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Modelling flock heterogeneity in the transmission of peste des petits ruminants virus and its impact on the effectiveness of vaccination for eradication

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ABSTRACT

Peste des petits ruminants (PPR) is an acute infectious disease of small ruminants targeted for global eradication by 2030. The Global Strategy for Control and Eradication (GSCE) recommends mass vaccination targeting 70% coverage of small ruminant populations in PPR-endemic regions. These small ruminant populations are diverse with heterogeneous mixing patterns that may influence PPR virus (PPRV) transmission dynamics. This paper evaluates the impact of heterogeneous mixing on (i) PPRV transmission and (ii) the likelihood of different vaccination strategies achieving PPRV elimination, including the GSCE recommended strategy. We develop models simulating heterogeneous transmission between hosts, including a metapopulation model of PPRV transmission between villages in lowland Ethiopia fitted to serological data. Our results demonstrate that although heterogeneous mixing of small ruminant populations increases the instability of PPRV transmission—increasing the chance of fadeout in the absence of intervention—a vaccination coverage of 70% may be insufficient to achieve elimination if high-risk populations are not targeted. Transmission may persist despite very high vaccination coverage (>90% small ruminants) if vaccination is biased towards more accessible but lower-risk populations such as sedentary small ruminant flocks. These results highlight the importance of characterizing small ruminant mobility patterns and identifying high-risk populations for vaccination and support a move towards targeted, risk-based vaccination programmes in the next phase of the PPRV eradication programme. Our modelling approach also illustrates a general framework for incorporating heterogeneous mixing patterns into models of directly transmitted infectious diseases where detailed contact data are limited. This study improves understanding of PPRV transmission and elimination in heterogeneous small ruminant populations and should be used to inform and optimize the design of PPRV vaccination programmes.

1. Introduction

Peste des petits ruminants (PPR) is an acute infectious disease of small ruminants, caused by the peste des petits ruminants virus (PPRV), a virus of the *Morbillivirus caprinae* species within the *Morbillivirus* genus which includes measles virus, canine distemper virus and the eradicated rinderpest virus. PPRV occurs in Africa, the Middle East and Asia, regions which account for 80% of the global population of small ruminants (FAO and OIE, 2015). PPRV outbreaks can cause high morbidity and mortality in affected flocks, and global economic losses due to PPRV are estimated to be between $1.5–2 billion USD annually with disproportionate impacts on subsistence farmers in low- and middle-income countries (Jones et al., 2016). In 2015, the Food and Agriculture Organisation (FAO) and the World Organisation for Animal Health (WOAH)

Abbreviations: PPR, *peste des petits ruminants*; PPRV, *peste des petits ruminants virus*; GSCE, Global Strategy for Control and Eradication.

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launched the Global Strategy for the Control and Eradication of PPR (PPR GSCE) targeting the global eradication of PPRV by 2030 (FAO and OIE, 2015). A core approach of the GSCE is mass vaccination of small ruminant populations using effective live-attenuated vaccines which provide long-term protective immunity after a single inoculation (Sen et al., 2010; Zhao et al., 2021).

The GSCE aims to reach a post-vaccination immunity rate of at least 70% in endemic small ruminant populations (FAO and OIE, 2015). However, between 2015 and 2018, 333 million doses of PPRV vaccine were distributed which constituted less than 25% of the target coverage (Zhao et al., 2021). In 2018, of 66 countries recorded as infected, only one country reported vaccine distribution reaching 70% of small ruminants and in countries with distribution approaching or exceeding 70%, PPRV outbreaks have been routinely reported (Zhao et al., 2021). These figures highlight the challenge of implementing large-scale mass-vaccination campaigns and indicate that very high vaccine coverages may be required to achieve elimination in some small ruminant populations.

Vaccination coverage targets (or critical vaccination thresholds) can be estimated using mathematical models which typically make simplifying assumptions about population mixing patterns, often assuming homogenous mixing where units (i.e., individuals or groups) mix randomly (Anderson and May, 1991). Departures from this assumption—to heterogeneous mixing—alter population-level disease dynamics and critical immunity thresholds for elimination with implications for the optimal vaccination strategy (Bansal et al., 2007; Hill and Longini, 2003). In heterogeneously mixing populations, vaccination may be targeted to sub-populations with high contact rates with the effect of lowering the population-wide critical vaccination threshold.

The mixing patterns of small ruminants in PPRV endemic regions are shaped by husbandry systems, trade, religious and cultural practices, and climatic and geographic factors (Apolloni et al., 2018; Bouslikhane, 2015). Serological studies from East Africa (Herzog et al., 2020, 2019; Kivaria et al., 2013; Megersa et al., 2011; Swai et al., 2009) and a PPRV transmission model in lowland Ethiopia (Fournié et al., 2018), provide evidence that pastoralist management systems have higher seroprevalence and increased risk of PPRV transmission than more sedentary agropastoralist or mixed farming systems. Under pastoralist husbandry systems, livestock mix with other flocks at common grazing and watering points resulting in high contact rates and high potential for PPRV transmission (Waret-Szkuta et al., 2011). Under sedentary mixed crop-livestock and agropastoralist husbandry systems livestock are much less mobile (Otte and Chilonda, 2002). Heterogeneous mixing patterns within and between flocks under different husbandry systems present an opportunity to target high-risk pastoralist populations for vaccination. However, these mobile pastoralist populations are common to geographically remote regions and areas of political or economic instability and therefore may be difficult to access for vaccination (Zhao et al., 2021). This can create a bias towards 'convenience vaccination' of the more accessible sedentary populations which have lower transmission potential, and a possible barrier to elimination as flocks which contribute disproportionately to transmission are systematically missed. Such problems were experienced during the rinderpest eradication programme where transmission was able to persist in sub-populations with low vaccination coverage despite high coverage of the overall population (Mariner et al., 2012).

Heterogeneous mixing may be integrated into mathematical models when detailed outbreak data or high-resolution contact information are available. Contact matrices incorporate heterogeneous mixing into compartmental models, accounting for variable contact rates between sub-populations (e.g. age-groups, sexual activity groups) (Garnett and Anderson, 1993; Glasser et al., 2012; Jacquez et al., 1988). Simulation of disease transmission on well-characterized contact networks (Kao et al., 2006; Milwid et al., 2019) or using spatially resolved data (Lambert et al., 2020; Mancy et al., 2022) has also been applied to understand transmission and the effectiveness of control interventions in heterogeneous populations and landscapes. However, when empirical contact data are scarce and transmission heterogeneity cannot be reliably estimated, studies may default to the homogeneous mixing assumption. In such contexts, a framework for incorporating different levels of transmission heterogeneity (heterogeneous mixing) would enable the sensitivity of model outcomes under different population mixing patterns to be explored. This approach would be particularly relevant in data-limited settings when assessing the likelihood of infectious disease emergence or eradication which is heavily impacted by transmission heterogeneity (Bansal et al., 2007; Lloyd-Smith et al., 2005).

