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A model exploration of carrier and movement transmission as potential explanatory causes for the persistence of foot-and-mouth disease in endemic regions

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Abstract

Foot-and-mouth disease (FMD) is a virulent and economically important disease of livestock, still endemic in many areas of Asia and sub-Saharan Africa. Transmission from persistently infected livestock, also known as carriers, has been proposed as a mechanism to support the persistence of FMD in endemic regions. However, whether carrier livestock can infect susceptible animals is controversial; recovered virus is infectious and there are claims of field transmission, but it remains undemonstrated experimentally. Alternate hypotheses for persistence include the movement of livestock within and between regions, and fomite contamination of the environment. Using a stochastic compartmental ordinary differential equation (ODE) model, we investigate the minimum rates of carrier transmission necessary to contribute to the maintenance of FMD in a region, and compare this to the alternate mechanism of persistence through cattle shipments. We find that carrier transmission can theoretically support persistence even at transmission rates much lower than the highest realistic rates previously proposed, and that the parameters with the most effect on the feasibility of carrier-mediated persistence are the average duration of both the carrier phase and natural immunity. However, shipment-mediated persistence remains a viable alternate mechanism for persistence without carrier transmission.

KEYWORDS
cattle, fomites, foot-and-mouth disease, livestock, maintenance

1 | INTRODUCTION

Foot-and-mouth disease (FMD) is one of the most important diseases of livestock in the world, causing billions of dollars in economic damage in low and middle income countries (LMIC) annually (Grubman & Baxt et al., 2004; Knight-Jones & Rushton et al., 2013). The causative agent of the disease is a virus, which can infect approximately 70 species of cloven-hoofed animals, including domestic cattle, sheep, goats and pigs (Grubman & Baxt, 2004). Although the disease results in low mortality in infected animals, it causes high morbidity and can result in painful lesions around the mouth and feet from which it takes its name. The disease is also incredibly transmissible, with estimates of the individual reproductive ratio (R_0) ranging up to 70 (Woolhouse et al., 1996).

Distribution of the disease is uneven globally, with many developed countries being free of the disease while in many LMICs the disease is endemic. The presence of FMD in these countries represents a risk of reintroduction into areas currently free of the disease, leading to substantial trade barriers in international livestock and livestock-derived markets. Countries where FMD is present experience losses in revenue from the trade barriers imposed, as well as impairment of their food

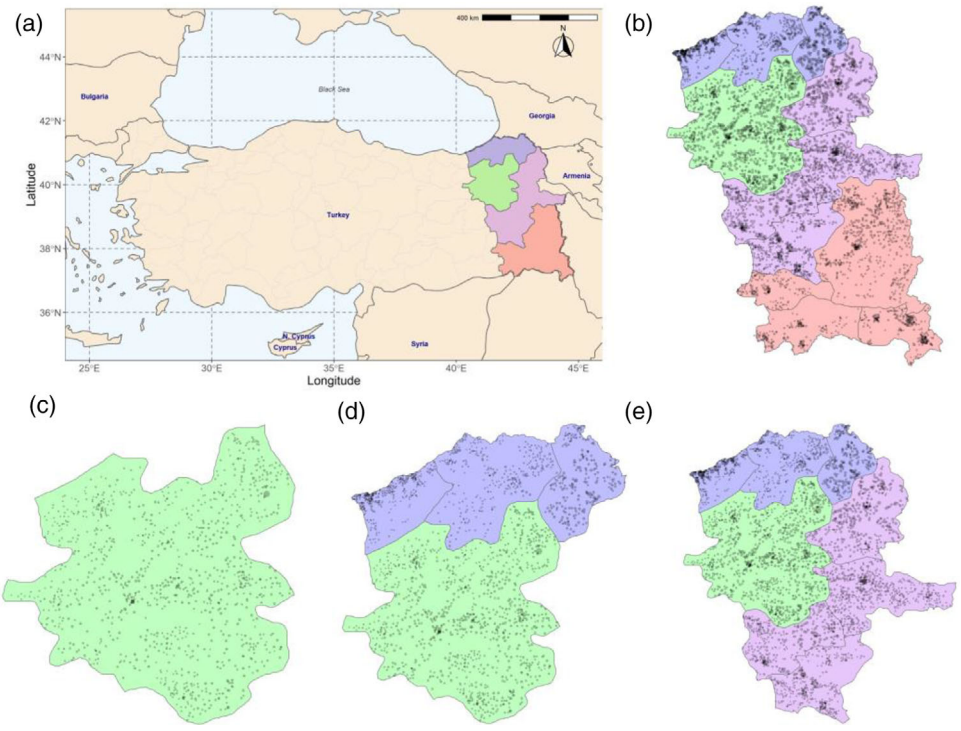

FIGURE 1 a) The regions of Turkey modelled, made up of sets of provinces. Four different areas were simulated, shown in different colours, relevant statistics for each of the regions being provided in Table 7. ER (red) contains I2, I2 (purple) contains I1, I1 (blue) contains EZ (green). (b) The Eastern Region (ER), shown with farm locations as points. This region contains all of the others. (c) Erzurum Province (EZ). (d) Intermediate 1 (I1) region, containing Erzurum. (e) Intermediate 2 (I2) region, containing the smaller I1 region

TABLE 1 Summary of the regions modelled, approximate area in square kilometres, the number of farms modelled and the number of cattle. The value of these statistics with reduced densities is also provided to avoid duplication

Region (code)	Area (~km^2)	Density (%)	Number of farms	Number of cattle
Eastern Region (ER)	120,305	100	5170	2,048,283
		75	3877	1,542,548
		50	2585	1,023,206
		25	1292	521,368
Intermediate 2 (I2)	81,537	100	4014	1,838,563
		75	3010	1,383,690
		50	2007	904,877
		25	1003	441,236
Intermediate 1 (I1)	42,083	100	2109	922,808
		75	1581	668,700
		50	1054	423,767
		25	527	217,682
Erzurum Province (EZ)	25,066	100	1108	605,177
		75	831	468,243
		50	554	298,569
		25	277	153,231

