A review of foot-and-mouth disease with special consideration for the clinical and epidemiological factors relevant to predictive modelling of the disease

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Abstract

Modelling the epidemiology of foot-and-mouth disease (FMD) has been undertaken since the early 1970s. We review here clinical factors and modelling procedures that have been used in the past, differentiating between those that have proved to be more relevant in controlling FMD epidemics, and those that have showed less significance. During the 2001 UK FMD epidemic, many previously developed FMD models were available for consideration and use.

Accurate epidemiological models can become useful tools for determining relevant control policies for different scenarios and, conversely, inaccurate models may become an abuse for disease control. Inaccuracy presents two opposing difficulties. Firstly, too much control (in terms of animal slaughter for 2001) would negatively impact the farming community for many subsequent years, whilst too little control would permit an epidemic to persist. Accuracy however, presents the optimal permutation of control measures that could be implemented for a given set of conditions, and is a prerequisite to boosting public confidence in the use of epidemiological models for future epidemics.

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1. Introduction

This review is presented as an interpretation of the 2001 foot-and-mouth disease (FMD) epidemic in the United Kingdom based upon findings that are available within the relevant literature. These findings take the form of both clinical and epidemiological factors that should be used to construct accurate predictive models of the disease. Initially the relevant clinical findings are examined, followed by a review of the key epidemiological factors, none of which should be considered in isolation when modelling FMD.

Between the 20th February and 30th September 2001, over four million animals were slaughtered in the UK in support of the programme to control an epidemic of FMD. In addition, a further 2.5 million animals were slaughtered on welfare grounds. Two thousand and thirty animal holdings were officially declared infected (four in Northern Ireland), and 8131 identified as dangerous contact premises (including 3369 contiguous premises) and subjected to pre-emptive culling (Anderson, 2002).
The total cost of the epidemic has not been fully quantified, but has been estimated at $4.7 billion to the food and farming sectors and another $4.5 billion to the leisure and tourism sector – plus $3 billion of other indirect costs (Thompson et al., 2002). Surprisingly, the estimated overall effect on the gross domestic product of the UK economy for 2001 was a reduction of less than 0.2% (Thompson et al., 2002). The magnitude of these figures alone – even without consideration of the major social effects the epidemic and the measures employed to bring it under control had on the rural communities affected – initiated a series of government inquiries into an alternative response to any future epidemics of FMD, or similar, highly infectious animal diseases.

The Royal Society Inquiry (Follet, 2002) addressed disease control strategies, while the “Lessons Learned” inquiry (Anderson, 2002) made recommendations for controlling future animal disease epidemics based upon what happened in the 2001 epidemic. Additionally, the inquiry under Curry (2002) considered the future of food and farming. It may be possible to determine whether the extensive slaughter that took place, and its consequential effects on the farming and tourist industries, were necessary. Could effective control have been achieved by following previously proven epidemiological principles, resulting in fewer economic and social costs?

2. Foot-and-mouth disease

2.1. The virus

Foot-and-mouth disease is a highly contagious disease of cloven-hoofed animals, in particular cattle, sheep, pigs, goats and domestic buffalo, as well as wild ruminants such as deer. It is characterised by fever and vesicles on the mouth, feet and udder of lactating ruminants. FMD is caused by strains of aphthovirus, in the family Picornaviridae, of which there are seven immunologically distinct serotypes, namely O, A, C, SAT1, SAT2, SAT3 and ASIA1. Animals that have recovered from infection with a strain of one serotype remain fully susceptible to infection with strains of the other six.

Within each serotype there are a substantial number of strains showing a variable degree of antigenic diversity. This is particularly evident within the A serotype, in which vaccines prepared using one strain of serotype A virus may provide almost no immunity against other serotype A strains of virus. The genome of the virus contains a single strand of positive-sense RNA, of approximately 8.2 Kb, and in common with other RNA viruses has a high mutation rate, which together with the apparent ‘plasticity’ of the major neutralising sites on its surface, explains a high antigenic variability (Domingo et al., 1985).

2.2. The disease

The clinical severity of FMD varies with the strain of virus, as well as the infecting dose, the species and individual susceptibility of the host. It is clinically most apparent in high-yielding dairy cattle and intensively-reared pigs, in which the lesions can be severe and debilitating. In adult sheep and goats, FMD is frequently only a mild disease, with transitory clinical signs which can easily be missed by the stockman or veterinarian, or confused with other diseases presenting similar lesions (De la Rua et al., 2001; Watson, 2002). However, even in some breeds of cattle, FMD can also be clinically difficult to recognise because of the mild appearance of the disease (Kitching, 2002a).

The virus replicates to a high titre in epithelial cells, particularly those undergoing repair, and consequently lesions may also be seen on the hocks or elbows of pigs being housed on concrete flooring where damage to legs is common. FMD virus will also destroy the replicating myocardial cells of young susceptible species, resulting in high mortality from heart failure (Kitching and Hughes, 2002; Kitching and Alexander, 2002).

2.3. Transmission

The most common method of spread of FMD virus is by contact between an infected and a susceptible animal. An infected animal produces a large amount of virus in exhaled breath, whilst cattle and sheep are particularly susceptible to infection by the aerosol route, requiring as little as 10 Tissue Culture Infective Doses 50 (TCID50). Pigs are considerably less susceptible to aerosol infection, possibly requiring as much as 6000 TCID50 (Alexandersen et al., 2002). However, all excretions and secretions from an infected animal will contain virus, and infection can occur either across damaged epithelium or orally. Although less susceptible than ruminants to aerosol infection, pigs produce up to 3000 times more aerosol virus per day during the acute stage of infection. Under the appropriate weather conditions, aerosol virus can potentially spread a considerable distance, particularly if the source is a large infected pig herd.

