Dynamics and control of foot-and-mouth disease in endemic countries: A pair approximation model

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HIGHLIGHTS

- Traditional models of FMD focus on control and dynamics in disease-free settings.
- We analyze long-term dynamics and control of FMD in endemic countries.
- Success of vaccination depends on rates of vaccine and natural immunity waning.
- Prophylactic vaccination performs better than ring vaccination.
- More mathematical models applicable to FMD-endemic countries need to be developed.

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ABSTRACT

Previous mathematical models of spatial farm-to-farm transmission of foot and mouth disease (FMD) have explored the impacts of control measures such as culling and vaccination during a single outbreak in a country normally free of FMD. As a result, these models do not include factors that are relevant to countries where FMD is endemic in some regions, like long-term waning natural and vaccine immunity, use of prophylactic vaccination and disease re-importations. These factors may have implications for disease dynamics and control, yet few models have been developed for FMD-endemic settings. Here we develop and study an SEIRV (susceptible-exposed-infectious-recovered-vaccinated) pair approximation model of FMD. We focus on long term dynamics by exploring characteristics of repeated outbreaks of FMD and their dependence on disease re-importation, loss of natural immunity, and vaccine waning. We find that the effectiveness of ring and prophylactic vaccination strongly depends on duration of natural immunity, rate of vaccine waning, and disease re-introduction rate. However, the number and magnitude of FMD outbreaks are generally more sensitive to the duration of natural immunity than the duration of vaccine immunity. If loss of natural immunity and/or vaccine waning happen rapidly, then multiple epidemic outbreaks result, making it difficult to eliminate the disease. Prophylactic vaccination is more effective than ring vaccination, at the same per capita vaccination rate. Finally, more frequent disease re-importation causes a higher cumulative number of infections, although a lower average epidemic peak. Our analysis demonstrates significant differences between dynamics in FMD-free settings versus FMD-endemic settings, and that dynamics in FMD-endemic settings can vary widely depending on factors such as the duration of natural and vaccine immunity and the rate of disease re-importations. We conclude that more mathematical models tailored to FMD-endemic countries should be developed that include these factors.

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1. Introduction

Foot and mouth disease (FMD) is a highly transmissible viral infection affecting cloven-hoofed animals, including domestic livestock such as cattle, pigs, goats, sheep (Baipoledi et al., 2004; Keeling et al., 2001; Wernery and Kinne, 2012; Ferguson et al., 2001) and some wild animals, e.g. buffaloes. The disease agent of FMD belongs to the picorna virus family (Belsham et al., 2011). There are seven known serotypes of FMD virus which vary according to geographical region (Rweyamamu, 1984; Alonso et al., 1992). The serotypes of FMD are classified as (a) European types O, A and C; (b) African types STA 1, STA 2 and STA 3 and (c) Asian type Asia 1 (Davies, 2002; Ding et al., 2013), and there are several (more than 60) subtypes of the virus (Alonso et al., 1992; Anderson et al., 1974; Belsham et al., 2011).
Vaccination against one serotype does not provide protection against other serotypes. This makes it difficult to control the spread of FMD by vaccination alone and adopting multiple control measures may offer better means of control.

The FMD virus can be found in secretions and excretions from infected animals, including expired air, saliva, milk, urine and semen. The virus is airborne and can also be transmitted through physical contact. Clinical symptoms of FMD include high fever, blisters inside the mouth, raptured feet and stunted growth (Rweyamamu, 1984; Baipoledi et al., 2004; Ferguson et al., 2001; Rae et al., 1999). However, animals rarely die from foot and mouth disease. Upon introduction, FMD virus spreads rapidly within a farm, and interaction between neighboring farms leads to a rapid spread of the disease to several kilometers (up to 6 km) from the source point (Enserink, 2001). Import–export routes also enhance the spread of FMD, potentially resulting in a highly damaging global economic impact.

FMD is one of the most economically important livestock diseases (Belsham et al., 2011; Cottam et al., 2008). Heavy import–export restrictions apply in countries that experience frequent FMD outbreaks (Rae et al., 1999). Thus, the cost–benefit ratio of an investment business in FMD-affected animal species is greatly affected by frequent disease outbreaks. Due to its economic impact, FMD remains the greatest and most feared vesicular diseases in India (Matthew and Menon, 2008). In livestock production, the economic loss due to FMD can be calculated by considering, e.g., milk loss, disease-induced abortions and treatment costs. By the time the 2001 UK FMD outbreak had been stopped, the government had spent nearly GBP 3 billion on the operation of containing and cleaning up after the disease (Thompson et al., 2002). Recent outbreaks in Botswana include in 2002, 2005, 2006, 2007, 2011 and 2012 (Baipoledi et al., 2004; Letshwenyoe et al., 2004; Mokopasetso and Derah, 2005).

There is no cure for FMD (Pharo, 2002; Wernery and Kinne, 2012). Infected animals usually recover to a health-compromised status that renders them less profitable. Conventional control measures against FMD are movement restriction; public education; veterinary boundaries; quarantine; vaccination and culling (slaughtering animals in order to reduce the number of susceptible or infectious animals, and hence reduce spread of the disease Barteling, 2002). Two basic forms of vaccination against foot and mouth disease are prophylactic vaccination (pre-outbreak: vaccination carried out prevent introduction of the disease) and ring vaccination (during an outbreak: carried out on farms neighboring infected farms). The Cedivac-FMD Double Oil Emulsion (DOE) vaccines (one of many types of FMD vaccines) confer a duration of immunity of at least 6 months in cattle, sheep and pigs (Chenard et al., 2007; Domenech et al., 2010). Some vaccines can provide prolonged immunity for up to 12 months, depending on, among others, the species affected and the virus serotype. Cattle which have recovered from infection with one of the seven serotypes of the FMD virus remain protected against that serotype for up 6 months to about 5 years, depending on the virus serotype (Doel, 1996). Methods of culling include contagious premises (CP) culling (slaughtering farms based on their proximity to infected farms) and infected premises (IP) culling (slaughtering infected farms).