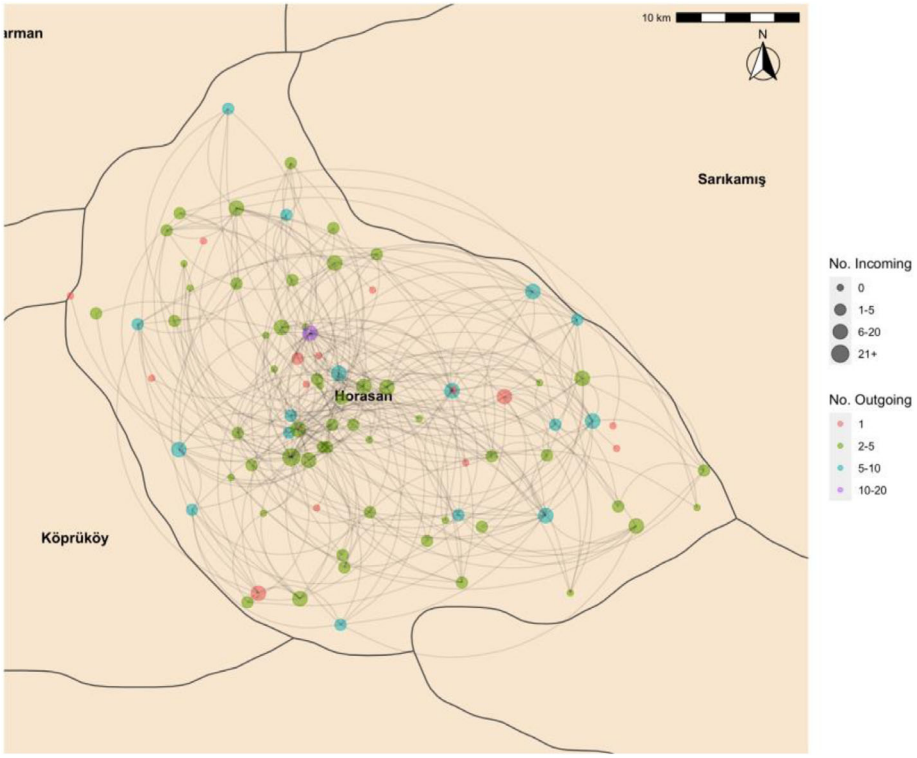

FIGURE 2 Individual cattle shipments within Horasan District, Erzurum Province, on 1 June 2012. Each point is a farm. The colour of a point indicates how many shipments leave the farm on that day (weighted outdegree), and the size of the point indicates the number of shipments received by that farm on that day (weighted indegree). Each line between points represents an individual cattle shipment. This example shows only 326 of the 19,486 shipments we have data for within Horasan district 2007–2012

security and the costs of measures to prevent and control the disease (Knight-Jones et al., 2017). Free countries experience costs related to the preventative surveillance and enforcement required to remain free, as the incursion of FMD into a free country can have devastating impacts on the country's agricultural industry (Knight-Jones & Rushton, 2013).

Research into FMD has historically focused on the disease in Western Europe and North America, regions where the disease was once endemic but is now extinct, and more recently the effect of reintroduction of the disease into these free regions on the agricultural industry (Björnham et al., 2020; Brown et al., 2003; Keeling, 2001; Tildesley et al., 2012). For a variety of reasons including lack of good quality data and the more complex dynamics of multiple circulating serotypes and natural immunity, less research has focused on the disease in endemic areas.

FMD exhibits several possible distinct phases of infection. Upon infection with foot-and-mouth disease virus (FMDV), animals enter a latent (or exposed) phase where the virus replicates within the host animal but the animal is not infectious and no symptoms are exhibited. In cattle, approximately 2 days before symptoms are shown, the animal begins shedding infectious virus, becoming sub-clinically infectious (Yadav et al., 2019). The vast majority of naïve cattle exhibit clinical symptoms: most commonly lesions around the mouth, tongue and feet, as well as a fever and possible lameness, during which they are clinically infectious (Stenfeldt & Arzt, 2020). Following this phase, a proportion of the cattle recover fully and generate immunity against the strain or serotype they were infected with, and the remainder become persistently infected—these animals are known as carriers. Persistently infected cattle display no symptoms, but have detectable levels of virus recoverable from the oro-pharyngeal fluid (OPF) more than 28 days post-infection; this period can potentially last up to 3 years, although most evidence suggests around 6 months to 1 year is likely (Stenfeldt & Arzt, 2020; Tenzin et al., 2008). Experimental evidence suggests that close to 50% of cattle become persistently infected, although field studies find lower proportions (Stenfeldt & Arzt, 2020; Stenfeldt et al., 2016, 2011; Sutmoller et al., 1968). Vaccination does not prevent an animal becoming persistently infected (Stenfeldt et al., 2016).

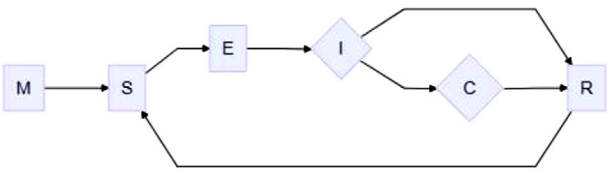

FIGURE 3 The basic disease compartments which animals in the model can be in. (M)aternal, (S)usceptible, (E)xposed, (I)nfectious, (R)ecovered and (C)arrier. Moving between these compartments is done at different rates, dependent on the population of each compartment as well as model inputs. These equations are described in Equation 1

TABLE 2 Relevant parameters of the ordinary differential equations (ODEs) and model, with their value(s)

Parameter	Parameter description	Value(s)	Source(s)
α	Per-capita birth rate	2%/year	
β_a	Acutely infectious transmission	6/11	(Yadav et al., 2019)
β_c	Carrier transmission	Variable	(Bertram et al., 2018; Parthiban et al., 2015; Tenzin et al., 2008)
γ	Recovery rate	1/11 days	(Yadav et al., 2019)
λ_r	Average duration of recovered state	Variable	(Doel, 2003)
λ_c	Average duration of carrier state	Variable	(Bertram et al., 2018)
μ	Rate at which maternal immunity wanes	120 days	(Nicholls, Black, & Rweyemamu, 1984; Tenzin et al., 2008)
σ	Symptomatic rate	1/1.5 days	(Yadav et al., 2019)
Ω_d	Infection mortality	2%	(Şentürk & Yalçin, 2008)
Ω_n	Per-capita natural mortality rate	2%/year	
k_c	Proportion infected that become carriers	50%	(Sutmoller et al., 1968; Stenfeldt et al., 2011, 2016)
T	Inter-farm per capita transmission	6.8e-6	(Keeling et al., 2001; Tildesley et al., 2006)
N_i^{inf}	Infectious population at farm i	Variable	
S	Per-capita susceptibility	1	
N_j^{sus}	Susceptible population at farm j	Variable	
$K(d_{ij})$	Distance-based kernel	Equation (2)	(Jewell et al., 2009)
d_{ij}	The distance between farms i and j	Variable	
Scale	Kernel scale parameter	1	(Jewell et al., 2009)
Shape	Kernel shape parameter	2	(Jewell et al., 2009)

TABLE 3 The parameter values investigated for carrier-induced persistence, carrier-1. The combinations of all of these values were simulated

Parameter	Value set
Population Multiple	x1, x2, x4
Shipments	Simulated, not simulated
λ_r	365, 730, 1095, 1460 (days)
k_c	0.0, 0.5
λ_c	180, 540, 900, 1260 (days)
β_c	2.67e-3, 1.33e-3, 6.67e-4, 3.33e-4, 1.67e-4, 8.33e-5, 4.17e-5

TABLE 4 The parameter values investigated for carrier-induced persistence, carrier-2. β_c was halved until all parameter sets no longer exhibited persistence. The combinations of all of these values were simulated. Population multiple, shipments, and k_c were no longer varied due to the results of carrier-1

Parameter	Value set
Population Multiple	x1
Shipments	Not simulated
λ_r	365, 730, 1095, 1460 (days)
k_c	0.5
λ_c	180, 540, 900, 1260 (days)
β_c	4.17e-5, 2.08e-5, 1.04e-5, 5.21e-6, 2.61e-6, 1.30e-6, 6.51e-7, 3.26e-7, 1.63e-7, 8.14e-8, 4.07e-8, 2.03e-8, 1.02e-8, 5.09e-9, 2.54e-9, 1.27e-9, 6.36e-10, 3.19e-10, 1.59e-10, 7.95e-11