In 1981, aerosol virus spread from Brittany in France from infected pigs, across the Island of Jersey (where it infected cattle) as far as the Isle of Wight off the coast of southern England: this was a distance of over 250 km (Donaldson et al., 1982). Knowing the number and species of animals infected, together with the weather conditions at the time of virus excretion, it is possible to predict a likely dispersion of aerosol virus. The animals at risk are usually cattle since they are especially suscep-
tible to infection by the aerosol route, and because they hold a higher respiratory volume than sheep.

An aerosol dispersion model had been used to predict the Isle of Wight outbreak (Donaldson et al., 1982). One dairy herd was infected, and following clinical diagnosis was slaughtered. A large pig herd was situated topographically adjacent to the cattle, and while predictions of the aerosol spread from the dairy herd had indicated that there would be insufficient virus to infect animals on the English mainland, the model also predicted that if the pig herd was infected, it would generate a plume of FMD virus that would cover a large area of southern England. Hence although the pigs were showing no clinical disease, it was decided to cull the herd because of the possible consequences of these animals being infected. When samples from the pig herd were tested for evidence of FMD virus, all were negative, yet it was still considered to have been a useful decision to employ slaughter, rather than have risked further spread. Such is the concept of pre-emptive slaughter that was implemented extensively during the 2001 epidemic.

When an animal infected with FMD virus is slaughtered, all meat and organs will contain FMD virus. Where the carcass is frozen prior to rigor mortis the virus will survive, and should any of the infected products be fed to a susceptible species (e.g., pigs) an outbreak of FMD would be likely. There remain numerous examples of FMD outbreaks initiated through ingestion of FMD virus-infected products by pigs (Kitching, 1998); hence countries frequently maintain strict regulations concerning the heat treatment of pig swill.

Foot-and-mouth disease virus is particularly susceptible to inactivation outside its host, for example by exposure to high temperatures, drying or where the pH is <6 or >10. When a carcass is permitted to mature after slaughter (at 2°C for 24 h), the lactic acid build-up will kill any virus in the meat by reducing the pH to <6. No reduction in pH occurs in the glands or bone marrow; however, with certain safeguards (in addition to allowing the carcass to remain at 2°C for 24 h (OIE, 2001a)), it is possible to safely import meat off the bone from countries where FMD is present. Milk from infected animals will also contain large quantities of live virus, sufficient to infect calves or pigs (if the milk is inadequately heat-treated or not diluted by uninfected milk). Semen from infected bulls and ova from infected cows may also be contaminated with live virus.

It is possible for virus to survive days or weeks in the environment if kept moist and at neutral pH. Personnel handling infected animals may become contaminated on hands, clothes or in nasal passages with live FMD virus, and mechanically carry virus to susceptible animals by close contact. Veterinary surgical instruments or artificial insemination equipment may likewise become contaminated and transmit the infection with improper cleansing and sterilisation; this occurred in Denmark (1982) and Italy (1993), respectively. Vehicles can carry infected material between farms, although there is the necessity that the material makes direct contact with a susceptible animal. Milk tankers were also associated with the spread of virus during the 1967/1968 epidemic: vehicles transporting infected milk vented tanks during refilling, thereby creating an aerosol of virus-infected milk droplets. Milk tankers were similarly implicated in the spread of disease during the 2001 epidemic (Gibbens et al., 2001).

Cattle, sheep, goats and other ruminant species that have recovered from FMD virus infection, as well as those that have been vaccinated against FMD and subsequently exposed to live virus, may remain infected for a variable period of time. Cattle may carry the virus for over three years, sheep for up to nine months and goats for up to four months in the epithelial cells of the pharynx, particularly the dorsal soft palate (Zhang and Kitching, 2001; Kitching, 2002b). These carrier animals hold a high level of neutralizing antibody within their sera and yet retain the live virus, which is detectable in scrapings taken from the pharynx (probang sampling). The mechanism by which the virus is protected from the host immune response is not understood (Salt, 1993). Nor is it known what risk these carrier animals represent in terms of causing new outbreaks of FMD. However, carriers following contact with live virus are not an exception, occurring in over 50% of exposed cattle and sheep, where a carrier is defined by the recovery of live virus from the pharynx at 28+ days post infection.

Although virus-laden oropharyngeal fluid from carrier animals can infect cattle and pigs experimentally (Van Bekkum, 1973), it has not been possible experimentally to show transmission from a bovine carrier animal to an in-contact susceptible animal. However there is circumstantial field evidence that carriers may initiate a new outbreak (Kitching, 2002b), notably in outbreaks in Zimbabwe due to the SAT2 serotype (Thomson, 1996). In spite of the uncertain role that carrier animals play, the existence of animals carrying live virus combined with a difficulty in reliably identifying them, prohibits the international trade of susceptible animals that have recovered from, or have been vaccinated against FMD. This includes porcine species that do not become carriers but do carry antibodies to FMD virus.

2.4. Diagnosis

Definitive diagnosis of FMD relies upon the identification and isolation of live FMD virus, and this is usually a requirement at the start of an outbreak in a country or region previously free of disease. Once the disease has started to spread, diagnosis may be based upon clinical signs alone, or on the basis of a known link to an existing infected premise (IP). There are a number
of diagnostic tests recommended for use in support of clinical diagnosis and in tracing the spread of disease, either to detect live virus, virus antigen or viral genome, or to detect serological evidence of the presence of the virus (OIE, 2001b). The perceived importance of the carrier animal, and the difficulty of reliably detecting these animals, led to the development of tests to distinguish animals that were antibody-positive through vaccination, from those that were antibody-positive following infection (Kitching, 2002b).