The aim of this study is to evaluate the impact of heterogeneous mixing on PPRV transmission dynamics and suggest optimal vaccination strategies for PPRV eradication. We first use a general model (Model I) of an unspecified, directly transmitted virus to explore the sensitivity of disease dynamics and the effectiveness of vaccination under different population mixing patterns (i.e., transmission heterogeneity). Here, the epidemiological unit is not defined but may be either an individual (human or animal) or a group of hosts in a metapopulation. We suggest the negative binomial distribution as a framework for incorporating transmission heterogeneity where empirical data are limited. We then adapt a stochastic meta-population model of PPRV transmission (Model II) in small ruminant populations, parameterized using serological data from pastoral flocks of lowland Ethiopia, to assess the effectiveness of competing vaccination strategies—including the GSCE vaccination strategy—in heterogeneously mixing populations. Our results are discussed in the context of eradicating PPRV by 2030.

2. Materials and methods

2.1. Model I: Dynamics of a directly transmitted virus in a heterogeneously mixing population

We developed an agent-based, continuous-time, stochastic Susceptible-Infectious-Recovered (SIR) transmission model to explore the impact of heterogeneous mixing on the transmission dynamics of a directly transmitted virus. Agent-based models explicitly represent each unit and its disease state over time, a unit being defined as an individual host or the smallest group of hosts that share approximately the same likelihood of exposure to a pathogen (World Organization for Animal Health, 2023). This approach enables specification of unit-level characteristics and is therefore suitable for modelling populations with a high degree of heterogeneity. Here, we consider 'transmission heterogeneity' to be driven by heterogeneity in unit contact patterns (i.e., heterogeneous mixing). We consider units to differ exclusively in their transmission potential v_i, the number of effective contacts (contacts resulting in infection if made with a susceptible unit) made by an infected unit i during its infectious period. The number of effective contacts made by a unit is determined by the contact rate (frequency of contacts) and, importantly, by the probability of a contact being effective i.e., resulting in infection, which is influenced by the type (closeness) and duration of contact (Sun et al., 2021). In this theoretical exploration, the pathogen is not specified (i.e., it may be any directly-transmitted pathogen) and the unit of the model is context-dependent, but could be an individual host (human or animal), or group of hosts (e.g. schoolchildren, livestock herd, or sub-population) that share similar risks of exposure.

In Model I, units move discretely between three mutually exclusive states: susceptible, infected and recovered. Briefly, a susceptible unit becomes infected following effective contact with an infectious unit, modelled as a stochastic process. An infected unit, i, makes v_i effective contacts which are randomly sampled from the population during its infectious period, τ. After τ days, an infected unit transitions to the recovered state and is protected against further infection for an immune period, γ. Parameters τ and γ were assumed uniform for all units and parameter α was defined as the ratio τ/γ, the relative duration of infectious to immune periods. Following the immune period, a recovered unit loses protective immunity, and returns to the susceptible state. A

loss of natural or vaccine-derived immunity may be driven by a waning of antibody response at the individual level, or population turnover at the group level as immune individuals are lost (e.g., through deaths, emigration or offtake) and replaced with susceptible individuals (e.g., through births, immigration or intake). This loss of protective immunity following infection permits replenishment of susceptible units without explicit consideration of demographic processes (e.g., births and deaths). A unit in any state can also be selected for vaccination with likelihood χ_i and, once vaccinated, is protected against infection for the duration of the simulation.

2.2. Modelling transmission heterogeneity

We assumed that unit transmission potential, v_i, followed a negative binomial distribution with mean, m, and dispersion parameter, k. Parameter m is the mean number of effective contacts made by an infected unit during its infectious period, hence $m = R_0$. The negative binomial distribution has been previously used to model the over-dispersed distribution of the number of effective contacts made by infected individuals for a range of human diseases (Allard et al., 2020; Lloyd-Smith et al., 2005). As $k \to 0$, the overdispersion of v_i increases (high transmission heterogeneity), and v_i is low or null for most units and very high for a small number of units (Fig. 1) (Lloyd-Smith et al., 2005). As $k \to \infty$, the overdispersion of v_i decreases (low transmission heterogeneity) and v_i tends towards a Poisson distribution. The geometric distribution is a further special case of the negative binomial distribution for $k = 1$ (Fig. 1).

2.3. Modelling vaccination strategies

Three vaccination strategies were assessed: (i) random vaccination, defined as random selection of units for vaccination, (ii) targeted vaccination, defined as biased selection of units with a high transmission potential, and (iii) convenience vaccination, defined as biased selection of units with a low transmission potential. For each of the targeted and convenience vaccination strategies, two levels of bias were investigated: extreme bias (denoted A) and intermediate bias (denoted B), with the level of bias defined by the vaccine bias index (x). Vaccination was implemented at time t_v, defined a-priori in the vaccination schedule. At t_v, a proportion V of units (i.e., the vaccine coverage) were sampled for vaccination with each unit assigned a probability weight χ_i given by:

$$\chi_i = \frac{(v_i)^x}{\sum_i (v_i)^x} \quad (1)$$

When $x = 0$, χ_i is equal for all units ($\chi_i = 1/N$) and vaccination is random (no bias). When $x < 0$ the likelihood of selection for vaccination decreases as v_i increases and vaccination is biased towards units with lower transmission potential (convenience vaccination). When $x > 0$, the likelihood of selection for vaccination increases as v_i increases and vaccination is biased towards units with higher transmission potential, (targeted vaccination) (Fig. 2). The absolute value of x was arbitrarily set to ± 4 or ± 0.5 to indicate extreme (A) and intermediate (B) bias respectively. The impact of biased vaccination is exacerbated as transmission heterogeneity increases; in more heterogeneous populations ($k = 0.1$) the probability of vaccination tends to 1 or 0 more rapidly as v_i increases for targeted and convenience strategies respectively.

2.4. Simulations to explore the impact of heterogeneous mixing on the dynamics of a directly transmitted virus

The impact of heterogeneity in v on the probability of stochastic extinction (p) was explored for a range of epidemiological scenarios correponding to different parameter combinations (R_0, k and α). For each scenario, a transmission potential was randomly drawn (without replacement) from a negative binomial distribution with mean $m = R_0$ and dispersion parameter k for each unit in the population. Each scenario was repeated for 1000 iterations over a 5-year (1825 day) simulation period. The probability of extinction (p) was the proportion of simulations with no infected units at the end of the simulation period. The population comprised 10,000 units and infection was seeded randomly at the start of the simulation in 1% of the population (100 units).