The availability of data for the 2001 FMD outbreak in the United Kingdom allowed the development of validated epidemiological models, making it possible to explore impacts of various control measures (Tildesley et al., 2001). For instance, Tildesley et al. (2001) used an individual-farm based transmission probability model, capturing spatiality by describing the probability of infection as a function of the distance between susceptible farms and infection source (transmission kernel), and also explored impacts of ring vaccination strategies. Using a stochastic individual farm-based model, Keeling et al. (2003) explored impacts of either national prophylactic vaccination campaigns, or combinations of reactive (during outbreak) vaccination and culling.

Compartmental models have also been used to study the dynamics and control of foot and mouth disease. In compartmental models, the host population is composed of subdivisions called compartments such that the nature and time rates of transfer from one compartment to another are defined (Brauer, 2006). Each compartment represents the disease status of farms (e.g. susceptible, infectious or recovered). Compartmental models are sometimes referred to as mean-field approximations as they typically assume that members of the host population mix homogeneously (Brauer, 2006). Thus spatial spread of the disease is neglected (Bunwong, 2010), since it is assumed that an infectious farm is equally likely to infect any of the susceptible farms in the population. Ref. (Mushayabasa et al., 2011) adopt this approach to model the spread of FMD and impacts of vaccination, by dividing the population of farms into susceptible (S), vaccinated (V), latentely infected (L) and infectious farms (I), and uses it to explore the impacts of births and deaths, culling, and vaccine waning.

Recently a number of foot and mouth disease transmission models have used moment closure approximations (pair approximation models in particular) to capture spatiality implicitly. Parham et al., 2008 design and analyze an SEI (susceptible, exposed but not infectious, infectious) pair approximation model of foot and mouth disease and explore impacts of IP culling and CP culling. They assume that the disease spreads on a network of farms represented by nodes (farms) and edges (links between farms). For many infectious diseases where spatiality is important for transmission and control, including foot and mouth disease, spatially structured models may provide advantages over mean-field approximations such as conventional compartmental models (Parham and Ferguson, 2005; Bauch, 2005). Ferguson et al. (2001) also present and analyze a pair approximation model of foot and mouth disease, employing data from the well-documented 2001 FMD out break in the United Kingdom, and explore impacts of ring culling and ring vaccination (both of which are applied during a single outbreak). In the study of Ferguson et al. (2001), the transmission rate is explicitly defined as a function of both local transmission between connected farms, and long range transmission due to transport since FMD virus can be transported to up to 60 km from the source point.

While mean field approximations are formulated under an assumption that individuals in the host population mix homogeneously, moment closure approximations capture the spatial spread of diseases by modeling states of neighboring members of the host population. This technique provides information about the spatial distribution of disease states on a network by employing pairs, triples, quadruples, and other higher-order correlations as state variables of ordinary differential (Bauch, 2005; Bunwong, 2010). Each ordinary differential equation (also referred to as equation of motion for a state variable) measures the expected rate of change of a state variable by averaging all possible events affecting the state variable (van Baalen, 2000). To do this, the first step is to write the equations of motion for the number of neighboring pairs of individuals or groups of individuals of a given state on a network; these equations will have terms involving triples (Bauch, 2005). The equations of motion for triples will involve quadruples while the equations of motion for quadruples will have terms involving five-order correlations. Essentially the procedure yields an infinite system of ordinary differential equations, each describing rates of change of state variables. However in order to solve the system analytically or using available computer software the system of equations needs to be finite. A closed, manageable system is obtained by truncating the hierarchy at some suitable level by a process known as moment closure (Bauch and Rand, 2000; Bauch, 2005; van Baalen, 2000;
Hiebeler, 2006). When the system is closed at the level of pairs, it is referred to as pair approximations. Pair approximations models track down the dynamics of neighboring pairs of members of the host population, capturing the correlations that develop when two individuals interact (Bauch, 2005; Ellner, 2001). Pair approximations also tend to be more analytically tractable than fully explicit network models.

Most models of FMD transmission are intended for epidemic settings, where control measures are designed to contain a single epidemic outbreak. However, FMD is an endemic problem in many countries. For example, in Botswana, FMD is endemic in some regions due to importation of FMD virus from wild African buffaloes and neighboring countries (Baipoledi et al., 2004). In endemic settings, long-term factors become important, such as waning of natural immunity, waning of vaccine immunity, and frequent disease re-introduction. Moreover, prophylactic and ring vaccination may become desirable control measures, under some circumstances. Despite the importance of such factors for FMD-endemic settings, they are not commonly included in spatial FMD transmission models. For example, to our knowledge there is no pair approximation FMD model that analyzes both ring and prophylactic vaccination. The same holds true for the impact of disease re-introduction. Our objective was to fill this gap in the literature by developing an SEIRV (susceptible, exposed but not infectious, infectious, recovered and vaccinated) pair approximation model to explore the impacts of prophylactic and ring vaccination, vaccine waning and loss of natural immunity as well as disease re-introduction from an external source, on the dynamics of foot and mouth disease in a fixed population of farms.