The vaccine against FMD is produced from a suspension of whole virus, inactivated with aziridine, and mixed with either an oil or aluminium hydroxide/saponin adjuvant. Since there is no replication of live virus in the vaccinated animal, there is likewise no expression of the eight viral non-structural proteins (NSP). Infected animals support live virus replication and expression of the NSP, and consequently recovered animals develop antibodies not only to the structural proteins of the viral capsid, but also antibodies to the NSP. The presence of these NSP antibodies, in particular to the L, 2C, 3A, 3B, 3C and 3D indicate that the animal has recovered from infection.

Although, the 3D NSP may contaminate the dead vaccine sufficient to induce antibodies to this protein, tests designed to detect antibodies to 2C or the polypeptide 3ABC are reliable indicators of previous infection. These latter two tests have improved the potential for identifying carrier animals, but they are not 100% sensitive in discovering the vaccinated animal that has had contact with live virus and become a carrier. Some of these animals, because of their immune status following vaccination, do not allow sufficient viral replication to induce detectable antibodies to NSP, and yet they are just as likely to become carriers as the animal that has recovered from frank disease. Until there is a test for carriers that will approach full diagnostic sensitivity, they will remain a constraint to trade (Kitching, 2002b).

2.5. Control and vaccination

Control of FMD in a country such as the UK, which had been free of the disease for several decades, is initially implemented by slaughter of all infected and susceptible in-contact animals, with a ban on movement of susceptible animals, disinfection in and around IPs and intense surveillance for evidence of further spread. Concurrently an epidemiological team of veterinarians with experience of FMD are required to examine the animals on the first IP. By estimating the age of clinical lesions observed on the infected animals, and inspecting the movement records of animals coming onto and off the farm, the team may advise as to the possible origin and potential spread of the outbreak.

The first identified case (index IP) during the 2001 UK epidemic was found in an abattoir in Essex, and while it was originally perceived that the infected pigs had carried the disease with them, an inspection of their originating farms showed no evidence of FMD. It therefore became apparent that the pigs were infected while awaiting slaughter, and it was necessary to back trace pigs that had been delivered and slaughtered during the previous week.

The primary case was identified as a farm of 500 adult sows and boars close to Newcastle, at Heddon-on-the-Wall. The pigs were fed waste food collected from restaurants and other sources in the area, and although there was a legal requirement that all waste food should first be boiled before feeding to pigs, heat treatment had not always been performed. Most of the pigs showed evidence of clinical lesions over seven days of age, some up to 12 days, indicating that the virus could have been present on the farm for up to three weeks. The origin of the infected food was not identified, but following closer inspection of container traffic coming into the UK, it was clear that an extensive illegal trade had existed in pork products from the Far East (DEFRA, 2002).

The FMD virus causing the epidemic was identified as a strain of the serotype O PanAsia topotype (Knowles et al., 2001), which during the previous year had caused outbreaks in South Korea (free of FMD since 1934) and Japan (free since 1908). It had also spread into South Africa by means of infected food collected from a ship in Durban harbour, which had then been fed to pigs; serotype O had never before been identified in this country. However, for none of these epidemics had there been evidence of significant aerosol spread of the virus, and consistent with this observation, the primary case in the UK (involving 500 adult pigs) caused only a few further outbreaks as a consequence of aerosol transmission – initial models of the predicted spread (using data for aerosol spread of other strains of FMD virus) suggested sufficient virus could have been produced to infect animals on the coast of Denmark (Mikkelsen et al., 2003).

Unfortunately, one of the nearby farms that had been infected (close to the primary case) sent sheep through two markets at Longtown and Hexham in the north of England, and as far south as Devon: potentially 25,000 sheep may have been infected in the Longtown market (Anderson, 2002). The movement of infected sheep established minimally eight separate foci throughout England, Wales and Scotland, prior to the total ban on movement of susceptible animals that was imposed on the 23rd February (three days after the initial diagnosis). However because of the occult nature of FMD in sheep, the magnitude of the spread was not immediately realised.

The UK maintains a bank of FMD virus antigen which may be rapidly formulated into FMD vaccine at its storage site in the Institute for Animal Health, Pirbright (IAH). Half a million doses of high potency vaccine (suitable for use against the PanAsia strain)
could have been made available within a few days; in addition a further five million doses were accessible from the EU FMD virus antigen bank held in France and Italy. The problem would have been where to vaccinate, since by the time it was realised that FMD was in the country, the epidemic was already widespread, and the likelihood of containment within a ring of vaccinated animals (as used by the Netherlands) was unrealistic.

The veterinary resources of the Ministry of Agriculture, Fisheries and Food (MAFF) were quickly consumed in tracing IPs and other salient tasks. Moreover the requirement that veterinary personnel could not visit another farm for three days following contact with infected animals further constrained their efforts.

A movement ban was in place, and it was known that the virus did not spread significantly as an aerosol, particularly from infected sheep (Donaldson et al., 2001). Additionally the farming community was alerted for evidence of infection, and it remains likely that the size and distribution of the epidemic would have subsequently been contained (with the virus eliminated) without the excessive slaughter that took place. Such had been the situation during the 1967/68 epidemic. On 21st March, Professor Roy Anderson (of Imperial College, London) stated that the epidemic was not under control (BBC Newsnight: reported in The Independent, 2001). This statement was based upon a model of inter-herd FMD spread that was constructed during the epidemic but had not been validated, particularly for the PanAsia strain.