The impact of heterogeneity in v on the effectiveness of vaccination was investigated by exploring the probability of elimination (p_v) at different vaccination coverage, V, under random ($x = 0$), targeted

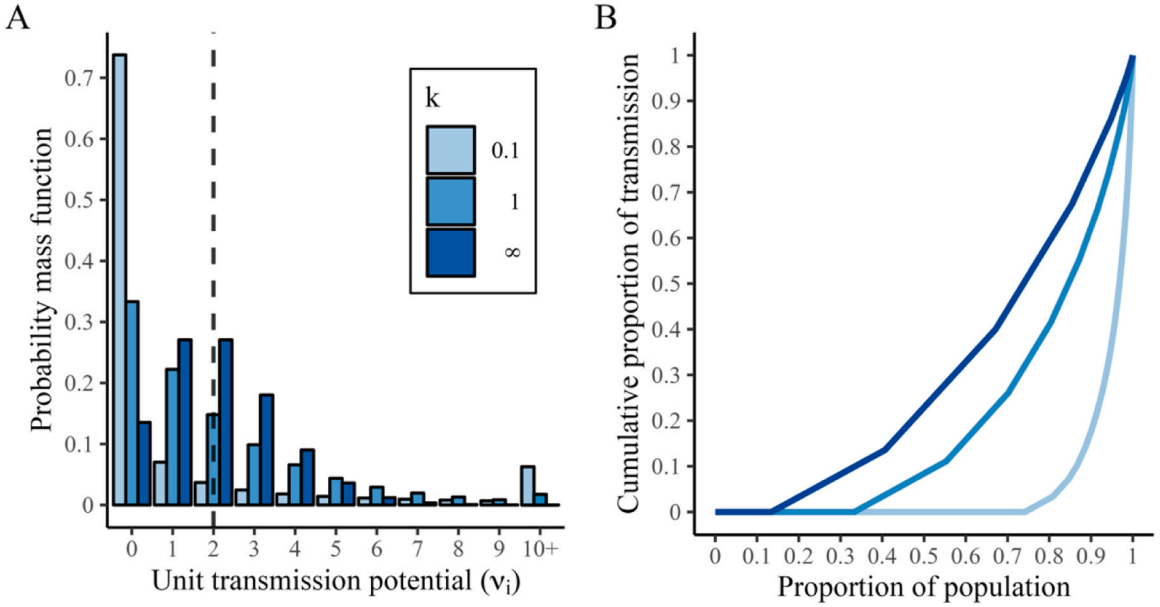

Fig. 1. | Transmission in heterogeneous populations. (A) The probability mass function of transmission potential (v) follows a negative binomial distribution with mean transmission potential $m = 2$ ($=R_0$) indicated by the dashed line, and dispersion parameter k. (B) The cumulative proportion of transmission accounted for by the proportion of the population; units are sorted in ascending order according to their transmission potential v, such that the cumulative proportion of transmission (C_i) for a proportion (i) of the population is expressed as $C_i = \sum_{j=1}^{iN} v_j / \sum_{j=1}^{N} v_j$.

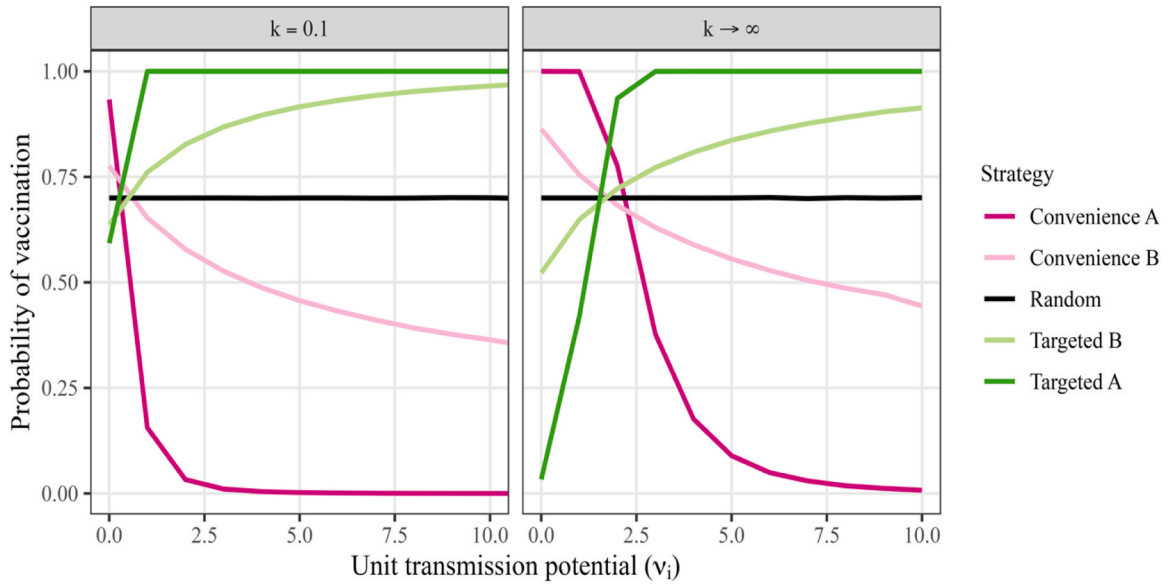

Fig. 2. | Mean unit probability of vaccination. The mean probability of a unit with a given transmission potential (v_i) being selected for vaccination with a vaccination coverage of 70% ($V = 0.7$) in populations with low ($k \to \infty$) and high ($k = 0.1$) transmission heterogeneity estimated from 10,000 iterations of a population comprising 10,000 units. The algorithm used to compute the probability of vaccination is included in Supplementary Methods 1.1.

($x > 0$) and convenience ($x < 0$) vaccination strategies. p_v was defined as the proportion of simulations for which the infection was endemic at the time of vaccination ($\geq$1 infected unit) but faded out by the end of the simulation. The total simulation period was 7 years (2555 days) and vaccination was implemented 3 years (1095 days) post virus introduction, the approximate mid-point of the simulation, to account for initial fade-out and allow sufficient time for elimination following vaccination. Each vaccination scenario (V, x) was repeated for 5000 iterations, and the probability of elimination following vaccination (p_v) was calculated from those simulations with active transmssion at the start of vaccination (i.e., at 1095 days). The parameters used for Model I simulations are defined in the Supplementary Material (Supplementary Tables, Table S1).

2.5. Model II: Metapopulation model of PPRV transmission and vaccination in lowland Ethiopia with heterogeneous mixing

We adapted a PPRV metapopulation model (derived from Fournié et al., 2018) simulating transmission within and between pastoral small ruminant village populations in lowland Ethiopia to incorporate heterogeneous mixing (transmission heterogeneity) between villages. The model extended our theoretical exploration (Model I) to the applied scenario of PPRV transmission in an endemic region, evaluating the impact of heterogeneous mixing on PPRV dynamics and the effectiveness of vaccination in the context of PPRV eradication. Here, the epidemiological unit of the model is defined as a population of small ruminants within a village, which are assumed to share equal risk of exposure to PPRV. Animals could pass through the mutually exclusive states of susceptible, infected, recovered and vaccinated. We assumed that recovered and vaccinated animals gain complete, lifelong immunity to PPRV (i.e., no return to the susceptible state). The demographic processes of births, non-PPR related mortality and ageing were incorporated, and two age categories included: young animals $<$ 12 months and adults $>$ 12 months, which differed in their reproductive capacity and non-PPR related mortality rate. Reproduction was modelled as uncontrolled and temporally constant which is a simplification of the seasonal birth peaks observed in pastoral Ethiopian small ruminants. The metapopulation comprised 10,000 villages with 17.4 million small ruminants.