It is uncertain (and controversial) whether or not carrier animals are infectious and can transmit the virus to other susceptible animals (Alexandersen et al., 2002; Stenfeldt & Arzt, 2020). Multiple experimental studies have failed to find evidence of transmission or viral shedding from carrier animals, and it has never been observed in the field, including recent field studies in Vietnam and India (Alexandersen et al., 2002; Bertram et al., 2018, 2020; Hayer et al., 2018; Moonen et al., 2004). Outbreaks of serotype SAT2 in Zimbabwe in 1989 and 1991 were blamed on carrier transmission; however, the truth of the matter is unclear and this has not been confirmed (Alexandersen et al., 2002). However, a summary of the experimental transmission studies by Tenzin et al. (2008) noted that after calculating a rate of transmission following a synthesis of multiple studies, the probability of not observing any transmission in those studies with the calculated transmission rate remained above 5%. More recently, research has demonstrated that the virus taken from the OPF can be infectious (Arzt et al., 2018). If carriers can transmit, it is clear that the per-capita probability of such an event must be very low. The possibility of carrier animals triggering a new outbreak after a contained outbreak is one of the reasons why the OIE-mandated trade ban lasts for 6 months if a vaccinate-to-live policy is used rather than the 3 months for a vaccinate-to-kill policy.

TABLE 5 The parameter values which were investigated for shipment-induced persistence, shipment-1. For all model simulations runs with these parameters, $k_c = 0.0$ (i.e. there were no carriers simulated)

Parameter	Values
Shipments	Simulated, not simulated
Area modelled	Erzurum Province, Eastern Region
Probability of fomite transmission	0.0, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Long range shipments	Simulated, not simulated
λ_r	365, 730, 1095, 1460 (days)

TABLE 6 The parameter values which were investigated for shipment-induced persistence, shipment-2. For all model simulations with these parameters long range shipments were simulated, but no carriers were simulated ($k_c = 0$). Each combination of these parameters was simulated. Area farm density refers to the percentage of farms randomly selected from each area to be included in the simulation

Parameter	Values
Shipments	Simulated
area modelled	Erzurum Province (EZ), Intermediate-1 (I1), Intermediate-2 (I2) Eastern Region (ER)
Area farm density	25, 50, 75, 100 (%)
Probability of fomite transmission	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0
Long range shipments	Simulated
λ_r	365, 730, 1095, 1460 (days)

Carrier animals being able to infect susceptible animals have been proposed as a mechanism supporting the persistence of the disease in currently endemic areas (Arzt et al., 2018; Condy et al., 1985; Moonen & Schrijver et al., 2000; Tenzin et al., 2008). In this proposed mechanism, carrier animals act as a reservoir for the disease after a prior wave of FMD has immunized a population, allowing reinfection once immunity in the non-carrier animals begins to decline.

An alternate proposed mechanism for persistence of FMD in endemic areas is the movement of infected animals into areas where the animal population is susceptible to the disease (Di Nardo et al., 2011; Fèvre et al., 2006; Rweyemamu et al., 2008). Depending on the farming practices of the region under investigation, this could be through the shipment of livestock between farms or transhumance. In this mechanism, the local population of susceptible animals replenishes after an outbreak via births, movements or waning immunity. The time delays between spatially separated outbreaks in a large area can, therefore, allow the infection to persist by moving between these partially connected and newly susceptible populations. Supporting this interpretation is the known effectiveness of movement bans in reducing the spread of the disease during ongoing outbreaks, although movement alone does not appear to be sufficient to maintain FMDV transmission in regions such as Cameroon (Kim et al., 2016; Tildesley et al., 2019)

Mechanistic mathematical modelling can be a useful technique for exploratory analysis of the emergent dynamics of diseases, without the ethical considerations or expense of real-world animal experiments, and allowing the dynamics of the system to emerge from the known characteristics of the disease in question. Much work has been done modelling FMD in epidemic settings (Björnham et al., 2020; Ferguson et al., 2001; Hayama et al., 2013; Kao, 2002; Keeling, 2001; Schley et al., 2009; Tildesley et al., 2008; Wada et al., 2017); however, relatively few studies have looked at FMD in endemic settings (Kim et al., 2016; McLachlan et al, 2019; Pomeroy et al., 2017; Ringa et al., 2014; Schnell et al., 2019). Of these, only Schnell et al. (2019) and McLachlan et al. (2019) investigate the possible role of carriers in persistence of the disease. In this study, we use the Republic of Turkey and seek to investigate and compare the plausibility of the outlined hypotheses using a stochastic compartmental ODE model.

2 | MATERIALS AND METHODS

2.1 | Data

Detailed agricultural data from 2010 were available from the Sap Institute in the Republic of Turkey. This data set consisted of 54,096 farm locations (longitude and latitude) and 47,804 cattle headcounts for these farms. Additionally, 14,261,447 daily farm-specific cattle shipment records were used, which covered the entirety of the Republic of Turkey between 2007 and 2012 and which contained the date of shipment, source and destination farms, and the number of animals moved. A subset of these farm data was used, shown in Figure 1 and outlined in Table 1. As an example of the shipment records, a subset of the records is displayed in Figure 2. Incorporating these records allowed for the seasonality of such shipments to be explicitly modelled. After cleaning and cross-referencing, only those data where a location and a headcount could be matched were used, reducing the number of farms to 40,208.