2.6. Predictive FMD modelling and effective control measures

Since epidemiological models may be fitted to historical data (essentially ‘re-running the past’) and when correctly formulated can simulate the future, they may be used as tutoring tools to assist in answering epidemiological problems: a knowledge of the biology for given diseases is also required. However, although veterinary epidemiological expertise has been available in the UK for several decades, a recent tendency for some modelling has been to skew perception towards the importance of mathematics, yet away from the reality (even constraints) of practical disease control. Lorenz (1977) has cited such a case as the specialist’s tendency to narrowly focus upon areas of interest. This in turn may engender not only a confidence in models that have been inappropriately constructed but also reliance upon such models as a substitute for analysis of field data (The Economist, 2002). Thus, whilst the predictive capabilities of biomathematical modelling may increase both the number and novelty of effective disease control measures that are available, models can also be misused by replacing previously evaluated and effective disease control strategies, with a stronger yet unnecessary form of control.

A number of objective FMD modelling reviews have already appeared in the literature, assessing the mathematical and predictive validity of the FMD models constructed during the 2001 UK epidemic (Green and Medley, 2002; Haywood and Haywood, 2002; Kao, 2002; Lusmore, 2002). Taken together, it is now possible to:

1. Review the predictive accuracy of FMD modelling solutions that were available prior to the 2001 epidemic,
2. Examine the events of the 2001 epidemic, in particular the sub-clinical (undetected) disease that determined its distribution prior to its diagnosis, and before control measures or the new FMD models were introduced, and
3. Assess empirical data to show that the previous experience (including the use of models) of MAFF, Veterinary Laboratories Agency (VLA) and IAH relating to FMD epidemics, had been effective in maximising balanced control of FMD epidemics. Conversely, the introduction of some newly constructed FMD models during the 2001 epidemic resulted in the culling of more than 989 clean herds (out of 1876 tested at IAH by May 2001) – an excess of 53% in terms of disease control measures beyond the removal of animals on (suspected) IPs (R.P. Kitching, unpublished data).

3. FMD modelling prior to the 2001 UK epidemic

Generally, epidemiological models have been constructed and used for a variety of reasons, but the most effective uses remain:

1. Predicting the duration, animal numbers involved (or prevalence) and geographical range (or the focus/foci) of an epidemic.
2. Identification of control measures that will effectively abate and rapidly control any given epidemic.

The starting point for any model of FMD should be at the farm level, focusing on intra-herd transmission (Hutber, 2001a). There are a number of reasons to ensure that intra-herd transmission should form the base of an inter-herd model:

(i) Contact spread has been the predominant mode of transmission at the farm level (Kitching and Hutber, 2002). This similarly applied to inter-herd spread during the 2001 UK epidemic (151 of the initially reported 160 outbreaks recorded on the
MAFF website were due to contact transmission: additional data provided by Marion Wooldridge, as well as for both hot and more temperate, humid climates such as the UK (Hutber, 2001b).

(ii) First day incidence (FDI) is a within-herd parameter based upon contact spread, that accurately predicts the final percentage of a herd (prevalence) that will become infected (Hutber and Kitching, 1996; Hutber, 2002); FDI can also be termed FDP or first day prevalence, since the parameter may at times include animals with aging lesions.

(iii) First fortnight incidence (FFI) is an inter-herd parameter, extending predictive capabilities (for prevalence and duration) beyond the farm level to regional and national foci (Hutber, 2001b). Significantly both FDI and FFI incorporate sub-clinical disease, applying to totally susceptible (unvaccinated) as well as vaccinated herds (Hutber et al., 1999). First day incidence and FFI will usually be measured accurately in that they can easily be monitored at the start of an epidemic, when the number of outbreaks is low, and manpower resources are less in demand. First day incidence and FFI are not only directly measurable, but also remove the need to assume, average or to estimate unknown, non-measurable values.

(iv) Typical unknown values (since they are clinical, highly variable, or often in a pre-defined range that requires averaging) include species susceptibility, infectious period, viral excretion levels and incubation period (Ferguson et al., 2001). The more central that unknown values are as input parameters to a model, the more probable that the model will run inaccurately. Accuracy can be mimicked (despite the estimates of the unknown values), by the use of a number of weighted values to fit the model to a particular scenario (Howard and Donnelly, 2000). Mimicked accuracy however, becomes a liability as the model overestimates or underestimates the appropriate level of disease control (such as culling), and exerts an unnecessary economic and logistical drain upon the farming industry and control authorities.

(v) Despite the culling of livestock from an IP, it remains within the interests of the farming community to reduce virus excretion from any given IP, thereby minimising the risk of disease spread to neighbouring (contiguous) premises (CPs), or to dangerous contact (DC) farms (which may or may not be contiguous). Only 13 of the 187 outbreaks recorded at VLA Starcross for South-West England (the second largest focus during the 2001 UK epidemic), were detected by veterinary surveillance (T. Crawshaw, personal communication) whilst the majority (153) were reported by farmers. This indicated that the farming community was continuing with control measures despite personal losses, in the long term interest of disease eradication. Biosecurity and farm management techniques have been found to abate FMD transmission (Hutber and Kitching, 2000), and can be implemented preventatively or as a means of regional control. Management techniques include:

(I) Creation of spatial bottlenecks between livestock pens or blocks of pens (by strategically removing or relocating animals).

(II) Use of unused housing for livestock.

(III) Re-use of animal housing to prioritise the protection of species shedding most virus.

(IV) Re-use of animal housing to prioritise the protection of more vulnerable age groups within bovine herds (in-calf heifers >4–16 month young stock >first/second lactation cattle >third/fourth/fifth lactation cattle >zero–three month calves >dry cows).