Within-village transmission between small ruminants was modelled as a deterministic process (based on simulations in Fournié et al., 2018) assuming homogeneous transmission among small ruminants within a village, reflecting the extensive pastoralist production system of lowland Ethiopia and regular mixing of flocks within villages (Fournié et al., 2018). Between-village transmission was modelled as a stochastic process with heterogeneous transmission, such that each village comprising the metapopulation had a unique transmission potential.

Briefly, in a village (i), a susceptible small ruminant could become infected due to contact with an infected small ruminant in the same village with the force of infection (λ_i) at time t as follows:

$$\lambda_{i,t} = 1 - e^{\frac{-\beta^w I_{i,t-\tau}}{N_{i,t-\tau}}} \tag{2}$$

Where β^w is the within-village transmission rate, $I_{i,t}$ and $N_{i,t}$ are the number of infected animals and the total number of animals in village i at time t, respectively.

In village i, the risk of viral incursion from exposure to infected small ruminants in other (infected) villages is computed as π_i:

$$\pi_{i,t} = 1 - e^{-\frac{S_{i,t-\tau}\sum_{j\neq i}\beta^b_j I_{j,t-\tau}}{\sum_{j\neq i} N_{j,t-\tau}}} \tag{3}$$

where $S_{i,t}$ is the number of susceptible animals in village i at time t and β^b_j is the between-village transmission rate associated with village j. In the absence of transmission heterogeneity $\beta^b_j = \beta^b$. The within-village and between-village transmission rates under an assumption of random mixing (β^w and β^b) were sampled from the approximate joint posterior distribution obtained in Fournié et al., (2018) which was estimated using an approximate Bayesian computation method based on a sequential Monte-Carlo algorithm (ABC-SMC), using broad uniform priors and summary statistics from model simulations matched to serological survey data. The posterior predictive value for the mean between-village reproduction number r^b was computed from β^b, and was defined as the average number of villages infected by a single infected village in an initially fully susceptible metapopulation, computed as follows:

$$r^b = (n-1)\left(1 - \exp\left[-\beta^b \int_{t=0}^{t=\infty} \frac{N_0 I_t}{(n-2)N_0 + N_t}\, dt\right]\right) \tag{4}$$

Where N_0 is the number of animals in a susceptible village that has never experienced a viral incursion, I_t and N_t are the number of infected and total number of animals in an infected village at time t, and n is the number of villages in the metapopulation. Between-village transmission heterogeneity is incorporated through r_i^b, the between-village transmission potential of village i (equivalent to v_i in Model I), which is drawn from a negative binomial distribution with mean r^b and dispersion parameter k, for k values between $k = 0.1$ and $k \to \infty$ (see Methods, *Modelling transmission heterogeneity*). For any village i, β_i^b is given by:

$$\beta_i^b = \frac{-1}{\int_{t=0}^{t=\infty} \frac{N_0 I_t}{(n-2)N_0 + N_t}\, dt} \log\left(1 - \frac{r_i^b}{(n-1)}\right) \quad (5)$$

Full details of the model structure are given in Fournié et al., (2018).

We explored the impact of heterogeneity in village transmission potentials on the probability of PPRV extinction p (with 5000 model iterations run for 25 years) in the absence of vaccination, to assess stochastic fadeout, and under the GSCE vaccination programme. The GSCE vaccination schedule recommends 4 years of vaccination, with 2 years of full vaccination targeting all immunocompetent animals aged over 3 months, and 2 years of partial vaccination targeting immunocompetent offspring aged 3–12 months (FAO and OIE, 2015). We simulated 4 consecutive rounds of vaccination: 2 years vaccination of all animals followed by 2 years vaccination of animals $<$ 12 months. Vaccination coverage between 0% and 100% was implemented at the village-level such that a proportion, V, of villages were selected for vaccination and within those villages all eligible animals (as defined by the vaccination schedule above) were vaccinated.

We assessed five vaccination selection regimes: the baseline random strategy, two targeted strategies with extreme (A) and intermediate (B) bias, and two convenience strategies with extreme (A) and intermediate (B) bias (see Materials and Methods, *Modelling vaccination strategies)*. Vaccination was implemented after 15 years of PPRV circulation as infection approached endemic equilibrium, accounting for initial stochastic fade-out (not due to vaccination) and allowing sufficient time for elimination to occur following vaccination. In each round, a vaccination campaign was implemented over 4 timesteps (40 days), with an equal proportion of villages vaccinated per timestep, to mimic the sequential vaccination of villages in the field. This vaccination timeframe is representative of a well-resourced intensive vaccination campaign of relatively short duration. An alternative scenario with vaccination over 12 timesteps (120 days) was included as a sensitivity analysis, representing a less intensive vaccination campaign spread over several months which may be necessary when essential resources, such as personnel, vehicles and vaccine cold-chain, are limited. For a given simulation, the identity of villages selected for vaccination remained constant for all 4 rounds, hence, if a given village was selected for vaccination in round 1 it was vaccinated for all subsequent rounds (i.e., rounds 2–4). The probability of PPRV elimination following vaccination p_v was defined as the proportion of simulations with no infected villages at the end of the simulation out of those where at least 1 village was infected at the time of vaccination.

3. Results

3.1. Model I: Endemicity and vaccine effectiveness in populations with transmission heterogeneity

Results from the theoretical model sensitivity analysis demonstrate that, in the absence of vaccination, the probability of stochastic extinction (fadeout) depends on R_0, the ratio between infectious and immune durations, a, and transmission heterogeneity, k (Fig. 3). Increasing R_0 increases the probability of fadeout due to the rapid infection, and subsequent immunity, of a large fraction of the susceptible population (i.e. depletion of susceptible units). Increasing a also increases the probability of fadeout as the relatively long immune period results in insufficient replenishment of susceptible units to sustain transmission. These results are not affected by the values of the infectious and immune periods for a given value of a (*Supplementary Results,* Fig. S1). All other parameters (R_0, α)being equal, the probability of stochastic extinction increases as transmission heterogeneity increases (i.e. $k \to 0$) as most units make insufficient contacts to sustain transmission (Fig. 3). For simulations resulting in stable endemic transmission, the median proportion of infected units over time is similar irrespective of heterogeneity (*Supplementary Results,* Fig. S2). Following vaccination, the probability of elimination depends on both transmission heterogeneity and the vaccination strategy, when R_0, α and vaccination coverage (V) are constant. Under random and targeted vaccination, the probability of elimination increases as transmission heterogeneity increases (aligning with simulation results in the absence

