proper scientific review, must be agreed with stakeholders in advance, and must emphasise the need for rapid action.*"

Contingency planning should be based on the wide range of available knowledge about disease epidemiology, disease control, the logistics of control and the economic consequences of disease and control. **Modelling can play an important part in combining all this knowledge together to produce useful output for decision support**.

Tactical decision making should be based more on real veterinary intelligence than on predictive modelling. However, **models can also play a role in interpretation of veterinary intelligence**.

However, it is stressed that modelling is only a part of the process, and is a possible tool among many that could be used to organise epidemiological knowledge. There have been suggestions that DEFRA should establish a dedicated modelling section at headquarters level. I would suggest that this is a bad idea. Modelling is a highly specialised area of work, in which techniques are various, constantly developing and becoming ever more sophisticated. Attempting to establish, within DEFRA, a group who's modelling work might be considered 'definitive', and given priority over the work of other groups outside DEFRA, is unrealistic and would also lead to an over-reliance on model-generated solutions. Rather, DEFRA should establish a core group with broad expertise in epidemiology, including quantitative epidemiology, which includes an understanding of statistical analysis and modelling. This group could consist of both headquarters and field based staff. The remit of this 'epidemiology group' would be to collate, analyse, and interpret all information on animal health issues about which decisions are to be made. The group, would, of course, call on

outside specialist expertise, for example in modelling, where necessary. The group would also be responsible for evaluation of all research which may have implications for animal health policy. With particular reference to FMD, establishment of such a group would ensure that all possible lessons are learned from the 2001 epidemic. In any future epidemic, such a group would be responsible for the rapid provision of real veterinary intelligence, based on targeted monitoring of key parameters of the unfolding epidemic.

The need for a structure to guide tactical decision making is being addressed. In a consultation document (DEFRA, 2003) a decision tree approach is described in which modelling and cost-benefit analysis (CBA) will be used as part of the process to decide whether to use vaccination and/or pre-emptive culling during a future epidemic. With regard to this it important to consider what the modelling approach can be expected to do and what its limitations are.

7.1.1 The scope of models in contingency planning and tactical decision support

In decision support, economic CBA is a way of quantifying the economic criteria involved in a decision (and there are usually criteria other than purely economic ones). CBA requires the comparison of outcomes resulting from different courses of action. CBAs may compare a before and after scenario, or, real with and without scenarios, or, sometimes, a known current *status quo* is compared with a projected outcome following a change. Because FMD epidemics are rare events and never occur more than once in directly comparable situations it is not possible to attempt CBA of different FMD control policies based on comparisons of real events alone, i.e. a model is required to fill in at least one side of the CBA. At best, a real situation can be compared with a projected outcome following a different set of control options. This approach is exemplified in the retrospective analysis of FMD in the UK (Ferguson and others, 2001b) and the retrospective analysis of CSF in the Netherlands (Nielen and others, 1999). During 2001, the decision to adopt the contiguous cull policy was made using models made in the first month of the developing epidemic, in which projected outcomes following different control scenarios were compared. This approach relied on the models being able to accurately predict the course of the real epidemic, under the prevailing strategies and circumstances and in response to various control strategy alternatives. With hindsight, it was unrealistic to accept the predictions of the models as accurate and therefore the quality of the decision made with the support of the models is questionable. **The conclusion of this report is that the use of predictive models to support tactical decisions is not to be recommended**.

The reliability of models as predictive tools in FMD epidemic is limited, especially when trying to make long term predictions from the early days of an epidemic. The modellers themselves say that two or three weeks' data are needed to begin to model a specific epidemic. Even given good 'start up' data, there are inherent difficulties in predicting the future course of an FMD epidemic. Important factors can change during the course of an epidemic, which alter the tendency of disease to spread, such as farmers' varying attention to biosecurity measures, which essentially cause the R_0 to change during the epidemic in an unpredictable way. Such variability could be included in stochastic models, but these then have the problem that each scenario may produce vastly different outcomes, any of which are possible, therefore presenting decision makers with information of limited predictive value.

The final phases of epidemics are particularly difficult to predict. Ferguson and others (2001b) point out that the duration of an epidemic tail depends largely on stochastic, low-probability, long-range transmission events causing significant outbreaks in new areas and that the unpredictability of these factors precludes making predictions of the extinction date of epidemics.

Measures like vaccination or pre-emptive culling are most efficient when implemented early in an epidemic, so decision support would be most needed at this time. Leforban (2002) suggests that the time taken to detect the primary outbreak should be the deciding element in the choice of control method. With particular reference to making a decision in the use of ring vaccination, James and Rushton (2002) say; "*The progress of an outbreak of FMD is extremely difficult to predict in the early stages of the disease. The course of an outbreak can be critically affected by minor and inherently unpredictable events, such as a single livestock movement. For this reason, predictive disease models, which depend on statistical probabilities of transmission, have not met with much success in predicting the spread of FMD from herd to herd, and still less the impact of control measures. Given these constraints on predicting the impact of ring vaccination on the progress and extent of an outbreak, it is difficult to envisage an economic analysis that would guide decisions on the possible use of ring vaccination. This leads to the rather unsatisfactory conclusion that, in most cases, the impact of using or not using ring vaccination is essentially unpredictable. By the time that it becomes apparent that ring vaccination would have been justified, it is likely to be too late to use this method of control*." (James and Rushton, 2002).

The most appropriate use of models is as tools in 'peacetime' to aid retrospective analysis of real epidemics to gain insights into behaviour of epidemics. Hypothetical scenarios can then be modelled to develop insights into the relative merits of different strategies in different situations. In this way decision makers can be provided with *a priori* supporting guidelines. As an example, modelling was used by Mourits and others (2002) to show that different control measures would be justified in different density livestock areas and this idea has been adopted within the Dutch contingency plans for CSF and FMD (Mirjam Nielen, pers. comm.). In a similar way, models may be used to suggest areas of the UK where vaccination would be a more or less appropriate strategy in case of FMD incursion.