2. Model

The state variables of pair approximation models are of the form [XY], where X and Y represent the status of farms with respect to the disease so that [XY] is defined as the expected number of status X and status Y pairs at a given time, t. The dynamics of state variables of pair approximation models are governed by the master equation:

\[
\frac{dg(t)}{dt} = \sum \tau(\epsilon) \Delta g(\epsilon),
\]

where \(g(t)\) is the state variable of interest, \(\tau(\epsilon)\) is the rate of event \(\epsilon\) and \(\Delta g(\epsilon)\) is the change this event causes in \(g(t)\).

As an example of pair approximation derivation, in Appendix A we derive the equation of motion for the number of susceptible–infectious, S–I pairs, \(d[SI]/dt\), for an SEIRV (susceptible, exposed, but not infectious, infectious, recovered and vaccinated) pair approximation model of FMD. We show how ring and prophylactic vaccination as well as vaccine waning and loss of disease induced immunity are incorporated and observe that

\[
\frac{d[SI]}{dt} = -\tau([SI]) + \nu[SE] - \sigma[SI] - \nu_p[SI] - \psi_p[SI] + \alpha_o[R] + \theta[V],
\]

where \(\tau, \sigma, \nu, \nu_p, \alpha_o\) and \(\theta\) are the transmission rate, recovery rate, rate of ring vaccination, rate of prophylactic vaccination, rate of loss of natural immunity and rate of vaccine waning, respectively. The number of I–S–I triples enters the equation of motion for S–I pairs because it is possible that transmission from one infected farm to a susceptible farm can destroy a S–I pair consisting of that susceptible farm and a second infected farm, creating an E–I pair in its place. The sign in front of the triple term is negative because an S–I pair is disappearing. The latent period of FMD is given by \(\nu^{-1}\), therefore S–E is converted to S–I (i.e. S–I bond is created), at rate \(\nu\), leading to the term \(+\nu[SE]\) on the RHS of this equation. The rest of the terms are developed in a similar manner.

If an equation of motion for [SI] is in turn formulated, it will involve quadruples and the hierarchy will go on to involve progressively higher order correlations. To truncate the hierarchy, we perform a moment closure approximation, a technique in which higher order correlations (order 3) are approximated in terms of lower order correlations (pairs and singletons). There exist various forms of moment closure approximations to the level of pairs which vary in the assumptions they make about the distribution of neighbors around a farm. Here we adopt the ordinary pair approximation (OPA) (Parham et al., 2008), and approximate the number of triples in terms of pairs and singletons, and the number of neighbors of a farm, \(n\), as

\[
[XY] \approx \frac{n - 1}{n} [XY][V]
\]

The ordinary pair approximation assumes that all individuals in the network have exactly \(n\) contacts. The approximation maintains pair correlations between \(X\) and \(Y\), and between \(Y\) and \(Z\), but assumes higher order correlations between \(X\) and \(Z\) are negligible. In practice, \(X\) and \(Z\) could be correlated because they are directly connected, forming a triangle, or because \(X\) and \(Z\) have influenced one another via \(Y\). The presence of triangles can be accounted for using a triangular approximation (Parham et al., 2008; Keeling et al., 1997). In contrast, in a mean field approach \([XY]\) is approximated by \([X][Y]\) while \([XY][Z]\) would be approximated by \([X][Y][Z]\).

2.1. Model equations

\(S, E, I, R\) and \(V\) respectively, represent epidemiological states of the host population (farms): susceptible, exposed, infectious, recovered and vaccinated. The full model equations are given by

\[
\begin{align*}
\frac{d[S]}{dt} &= -\tau[S] - \psi_p[S] - \psi_r[S] - \alpha_o[R] + \theta[V] \\
\frac{d[E]}{dt} &= \tau[S] - \nu[E] - \psi_p[E] \\
\frac{d[I]}{dt} &= \nu[E] - \sigma[I] \\
\frac{d[R]}{dt} &= \sigma[I] - \alpha_o[R] \\
\frac{d[V]}{dt} &= \psi_p([I][E]) + \psi_r[S] - \theta[V] \\
\frac{d[SS]}{dt} &= -2\tau[SS] - 2\psi_p[SS] - 2\psi_r[SS] + 2\alpha_o[SR] + 2\alpha_o[V] \\
\frac{d[SE]}{dt} &= -\tau[ISE] - \psi_r[I][SE] + \psi_p[SE] + \psi_p[SE] + \alpha_o[ER] + \theta[EV] \\
\frac{d[SI]}{dt} &= -\tau([SI] + [SI]) + \nu[SE] - \sigma[SI] - \psi_r([I][SI]) \\
&\quad - \psi_p[SI] + \alpha_o[R] + \theta[IV] \\
\frac{d[SR]}{dt} &= -\tau[SR] + \sigma[R][SI] - \psi_r[S][SR] - \alpha_o[SR] - \alpha_o[SR] + \theta[RV] \\
\frac{d[SV]}{dt} &= -\tau[SV] - \psi_p[I][SV] - \psi_r[I][SV] - \psi_r[I][SV] \\
&\quad + \alpha_o[SV] + \theta[V][V] + \theta[SV] \\
\frac{d[EE]}{dt} &= 2\psi_p[EE] - 2\nu[E][E] - 2\psi_r[EE] \\
\frac{d[I][E]}{dt} &= \tau([I][E]) + \nu[I][E] - \sigma[I][E] - \psi_r[I][E] + \psi_p[I][E] \\
\frac{d[ER]}{dt} &= \tau[SR] - \nu[ER] + \sigma[ER] - \psi_r[ER] - \alpha_o[ER] \\
\frac{d[EV]}{dt} &= \tau[SV] - \nu[EV] - \psi_p[I][EV] - \psi_p[I][EV] + \psi_p[SE] - \theta[EV]
\end{align*}
\]
\[
\frac{d[V]}{dt} = \gamma\{[E] + [EI]\} - \gamma[V][E] - \gamma[V][I] - \lambda[I] + \delta[V] - \alpha[V][R] - \beta[V][S] - \theta[V][R]
\]