(V) Removal of animal access to the back of buildings, where air flow carries viral plumes.

(VI) Use of physical or natural barriers between livestock and the direction of known IPs, and movement of livestock to farm areas at the greatest distance from the direction of known IPs.

The mathematical algorithms for FMD models should not become cumbersome. Concise algorithms ensure that the complexity of the epidemiology does not have to be simplified (nor the accuracy compromised) to maintain complex mathematics. For example, conventional state-transition methodology within predictive simulation models, can be condensed through the use of vectors. Vector-transition models combine several factors such as immunity levels and disease states, within a single vector (Hutber and Kitching, 1996; Keeling et al., 2001) where only a small number of vectors are required to run the model. Biomathematical models (James and Rossiter, 1989) use mathematics only to highlight the clinical and epidemiological aspects of an epidemic, whereas mathematical models (Ferguson et al., 2001; Howard and Donnelly, 2000) highlight the mathematical aspects of their proposals.

Prior to 2001, there were a number of FMD models and modelling related papers in the literature that added significant advances to the way in which relevant institutions understood the epidemiology of FMD. These included economic FMD modelling (Carpenter and Thieme, 1979; Teclaw, 1979; Thieme, 1982; Berentsten et al., 1992), modelling FMD vaccination programmes (Hingley, 1985; Cleland et al., 1993), regional FMD models (Pech and Hone, 1988; Garner, 1992), spatial FMD modelling (Hugh-Jones, 1976; Pech and McIroy, 1990), modelling antigenic drift (Hugh-Jones, 1986), FMD model simulations (Tinline, 1972; Woods, 1974; Miller, 1976) and tutorial FMD modelling (Baldock,
1992; Moutou and Durand, 1994). Hence FMD models were not novel prior to 2001. However, it was recognized before 2001 that models carried inherent strengths and weaknesses. Their strengths were usually found within the areas of investigation listed above, although more generally, significant advances were also made in other areas, such as the development of the modelling methodologies employed.

One of the areas of weakness was human error. In 1996, Woolhouse and his colleagues proposed a model that concluded vaccination was inappropriate amongst intensively farmed dairy herds, since they stated the critical inter-vaccination period (CIP) was too short (Woolhouse et al., 1996). Subsequently it was pointed out (Hutter et al., 1998) that the infected animals had not been isolated from the herd, therefore the transmission rate was not at the (high) levels as modelled by Woolhouse and his co-workers, and the CIP was longer than their (low) estimates. The appropriate CIP was shown to be 75 days with the vaccine efficacy at 81–98%. A further potential area of weakness for models is epidemiological change.

Following the 1981 FMD outbreak on the Isle of Wight, the IAH prepared a model (EpiMan) to predict wind borne spread of FMD virus (Sanson et al., 1999): NAME (Gloster et al., 2001) and ‘Rimpuff’ (Sorensen et al., 2000) were similar models produced for the same purpose. However, whilst these models successfully simulated an aerosol plume affecting nine of the initial 160 outbreaks in the 2001 UK epidemic, the remaining 151 outbreaks were initiated by various means of contact spread (physical proximity of livestock, fomites, etc., Marion Wooldridge, personal communication).

The likely reason for the limited relevance of these models was the species involved. Pigs can excrete sufficient levels of FMD virus to create infective plumes, as indicated by the source herds (porcine) for both the 1981 outbreak and the 2001 epidemic. Beyond the source herd however (during 2001), the majority of IPs had farmed sheep (also cattle) rather than pigs. Moreover, experimental work (from the IAH) later indicated that the 2001 PanAsia strain was excreted only in relation to clinical inter-vaccination period (Kitching, 2002c) the epidemic was under control by 22nd March: this preceded the introduction of rapid (suspected) IP culling as well as pre-emptive culling from 23rd March (EI 2001/62), or rapid pre-emptive slaughter from 26th March (EI 2001/73). The initial modelling undertaken by Ferguson, Donnelly and colleagues (Ferguson et al., 2001; Kao, 2002) for premises contiguous to an IP (CPs) as well as dangerous contacts to an IP (DCs). Rapid slaughter had been advocated earlier (Howard and Donnelly, 2000) and removed the option to differentiate between clean and affected farms using laboratory tests. This had a significant impact because of the difficulty in clinically identifying FMD in sheep. Whilst the abatement of disease transmission through thinning the susceptible pool was not a novel solution, models should add refinement to disease control: unnecessary slaughter of unaffected herds is as much an economic drain upon the farming industry as an epidemic that is ‘out of control’.

After the epidemic was declared ‘not under control’ (BBC Newsnight, 21st March 2001), susceptible stock on all premises contiguous to an IPs were regarded as dangerous contacts, and subject to pre-emptive slaughter from 23rd March (EI 2001/62), or rapid pre-emptive slaughter from 26th March (EI 2001/73). The initial modelling undertaken by Ferguson, Donnelly and Anderson predicted that 61–97% of farms would be lost.

5. Unbalancing of the 2001 epidemic control measures

Whereas, previous FMD models had become tools for institutions with experience of FMD, the 2001 models were constructed to substantiate or justify particular forms of control. Some of these were farm-level based constructions, providing valuable insights into the possible outcome of alternative control strategies (Morris et al., 2001), whilst others were more controversial.