The use of models during 'wartime' should then be restricted to monitoring the epidemic and aiding short term fine adjustments to strategies. 'Wartime' models should be one of several tools available to the epidemiologists to aid them in analysing and understanding the behaviour of the epidemic. Comparing real behaviour to 'expected' (model-generated) behaviour could alert epidemiologists to unexpected circumstances in the field which could then be targeted for action. 'Wartime' models could also be used to carry out limited 'what-if' simulations, to assess risks associated with various developments of the epidemic, so that appropriate contingencies could be made in resource planning.

The rest of this chapter provides more detailed suggestions of the research required to inform FMD contingency planning and the types of decision support tools that could usefully be developed in the coming years. It should be understood that modelling is not the only method relevant to this research. Modelling is but one method within the wide range of quantitative epidemiological tools. **When commissioning research therefore, the desired output is what should be specified, with the methodology left open to the researchers, unless of course, a working model forms part of the desired output**.

7.2 Contingency planning ('peacetime')

7.2.1 The key questions

Questions for research to address include the following:

1. What are the relative merits of different control strategies?

   i) Vaccination (various strategies) and culling (various strategies) are the obvious strategies requiring attention. However, other control measures such as improving

biosecurity and controls on different kinds of agricultural and livestock movements should be looked at – the fact that these measures are more difficult to model makes it more important that they are not overlooked. Perhaps novel approaches will be needed to evaluate the potential effects of biosecurity measures.

ii) There are several criteria for 'merit'. Analyses should look at the resource, logistic and economic consequences of different strategies. It is interesting to note that the InterCSF model used by the Dutch to analyse control measures used in the 1997-98 CSF epidemic included limits on pig rendering capacity, so that slaughtering delays would be modelled if too many farms were to be culled and slaughter capacity would run out. This was not a feature of models used during the UK FMD epidemic in 2001, but is very important in contingency planning, which should prepare the authorities not only for what will need to be done, but how to do it.

2. What factors influence the appropriateness of different strategies?

i) What is the relationship between the characteristics of disease spread, as indicated for example by such things as the spatial transmission kernel (or, plainly, the relative importance of spread over different distances) and other factors such as livestock density and type, and the effectiveness or otherwise of local vaccination or culling? General models could be used to answer this question, as opposed to models specifically reproducing the 2001 epidemic. In a discussion at the Royal Society Inquiry (Royal Society, 2002) the suggestion was made that a 'general theory for neighbourhood control' could be developed. Woolhouse (2002b) similarly suggests, "*Development of a formal quantitative understanding of the impact of neighbourhood disease control policies, e.g. ring culling or ring vaccination, on disease spread*." As an example of modelling addressing this issue see Matthews and others (2002). This is an interesting idea but care would be needed when transferring 'generalised' ideas to specific situations.

ii) Can 'triggers' be identified which would lead to the choice of one strategy over another? Triggers should be parameters easily measurable in real epidemics. For example, are different measures appropriate to fight disease in different areas, or at different times in an epidemic. When is pre-emptive culling appropriate or not?

3. Can measures be effectively targeted? For example see the current work of Keeling and others (2003) on targeting vaccination.

Note that on the question of vaccination or extended pre-emptive culling the decision of whether to apply a measure or not can not really be left to a 'wartime' model. The contingency planning should therefore have developed *a priori* decision rules (or triggers) leading to application of the measures. If the decision depends partly on economic or logistic factors then a model or spreadsheet framework should be set up in advance so that these factors can be rapidly evaluated. Such a framework would include the potential economic effects of changes in trading arrangements, resource and economic costs of switching resources to vaccination duties, costs of 'knock on' consequences such as changing requirements for serological monitoring etc.. Once the decision to apply measures is made, 'wartime' models may assist in deciding where and what to vaccinate or cull.

An important consideration on the vaccination modelling issue is that there is also a need for more detailed data on the responses of animals to vaccination. This points to a need for further research on vaccines and vaccination, for example, the development of protection after

vaccination and the possible levels of infectivity of animals themselves exposed to infection shortly after vaccination etc..

7.2.2 Use of models in training

Realistic stochastic spatial simulation models may be useful as a means of carrying out 'virtual reality training'. This would allow people to build up 'virtual experience' to draw on in case of real disease. Also the results of many virtual exercises can be analysed and documented to provide 'collective experience' which may be used in refining contingency plans, which should be built up to prescribe courses of action to take in case epidemics develop in certain ways. Data from virtual epidemic runs can thus be used, in the absence of real epidemic data, to look for key epidemiological indicators with some predictive value, or particular value in decision support (as decision triggers).

7.3 'Wartime' – Veterinary intelligence – Development of an 'epidemic management system'

Tactical decisions, which would direct courses of action within various options already set up by contingency planning, should be based as far as possible on real information about the progress of the epidemic, i.e. veterinary intelligence. Wartime modelling could be one of several tools used to analyse this veterinary intelligence.

The objectives of 'wartime' modelling should be to provide short and medium term projections, specifically to allow resources to be efficiently targeted. These projections would also be used to alert authorities to potential risky situations, so that adjustments aimed at risk reduction can be made. **It is particularly important that such models are used in parallel with routine and 'real time' analysis of field data to monitor the progress of the epidemic**. Divergence of the 'expected' course, as predicted by the model, and the actual course as revealed by analysis of real data would highlight where tactical adjustments to control measures may be needed.

Once an epidemic has generated sufficient data to allow longer term predictions to be made from models, **these alone should not be relied on to support dramatic changes in policy** that are not foreseen in contingency planning, but regularly updated **predictions would be useful in forward planning of resource requirements**.

Of particular value during epidemics would be individual farm level 'models' which would provide a framework within which to combine field data with knowledge of epidemiological risk factors to derive an assessment of risk of onward transmission from IPs. The airborne spread models are a special case of this kind of model, and the EpiMAN system also includes this feature (Sanson, 1993). Hutber (2001) is also working on models with this objective.