The factor two in the equations of motion pairs of the form \( XX \) comes from the counting convention of same-status pairs, wherein pairs of type \( X-X \) are counted twice. The ordinary pair approximation has been used to close the equations of motion.

During an outbreak of foot and mouth disease, transmission at rate \( \tau \) takes place between an infectious and a susceptible farm, moving the latter to the exposed compartment. A farm stays in the exposed state for \( \nu^{-1} \) days (latent period), after which it becomes infectious. The recovery rate (transition from infectious state to recovered compartment) is given by \( \sigma \). Loss of natural immunity (disease-induced immunity) takes place at rate \( \omega \), enabling transition of farms from \( R \) to \( S \) compartments. Prophylactic vaccination and ring vaccination at per capita rates \( \psi_v \) and \( \psi_r \), respectively, transfer vaccinated susceptible and susceptible and/or exposed farms to the vaccinated compartment. The rate of loss of vaccine-induced immunity (vaccine waning) is given by \( \theta \) (where farms lose protection from the vaccine, becoming susceptible again).

### 2.2. The basic reproduction number

The basic reproduction number, \( R_0 \), is defined as the expected number of secondary cases produced by a single infection in a completely susceptible population (Hethcote, 2000; Bauch, 2005; Li et al., 2011; Schmitt and Monteiro, 2012). An epidemic is expected if \( R_0 > 1 \) and the infection is expected to die out if \( R_0 < 1 \) (Schmitt and Monteiro, 2012; Heffernan et al., 2005). In Appendix B we illustrate the derivation of a spatially oriented basic reproduction number for a pair approximation model without control measures:

\[
R_0 = \frac{\beta(n_1 - 1)^2}{\sigma n(n - 1 + \frac{P}{\nu})}
\]

where \( \beta = \tau n \) is the number of neighboring farms. The basic reproduction number increases with the number of neighbors, \( n \), on account of decreased opportunities for localized clustering of infected individuals to interfere with further transmission.

The basic reproduction number with ring vaccination as the only control measure is

\[
\frac{m_3 \tau (m_1 \nu + m_2 \psi_r)}{m_1 \nu + m_2 \psi_r + (m_1 \nu m_2 + m_3 \psi_r) \left( \frac{\sigma(m_1 \mu + m_2 \tau)}{\nu} + m_1 \alpha \frac{\sigma \psi_r \mu}{\nu} \right)}
\]

where \( m_i , i = 1...5 \), are constants \( (n-1)/n+1 \), \( (n-1)/nNq \), \( n(n-1)^2 \), \( n(n-1) \) and \( n^2 \), respectively. In our model \( n=4 \) neighbors per farm, \( N=40,000 \) farms and \( q=1.5 \) (\( q \) represents a ratio, \( [EI]/[E] \) and converges to 1.5 as \( t \rightarrow \infty \), on a square grid). Therefore \( m_1 = 1.75 \), \( m_2 = 4.5 \times 10^5 \), \( m_3 = 36 \), \( m_4 = 12 \) and \( m_5 = 16 \). The basic reproduction number with prophylactic vaccination only is

\[
\frac{m_3 \tau (m_1 \nu + m_2 \psi_r)}{(m_1 \nu + m_2 \psi_r) \left( \frac{\sigma(m_1 \mu + m_2 \tau)}{\nu} + m_1 \alpha \frac{\sigma \psi_r \mu}{\nu} \right)}
\]

where \( m_6 = (n-1)^2 = 9 \). The appearance of quadratic form of vaccination terms, \( \psi_v \) and \( \psi_r \), in the denominators of these expressions, guarantees that vaccination will decrease the basic reproduction number exponentially.

The basic reproduction number in the presence of prophylactic, \( \psi_v \) and ring, \( \psi_r \) vaccination (see Appendix B) is considerably more complicated and is given by

\[
R_0 = \frac{m_3 \tau (n-1)^2 + m_4 \tau (n-1)^2}{m_3 \nu(n-1)^2 + (m_6 \nu \mu(n-1)^2 + m_6 \alpha \nu \psi_r \mu(n-1)^2)}
\]

where \( m_7 = \nu + \nu \psi_r + \psi_r \), \( m_8 = \nu + \nu Nq \), \( m_9 = \tau \psi_r \), and \( m_{10} = (\tau + \psi_r)/\nu \).

### 2.3. Baseline parameters

Cattle, swine, sheep, goats and deer exhibit signs of clinical illness from FMD after an incubation period of about 2–14 days, (Mushayabasa et al., 2011). The latent period of foot and mouth disease is 3.1–4.8 days in cattle (Mardones et al., 2010). Upon contact with the FMD virus, animals show clinical signs and are able to transmit the virus after 4–5 days (Keeling et al., 2001). Therefore we assume that the latent period is 4 days, thus \( \nu = 1/4 = 0.25 \) day\(^{-1} \). Once in the infectious compartment, cattle show symptoms and remain infectious for about 7–8 days before they recover, (Parham et al., 2008). Our baseline choice of the recovery rate is \( \sigma = 1/70 = 0.0143 \) day\(^{-1} \).