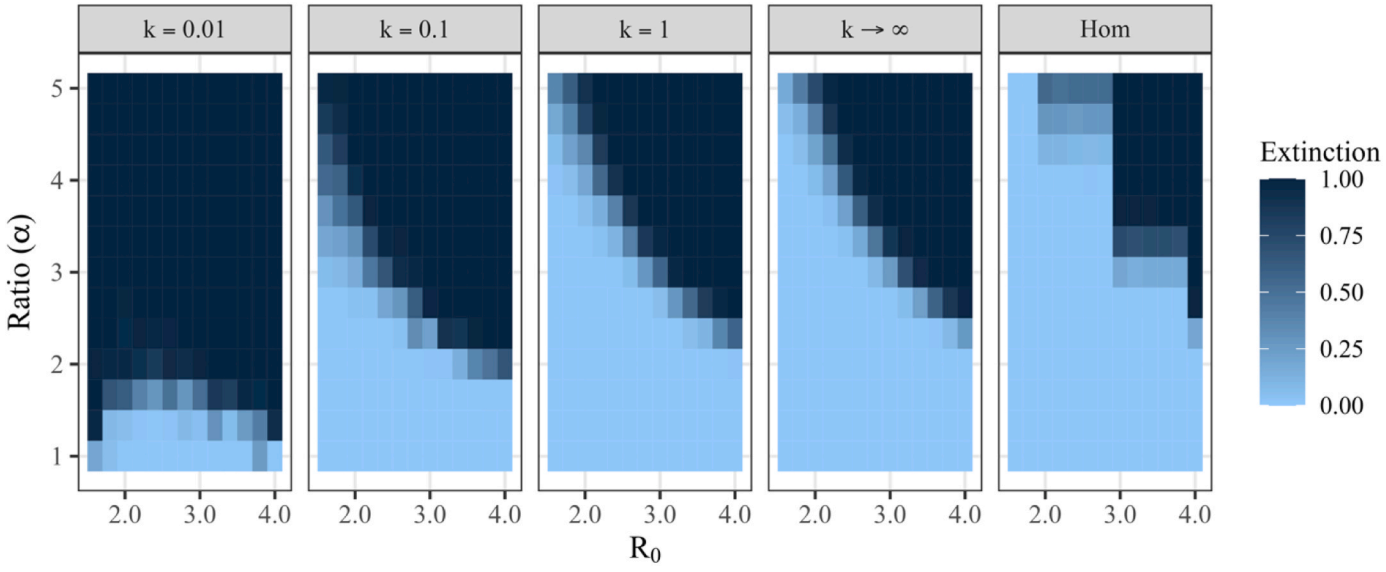

Fig. 3. | The probability of stochastic extinction as a function of R_0, the ratio between the infectious and immune period $\alpha = \tau/\gamma$, and transmission heterogeneity, k. Heterogeneity in unit transmission potential, v_i, increases as $k \to 0$. "Hom" denotes homogeneous transmission (i.e., v_i is constant for all units). The simulation period was 5 years with a population of 10,000 units, each scenario was repeated for 1000 iterations.

of vaccination). In contrast, under convenience vaccination, the probability of elimination decreases as heterogeneity increases. Relative to random vaccination, the minimum coverage required for elimination is lower under targeted vaccination strategies and higher under convenience strategies, with more extreme differences in more heterogeneous contexts ($k = 0.1, k = 0.3$) (Fig. 4).

3.2. Model II: The impact of heterogeneous transmission on PPRV endemicity and vaccine-based elimination in lowland Ethiopia

Under the assumption of a homogeneously mixing metapopulation of small ruminant village flocks and in the absence of control interventions, 99% of simulations result in stable endemic transmission at the end of the 25 years. By contrast, in heterogeneously mixing small ruminant populations, the probability of stable endemic transmission ranges from 94% ($k \to \infty$) to 66% ($k = 0.1$) in the absence of vaccination (*Supplementary Results,* Fig. S3). For simulations resulting in stable endemic transmission, the median prevalence of infected and immune small ruminants over time and across simulations is similar, irrespective of heterogeneity (*Supplementary Results,* Fig. S4).

Under the PPR GSCE vaccination strategy with $V = 70\%$ (FAO and OIE, 2015) and assuming true random selection of vaccinated villages, elimination is achieved in 95% of simulations for a homogeneously mixing metapopulation. In heterogeneously mixing populations, the probability of PPRV elimination ranges from 94% to 97% for $k \to \infty$ and $k = 0.1$ respectively. The minimum vaccination coverage required to achieve elimination in 100% of simulations under a random vaccination strategy is 80% in homogeneously mixing populations and ranges from 76% to 80% when heterogeneity in transmission is incorporated (Fig. 5).

The impact of biased vaccination strategies on the probability of elimination increases as transmission heterogeneity increases. Under targeted vaccination strategies, with $V = 70\%$, elimination is achieved in $> 99\%$ of simulations in heterogeneously mixing populations (from $k \to \infty$ to $k = 0.1$). Under convenience vaccination, at $V = 70\%$, elimination is achieved in $< 80\%$ of simulations when $k \to \infty$ and in less than 21% of simulations when $k = 0.1$ (Fig. 5a).

As the degree of heterogeneity increases ($k \to 0$) the disparity between the targeted and convenience strategies with respect to the minimum coverage required to achieve elimination in 100% of simulations (100% elimination) increases (Fig. 5b). As $k \to \infty$, 100% elimination is achieved at $V = 58\%$ under targeted vaccination (extreme bias, A) and at $V = 92\%$ under convenience vaccination (extreme bias, A). When heterogeneity increases ($k = 0.1$), $V = 10\%$ is required for 100% elimination for targeted vaccination (extreme bias, A) and $V > 99\%$ for convenience vaccination (extreme bias, A). The targeted strategy with intermediate bias (B) indicates a reduction in the minimum coverage to achieve 100%