7.3.1 InterSpread / EpiMAN?

The use of the simulation model, InterSpread, as an epidemiologists' tool during 2001 has been discussed. This type of model clearly has potential value as part of an overall epidemic management system. With reference to further development for UK, Morris (2002) suggested that a demographic farms database including farm polygons would be better than point references and strongly encourages the development of a national spatial farms database for the UK similar to the New Zealand Agribase. Morris also points out that, "*In order to produce useful conclusions, modellers must work closely with epidemiologists who are analysing the epidemic, and the modelling and analysis must go hand in hand, or else the modelling results may produce quite misleading predictions on the scale and pattern of the epidemic, and the impact of control measures.*" Morris (2002). This means that any model which is to be used as

a ‘wartime’ tool needs to be transparent so that interaction with epidemiologists is easy and such a model should have an interface making it amenable to ‘tinkering’. Such tinkering is the means by which the people involved on the ground can use the computer model as an aid to understanding the interacting processes of the epidemic and the effects of control measures on it.

7.3.2 Logistics/resource models

Linking short term predictions made by ‘wartime’ models to simple models which estimate future resource requirements would be an invaluable asset in disease management. Such models should be developed to work as integrated parts of the epidemic database (e.g. the DEFRA disease control system (DCS)).

7.3.3 Databases, simple analyses, key predictive parameters

In both the Dutch CSF epidemic of 1997-98 and the UK FMD epidemic of 2001, problems were encountered because databases were not linked up where necessary. Policy-makers complained about the adequacy of the information provided to base policy decisions on. This highlights the need for real time data collection and analysis during an epidemic. This need is addressed by systems like EpiMAN, though custom built data management systems could also be developed to address this need (such as DCS).

There are gaps in the currently available data that have been identified as important to modelling and management of FMD epidemics. In addition to deficiencies in the geospatial aspect of the farm database referred to above (i.e. point data to be replaced by polygon data) the fact that small farm units are missing has also been pointed out. The current census data excludes farms employing less than a certain number of labour units, but small ‘hobby’ farms could be particularly important in FMD epidemiology. Another area where data are currently lacking is that of livestock movement. In 2001, the lack of a comprehensive animal movements database made tracing of dangerous contact stock that had passed through various markets extremely difficult.

The potential economic benefit of more rapid tracing of animal movements, resulting in more rapid control of an epidemic, could be demonstrated using a model. The purpose of this would be to compare the cost of introducing a comprehensive animal movements database with the potential benefits, therefore providing economic justification for such a system.

The key role of simple analysis of data, perhaps carried out at local disease emergency control centres (LDECC) would be to produce veterinary intelligence, and in particular, key epidemiological parameters which have been identified during contingency planning as having particular relevance to decisions taken in epidemic management. For example, a particularly important indicator would be the delay between report of disease and slaughter of livestock. This parameter has been shown to have value as a short term predictor of case incidence (Honhold and others, 2003). If the idea of local analysis of data is accepted then there is clearly a staff/skill resource and training implication.

Another important epidemiological activity is the tracing of sources of infection. Back tracing was not prioritised in 2001 but the information on sources of infection was required by all the models and would also have provided much needed veterinary intelligence on the mechanisms by which disease was spreading, allowing appropriate control measures to be used.

Much was made of estimating the *R* value through the 2001 epidemic as an indicator of the level of control being achieved. However, parameters which can be simply calculated from the raw epidemic data, such as the EDR (basically a rolling ratio of cases occurring in

consecutive periods of time, e.g. 4 days, 7 days), are just as useful as monitors of the progress of epidemics (Morris and others, 2002). When epidemics are widespread in different locations it is important that the key epidemiological parameters are monitored locally, as aggregating data for the whole country would be misleading if sub-epidemics are progressing at different rates and 'out of synchrony' in the different areas.

There is much to be gained from retrospective study of FMD epidemics worldwide, wherever good quality data are available, with the objective of identifying simple, readily measurable parameters, such as early disease incidence, which may have value as indicators of the risk of local spread of disease (Hutber and others, 1999). Such indicators could be useful in local veterinary decision making and local tuning and targeting of control measures.

7.3.4 Airborne spread

Of particular interest with regard to local tuning and targeting of control measures is assessment of the potential for direction and magnitude of airborne spread of FMD. DEFRA should work closely with developers of airborne spread models (UK Met Office) to ensure that appropriate output is produced in a form that is needed for tactical decision making at times of outbreak. When formulating contingency planning it must be remembered that the outputs of meteorological models will always require expert interpretation. Inclusion of meteorologists and epidemiologists in the evaluation of model output and its impact on decision making should be built in to contingency plans.

Although airborne spread models are well developed, particularly the meteorological atmospheric dispersion components, there are still areas where they can be improved. Donaldson and Alexanderson (2002) state that further research is needed to refine the input data and improve the accuracy of these models. These are mainly the areas concerning virus emission to the air and infection of animals by airborne virus, but there is also potential to improve understanding and prediction of localised variations in dispersion of virus. John Gloster (UK Met Office) provided the following summary of potential research areas:

Virus emission

Although emission of virus in the breath of animals is being well researched are there ***other important ways in which virus gets into the atmosphere*** (e.g. splashing, evaporation from contaminated surfaces)?

Animal experiments are conducted to quantify virus excretion (animal species, virus strain, stage of disease), but other factors could also be important (e.g. time of day, stress, size of animal).

At the moment the models deal with the excreted virus as if it were 'dissolved' in the atmosphere, therefore as an air plume widens the virus is 'diluted'. However, virus may be excreted associated with particles of epithelium etc., each containing large amounts. These particles could be carried long distances unchanged, therefore allowing infection to take place further away than a model based on dilution of virus along a plume would predict. Research should be carried out on this.