Cattle which have recovered from infection with one of the seven serotypes of FMD are not immune to other serotypes but remain protected against the first serotype for a considerable period of time. Laboratory experiments show that the length of natural protection may range from 6 months to 5.5 years, depending on the serotype (Doel, 1996). Using this observation as a guide, and considering the possibility for transmission of multiple serotypes in the same population in succession, our baseline choice of the duration of natural immunity is 6 months (\( \approx 0.5 \) years, or \( \omega = 0.0056 \) day\(^{-1} \)), but we also explore scenarios of \( \approx 1 \) year (\( \omega = 0.0030 \) day\(^{-1} \)) and \( \approx 2 \) years (\( \omega = 0.0015 \) day\(^{-1} \)).

Cattle remain protected by FMD vaccine for up to 6 months (Keeling et al., 2003), therefore \( \theta = 0.0056 \) day\(^{-1} \). We assume that per capita prophylactic and ring vaccination rates are \( \psi_v \approx 0.005 \) day\(^{-1} \) and \( \psi_r \approx 0.005 \) day\(^{-1} \), respectively. In some countries, foot and mouth disease can spread across borders through animal movement or trade. In some parts of Botswana FMD is imported from Zimbabwe or South Africa resulting in a series of outbreaks almost every 2 years (Mokopasetso and Derah, 2005).

In our model simulations, the disease is re-introduced into the population of farms every \( \delta = 800 \) days (just over 2 years). The baseline transmission parameter is \( \tau = 0.6 \) day\(^{-1} \). In Appendix C we estimate this parameter value from the expression of the basic reproduction number (Eq. (5)). We present all baseline parameters in Table 1. Finally, to partially account for the effects of stochastic fadeout in our deterministic framework, when the total number of infectious farms falls below 1 in the simulation (less than one infected farm left), the infection is forced to die out, so that any subsequent outbreaks are the result of disease re-importation. The population size is \( N=40,000 \) farms.

In the model equations, prophylactic vaccination of the susceptible farm in a susceptible-infected pair occurs at rate \( \psi_v \) and converts SI to VI, creating the terms \( -\psi_v [SI]/[dSI]/dt \) and \( +\psi_v [SI]/[dVI]/dt \). However prophylactic vaccination is a pre-outbreak vaccination strategy and we assume that, in practice, authorities would switch all resources to ring vaccination in the event of an outbreak. To capture this in the model simulations, we assumed that \( \psi_v \) is set to zero whenever \( [I] > 0 \), and it remains zero
for the duration of the outbreak, after which it is returned to baseline levels.

3. Results

We focus on the impact of loss of natural immunity, \( \omega \), vaccine waning, \( \theta \), and disease re-introduction frequency, \( \delta \), on the number of outbreaks, average peak size of outbreaks, and cumulative number of infected farms over a given time period. We also consider impacts of prophylactic vaccination, \( \psi_p \), and ring vaccination, \( \psi_r \), on disease incidence, cumulative infections and the basic reproduction number, \( R_0 \).

Fig. 1 shows the impact of loss of natural immunity, \( \omega \), on disease re-introduction in the absence of control measures. For higher values of \( \omega \), natural immunity is short-lived causing the pool of susceptible farms to be rapidly replenished. Hence, epidemics do not fade out and the infection prevalence converges to an endemic equilibrium (Fig. 1a,b). In contrast, if \( \omega \) is low, corresponding to long-lived natural immunity, epidemics fade out and prevalence goes to zero after an outbreak. After some time, a subsequent disease introduction sparks a new outbreak. As a result, the epidemiology is characterized by sustained outbreaks every 3–5 years (Fig. 1c,d). However, because the susceptible pool is relatively slow to replenish, not every disease re-introduction is successful in starting an outbreak, meaning that outbreaks are spaced further apart when natural immunity wanes more slowly (Fig. 1d versus 1c).

As a result of interactions between timing of disease re-introduction and rate of natural immunity waning, the dependence of the size and number of outbreaks on the natural immunity waning rate is not linear (Fig. 2). As the rate of waning natural immunity, \( \omega \), increases, so does the number of outbreaks over a fixed time window of 20 years, through a series of plateaus (Fig. 2a). The average peak size of all outbreaks in this period of time also increases with \( \omega \), although beyond a certain point, further increases in \( \omega \) do not change the average peak size (Fig. 2b).

The effectiveness of prophylactic vaccination, \( \psi_p \), and ring vaccination, \( \psi_r \), is strongly determined by the presence or absence of vaccine waning, \( \theta \), and natural immunity waning, \( \omega \) (Fig. 3). If both vaccine immunity and natural immunity wane after 6 months, then a vaccination strategy with \( \psi_p = 0.005 \text{ day}^{-1} \) and \( \psi_r = 0.01 \text{ day}^{-1} \) fails to prevent the infection from becoming endemic (Fig. 3a). However, if vaccines were to provide life-long immunity (i.e. \( \theta = 0 \text{ day}^{-1} \)), vaccination prevents future outbreaks (except for a small second outbreak due to re-importation) and eventually leads to eradication (Fig. 3b). Similarly, if natural immunity were lifelong (Fig. 3c) or if both natural and vaccine immunity were lifelong (Fig. 3d), the infection is eradicated even more quickly.