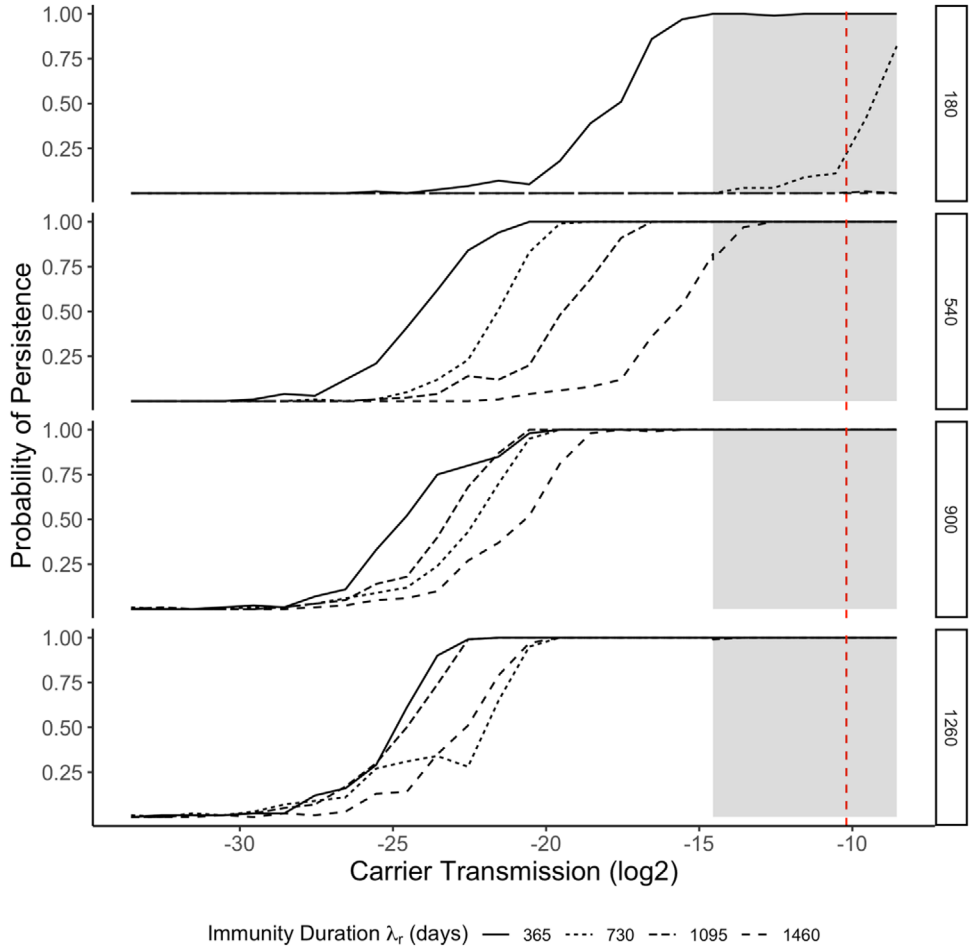

FIGURE 4 The observed relationship between the probability of persistence and carrier transmission for four different values of carrier duration (indicated on the right). Each type of line represents a given immunity duration (λ_r). The red vertical line indicates the estimated carrier transmission value by Tenzin et al. (2008). The values explored in carrier-1 lie in the grey area to the right. For any given value of immunity duration (λ_r), an increase in the duration of the carrier state (λ_c) increases the probability of persistence. For any given duration of the carrier state (λ_c), an increase in the duration of immunity decreases the probability of persistence

In order to attain reasonable model running times, only a geographical subset of Turkey was used, corresponding to those data in the 13 easternmost provinces, into nested regions (Figure 1, Table 1). The smallest region modelled was Erzurum Province (EZ); the next largest was Intermediate 1 Region (I1) which contained EZ and added Rize, Artvin and Ardahan. Intermediate 2 Region (I2) contained I1 and added Kars, Igdir, Agri, Mus and Bitlis. Finally, the largest region modelled contained I2 as well as Hakkari, Siirt, Sirnak and Van, and was referred to as Eastern Region (ER).

2.2 | Model

In this study, we utilize a metapopulation model where each farm is considered a separate population and the within-farm and between-farm dynamics are modelled interdependently. This provides an advantage in modelling potential carrier transmission—any such transmission would almost certainly be constrained to those animals closest to the carrier. Figure 3 describes the progression of disease states for each infected animal. At the beginning of the model timeline, it is assumed that all animals are in the susceptible compartment, and infection is seeded at a random farm or farms. Within each population, progression to the exposed/latent stage is dependent on contact rates with infectious cattle (β_a) and carrier animals (the much smaller β_c). Once exposed, cattle proceed to become infectious dependent on rate σ, and then either recover or become carrier animals. Recovered animals are considered immune to the disease, but this immunity decays over time to become susceptible again. Carrier animals are modelled if the proportion of carriers (k_c) is above 0, and will gradually proceed to the recovered compartment, simulating the final clearance of the virus. Natural mortality and natality are modelled, with maternally immune offspring dependent on the proportion of the population with some immunity to the disease. For infected stages (exposed/latent and infectious), disease mortality is also simulated. Progression between these compartments is described by ordinary differential equations (ODEs) outlined in Equation (1). The meaning of each term and the values used are described in Table 2. Stochastic simulation of these ODEs was done via the τ-leap approximation (Keeling & Rohani et al., 2008).

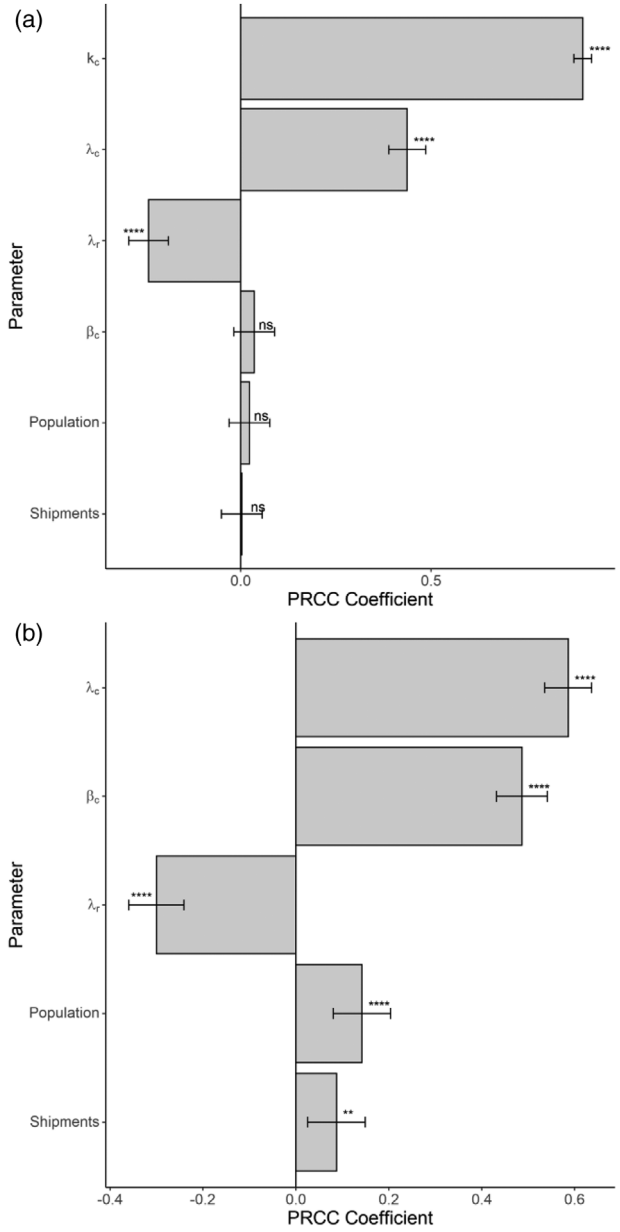

FIGURE 5 The partial rank correlation coefficients (PRCC) for the carrier parameter sets, with error bars indicating the 95% confidence intervals, and stars indicating significance. (a) PRCC for carrier-1 parameter sets. k_c is strongly positively correlated with the probability of persistence. (b) PRCC for carrier-2 parameter sets. β_c is now moderately positively correlated with the probability of persistence

The virus is transmitted between farms either by local spread or the shipments of cattle. The probability of spread from an infected farm to a susceptible farm (defined as a farm where the number of susceptible animals is greater than or equal to 1) via local spread is calculated by Equation 2. This depends on the number of infectious animals on the infecting farm, the number of susceptible animals on the susceptible farm and the distance between them, scaled via a power-law distance-dependent kernel $K(d_{ij})$. This kernel describes how transmission decreases with increasing distance, and is taken from Jewell et al. (2009), but has been used to flexibly describe the spread of FMD in many different regions such as Japan and the United States (Probert et al., 2018; Tsao et al., 2020). To explore uncertainty in the kernel parameterization for Turkey, an assessment of sensitivity of the results to the kernel parameters can be found in the supporting information. For the purpose of computational speed, local spread is done in a grid, using the algorithm outlined in Sellman et al. (2018). If infection was adjudged to happen, the susceptible farm has a number of susceptible animals proceed to the exposed/latent stage, drawn from a binomial distribution.

$$P_{ij} = 1 - e^{-TN_i^{inf} SN_j^{sus} K(d_{ij})} \quad (1)$$

$$K\ (d_{ij}) = \frac{1}{1 + \left(\frac{d_{ij}}{\text{scale}}\right)^{\text{shape}}} \quad (2)$$

Livestock shipments are modelled on a daily basis utilizing the animal movement data provided by the Republic of Turkey. Transmission via cattle shipments occurs in two ways, direct shipment of infected animals to the destination farm or indirect transmission via fomite contamination of the vehicle, driver or surroundings. Shipments are modelled as a random sample of cattle without replacement from the source farm; hence, the probability of selecting at least one infected animal for shipment (and therefore direct transmission occurring) is proportional to the shipment size and number of infected animals on the farm. Indirect fomite transmission can also occur when the source farm is infected and is modelled as a simple probability that fomite transmission occurs given that the source farm is infected. This probability is a model parameter input and can be toggled off by setting the parameter to 0.