Airborne transport

Possible effects of local topography and day/night effects at the moment are assessed by experts on a case by case basis when interpreting output of meteorological models.

Ongoing research will improve interpretation of these models.

A significant limitation of the dispersion models at present is that they produce output in terms of average concentrations in a plume over a 24 hour period. This misses potential short

term peaks (which could lead to transmission of infection). Therefore it would be useful to develop models with more detailed output.

Infection

Doses of virus required to infect animals has been researched In general. However, variations associated with different factors such as stress, local conditions (in fields or buildings), the period of challenge (short high dose or long low dose) are not fully understood.

Short range airborne spread and 'local spread' - the need for more detailed understanding:

During the epidemic of 2001 it was concluded that airborne spread of the PanAsia type of the FMD virus was unlikely to occur over a few hundred metres unless large numbers of animals were emitting virus at the same time. However, much of the transmission of disease in 2001 was recorded as 'local spread', which was assumed to be effected by virus carriage by moving fomites. In many cases the fomites responsible and the linking movement could not be identified, which left the actual source and route of infection of many IPs inadequately explained. It is suggested that if virus were carried in the air associated with particles each harbouring large amounts of virus, and if other localised effects were important, such as topographical features, animal stress etc., then more of the 'local spread' could be attributed to airborne than first thought. In order to assess this possibility research addressing the details indicated above would be necessary.

7.4 Risk modelling

The risk assessments carried out during 2001 were undoubtedly useful but having to carry them out in the heat of the epidemic was not ideal. As contingency plans are now developed in 'peacetime' it would be beneficial to revisit many of these risk assessments as they could well assist in formulating criteria for different courses of action that could be built into the contingency plans. The precise risk assessments to be carried out would depend on the particular critical issues identified in contingency planning, for example, how to deal with public access to the countryside. If quantitative data unavailable during the 2001 epidemic becomes available (see below) some of the previously qualitative assessments could be quantified, providing planners with more information on the relative importance of different risks.

The regular assessment of risk of disease incursion from different regions of the world can help to focus surveillance and protection activities and alert the authorities to emerging potential risks so that contingency plans can be updated accordingly. A project of this type is already set up by the VLA risk research department (see section 6.2.5). It should be understood, however, that although risk assessment exercises of this type may produce quantified estimates of the average annual risk of disease, they should not be used as forecasting tools. There are always uncertainties in these assessments and, in addition, the fact that an assessment may suggest that an outbreak may occur, on average, every 5 years would be no basis to expect an outbreak if 5 disease-free years have passed. As with models in general, the rule should be to use the quantitative output of such models to gain qualitative insights into the situations studied.

7.5 Experimental epidemiology

The very precise data needs of disease spread modelling and risk modelling, highlight the gaps remaining in knowledge about FMD epidemiology. Kitching (2002) comments that "*much still remains unknown about the natural history of FMD virus*". For example, Bartley

and others (2002) describe the shortcomings of currently available data on virus amounts and survival in excretions and on fomites. Such data are crucial to risk assessments and disease modelling. Much of the spread of disease in 2001 was attributed to 'local' spread mediated by fomites, and yet the precise mechanisms of spread are poorly understood.

Ferguson and others (2001a) point out the need for research to quantify how farm infectiousness depends on time from initial FMD infection. More specifically, Woolhouse (2002b) suggests that further studies are needed "*with particular attention to variability in the time course of viraemia, seroconversion and clinical signs, effects of different doses and routes of transmission, the time course of the response to vaccination and result of exposure to virus at different times post-vaccination. These experiments need to be carried out in different livestock species (including deer) and with different strains of virus. The emphasis throughout should be on quantifying rates of onward transmission of infection.*"

Work is being carried on at the Institute for Animal Health, Pirbright laboratory which focuses on the development of infectivity in the individual animal, and this work could contribute to answering the question about farm infectivity. In addition to this, there is a need for more experimental work aimed at providing quantitative data on viral excretion and transfer by various fomites.

The FMD models developed during 2001 are specific to the strain of virus causing that epidemic. It will be important to carry out comparative research on other strains of FMD virus so that the implications of strain variations (e.g. in tendency for airborne spread, species differences in susceptibility and infectivity etc.) for choice of control strategies can be explored in models.

The development of immunity after vaccination is another area where detailed quantitative data are needed for inclusion in models addressing the issue of vaccination.

Molecular epidemiology is an ongoing activity at the Institute for Animal Health Pirbright laboratory. This activity maintains a watch on the strains of virus circulating and will identify the emergence of new strains. Unfortunately genotype is no predictor of phenotype, so the characteristics of new strains, for example the tendency for airborne spread, cannot be predicted from the molecular work.

7.6 Quantitative epidemiology – analysis of real epidemics

Much can be learned from experience and the UK FMD epidemic of 2001 could prove to be a valuable experience. As much as possible should be learned from the 2001 data. The epidemic needs to be studied particularly in order to learn about the factors which determined the behaviour of the epidemic in the different affected areas. Quantitative epidemiological analysis can be used to identify risk factors for the spread of FMD between farms and develop hypotheses about disease spread which will be useful in future decision making. Not least, better understanding of risk factors would allow local control measures such as pre-emptive culling or local vaccination to be targeted and carried out in a prioritised way, resulting in the most efficient use of resources.

Of particular relevance to FMD contingency planning, it may be possible to identify key epidemiological parameters that are available in real-time and early in an epidemic, and have some value as predictors of the likely size of regional foci or whole epidemics. These parameters would be the triggers which could determine which of several predetermined choices of action might be taken, e.g. the choice of vaccination over culling only policies. Obvious examples might be the time taken to identify the primary case (as suggested by Leforban, 2002) or the number of regional foci at the beginning of the epidemic.

Modelling is only one tool in the range available to quantitative epidemiology, so many analytical approaches should be encouraged.