Both prophylactic and ring vaccination decrease the cumulative number of infected farms (see surface plots of cumulative infections versus \( \psi_r \) and \( \psi_p \), Fig. 4). However, at similar per capita rates

<table>
<thead>
<tr>
<th>Table 1 Baseline parameters for our model.</th>
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<tbody>
<tr>
<td>Parameter</td>
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<tr>
<td>-------------------------------------------</td>
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<tr>
<td>Transmission rate, ( r )</td>
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<tr>
<td>Rate of moving from latent to infectious, ( \nu )</td>
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<tr>
<td>Rate of moving from infectious to recovered, ( \sigma )</td>
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<tr>
<td>Rate of loss of disease-induced immunity, ( \omega )</td>
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<tr>
<td>Rate of loss of vaccine-induced immunity, ( \theta )</td>
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<tr>
<td>Rate of ring vaccination, ( \psi_r )</td>
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<tr>
<td>Rate of prophylactic vaccination, ( \psi_p )</td>
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<tr>
<td>Frequency of disease re-introduction, ( \delta )</td>
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![Fig. 1. Time series of the number of infectious farms where rates of natural immunity waning, \( \omega \) are 0.0055 day\(^{-1}\) (a), 0.0042 day\(^{-1}\) (b), 0.0014 day\(^{-1}\) and 0.00055 day\(^{-1}\) (d). \( \psi_p = \psi_r = 0 \text{ day}^{-1} \) and all other parameters are as in Table 1.](image_url)
of vaccination, prophylactic vaccination appears to be more effective. This simply reflects the fact that more farms in total are vaccinated under prophylactic vaccination, for the same per capita vaccination rate. However, it may also reflect the fact that prophylactic vaccination is a preventive (pre-outbreak) form of vaccination that can delay or prevent outbreaks altogether. Almost all of the variation in the effectiveness of prophylactic vaccination occurs in a range of values from $\psi_p = 0$ day$^{-1}$ to $\psi_p = 0.005$ day$^{-1}$ (the upper limit corresponds to being able to vaccinate all farms after about 200 days).

Both vaccine waning, $\theta$, and natural immunity waning, $\omega$, affect the number of epidemics, average size of infection peaks and cumulative number of infected farms over a 20-year time window (Fig. 5). The number of epidemics (Fig. 5a), average infection peak (Fig. 5b) and cumulative infections (Fig. 5c) are highest when both natural immunity and vaccine waning rates take values close to the baseline parameters ($\omega = \theta = 0.0055$ day$^{-1}$, corresponding to lowest immunity duration considered here: 6 months). Generally speaking, the number of epidemics, average infection peak and cumulative infections depend more sensitively on changes in the rate of natural immunity waning, $\omega$, than they do on the rate of vaccine waning, $\theta$ (the height variation is greater along the $\omega$ axis than the $\theta$ axis).

When the frequency of disease importation $\delta$ is low (i.e. there is a long time interval between re-introductions), long periods of zero disease prevalence are interspersed with sharp epidemic outbreaks (Fig. 6a). After an outbreak is finished, vaccination is sufficient to prevent FMD from becoming endemic, but not sufficient to prevent an outbreak after the next re-introduction. As the frequency of disease re-importation increases, outbreaks occur closer together, but they are smaller in magnitude (Fig. 6a). However, despite the smaller magnitude of epidemic peaks, the cumulative incidence is nonetheless higher when re-introductions are close together (Fig. 6b). Thus despite its capability to yield high-peak outbreaks, a lower rate of disease re-introduction produces fewer cumulative infections. Interestingly, when the rate of re-introduction is every 8 years, there is an outbreak every 8 years, but when the rate of re-introduction is only 3 years
Foot and mouth disease has both economic and social impacts in many countries. Even though it has since been eradicated or is under control in most developed countries, the occurrence of foot and mouth disease in the developing world can, and does, create global impacts. To avoid introduction of FMD into disease-free countries, heavy import-export restrictions apply on trade of animals and their products.

Here, we applied moment closure techniques to construct and analyze a pair approximation model of foot and mouth disease and explored impacts of loss of natural immunity, vaccine waning and disease re-introduction on infection dynamics and the basic reproduction number. At biologically plausible parameter values, both waning natural and vaccine immunity had significant impacts on the number and magnitude of outbreaks, cumulative number of infections, and feasibility of disease control. The impact varied according to the precise parameter values, over biologically plausible parameter ranges. Hence, these factors are important to consider in any transmission model of FMD in an endemic country. These outcomes are somewhat more sensitive to the rate of
waning natural immunity than the rate of waning vaccine immunity.

We also found that vaccination is more effective if loss of natural immunity is low (i.e. recovered farms remain in ‘recovered’ compartment longer due to longer-lasting natural immunity). However, if farms lose natural immunity at a higher rate then it will be difficult to eliminate the disease. For the same per capita vaccination rate, prophylactic vaccination appears to be more effective than ring vaccination, partly because prophylactic vaccination better delays the occurrence of outbreaks, leading to smaller and less frequent subsequent outbreaks, and ensuring that the basic reproduction number stays below unity.

In most developing countries, vaccination capacity may be constrained by many factors including cost. Therefore as part of future work, this model can be modified to explore optimal and/or cost-effective prophylactic and ring vaccination strategies where control measures are forced to operate within constraints such as cost, availability of vaccine and manpower. Empirical data are generally lacking in FMD-endemic settings and this must also be addressed in order to better validate country-specific FMD models.