2.3 | Design

2.3.1 | Investigating carriers

The model was run using different sets of parameters to investigate each hypothesis, referred to as carrier-1. For each combination of the parameter values outlined in Table 3, the model simulated a 5-year period (2007–2012) 100 times. Five years was chosen as the maximum time-period for which full data were available, and for which it could be reasonably assumed that disease persistence indicated endemicity. The population multiple indicates whether the population of each farm had been multiplied, as a test of the effects of farm and overall population on persistence. Shipments not being simulated and carriers not being simulated ($k_c = 0$) are included as null tests to be certain that the effect seen can be attributed to the shipments or carriers being simulated. The proportion of these simulations where FMD was still present at the end of the year was assumed to approximate the probability of persistence given those parameters.

Subsequent to the carrier-1 parameters being simulated, and as an extension to it, the values of β_c investigated were extended by repeatedly dividing by 2 until all parameter sets no longer exhibited persistence, extending down to 7.951400e-11; these values are outlined in

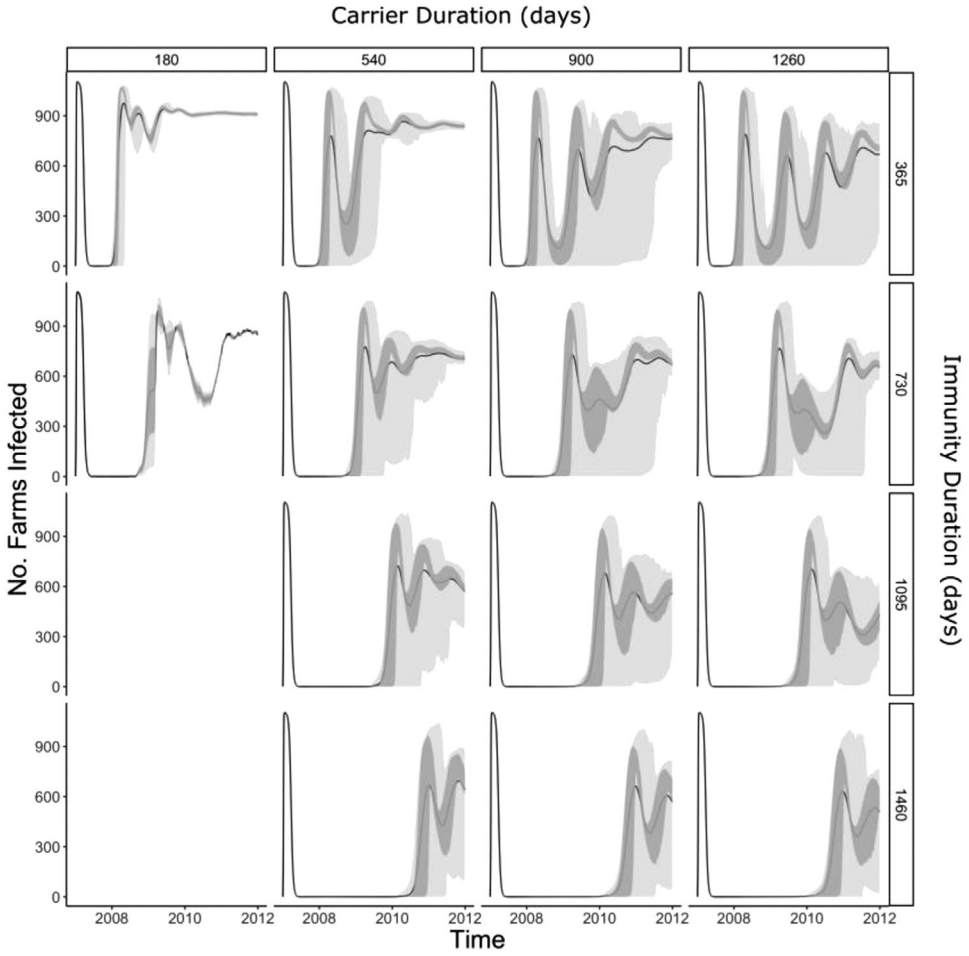

FIGURE 6 Simulated prevalence of foot-and-mouth disease (FMD) over time in simulations where the disease does persist over the 5-year period, organized by carrier (columns) and immunity (rows) duration, taken from the carrier-1 and carrier-2 results. Carrier duration and immunity duration were used as two of the most important parameters to illustrate the trends. Prevalence is defined as the number of farms where at least one animal is acutely infected. The black line indicates the average prevalence for simulations at that time point, the grey area is the interquartile range, and the light grey indicates the 5%–95% range of results at that timepoint. Blank plots indicate combinations of carrier and immunity duration where no simulation exhibited persistence. Where persistence occurred, there is a clear oscillation around a long-term endemic equilibrium, and there is a large time lag between the initial outbreak before the carrier animals re-seed the outbreak and it proceeds towards endemicity. The size of the time lag depends on the duration of immunity

Table 4. Values of β_c below 4.17e-5 were investigated with the population multiple set to 'x1', k_c at 0.5, and no shipments modelled due to the results obtained for carrier-1. λ_r and λ_c were investigated using the same values used in Table 3. This set of parameters is referred to as carrier-2.

2.3.2 | Investigating shipments

The ability of shipments to allow for FMD to persist over the 5-year period was investigated in a similar manner by running the model 100 times with every combination of the parameter values outlined in Table 5, with no carriers modelled ($k_c = 0.0$) for all of these parameter combinations. The probability of fomite transmission represents the probability that a shipment from an infected source farm would transmit infection via fomites to a susceptible destination farm.

Long range (LR) shipments were defined as those shipments where the distance traversed was over 40 km (25 miles). This was arbitrarily chosen as the distance where a completely infected farm of median size (141 cattle) would have a 0.01 probability of infecting a completely susceptible farm of median size via local spread, given the power law distance kernel uses values $a = 1$, scale = 1 and shape = 2. For EZ, excluding LR shipments reduced the number of records from 336,522 to 207,589 (−38.3%); for ER, it reduced the number of records from 2,291,913 to 1,043,478 (−54.5%). The parameter sets outlined in Table 5 are referred to as shipment-1.