Further analysis of field data and individual case reports of the 2001 epidemic (final reports database) may provide improved assessments of the infection sources, links and routes of infection for IPs. **This analysis should preferably be carried out by those with first hand experience of the epidemic, and would be a logical task for a DEFRA epidemiology group.** Analysis should be aimed at allowing better quantification of mechanisms of spread between farms. This would allow more accurate 'epidemic trees' to be constructed for the epidemic. Such epidemic trees have the potential to provide great insights into the dynamics of the epidemic, see for example Haydon and others (2003).

7.7 Summary of requirements for specific DEFRA research

7.7.1 The policy making process and the integration of modelling within the process

Several of those consulted during the preparation of this report pointed out a lack of dialogue among scientific advisers, policy advisers and field staff within DEFRA and scientists from different disciplines outside DEFRA. Possible results of this might be that the wrong policies are evaluated, inappropriate questions are asked of models, data limitations and analytical constraints are misunderstood and conclusions are wrongly interpreted. **Current moves to make the contingency planning process more open and consultative are to be encouraged**.

Specifically on the use of modelling, the Royal Society Inquiry (Follet, 2002) has the following on page 70: "*If models are to be used to support decisions on control policies, DEFRA needs to develop a process that highlights their strengths and weaknesses for use in disease control*." An ideal way of developing an understanding of the strengths and weaknesses of models is to be involved in the model's development. In this way modelling becomes an integral part of decision making process – model development and use of the model should be an interactive process involving close collaboration between the model builders, subject matter experts, data managers, policy makers and their advisers. **DEFRA needs to make sure that it has staff with adequate skills, in particular quantitative epidemiology, of which modelling is just a part, so that they can better integrate scientific advice with policy making**. **The establishment of an epidemiology group has already been suggested as a means to address this need.**

The interaction can begin with the framing of the specific questions to be answered by the research. Both risk assessment models and disease models are constructed to answer specific questions and may not easily be able to be adapted to answer different questions. Model builders will have the best idea of how questions need to be framed in order to be answered by their models. So it would be useful to build into any research project an initial phase when the exact questions to be addressed by models are decided upon in a consultative process involving the modellers and the policy makers.

One of the difficulties encountered during 2001 was the lack of constructive dialogue between field veterinarians, FMD experts and modellers. Modelling groups should be multidisciplinary and where possible seek the input of different groups with knowledge of the particular problem.

While disease spread models, economic models and risk models provide useful information which contributes to the decision making process, there are frequently other factors pertinent to a decision which are not accounted for in models, e.g. social factors, political considerations etc.. **Models will therefore never provide complete and unequivocal**

answers to a decision making problem. Models should therefore be seen as tools for exploring some of the issues involved, but the criteria on which the decision will be based should include other issues not addressed by the model.

7.7.2 The main areas for epidemiological (including modelling) research

The following are suggested as specific issues for DEFRA to address:

* quantitative analyses of real FMD epidemics;
* 'basic' epidemiology of FMD – experimental studies.
* commissioning of work to address specific policy questions as an ongoing, reviewing and updating, contingency planning process, this to include economic and practical logistic considerations;
* development of an 'in-house' simulation model for use as part of an epidemic management system and for training exercises;
* development of other tools for 'wartime' epidemic management – e.g. logistics models, risk assessments, airborne spread models;

Finally, DEFRA should maintain an informed watching brief on 'outside' research. All research, but particular that based on modelling, requires careful assessment. The models developed during 2001 are still being used to explore aspects of FMD epidemiology and control (e.g. Keeling and others, 2003). Modelling methodology is also being developed and opportunities to use novel approaches to explore old issues may arise. Researchers whose work may be relevant to DEFRA policy should be invited to discuss their work in a forum including DEFRA and independent scientists. One suggestion would be to maintain a standing committee to regularly review FMD epidemiological research, including modelling, being carried out in the wider scientific community, so that, where possible the results of good research may be incorporated into policy. The suggested DEFRA epidemiology group could play a key role in coordinating and contributing to this activity.

8. A guide to 'good practice' when using models in decision making

8.1 Quality assurance of models:

If models are to be used in decision making with confidence, then verification and validation are key issues. Decision makers must be assured of the quality of models. Unfortunately there are no hard and fast rules regarding quality assurance of models. Guidelines have been broadly discussed in sections 3.6.4, 3.6.5 and 3.6.6. The important issues will be summarised here.

8.1.1 Verification

Verification of a model refers to internal checks to ensure that the 'mechanism' of the model (i.e. the mathematics and programming) are correct. This means that the mathematics and programming should correctly reproduce the mechanisms of the model, as conceived by the model's creators, in computerised form.

Such verification requires intimate knowledge of the model's processes and can only really be carried out by those with mathematical and programming expertise. It is often the case that the verification of a model has to be taken on trust, assuming that the model's creator has carefully checked things as the model was constructed. An independent review of the model's mechanisms might be carried out by another modeller, but under time constraints it is not easy to check every single process within a complex model.

8.1.2 Validation

Validation of a model refers to checking that a model is 'realistic'. An analogy may be helpful here. Think of viewing a film on a television set. The film is supposed to be a representation of a real situation. Validation would involve assessing how realistic the film is. To make this assessment does not require any knowledge of the electronics inside the television. Checking the wiring and electronics of the television is analogous to model *verification*, and requires an electrician (modeller). But anyone who has knowledge of the film's subject matter can *validate* the film. Problems with film validity may stem from internal verification problems (the television may be incorrectly wired such that colours are incorrectly rendered), or wrong assumptions may have been made by the film makers about the film's subject. Realism may be compromised if the film uses cartoon animation rather than live action, and part of the validation process would involve an assessment of whether the cartoon representation is adequate for the purposes of the film.