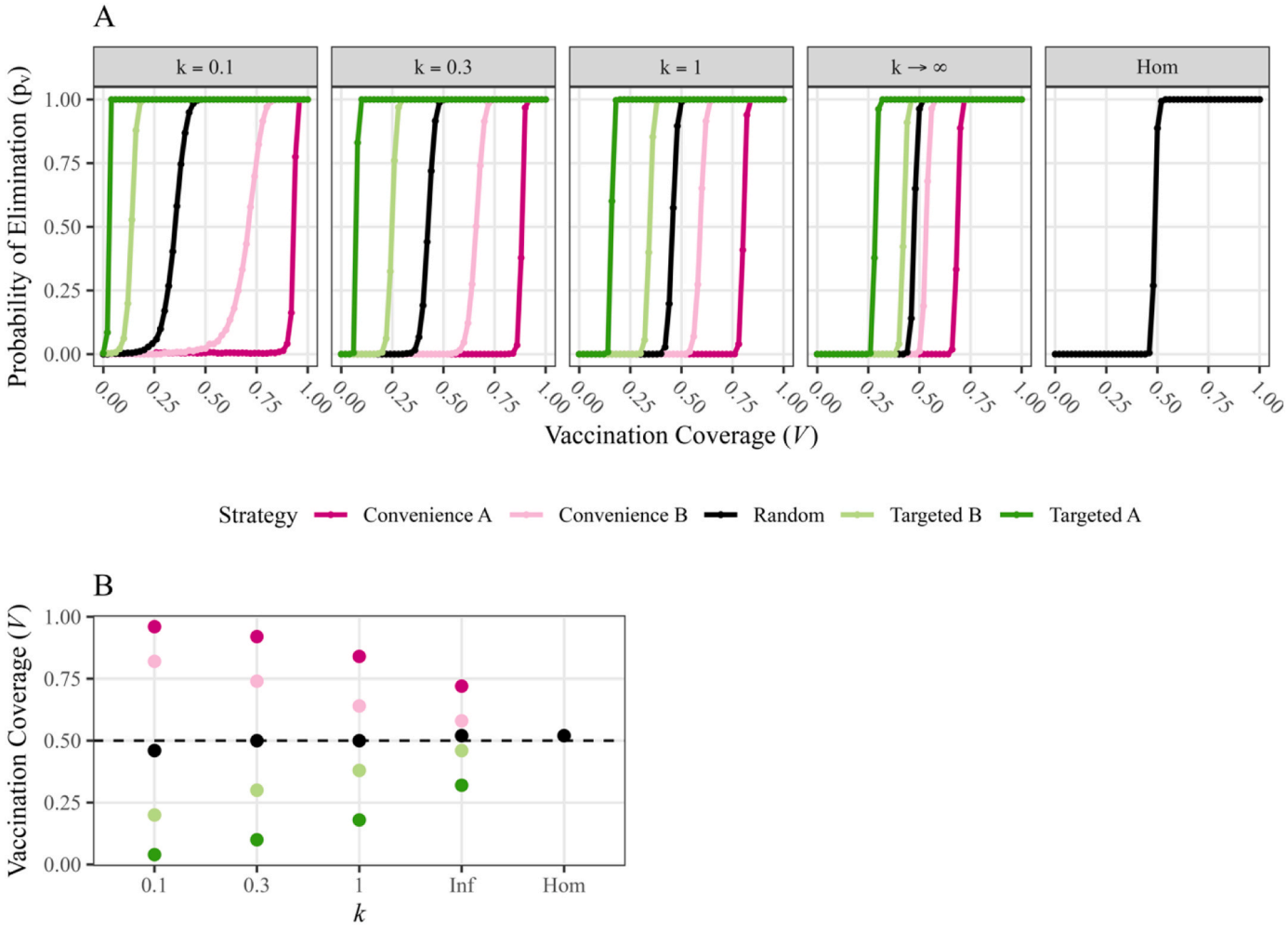

Fig. 4. | The probability of disease elimination following vaccination in heterogeneous populations. (A) At different vaccine coverage levels (V). **(B)** The minimum vaccination coverage required to eliminate infection in 100% of simulations. "Convenience A" and "Convenience B" are the extreme and intermediate convenience strategies respectively, "Targeted A" and "Targeted B" are the extreme and intermediate targeted strategies respectively. Dispersion parameter k values of "Inf" and "Hom" are the $k \to \infty$ and homogeneous transmission scenarios respectively. The simulation period was 7 years with vaccination in year 3, the population was 10,000 units and each scenario was repeated for 5000 iterations.