Two controversial policies included the culling of suspected IPs (optimally within 24–48 h) without waiting for laboratory confirmation, and the introduction of pre-emptive culling (Ferguson et al., 2001; Kao, 2002) for premises contiguous to an IP (CPs) as well as dangerous contacts to an IP (DCs). Rapid slaughter had been advocated earlier (Howard and Donnelly, 2000) and removed the option to differentiate between clean and affected farms using laboratory tests. This had a significant impact because of the difficulty in clinically identifying FMD in sheep. Whilst the abatement of disease transmission through thinning the susceptible pool was not a novel solution, models should add refinement to disease control: unnecessary slaughter of unaffected herds is as much an economic drain upon the farming industry as an epidemic that is ‘out of control’.

Modelling is not required to determine the fact that rapid culling of (suspected) IPs and additional slaughter

4. Sub-clinical spread of the 2001 UK FMD epidemic

As events of the 2001 epidemic unfolded, significant criticism of MAFF ensued, probably due to an apparent lack of reduction in number of daily outbreaks being recorded. Kitching and Hughes (2002) indicate that transmission between sheep is very low, that the transmission rate is also slow and that FMD in unvaccinated ovine flocks is frequently sub-clinical. Since potentially 82% of the (suspected) infected animals during the 2001 epidemic were sheep (3.3 million animals: Crispin et al., 2002), it is not surprising that FMD was not diagnosed until sub-clinical disease had become clinical disease, some time after the initial spread of the epidemic, and frequently only after it had spread to cattle on the same premises. Hence, Gibbens et al. (2001) indicated that eight of the 12 major foci (accounting for 89% of IPs by 15th July) were initiated before the first epidemic IP was diagnosed. The criticism of MAFF was therefore unjustified, yet produced significant changes to the organisation of the Government response to the epidemic.
(of DCs traced by veterinary surveillance and CPs) will impact the control of an epidemic. However, it is important whether pre-emptive slaughter had impacted with a net positive effect or a net negative effect. Hence, were more clean herds removed than necessary to halt the epidemic? Only 20% of the total culled herds during 2001 were (suspected) IPs (including DCs and CPs), with 80% unaffected (Anderson, 2002), so was a fourfold thinning of (clean) herds necessary to rapidly halt the disease transmission? Moreover if more IPs would have been created had the thinning been reduced, what rate of thinning (if any) would have produced the least number of culls (of IPs plus clean herds)?

6. Ineffective pre-emptive culling

The impact of thinning is greatest when the inter-herd transmission rate is high, since without susceptible herds, disease spread is abated. However, the 2001 transmission rate was low as the predominance of IPs contained sheep and cattle that produced sub-clinical disease and little aerosol virus (Donaldson et al., 2001). The manifestation of an apparently high transmission rate in the first few months of the 2001 epidemic, coincided with the development of clinical signs from previously sub-clinically infected animals (Hutber, 2001b). The source of FMD for IPs with sub-clinical disease is manifest by clinical signs only after sub-clinical disease has spread, where the cumulative effect of the sub-clinical challenge eventually produces clinical signs – hence the FDI for sub-clinically affected herds is usually high (Hutber et al., 1999).

The same principle applies to both vaccinated animals with sufficient vaccine protection to suppress clinical signs (such as vaccinated cattle), as well as unvaccinated species with high innate immunity, such as sheep, where clinical signs are likewise suppressed (Hutber et al., 1999). Significantly, the removal of the disease source has been shown to be effective in controlling FMD outbreaks with sub-clinical disease (Hutber et al., 1998). The reasons for successful control (by removing the infected animals from sub-clinically infected herds) are summarised below:

- Sub-clinically infected herds are sub-clinical due to a suppression of clinical signs through high levels of immunity (innate or vaccinal),
- High levels of immunity lead to low disease transmission rates,
- Low transmission rates remove the need for heightened speed in the implementation of control measures,
- Low transmission rates enable herd or animal disease status to be monitored by serology, without a consequent risk of rapid unabated disease transmission,
- Sub-clinical disease acts cumulatively to subsequently produce clinical signs that may be diagnosed, and infected animals or herds can be removed by culling as the outbreak, focus or epidemic progresses,
- Continued low transmission rates ensure that once the pre-seeded sub-clinical disease has manifest itself in subsequent clinically infected animals, the disease incidence will have peaked, and the epidemic will no longer appear to be out of control.

It is therefore probable that the MAFF strategy of culling IPs had successfully created the decrease in new daily IPs observed on 27th March, only five weeks after the diagnosis of the first IP. This is consistent with previous findings that for sub-clinical FMD, when clinical disease does later appear, it may run unchecked for many weeks despite strong control measures (Kitching and Hutber, 2002).

Ferguson et al. (2001) reported that the majority of secondary infections were within 1.5 km of an IP and this was due to the seeding of foci by sub-clinically infected animals; but the slow transmission of FMD amongst sheep permitted adequate time to identify sub-clinically affected flocks by serological monitoring, before additional inter-flock spread would have occurred (Hutber, 2001c). This remains inconsistent with a policy of 24/48 h rapid slaughter. Moreover the level of post diagnosis control measures that minimise the susceptible pool (equivalent to thinning), has been proven to be independent of prevalence whenever slowly transmitted, sub-clinical disease is present (Hutber et al., 1999). Therefore it is also likely that due to the high levels of sub-clinical (rather than clinical) disease amongst sheep, CP culling and rapid-slaughter policies would not have significantly abated the epidemic through thinning effects. It is also probable that rapid pre-emptive slaughter would have removed mostly clean herds for minimal benefit in terms of epidemic control (Hutber, 2001b).