As an extension of shipment-1, and to disentangle the effect of the area modelled from the number of farms modelled (which are correlated) on the probability of persistence, the area was split into four areas as previously defined (ER, I2, I1 and EZ), and simulated with either 25%, 50%, 75% and 100% of the farms in that area included. Farms were selected randomly with probability equal to 25%, 50%,

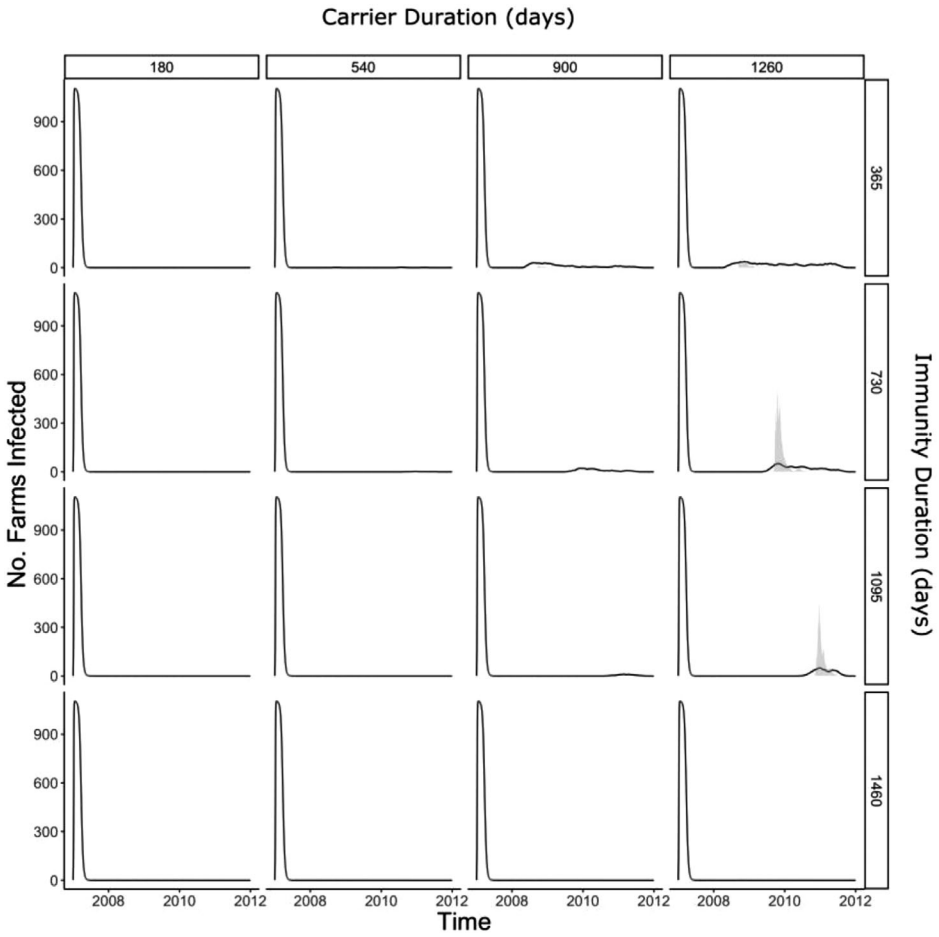

FIGURE 7 Simulated number of farms infected with foot-and-mouth disease (FMD) over time in simulations where the disease does not persist over the 5-year period, organized by carrier (columns) and immunity (rows) duration, taken from the carrier-1 and carrier-2 results. Carrier duration and immunity duration were used as two of the most important parameters to illustrate the trends. Prevalence is defined as the number of farms where at least one animal is acutely infected. The black line indicates the average prevalence for simulations at that time point, the grey area is the interquartile range, and the light grey indicates the 5%–95% range of results at that timepoint. Blank plots indicate combinations of carrier and immunity duration where no simulation exhibited persistence. In these cases, after the initial outbreak burned itself out, there was often no revival of the disease. With some combinations of parameters, there was occasionally a small outbreak following the decline in immunity, but this did not last to the end of the 5-year period

75% or 100%; a set of farms was only accepted if the convex hull area was within 1% of the actual approximate area covered by the 100% set of farms. For each parameter set with density <100%, four replicates were taken and simulated to eliminate the effect of randomly missing possibly important nodes in the shipment network. Each combination of area and density was simulated for 5 years, and the probability of persistence assessed as previously and averaged for the replicates. These parameter sets were referred to as shipment-2 and are shown in Table 6.

2.3.3 | Analysis

Analysis was done in R 4.0.2 (R Core Team et al., 2020). Partial rank correlation coefficient (PRCC) analysis, a sensitivity analysis index, was done using the package epiR 2.0.19 (Marino et al., 2008; Stevenson et al., 2021). Plots were done using ggplot2 3.3.3 (Wickham, 2016).

3 | RESULTS

3.1 | Carrier-induced persistence

Simulating the model with the combinations of parameters found in Table 3, it was found that combinations of parameters with infectious carriers could lead to the persistence of FMD in the population over the 5-year period simulated. This was true with values of β_c (carrier transmission) much smaller than estimated by Tenzin et al. in 2008.

In the carrier-1 parameter set, β_c took the values on the furthest right in Figure 4, extending from 2.67e-3 down to 4.17e-5, whereas carrier-2 included values down to 7.95e-11. Due to the range restricted values, no association of carrier transmission with persistence was found for the carrier-1 parameters, as shown in Figure 5a. As shown in Figure 7, this is due to all the values chosen resulting in persistence being certain. However, with values of β_c extended in the carrier-2 parameter set, a clear relationship between β_c and the probability of