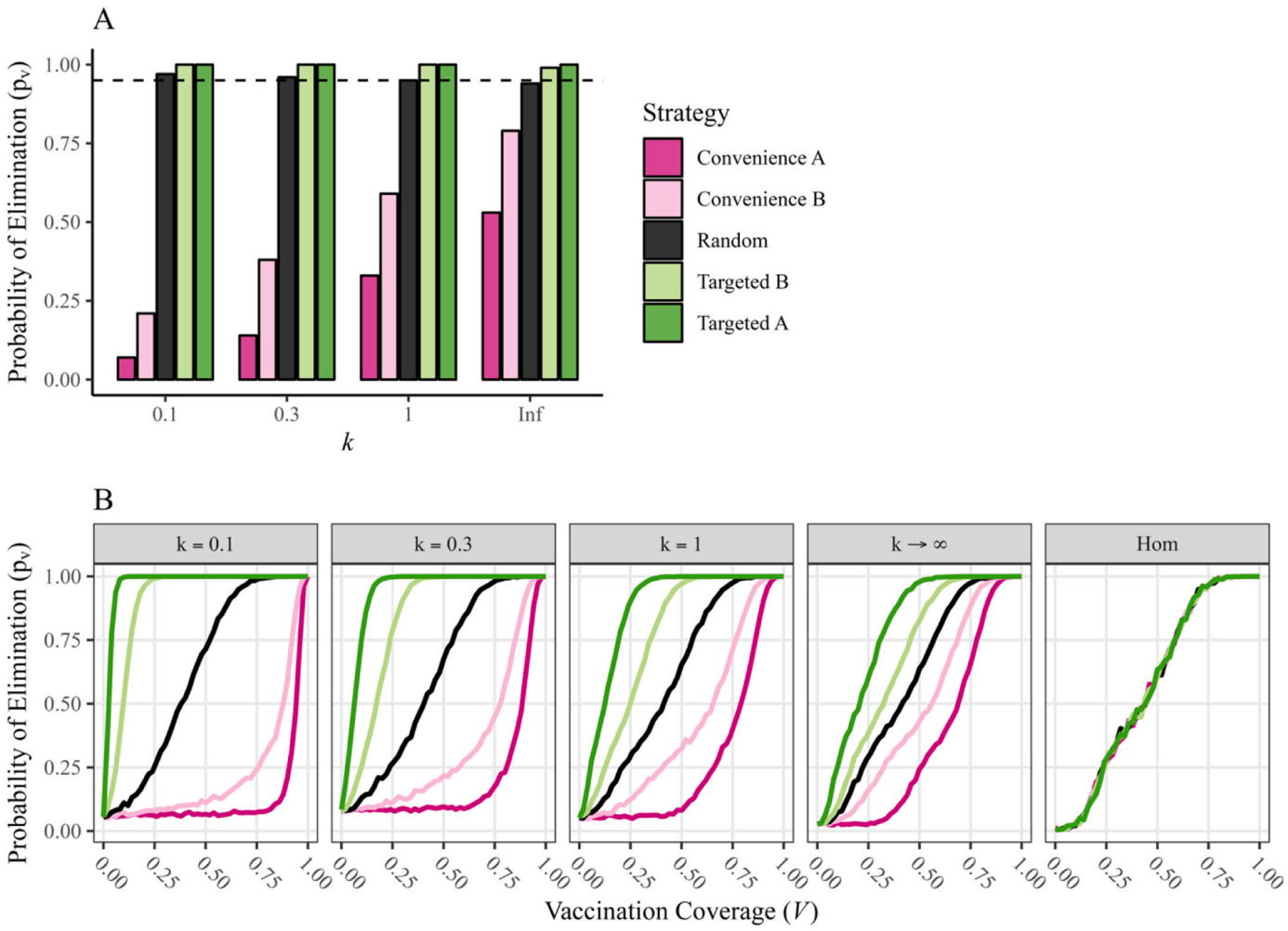

Fig. 5. | The probability of PPRV elimination in pastoral small ruminant populations of lowland Ethiopia with transmission heterogeneity following vaccination of **(A)** 70% of small ruminant villages, black dashed line indicates $p_v = 0.95$ and **(B)** 0–100% of small ruminant villages. "Convenience A" and "Convenience B" are the extreme and intermediate convenience strategies respectively, "Targeted A" and "Targeted B" are the extreme and intermediate targeted strategies respectively. Transmission heterogeneity increases as $k \to 0$, "Inf" and "Hom" are the $k \to \infty$ and homogeneous transmission scenarios respectively. The model simulation period was 25 years with vaccination from year 15. The metapopulation comprises 10,000 villages and each scenario was repeated for 5000 iterations.

elimination from $V = 70\%$ to $V = 26\%$ as heterogeneity increases (from $k \to \infty$, to $k = 0.1$), whilst the convenience strategy with intermediate bias (B) requires an increase from $V = 86\%$ to $V > 98\%$. The coverage required to achieve 100% elimination is reduced by between 27.5% (for $k \to \infty$) and 86.8% (for $k = 0.1$) using a targeted strategy (extreme bias, A) and increases by between 15% (for $k \to \infty$) to 31.6% ($k = 0.1$) under a convenience vaccination strategy (extreme bias, A) relative to random vaccination. These results are consistent when vaccination campaigns are implemented over 120 days (12 timesteps) (*Supplementary Results, 3.1;* Fig. S5).

4. Discussion

Our findings demonstrate that heterogeneous mixing among small ruminant flocks drives instability in PPRV transmission and can profoundly impact the effectiveness of vaccination programmes aiming for global eradication. This underscores the importance of (i) robust surveillance systems to rapidly identify new infections in disease-free flocks, and (ii) the optimization of vaccination strategies. Our results indicate that the current GSCE vaccination programme, targeting 70% post-vaccination immunity rates, may fail to eliminate PPRV under random or convenience vaccination strategies. Maximizing the effectiveness of vaccination—to increase the likelihood of local elimination and global eradication—could be achieved through targeting small ruminant populations with high effective contact rates, potentially using contact tracing and mobility data.

PPRV transmission dynamics—like other infectious diseases—are sensitive to heterogeneity in transmission, here driven by heterogeneity in effective contact rates among pastoral village flocks in lowland Ethiopia. The decreased stability of PPRV transmission under heterogeneous mixing is consistent with previous research (Britton et al., 2020; Lloyd-Smith et al., 2005) and is characterized by extreme peaks and troughs in cases. This has practical implications for PPRV surveillance following local elimination since viral introductions may occur repeatedly but remain undetected due to limited spread and rapid fadeout (Lloyd-Smith et al., 2005). However, when transmission becomes established, populations are vulnerable to explosive epidemics with high incidence peaks. Such dynamics were observed during the COVID-19 pandemic across epidemiologically similar settings (including groups of cruise ships, prisons, and long-term care facilities) where most infected sites reported low case numbers whilst a few experienced large outbreaks resulting from super-spreading events (Althouse et al., 2020; Mizumoto et al., 2020). Hence, a key component of PPRV eradication will be the strengthening of surveillance systems to enable early detection of recent PPRV incursions in disease-free populations enabling rapid containment and elimination.

Our model indicates that in the pastoralist villages of lowland Ethiopia, the GSCE vaccination strategy, assuming random vaccination, may achieve elimination with $>94\%$ probability. Whilst this result suggests that random vaccination could be effective for achieving eradication, in practice, a truly random strategy is likely unattainable and, therefore, rarely implemented. A more straightforward, widely adopted, strategy is to aim for complete coverage of populations (i.e., 100% coverage), although full coverage is rarely achieved. Moreover, in heterogeneously mixing populations, PPRV elimination thresholds are impacted by any bias (intended or otherwise) in the selection of villages for vaccination and therefore failing to vaccinate even a few high-risk hard-to-reach populations may facilitate long-term viral circulation despite high overall population immunity levels.

Empirical evidence for heterogeneous mixing in livestock populations, and its implications for disease dynamics, is well-documented. Descriptive analysis of contact networks shaped by the trade of cattle and small ruminants in the UK (Volkova et al., 2010; Woolhouse et al., 2005) and the use of shared grazing and watering points by small ruminants in Ethiopia (Waret-Szkuta et al., 2011) have also indicated that contact rates are highly heterogeneous between populations (farms, flocks), typically with a small subset of groups accounting for the vast majority of contacts in a network.

A comprehensive network of flock contacts including transhumance movements between villages, use of shared grazing or watering points, and trade at markets would provide detailed information about mobility patterns to both quantify heterogeneity and enable targeting of specific high-risk populations or sites. However, the collection of such high-resolution data is resource intensive and requires longitudinal monitoring of highly mobile populations. More limited data collection activities detailing flock structure and demographics, husbandry practices, trading behaviour and use of common resources using participatory methods to draw on the knowledge and experience of livestock owners (Mariner et al., 2012) could be used to infer flock dynamics and contact patterns enabling characterization of high-risk (high-contact) populations. When defining contact patterns, it will be critical for studies to consider both (i) the frequency of contacts and (ii) the type and duration of contact as key determinants of the probability that a contact is effective (Sun et al., 2021). Combining mobility data with virus genetic data can also help to elucidate transmission dynamics, including source-sink transmission processes and the identification of "hotspots" which facilitate the incursion and transmission of different PPR viral lineages (Bataille et al., 2021).

Despite these advantages, attempting targeted vaccination may be counterproductive in the absence of reliable data to identify high-risk units (i.e., if targeting is unsuccessful and true high-risk populations are missed). In this context, mass vaccination—aiming for the highest attainable coverage—may be more pragmatic, although also resource-intensive. To maximise the effectiveness of mass vaccination, known high-risk populations should be prioritized whilst high overall coverage is maintained. As progress is made towards eradication, targeting of high-risk populations and localized hotspots will become increasingly important as mass vaccination efforts are deescalated.

The success of the PPR GSCE will depend on the delivery of vaccination to populations in remote, or conflict-affected regions. This demands additional resources and innovation to tackle both social and technical challenges. Community-based animal health services can support work within pastoralist communities to plan and deliver vaccination to less-accessible populations (Jones et al., 2002; Mariner et al., 2016; Nkamwesiga et al., 2019) and the development of thermotolerant vaccines, which are more stable in the field, will reduce the constraints of vaccine cold-chains (Baron et al., 2017; Zhao et al., 2021). These innovations proved critical to the eradication of rinderpest in similar settings (FAO, 2012; Jones et al., 2022; Mariner et al., 2012) and will likely underpin PPRV eradication.