Furthermore, it is not correct to assume that pre-emptive CP culling/rapid slaughter would have removed animals that were both incubating FMD and posing a threat to susceptible farms (Woolhouse et al., 2001). Whilst incubating animals may have been removed by pre-emptive culling, the long mean incubation period amongst sheep ensured that it remained primarily a non-infectious (therefore non-threatening) period. With an extended, chiefly non-infectious incubation period, the available timescale for serological surveys of sheep (rather than pre-emptive culling) was similarly extended, thus enabling differentiation between clean and infected flocks. Serological surveys were more appropriate for sheep during the 2001 epidemic than CP culls/rapid culling.

It may be inappropriate to assume that the impetus for the CP culling/rapid culling was derived from an in-
ward 3 km transmission route rather than the outward 3 km inter-herd/inter-flock spread (Ferguson et al., 2001). An inward 3 km transmission rationale is focused upon an IP involving cattle, with the reasoning that cattle, as a secondary infection from sheep (within a radial distance of 3 km), may show clinical signs before the sheep (primary infection). Thus where the disease is sub-clinical in sheep, it may be argued that the primary infection could be any sheep within 3 km distance of the identified IP. However, under these circumstances it would be important to identify the primary infection IP by serological surveys around the secondary infection, since the 3 km around the primary IP would be at risk, and slaughtering at 3 km around the secondary infection would remove the ability to identify the primary IP. Moreover, unlike outward 3 km cull where the entire area is at risk, with inward 3 km cull only a small area of overlap between the 3 km around the primary IP and the 3 km around the secondary IP, is the area of possible transmission. Hence, unlike outward transmission most of the slaughter area for inward transmission is not at risk. Incidentally, any subsequent 3 km outward transmission to sheep (around the secondary IP bovine herd), would not be rapid (unless FDI was particularly high), and could not justify the 3 km cull around the secondary IP. Therefore any 3 km cull based upon inward transmission would have been significantly negligent in terms of unnecessary slaughter control, so remains less likely to have driven the 3 km cull/rapid cull policy, rather than outward 3 km transmission (Ferguson et al., 2001). Whatever was the case, both rationales for CP culling would have resulted in a significant net negative effect upon the farming community, in terms of unnecessary slaughter.

The likelihood that the CP culling/rapid slaughter policies had a net negative effect upon the farming industry, stemmed from an over-estimation of the transmission rates for the 2001 epidemic. In turn, an over-estimated transmission was based in a failure to recognise that FMD in sheep is frequently sub-clinical, and the transmission rates are particularly slow. Moreover, $R_0$ must be estimated indirectly from a large assortment of non-measurable parameters, or parameters with a range of values, or values that become variable with time. $R_0$ has been defined (Ferguson et al., 2001) as "the average no. of infectious days x the average no. of farms infected per infectious day", "assuming constant infectiousness".

Infectivity levels (dependent upon viral excretion) are not constant, nor are the time periods constant for infectiousness (ranging from one pre-clinical day to maximal-12 days after initial clinical signs). Hence the simplistic $R_0$ estimate of "an average of eight infectious days" is epidemiologically inaccurate and misleading. The success of a challenge between or within farms, is dependent upon factors including herd immunity, the strength of the challenge, species’ innate susceptibility and reproductive status. Any models using only infectivity for $R_0$ will require "mathematical weightings" to achieve their accuracy (Ferguson et al., 2001).

The situation is complicated by additional factors that would have decreased the accuracy of $R_0$ estimations, including low aerosol transmission for the Pan Asia 2001 strain, low transmission rates between sheep, poor transmission from sheep to pigs, false-positive diagnosis in the field, and many others. Identifying additional factors is not a difficulty, but quantifying their respective effects is problematic.

7. Contingency planning

The solution for future FMD contingency planning perhaps lies in identifying epidemiological factors that lie in the past, are available in (present) real-time, and have been proven to accurately predict prevalence/duration for future outbreaks, for regional foci or for epidemics. FDI and FFI as an example, are dependent upon the amount of sub-clinical disease transmitted (in unvaccinated sheep and unvaccinated/vaccinated cattle) before FMD is diagnosed. Both may be measured either when clinical signs are subsequently identified, or through serological surveys. Since the transmission rate for sub-clinical disease is slow, adequate scope remains for effective disease control, yet where sub-clinical disease can also be extensive, FDI/FFI can accurately predict the likely prevalence and duration of outbreaks/regional foci.

Empirical data to date (Kitching and Hutber, 2002; Hutber et al., 1999) have provided predictions for unvaccinated sheep flocks and unvaccinated/vaccinated cattle herds, but additional values for permutations with alternative control strategies can be obtained. First day incidence/FFI provide a direct measure for effective contact rate (ECR: Hutber, 2001b), thus enabling an accurate model of an FMD epidemic (with respective regional foci) to be simulated.

Where FDI/FFI are the consequence of sub-clinical disease transmission, there is no requirement to estimate ECR from factors, or epidemiological changes or other relevant conditions that may affect its value, since these have pre-determined the level of ECR prior to the initial disease diagnosis. First day incidence/FFI accurately predict the duration and prevalence of outbreaks (at the farm level) and for foci (at the regional level). Using these values the economic viability of a vaccination programme can be assessed (where the ban length tends from any value, currently six months with vaccination to live, down to zero).

Viability = [(prevalence without vaccination x unit compensation costs for culling) + export loss for epidemic duration + export loss during post epidemic ban due
to culling] – [cost of targeted vaccinations + cost of lost exports during ban due to vaccination].

The above assessment assumes that agricultural produce during a ‘vaccination to live’ policy, could enter the UK food chain, otherwise an additional subtraction must be made with vaccination of ‘export loss for epidemic duration’. Since the 2001 epidemic data used to derive correlations between FFI and prevalence/duration included the effect of culling on prevalence, then the above assessment likewise incorporates any IP culling effects. However, whilst it remains probable that the 3 km culls and CP culls merely removed clean herds (rather than abating prevalence for the 2001 epidemic), both possibilities are incorporated within the above assessment.