So, model validation should involve subject matter experts and decision makers who do not necessarily need to have modelling expertise. The discussion in section 3.6.5 highlighted three issues to be addressed:

1. Models should make biological sense:

   i) Subject matter experts should be happy that the conceptual framework of the model is biologically correct. In particular, all the assumptions and simplifications should be checked and agreed upon. For example, in a disease epidemic model, all of the known methods of disease transmission should be adequately accounted for in the model and the epidemiological processes of infection, incubation, and recovery should be adequately realised.

   ii) Subject matter experts should be happy that the model output can be explained in terms of current epidemiological knowledge. This is not to say that unexpected results automatically invalidate a model. It may be possible to interpret current

epidemiological knowledge in different ways and an unexpected model result may lead to novel interpretations of current knowledge.

2. Models should mimic real life:

   i) It seems an obvious statement that a valid model should be able to reproduce recorded reality. However, the fact that a disease model reproduces a recorded epidemic reliably does not necessarily prove validity. A model may contain internal errors within the conceptual framework which compensate, cancelling out the errors in a particular situation. This makes the checking of the conceptual framework of the model mentioned at 1.i) above essential.

3. Models should be fit for the use required of them:

   i) This is perhaps the most important issue of the three. There are no hard and fast rules about model validity. This discussion has used phrases such as, "disease transmission should be *adequately* accounted for". The word, "*adequately*" reflects the fact that simplification in models is inevitable. The final criterion of adequacy concerns utility of the model. This point is also made in the report of the Royal Society Inquiry, which says on page 70, "the quality of a model can be judged only in the context of the question that it sets out to address" (Follet, 2002). Provided the simplifications in the model do not compromise the value of the model outputs to the decision making process then the model can be judged as valid.

   ii) Decision makers and subject matter experts should jointly assess what information is critical in the decision to be taken. The utility of the model then depends on how well it can provide that information. The information provided should be judged for accuracy and precision. Accuracy depends on the validity issues already covered in points 1. and 2. above. The precision will depend on the inherent variability of the system it represents and also on the availability of precise data with which to quantify parameters in the model. The situation has already been described where stochastic models based on imprecise data may produce such a wide range of possible outcomes as to be useless in decision making.

   iii) Components within a model may be questionable from a scientific point of view, either because they are simplifications of reality or because the quantification of parameters has to be based in imperfect knowledge. If these components have little influence on the outputs of the model which are critical to the decision then the model is still useful and therefore 'valid'. **Sensitivity analysis is the process by which the influence of model components on the final outcomes (in terms of information provided for decision making) should be judged**.

It is important to realise that model validation depends on a weight of evidence, rather than a single proof. It is easier to invalidate a model than to validate it. That model output matches life and can be explained biologically does not prove that a model is valid, but if model output cannot be explained and does not match real life experience then it is likely to be invalid.

8.2 Checklist of issues to address and questions to ask when using models in decision making

1) The problem to be solved, or the decision to be supported by the model, must be clearly defined and the detail of information required from the model must be specified in advance. For example, if economic information is needed the model must be able to provide it or contribute to its provision. Models are constructed to serve a particular purpose and simplifications are made on the basis of the degree of complexity required to

fulfil the final goal. This means that 'general models' may be of limited use for particular decisions, hence the need to discuss particular decisions with modellers at the commissioning stage.

Discussions at this stage should cover both the requirements of the decision and the potential and limitations of a model to meet those requirements. It may even be concluded at this stage that alternative approaches to decision support, not involving modelling, are more appropriate.

Close collaboration between the decision makers, subject matter experts and model builders is important here.

2) As mentioned above, validation of models is difficult. Dent and Blackie (1979) point out that "*the process of gaining confidence in the model is a slowly emerging one over the period of model construction, through formal validation, to application of the model.*" This implies that for the decision makers to have maximum confidence in the model they, and their close advisers, should be involved in all of these steps.

   Close collaboration between the decision makers, subject matter experts and model builders is also important here.

   While the modellers may be experts in the field of mathematics and computing they should maintain a dialogue with subject matter experts throughout the process of model building so that the biological validity of the model becomes 'built-in'. Dialogue should also be maintained with those providing data for the model, so that the modellers and subject matter experts understand any limitations of the data.

   Maintaining such dialogue during model building should ensure model transparency, such that the simplifications, assumptions and limitations of the model do not become hidden to be overlooked during final validation and are fully appreciated by all involved in the decision.

   Since the process of model building can itself be a learning process there is much to be said for the idea that the decision makers and their advisers themselves should be involved with or interact with the process.

3) When the model is finally to be used in decision making a formal verification and validation process should be followed – see the discussion at 8.1 above.

   Verification requires the services of an expert in mathematical or computer simulation modelling.

   Validation can be carried out by subject matter experts in collaboration with the decision makers.

   Important in validation would be a full examination of all assumptions and simplifications made in the model. Where the values of parameters have been assumed or approximated **sensitivity analysis must be carried out to assess the influence of assumptions and simplifications on the final model outcome**.

   Prediction models have to either assume that model input parameters remain unchanged into the future, or change in an assumed way. The validity of such assumptions must be checked.

   Models require that input parameters be quantified. Very often the quantification of parameters has to be based on assumption or expert opinion. The validity of parameter quantification must be checked. Sometimes, parameters are 'fitted'. This means that the model outcome is assumed, or fixed according to some recorded reality, and parameters

are given values to 'fit' this outcome. A potential problem with this method is that several combinations of 'fitted' values may all produce the same desired outcome and there is no way of knowing which combination is biologically correct. Finding out how parameters are quantified is therefore an important part of the validation process.

4) It is extremely important that any interpretation of model output is made with reference to the assumptions and simplifications inherent in the model – **sensitivity analysis should be carried out to assess the potential influence of assumptions and simplifications on critical decision support information**.

5) When dealing with stochastic models the range of outcomes for each scenario should be considered, not simply an average or median outcome. This is best done using frequency distribution charts.