The results presented here are not intended to provide precise vaccine coverage targets, but rather to indicate the degree to which heterogeneous transmission can impact the effectiveness of vaccination under different strategies. The widespread evidence for heterogeneously mixing populations and heterogeneous transmission (Endo et al., 2020; Kao et al., 2006; Kiss et al., 2006; Kucharski and Althaus, 2015; Liljeros et al., 2001; Lloyd-Smith et al., 2005) indicates that the (default) simplifying assumptions of homogeneous mixing may not be appropriate when modelling the effectiveness of vaccination in different populations. We suggest that when detailed contact data is lacking, the modelling framework presented in the paper—using the negative binomial distribution (Lloyd-Smith et al., 2005)—offers a flexible approach for incorporating alternate mixing patterns into model structures and can be used to assess the sensitivity of model outcomes to heterogeneity in transmission. Whilst sensitivity analysis on model input parameters has been widely studied, the sensitivity of outputs to changes in model structure (structural uncertainty) is less often considered; the method presented here should support future studies within this field.

Targeting vaccination to high-risk groups has an effect similar to the selective immunization of high-contact nodes demonstrated as infections spreads on scale-free contact networks (Ferrari et al., 2006; Kiss et al., 2006). Highly connected nodes in such networks have a higher likelihood of being exposed to, and spreading, infection throughout populations. The association between exposure and transmission on contact networks drives the rapid spread of infection through the most highly connected portions of the network; immunising high-contact units and reducing network susceptibility to future outbreaks (Ferrari et al., 2006; Kiss et al., 2006; May and Lloyd, 2001). There are few empirical or mathematical studies addressing heterogeneity in unit susceptibility or exposure potential on infectious disease dynamics for directly transmitted pathogens, although Gomes et al. (2022) determined that individual variation in susceptibility or exposure to COVID-19 lowered the herd immunity threshold through selective depletion of the susceptible population. Rose et al., (2021) explored the impact of heterogeneity in susceptibility on transmission processes, supporting the conclusion that herd immunity estimates can be drastically altered when accounting for non-homogeneous transmission processes. Whilst the importance of contact heterogeneity in disease transmission, and the associated heterogeneity in exposure, has been the subject of theoretical network analysis (Ferrari et al., 2006; Meyers et al., 2005; Newman, 2005), further empirical and mathematical study could provide insights into the impact of exposure heterogeneity on epidemiological outcomes, accounting for contact frequency, type and duration of exposure as determinants of exposure potential.

In our simulations, we assumed that the transmission potential of a unit (Model I) or a flock (Model II), ν_i, was fixed for the duration of the simulation. During infectious disease outbreaks, population mixing patterns may be altered through behavioural changes and enforced restrictions such as self-isolation, social-distancing, movement restrictions or quarantine (Haydon et al., 2004; Imai et al., 2020; Seale et al., 2020). Such measures aim to reduce effective contact rates and transmission potential but may either increase or decrease population heterogeneity depending on the uniformity of, and adherence to, the imposed measures (Lloyd-Smith et al., 2005; Seale et al., 2020) which may alter epidemic outcomes.

The infectious and immune periods of each unit (in models I and II) were assumed to be fixed and equal for all units for the duration of the simulation. Instead, considering that these parameters may vary between units could impact PPRV transmission dynamics and vaccination effectiveness. Whilst heterogeneity in infectious periods is not explicitly considered, our definition of transmission potential ν_i – the number of effective contacts made by an infected unit i during its infectious period – could be considered to encompass heterogeneity in unit infectious periods if the number of effective contacts made by a unit is positively correlated with the duration of its infectious period. Heterogeneity in individual or group-level immune periods is particularly relevant to the design of vaccination programmes. For PPR, previously infected or vaccinated animals gain lifelong immunity (Methods, *Model II*),

however, at a flock-level the duration of immunity (following infection or vaccination) may vary due to different husbandry practices or seasonality shaping flock dynamics. Demographic processes such as births or offtake rates also influence immunity levels through the loss of immune individuals and influx of susceptible animals, affecting PPRV transmission and immunity dynamics with important impacts for the optimal time and schedule of vaccination (El Arbi et al., 2019; Hammami et al., 2018, 2016).

In our simulations, vaccination was assumed to confer complete, lifelong, immunity to all vaccinated animals. However, in practice a proportion of vaccinated animals may not gain protective immunity due to failure to mount an immune response or incorrect storage or administration of the vaccine (Fournié et al., 2018; Hammami et al., 2016; Yirga et al., 2020). A higher vaccination coverage would be required to account for this reduced vaccine efficacy. Finally, while our assumption of homogeneous mixing of small ruminants within villages is reasonable, due to attendance at shared grazing and watering points, and communal herding (Abdulatife and Ebro, 2015; Otte and Chilonda, 2002; Waret-Szkuta et al., 2011), different breeds of sheep and goats vary in their susceptibility to PPRV infection and virus excretion (Baron et al., 2017; Kihu et al., 2015; Swai et al., 2009; Waret-Szkuta et al., 2011), impacting PPRV dynamics. Species and breed-specific model parameters would enable these differences to be more accurately represented but would increase model complexity and would require detailed, reliable data on PPRV infection and excretion in different hosts.

5. Conclusion

Our results support previous work demonstrating the impact of heterogeneous transmission on the dynamics, control and eradication of infectious diseases. The framework presented here, which has been previously applied to model heterogeneous transmission, provides an accessible approach to exploring the sensitivity of model outputs to assumptions about population mixing patterns, even in the absence of detailed contact data. The PPRV metapopulation model results—calibrated to pastoral village flocks in lowland Ethiopia—indicate that the success of the PPR GSCE will critically depend on population mixing patterns and the selection strategy for vaccination. Where small ruminant populations mix heterogeneously, PPRV eradication will likely require identification and vaccination of “high risk” communities with high contact rates. Transmission may persist despite high coverage if vaccination is biased towards more accessible but low-risk populations. During its next phase, the focus of PPR GSCE should shift from attaining high overall vaccination coverage rates to risk-based approaches which can reduce resource requirements whilst increasing the likelihood of local elimination and, ultimately, global eradication.

Supplementary Materials

Further methods and results providing supporting information for the article.

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CRediT authorship contribution statement

Bethan Savagar: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Guillaume Fournié :** Conceptualization, Methodology, Software, Visualization, Supervision, Writing-review & editing. **Mark Arnold:** Conceptualization, Methodology, Supervision, Writing-review & editing. **Bryony A. Jones:** Conceptualization, Methodology, Supervision, Writing-review & editing. **Martin Walker:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare no known conflict of interest.

Data Availability

All computer codes associated with Models I and II are available GitHub online at: https://github.com/BethSavagar/transmission_heterogeneity_Sep23.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2023.100725.

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