The outcomes of this analysis provide spatially oriented insight into the dynamics of foot and mouth disease and its control in FMD-endemic countries. The dependence of disease control effectiveness on loss of natural immunity and vaccine waning has not been well explored in the literature of foot and mouth disease models, but our analysis suggests that these factors are influential enough to necessitate inclusion in any mathematical model of FMD transmission and control in endemic countries.

Appendix A. Derivation of the equation of motion for [SI]

We proceed with the derivation of a SEIRV pair approximation model of FMD as follows, using a similar approach to Refs. Bauch (2005) and Keeling et al. (1997). We demonstrate the derivation of the equation of motion for [SI].

The dynamics of [SI] are governed by the equation:

\[
\frac{dg(t)}{dt} = \sum r(e) \Delta g(e),
\]

where \(g(t)\) is the state variable of interest (i.e. [SI]), \(r(e)\) is the rate of event \(e\) and \(\Delta g(e)\) is the change this event causes in \(g(t)\) (i.e. [SI]).

As the disease progresses, [SI] is affected by the following events.

Infection of the susceptible farm by the infectious farm in the S-I edge converts S into E, i.e. \(S \rightarrow E\), where \(\rightarrow\) means ‘transformed to’. This adds \(-\tau[SI]\) into the equation of motion for [SI]. The negative sign \(-\) in the coefficient is a result of this event ‘destroying’ S-I edges.

Infection of the susceptible farms ‘from the left’ in a triple I-S-I, i.e. \(I \rightarrow SI\) gives rise to \(SI \rightarrow EI\), contributing the term \(-\tau[SI]\) into the equation of motion for [SI].

Latent period is \(1/\nu\), therefore \(SE \rightarrow SI\) and the process ‘creates’ SI (hence positive coefficient). Thus we add \(\nu[SE]\) into the equation of motion for [SI].

A infectious farm recovers at rate \(\sigma\), therefore \(SI \rightarrow SR\) contributing \(-\sigma[SI]\) into the equation of motion for [SI].

Ring vaccination (defined as vaccination of exposed and susceptible farms that have links with infected farms) in the susceptible farm in a pair S-I, at rate \(\psi_r\), converts SI to IV and adds \(-\psi_r[SI]\) to \(d[SI]/dt\).

Ring vaccination in the susceptible farm in a triple I-S-I, at rate \(\psi_r\), converts SI to IV and adds \(-\psi_{ir}[SI]\) to \(d[SI]/dt\).

A recovered farm in an I-R pair loses natural immunity at rate \(\omega\) to form an S-I pair, thus adding \(\omega[IR]\) to \(d[SI]/dt\).

A vaccinated farm in an I-V pair loses vaccine protection at rate \(\theta\) to form an S-I pair, thus adding \(\theta[IV]\) to \(d[SI]/dt\).

Therefore the equation of motion for [SI] is

\[
\frac{d[SI]}{dt} = -\tau([SI]+[I]+[E]) - \sigma[SI] - \psi_r([SI]+[ISI]) - \psi_{ir}[SI] + \omega[IR] + \theta[IV].
\]

Appendix B. Derivation of the basic reproduction number

We derive the expression of the basic reproduction number for a pair approximation model of foot and mouth disease without control. The equations of motion for the number of exposed and infectious farms are important in the derivation of the basic reproduction number:

\[
\frac{d[E]}{dt} = \tau[SI] - \nu[E]
\]

and

\[
\frac{d[I]}{dt} = \nu[E] - \sigma[I].
\]

An epidemic is expected if \(d/dt[E] + d/dt[I] > 0\) and the disease is expected to die out if \(d/dt[E] + d/dt[I] < 0\). Using the correlation function between susceptible and infectious farms, \(C_{SI} = N/[n[SI]/[SI][I]]\), we re-write the equation of motion for the number of exposed farms as

\[
\frac{d[E]}{dt} = \beta E SI - \nu[E],
\]

where \(\beta = \nu n\).

At the beginning of an epidemic almost all farms are susceptible, i.e. \([SI] \approx N\). Therefore we simplify the equation of motion for the number of exposed farms further:

\[
\frac{d[E]}{dt} = \beta SI - \nu[E].
\]

An epidemic is expected if \(d/dt[E] + d/dt[I] = \beta SI - \nu[E] + \nu[E] - \sigma[I] > 0\), i.e.

\[
\beta SI - \sigma[I] > 0.
\]

Thus there will be an epidemic if \((\beta/\sigma)C_{SI} > 1\). Therefore the expression of the basic reproduction number is

\[
R_0 = \frac{\beta}{\sigma} C_{SI}.
\]

The correlation between susceptible and infectious farms, \(C_{SI}\) is not constant but it changes from \(C_{SI} \approx 1\) at the beginning of the infection, decreasing as more individuals become infected (Bauch, 2005). An increase in the number of infected farms leads to reduction of the infection rate in the long run, and at this point the epidemic may fade out. This is a local minimum of \(C_{SI}\). The dynamics of the disease at this point are important in deriving an explicit form of the basic reproduction number. Therefore we seek \(C_{SI}^{(\text{ma})}\), the local minimum value of \(C_{SI}\), obtained by solving \((d/dt)C_{SI} = 0\).