It is noteworthy that the above assessment is a conservative measure of economic viability for a vaccination programme. Where the effect of introducing vaccination may reduce prevalence, then the economic viability of a vaccination programme will also increase. Moreover, using the above information a refinement of viability of a vaccination programme will also increase. Vaccination may reduce prevalence, then the economic benefit from pre-emptive culling of CPs is dubious.

6. Ring culling (in various forms) appears to be economically counter-productive, particularly in light of the more refined control approaches available.

7. Low FFI for a regional focus (with consequent low regional prevalence, as well as short focus duration) indicates that IP culling with DC tracing, and serological monitoring may be sufficient to control inter-herd transmission.

8. High FFI (with consequent high regional prevalence, accompanied by long focus duration) for a region suggests the need to consider a vaccination programme for the focus. Vaccination holds advantages as a control measure in terms of its rapid administration, reduced manpower requirements, decreased viral excretion from IPs and possible retention of livestock. Both ring vaccination to live, as well as ring vaccination to cull (with differing export ban restrictions) could be considered for economic viability. Prophylactic vaccination (for non-endemic countries such as the UK) is unlikely to become an effective control policy where sub-clinical disease is a probability. Whilst the risk of transmission via (vaccinated plus challenged) carrier animals may be reduced through the development of polymerase chain reaction testing for non-structural viral proteins, the detection of sub-clinical disease is greatly hampered with blanket vaccination (Kitching and Hutber, 2002). Vaccinated bovine herds can produce sub-clinical transmission for three weeks or more, before clinical signs become apparent. Combined with the extensive sub-clinical disease observed in sheep during 2001, blanket vaccination would require constant serological monitoring of all vaccinated (to live) herds. Nevertheless for ring vaccination, within vaccinated bovine herds calves<four months could be used to protect more vulnerable age groups (Kitching and Hutber, 2002). Moreover, priority vaccination should be administered to protect the most vulnerable age groups (Kitching and Hutber, 2002). Nevertheless for ring vaccination, within vaccinated bovine herds calves>four months could be used to protect more vulnerable age groups, namely in-calf heifers>4–16 month young stock>first/second lactation cattle>third/fourth/fifth lactation cattle>0–3 month calves>dry cows.

8. Selection of useful models

When debates over the most appropriate FMD modelling approaches has abated, a criterion may be used to distinguish the more useful models from less useful ones.
Namely, whether any given model has generated or has proven that it will generate, economic benefit for the farming industry, above and beyond any economic drain for which it may be liable: welfare issues (Crispin et al., 2002) should also be considered.

Where the debated net gain is dubious, then the advised usage of that model (as a tool by institutions with experience of FMD) is also dubious. Useful modelling tools for future FMD contingency planning should be those that are clearly understood with accepted economic benefits.

Whilst this review has critically examined some of the models constructed during and prior to the 2001 UK FMD epidemic, the paper’s conclusions remain the authors’ interpretations of the findings within the literature, and the authors would also wish to acknowledge the work of all colleagues within this field.

9. Note

Ro has traditionally been defined as the average number of secondary cases caused by one typical infectious individual during its entire infectious period.

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References


Book review


In 1995, the fifth edition of this book was renamed the Essentials of Veterinary Microbiology and included, for the first time, a section on virology. This made it an all encompassing, general text for the undergraduate audience at which it was aimed. It is therefore regrettable that this latest edition has reverted to cover just bacteriology and mycology.

The book is divided into three sections, the first dealing with general aspects of bacteriology including morphology and classification, nutrition, growth and metabolism, molecular genetics and genetic engineering, epidemiology, pathogenicity, chemotherapeutics, sterilisation and disinfection, and a diagnostic overview. So many areas of microbiology are now reliant, albeit at different levels, on aspects of genetics and genetic engineering and it is particularly good to see that the authors have expanded these important topics to take this into account. Items covered include cloning, the polymerase chain reaction and DNA microarrays.

The second, and largest, section looks at the bacteria themselves. As in previous editions, these chapters cover laboratory diagnosis, pathogenicity, immunity, treatment and control, and, where applicable, the public health significance. The order in which the bacteria are presented is, however, slightly different. Bacteria are studied in taxonomic groups, enabling a correlation between genetic relatedness and disease type, an approach which seems to work well. The final section covers fungi in a similar manner, with an introductory chapter followed by those on the dermatophytes, yeasts, and the skin, respiratory and systemic mycoses. This format is especially good because it is in line with the way in which the majority of veterinary schools still teach their undergraduate students, providing a sound grounding in the subjects rather than just their clinical applications.

Overall, this book is well written and presented but there are, in my mind, two main areas which detract from its usefulness as an undergraduate text in this country. Firstly, in order to keep down the cost of the book, the authors have omitted references at the end of each chapter, removed the colour plates of bacterial and fungal morphology, and over-simplified many of the figures. This all appears to compound the fact that the concise, summarised format of the text can, in places, be rather limiting. Whilst acting as a good revisionary aid, this book therefore lacks the depth required to support a lecture course fully. Secondly, where epidemiological and legislative aspects of diseases are quoted, these are largely for the USA. Notifiable diseases in the UK, such as bovine tuberculosis and the potential for anthrax, and problems of increasing importance such as MRSA, are not covered in the detail required by our undergraduates. Students would also need to be informed that a number of the antimicrobial agents and vaccines mentioned may not be licensed for use in this country.

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