   It is important to appreciate that there are three distinct sources of variability of outcomes from stochastic models. Natural variability of biological parameters, the effect of chance and data uncertainty. If huge variability of outcome results from known natural variability and chance alone (i.e. data are as certain as reasonably possible) then the conclusion should be that the system is essentially unpredictable (chaotic) and therefore modelling may be of little help to decision making. However, modelling chaotic systems, such as the risk of FMD introduction to UK, for example, can be useful for certain decisions or policy development. Even though a meaningfully precise assessment of the expected frequency of introductions may be impossible, modelling can serve to highlight the factors which are most influential in the final outcome (through sensitivity analysis). this might lead to better targeting of protection and surveillance programmes.

   A model with a large amount of variability in the outcome due to data uncertainty is also of limited use in decision making but could become useful if more precise data could be obtained. A judgement would have to be made as to the relative benefit of obtaining that data, compared to supporting a decision in a different way (without modelling).

   The fact that a stochastic model predicts a range of possible 'futures', reflecting the unpredictability of real life, means that it must be used with care as a decision support tool. Decision makers must not rely on the model to make a decision for them but be prepared to use it as part of a process in which other factors, such as the 'riskiness' of a policy, are weighed.

   It is especially important that decision makers understand that the range of outcomes predicted by a stochastic model may also be, at least in part, a reflection of data uncertainty. This again means that models cannot always be expected to provide definitive guidance in decision making. In the past decisions have often been made in the face of imperfect data, and the skills involved in this process must not be forgotten – models must not be seen as a tool to produce knowledge without data.

6) Bearing in mind issues raised above, decision makers need to be prepared in advance for the probability that models will come up with imprecise results which are also conditional on assumptions about uncertain input data items. Sensitivity analysis may suggest that the model result is sensitive to one or more uncertain assumption. Results may therefore be presented for a range of scenarios based on different assumptions, without any indication of which assumption is likely to be correct.

   Decision makers require some sort of framework within which model results can be combined with other quantitative and qualitative criteria to guide the decision. Development of such a framework may be a useful topic for future research.

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10. Appendix 1: People consulted

The following people were consulted with during the course of this work:

Name	Date of meeting
Dr. Marcus Hutber, EpiVet	November 21st 2002
Prof. John Wilesmith, VLA	January 22nd 2003
Mr. Ed Van Klink, Dutch Ministry of Agriculture	January 24th 2003
Prof. Neil Ferguson, Imperial College	February 18th 2003
Mr. Fred Landeg, DEFRA	February 18th 2003
Dr. Rowland Kao, University of Oxford	February 20th 2003
Dr. Graham Medley Dr. Laura Green Dr. Matt Keeling, University of Warwick	February 24th 2003
Mr. John Gloster, UK Met Office	February 27th 2003
Dr. Soren Alexandersen, Dr. David Paton, Pirbright Laboratory, IAH	February 27th 2003
Dr. Marion Wooldridge, Risk Research, VLA	March 14th 2003
Prof. Roger Morris, Massey University, NZ	March 26th 2003 (by telephone)
Prof. Mark Woolhouse, University of Edinburgh	by e-mail – see correspondence at Appendix 3
Dr. Mike Thrusfield, University of Edinburgh	by e-mail
Dr. Mirjam Nielen, Wageningen Agricultural University, The Netherlands	by e-mail
Dr. Sunetra Gupta, University of Oxford	by e-mail

11. Appendix 2: Veterinary risk assessments

Risk assessments carried out for DEFRA during the 2001 FMD epidemic in UK. (source of list: http://www.defra.gov.uk/footandmouth/disease/risks/index.htm)

11.1 Numbered Risk Assessments

1. Moving livestock directly from farm a to farm b
2. Moving livestock (sheep, cattle, pigs) carcases from their place of slaughter to a different place for disposal (22 March)
3. Bulk Feed Delivery to Form D premises by lorry (22 March)
4. Opening footpaths to the public Revised (January 2002)
5. Feral Deer on infected premises (22 March)
6. Moving sheep to an alternative place of slaughter, and from there to a further place for disposal (26 March)
7. Feral wild boar and domestic livestock (9 April)
8. Meat and waste products distribution (9 April)
9. Opening deer parks to the public (31 May)
10. Horse racing meetings (January 2002)
11. Farm visits by DEFRA personnel (10 October)
12. Specified equestrian events? (January 2002)
13. Moving hay and straw onto a farm (26 April)
14. Official equestrian events on non-agricultural land (January 2002)
15. Sheep shearing (revised) (07 February 2002)
16. Opening farm shops (4 June)
17. Car boot sales on agricultural land (31 May)
18. Collection and transport of bull semen and artificial insemination of cows (6 June)
19. Grouse shooting (16 July)
20. Sheep dipping (revised) (07 February 2002)
21. Vaccination of TSE experimental animals (26 July)
22. "Pick Your Own" operations on farms (1 August)
23. Shooting Pheasants and Partridge (6 August)
24. Wildfowling (24 August)
25. Falconry (15 November 2001)
26. Hunting with dogs (revised) (07 February 2002)
27. The risk of causing new outbreaks of FMD if the wildlife unit resumes work on the randomised Badger Culling Trial? (14 November)
28. What is the risk of causing new outbreaks of FMD if livestock are sold in markets? (January 2002)

11.2 Un-numbered Risk Assessments

* Preliminary discussion of the risk assessment for the resumption of hunting with dogs.(14 October)
* Autumn movements (2 August)
* Transmission of Foot and Mouth Disease by Birds. (23 April)
* Assessment of risk due to BSE infectivity from burning cattle (revised 7 April)
* Addendum to Assessment of risk due to BSE infectivity from burning cattle (24 May)

12. Appendix 3: Specific questions and responses on modelling issues; Professor Mark Woolhouse

Dear Professor Woolhouse,

Here are the specific questions I would appreciate your feedback on, if possible: (Professor Woolhouse's written responses are reproduced in Arial font):

1. Modelling and decision making during the 2001 epidemic:
   a. What were the key items of field data required to make the models? Were these data available in time and of sufficient quality (accuracy and completeness)?
   b. In case there was a shortfall in data required for the models, did this lead to limitations in the value of the models for decision making on policy – e.g. the decision that culling of contiguous premises was essential?
   c. How were any model limitations taken account of in the decision making process? Do you think sufficient sensitivity analysis of the model outputs to uncertain inputs was carried out? Do you think DEFRA/other govt. bodies possessed and used staff with the right types and level of skills to appreciate the limitations of modelling at that time?
   d. Do you have any specific suggestions as to how the use of models in the decision making process could have been improved?