The derivative of the correlation function between the number of susceptible and infectious farms is given by

\[
\frac{dC_{SI}}{dt} = \frac{N}{n(S[I])} \frac{d}{dt}[S[I]] + \frac{N}{n(I)[S]} \frac{d}{dt}[S[I]].
\]

This expression is equivalent to

\[
\frac{dC_{SI}}{dt} = \frac{N}{n(S[I])} \frac{d}{dt}[S[I]] + C_{SI} \left( \frac{1}{n[I][S]} \frac{d}{dt}[I] - \frac{1}{n[S][I]} \frac{d}{dt}[S] \right).
\]

Substituting the equations of motion for \([SI], [I]\) and \([S]\), into the equation above, applying the ordinary pair approximation to express the number of triple as pairs and singletons, and noting
that at the initial stages of the disease there are no recovered farms \([i.e. \{R\} = 0]\), yields
\[
\frac{d}{dt} C_{SI} = -\tau (n-1) \frac{C_{SI}}{N} - r C_{SI} + \frac{[E]}{[I]} C_{SI} - \frac{[E]}{[I]} C_{SI} + \frac{\tau n}{N} \frac{C_{SI}}{C_{SI}}.
\]
Note that at the initial stages of the infection \([S] \approx N\); a simple analysis of terms involving \([I]/NC_{SI}^2\) shows that they are too small to have significant impact on the correlation between susceptible and infectious farms. We let \([I]/NC_{SI}^2 \rightarrow 0\) so that the equation of motion for \(C_{SI}\) becomes
\[
\frac{d}{dt} C_{SI} = -\tau C_{SI} + \frac{[E]}{[I]} - \frac{[E]}{[I]} C_{SI}.
\]
To solve for \(C_{SI}^{\text{eq}}\), explicitly, we need simpler representation for \(C_{SE}\) and \([E]/[I]\).

In a network where there are no ‘triangles’, when a susceptible farm becomes exposed, this newly exposed farm inherits the neighborhood of the susceptible (Parham et al., 2008; Keeling et al., 1997). Thus
\[
C_{SI} \approx \left(\frac{(n-1)}{n}\right) C_{SS}.
\]
Adopting arguments by Parham et al. (2008) we assume further that the host population space is such that \(C_{SE} \approx 1\), so that
\[
C_{SI} \approx \frac{(n-1)}{n} C_{SS}.
\]
The process of a farm moving from the exposed to the infectious state implies that the farm now inherits a fraction \((n-1)/n\) of the neighborhood it had previously (Parham et al., 2008; Keeling et al., 1997). Thus
\[
\frac{[E]}{[I]} \approx \left(\frac{n-1}{n}\right).
\]
Therefore the equation of motion for \(C_{SI}\) is
\[
\frac{d}{dt} C_{SI} = -\tau C_{SI} + \frac{\beta (n-1)}{n} \frac{C_{SI}}{n} - \frac{\nu (n-1)}{n} C_{SI}.
\]
We obtain \(C_{SI}^{\text{eq}}\) by letting the left hand side of the equation above equal zero and solve for \(C_{SI}\). It follows that
\[
C_{SI}^{\text{eq}} = \frac{(n-1)^2}{n (n-1) + \left(\frac{\beta}{\nu}\right)}
\]
where \(\beta = r n\). Under mean field approximation, the corresponding expression of the basic reproduction number is \(R_0 = \tau/\sigma\). This overestimates the true \(R_0\) in a spatially structured population of farms because it does not take into account the slowing effects of spatially localized transmission (Bauch, 2005). On the other hand, the expression of the basic reproduction number derived under moment closure techniques provides a better estimation of the true value of \(R_0\) because of the pair approximations’ capacity to capture the time evolution of local spatial structure. Here transmission can only take place between neighboring farms.

Appendix C. Derivation of the transmission parameter, \(\tau\)

We derive the baseline transmission rate, \(\tau\) from the expression of the basic reproduction number, Eq. (5). Substituting \(n=4, \beta = r n = 4 r, \nu = 1/4\) and \(\sigma = 1/7\) into this expression yields
\[
R_0 = \frac{63 r}{3 + 16 \tau}.
\]
Changing the subject of this formula to \(\tau\) gives
\[
\tau = \frac{3 R_0}{63 - 16 R_0}.
\]
\(\tau\) takes positive values only when \(R_0 > 0\) and \(63 - 16 R_0 > 0\). Thus transmission will take place when \(0 < R_0 < 63/16\), i.e. \(0 < R_0 < 3.9375\).

The corresponding baseline choice of \(\tau\) should be based on the choice of \(R_0\) in this interval.

Also on a square grid, if recovery rate, \(\sigma = 0\), an infected farm can infect no more than \(n-1\) neighbors, none of whom ever recover (the farm became infected through one of its neighbors, so no more than \(n-1\) neighbors can be susceptible) (Bauch, 2005). Thus \(R_0 \leq n-1\). If infectious farms recover (to recovered compartment), i.e. \(\sigma > 0\), then the susceptible denominator is still at most \(n-1\), i.e. \(R_0 \leq n-1\).

Thus if each farm has \(n=4\) neighbors, then \(R_0 \leq n-1 = 3\), for all \(\tau\) and \(\sigma\).

Therefore on a squares-grid torus, an infected farm can infect at most 3 of its 4 neighbors.

If \(R_0 = 1\), then \(\tau = \frac{3 \times 1}{63 - 16 \times 1} = \frac{3}{47} \approx 0.064\);
If \(R_0 = 2\), then \(\tau = \frac{3 \times 2}{63 - 16 \times 2} = \frac{6}{31} \approx 0.194\);
If \(R_0 = 3\), then \(\tau = \frac{3 \times 3}{63 - 16 \times 3} = \frac{9}{15} \approx 0.600\).

Our baseline choice of the transmission rate is \(\tau = 0.600\).

References