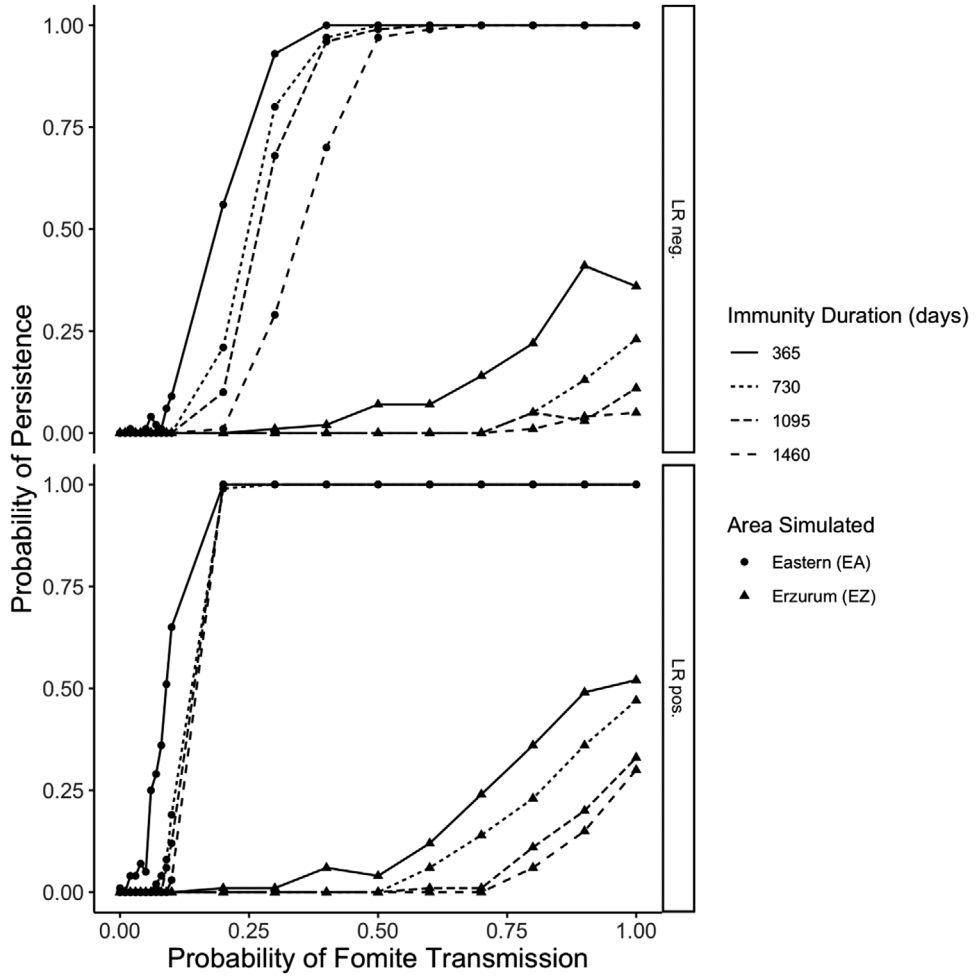

FIGURE 8 The observed relationship between the probability of fomite transmission and the probability of persistence for shipment-1. The top half of the plot contains results when no long-range shipments were simulated, the bottom half when long range shipments were simulated. Each line type indicates a different duration of immunity (λ_r), and each point type the area being simulated. As the probability of fomite transmission increases, the probability of persistence also increases. Erzurum Province (EZ) requires much a higher probability of fomite transmission for persistence than Eastern Region (EA), as it has both a smaller area and fewer farms. Within each area, increasing immune duration increased the probability of fomite transmission required for persistence by a small amount. There is little difference whether long range shipments are simulated or not

persistence is visible. Additionally, a pattern is visible in the relationship between λ_c and λ_r and the probability of persistence in Figures 4 and 5b. Population and the presence/absence of shipments remain uncorrelated with persistence. λ_r is weakly negatively correlated with persistence, as shown in Figure 4 where after holding λ_c constant, a longer duration of immunity decreases the probability of persistence. β_c and λ_c are moderately positively correlated with persistence, also shown in Figure 4.

When $\lambda_c = 1/180$, the probability of persistence = 0 at values of $\beta_c < 2e{-}08$. When $\lambda_c = 1/540|900|1260$, the probability of persistence is close to 0 at values of $\beta_c < 6e{-}10$.

PRCC analysis was performed on these data, as shown in Figure 5a. It was found that the parameter most strongly associated with changes to the probability of persistence is the presence or absence of carriers in the population (k_c). Significantly associated but weakly correlated are λ_r (immunity duration) and λ_c (carrier duration). Figures 6 and 7 show the average prevalence of the disease in the population over the 5-year period simulated, organized by these two parameters and demonstrating the relatively minor effects they have on the probability of persistence. No significant association was found between persistence and population size, the presence/absence of shipments or β_c. These results remain when restricting analysis to parameter sets where $k_c = 0.5$.

3.2 | Shipment-induced persistence

Investigating scenarios where shipments can spread disease and fomite transmission is simulated, we see that no persistence appears to be possible when the probability of fomite transmission = 0, even when simulating the Eastern Region (the largest region). The minimum value of the probability of fomite transmission where persistence is observed

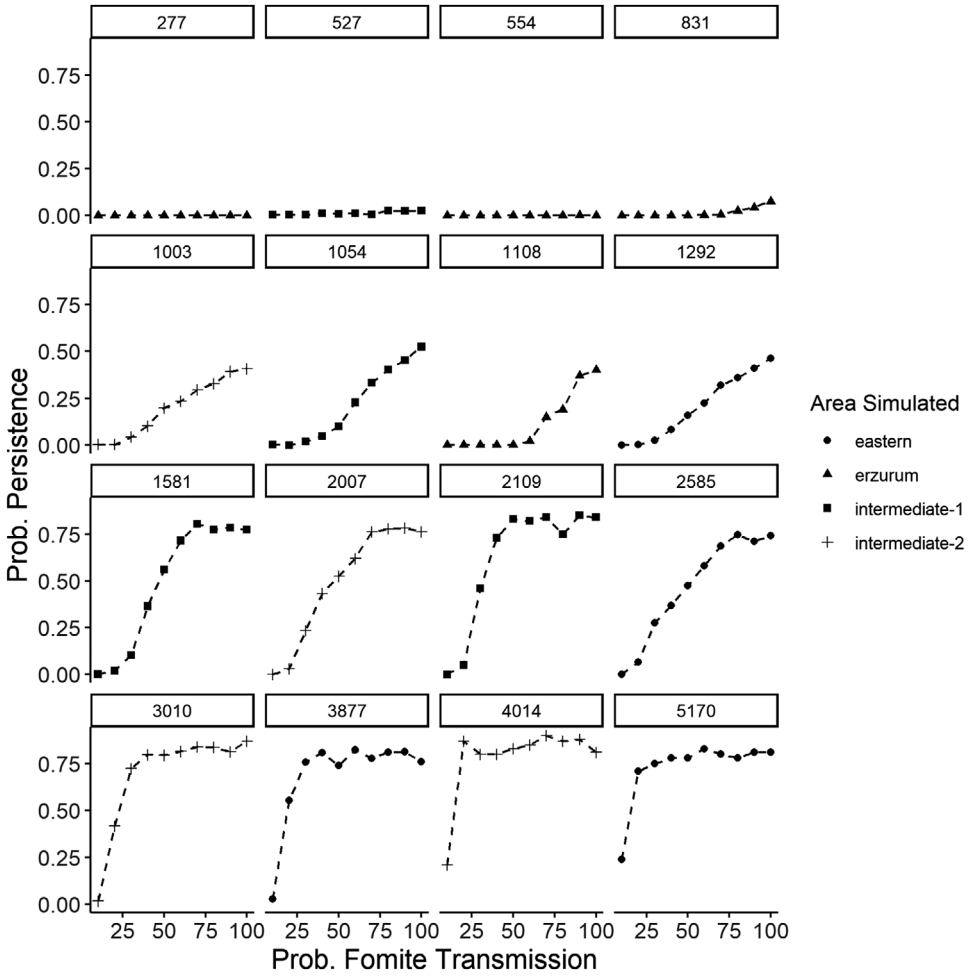

FIGURE 9 The observed relationship between the probability of fomite transmission and the probability of persistence for shipment-2. Each mini-plot indicates the number of farms simulated for these results above it, and the point type indicates the region simulated. Simulating a greater number of farms leads to a greater probability of persistence for a given probability of fomite transmission, with the actual area (km^2) simulated being less important. Persistence curves are most similar to each other when the number of farms simulated is similar, with the different areas (point-type) not clustering together in the same manner

is 0.05 for the Eastern Region, and for Erzurum Province the minimum is 0.5.

Figure 8 demonstrates clearly the relationship between the probability of fomite transmission and persistence for the shipment-1 parameter set, with the persistence curve seen depending in large part on the area simulated. For the Eastern Region (EA), persistence is very likely at low probabilities of fomite transmission, reaching 1 at probabilities of fomite transmission of approximately 0.2–0.3. For Erzurum Province, there is a large difference, with persistence rarely exhibited until the probability of fomite transmission >0.5. A small reduction in persistence is seen from removing long range transmission, as well as a slightly larger reduction from increasing the duration of immunity.

PRCC analysis of the shipment-1 parameter set suggests that the area simulated and the probability of fomite transmission are significantly positively associated with the persistence measure when shipments are simulated, as shown in Figure 9. The presence of long-range movements is not correlated, although the coefficient is significantly different from 0. The duration of immunity was not significantly associated with persistence in this analysis.