1. This section refers to modelling and decision making. These are two separate activities and, as I understand it, remained separate during the 2001 epidemic. Models were used as part of the advice given to both the Chief Veterinary Officer and the Chief Scientific Advisor, who passed this advice on as they saw fit. None of my immediate colleagues, nor myself, was present at any 'decision-making' committees at any stage. These comments are therefore confined to modelling activities.
   - The specific aspect queried, regarding the 'contiguous cull', was found at the time to be robust both to modelling approach (four different models were being used at one stage) and to uncertainties in the data (the effects of both noise and bias were extensively explored, often specifically to address questions raised from the field). Subsequent analysis and, indeed, independent analyses carried out even before 2001, confirm the potential effectiveness of this measure. Contrary opinions have been expressed but, so far, we are aware of none which is 'evidence-based', i.e. follows from a quantitative analysis of field data. A particular concern is criticism based on invalid analyses published without peer-review (e.g. Vet. Rec. 10/11/01, p600), which does nothing to advance what is a necessary and important scientific debate.
   - That said, there were identifiable deficiencies in the data available, especially in the census data describing the distribution of livestock and livestock farms (see Supplement to Keeling and others, 2003). For this reason, it was advised that while models could be used for strategic planning they could not be used for local decision making (e.g. which farms were 'contiguous' in practice); hence the importance of local input for the implementation of control measures on the ground.
   - Another practical problem was that, although data on infected premises was made available promptly (often within 24-48 hours) data on premises included in the extended culls took longer to appear and, for the 'welfare' culls may still be incomplete even now. This underlines the importance of comprehensive 'real time' record keeping to keep track of what is actually going on on the ground.
   - It is unclear what is meant by the 'limitations of modelling' in this context. The strengths and weaknesses of the various models were extensively discussed at the time and continue to be discussed. In the event, the outcome was that the models correctly indicated that the epidemic was 'out of control' in mid-March, provided accurate short-term predictions throughout the epidemic, and have since proved capable of reproducing the epidemic with considerable accuracy (allowing for the actual rather than intended

implementation of culling effort). All of these outputs proved useful to senior advisors and decision makers.

2. Current modelling. I have seen the note describing your current project, which you recently supplied to the DEFRA Science Group. This has among its stated aims/benefits, "the results will inform policy makers regarding the control of FMD…" and, "to develop … computer model … which will inform the design of disease control policies and significantly improve the management of individual disease outbreaks."
   a. Has there been any dialogue with DEFRA regarding any particular control policies they may be seeking guidance on, or is your aim to explore novel control strategies with the model which may then be suggested to DEFRA?
   b. Whilst development of the model is being progressed independently of DEFRA, would you envisage working more closely with DEFRA, using the model to address specific policy questions in future? If so, would you envisage that as part of this process the model itself would be 'opened up' for critical review, so that its limitations, sensitivities etc. could be fully appreciated by decision makers and their advisors?
   c. Do you envisage the model being used as a tactical tool in any future FMD outbreak? If so, how would this be managed – should DEFRA be training staff in its use or would the use of the model be supplied as an 'outside service' in case of need?
   If the use of the model in an outbreak is foreseen, is there need for supporting work to make this achievable – e.g. development of specific databases, development of new disease data management systems to be in place during outbreaks?

2. This set of questions refers to the Wellcome Trust-funded FMD modelling project with which we are currently engaged.
   - The results of this work will be published in peer-reviewed scientific journals and, as such, will be generally available to DEFRA. Should DEFRA, or any other agency, wish more detailed briefings and discussion regarding the results then we will be happy to provide these. We have willingly agreed to keep DEFRA informed regarding progress with this project.
   - The major difference between this work and a project aimed at specific policy questions is that we will not be limited by current policy options. For example, we will consider in some detail the potential of prophylactic vaccination to prevent FMD epidemics, even though this is not a policy option within the UK at the present time.
   - Translation of the models developed during our project into tactical tools for use during future FMD epidemics would require significant additional investment.
   - We emphasize that there will never be a 'definitive' model of FMD. Different modelling approaches have different strengths and weaknesses and it is generally advisable to have more than one model operating in parallel.

3. Other required research:
   a. Would you say that the basic model building methodology is already available to produce models of optimal complexity, accuracy, precision etc. for decision support roles – or is there still need for research/development in the basics of model building?
   b. It would seem an obvious statement that there is always a need for accurate data and good knowledge in order to produce accurate model output. Would you identify any particular aspects of FMD epidemiology which require research in order to provide better model input?

3. I agree strongly with the suggestion that model building methodology requires further development. At present, many modelling exercises are more or less ad hoc. This does not in itself negate their value, but the absence of a recognised methodological framework hampers both model development and evaluation. This is an issue which will be addressed in future work.

   Particular aspects of FMD epdemiology which require attention are discussed at length in the Royal Society report on 'Infectious Diseases of Livestock'. Topics of particular relevance to my own work include:

- further quantification of risk factors for the spread of FMD between farms (noting that susceptibility is only half the story; we also need information on risk factors for infectiousness)
- quantitative information on livestock movement patterns;
- quantitative experimental information on the short term impact of vaccination on livestock exposed shortly afterwards (and shortly before), again with emphasis on the potential for transmission.

Mark Woolhouse
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Thank you for your time,

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