Figure 10 outlines the relationship between the probability of fomite transmission and persistence for the shipment-2 parameters, disentangling the effect of greater simulated area from simulating a larger number of farms. An increasing number of farms simulated leads to a greater probability of persistence for a given value of the probability of fomite transmission, independent of the area simulated. This can be seen in the first two mini-plots, where despite having simulated an area twice the size of the first, the second plot has a similar persistence curve because it has a similar low number of farms.

PRCC analysis on the results of shipment-2 parameter sets (including the four-region simulations ER, I2, I1, EZ) revealed a strong positive correlation with the number of farms simulated, in addition to a moderate-to-strong positive correlation with the probability of fomite transmission (Figure 8b). No correlation between the area simulated and persistence was observed.

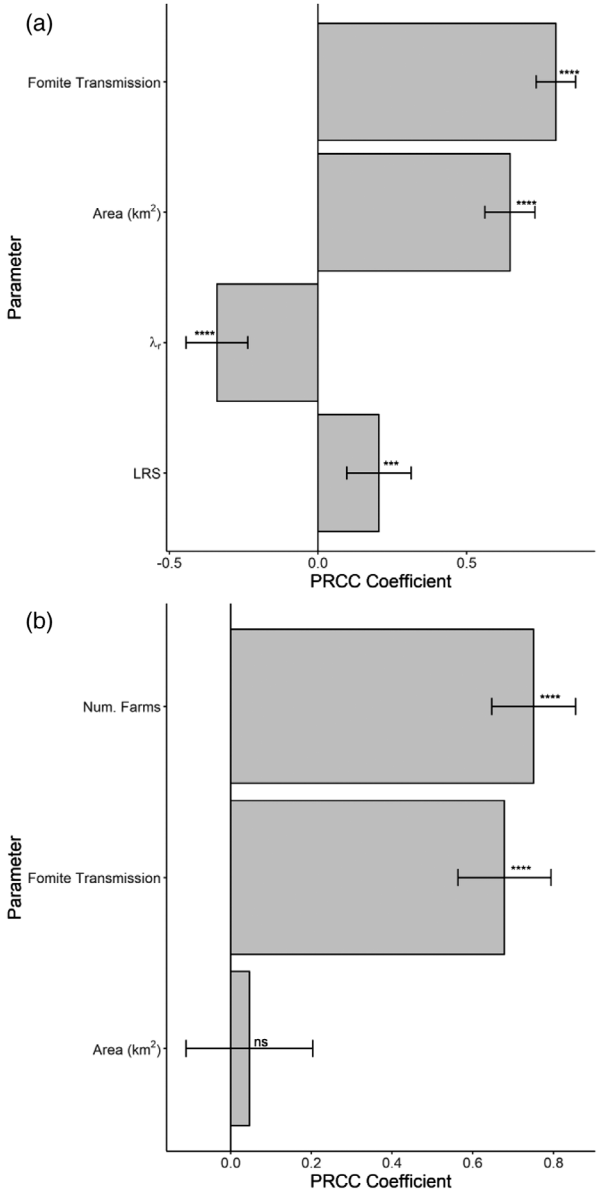

FIGURE 10 The partial rank correlation coefficients (PRCC) for the shipment parameter sets, with error bars indicating the 95% confidence intervals, and stars indicating significance. (a) Results of the shipment-1 PRCC analysis, assuming shipments are occurring. (b) Results of shipment-2 shipment-only PRCC analysis

4 | DISCUSSION

The results presented here suggest that persistence of FMD in populations is possible even with very small per-capita probabilities of transmission and no other pro-persistence factor, and that carriers therefore cannot yet be set aside as a possible cause for the persistence of FMD. This effect seemed to be independent of greater population size, suggesting that current realistic farm sizes are already large enough for this effect to take place.

The values of β_c (carrier transmission) investigated are much smaller than the value estimated by Tenzin et al. (2008), itself an overestimate due to an inability to calculate species-specific β_c due to a lack of experiments. Although that analysis could not explicitly rule out carrier transmission occurring, more studies have been carried out since that might be able to provide greater statistical certainty (Bertram et al., 2018; Hayer et al., 2018; Parthiban et al., 2015). It is unlikely, however, that statistical certainty could be provided for values of β_c as low as seen in these experiments.

Focusing on carriers, the two main factors relating to carrier-induced persistence appear to be the average duration of immunity to FMD, and the average duration of the carrier state. Realistic estimates of these parameters may therefore be important in determining whether carrier-induced persistence is a realistic proposition. Many different studies support different values, with some supporting shorter durations of 6–12 months and others supporting longer durations of up to several years (Bertram et al., 2020; Hayer et al., 2018; Moonen & Schrijver, 2000). Assuming a shorter carrier duration of 6 months, durations of natural immunity longer than 1.5 years appear to rule out undetected transmission from carrier animals, and evidence suggests immunity can last much longer (Doel et al., 2005). However, assuming a longer duration of the carrier state relaxes this, with realistic durations of immunity theoretically allowing both carrier transmission to be happening and to have remain undiscovered by experiments to date.

An important assumption of this study is that carrier transmission is homogenous through time, meaning that a persistently infected animal is as likely to infect a nearby susceptible animal 1 day before it clears the infection as it is 28 days after infection. This is to some extent unavoidable through the use of the τ-leap algorithm, which is memoryless and so has difficulties achieving this. Additionally, since we have difficulty demonstrating carrier transmission at all, there is no evidence that might inform whether or how transmission changes over time. Further work is needed here and it is important to establish whether our results hold under a more pessimistic assumption.

In the absence of explicitly modelled fomite transmission, the shipment of potentially infected cattle from infected farms to susceptible farms did not lead to persistence. This suggests either that the mechanism of persistence in this case is not asynchronous outbreaks in spatially separated areas, or that fomite transmission is necessary to achieve those asynchronous outbreaks.

The minimum probability of fomite transmission necessary for the probability of persistence to be greater than 0 declined as the number of farms modelled increased, suggesting that even small probabilities of fomite transmission would be sufficient for persistence to happen in regions with greater numbers of farms, or larger regions. Shipments therefore appear to represent a viable alternate mechanism for supporting persistence when fomite transmission is explicitly modelled. This model's estimation of the effect of fomite transmission via this route is also likely an underestimate, as it assumes that fomites are only transmitted when the source farm is actively infected. In reality, fomites can survive for up to 6–9 months in the environment given favourable conditions, expanding the time period where fomites might contaminate vehicles and likely reducing further the necessary to contribute to persistence (Mielke & Garabed et al., 2020).

In conclusion, this study suggests that carrier-induced persistence cannot yet be discounted as a possibility, with our modelling approach demonstrating the ability of even very sporadic carrier transmission events that are unlikely to be detected to support persistence within a greater population. The main factors that affect the plausibility of carrier transmission being epidemiologically relevant to persistence are the duration of the carrier state and the immune state—further work on elucidating those are likely to narrow the range of values at which potential carrier transmission can be epidemiologically relevant and simultaneously undetected. However, shipment-induced persistence is a viable alternate mechanism by which persistence might occur and requires only small probabilities of fomite transmission. As fomite transmission is a recognized and well-studied mechanism, whereas carrier transmission has still not been shown to occur in the field, this study suggests that shipment-induced persistence remains the more likely of the two hypotheses to be occurring.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a modelling article with no original research data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.4926098. Model code is available at https://doi.org/10.5281/zenodo.4926103.

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