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Projecting vaccine demand and impact for emerging zoonotic pathogens

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Abstract

Background: Despite large outbreaks in humans seeming improbable for a number of zoonotic pathogens, several pose a concern due to their epidemiological characteristics and evolutionary potential. To enable effective responses to these pathogens in the event that they undergo future emergence, the Coalition for Epidemic Preparedness Innovations is advancing the development of vaccines for several pathogens prioritized by the World Health Organization. A major challenge in this pursuit is anticipating demand for a vaccine stockpile to support outbreak response.

Methods: We developed a modeling framework for outbreak response for emerging zoonoses under three reactive vaccination strategies to assess sustainable vaccine manufacturing needs, vaccine stockpile requirements, and the potential impact of the outbreak response. This framework incorporates geographically variable zoonotic spillover rates, human-to-human transmission, and the implementation of reactive vaccination campaigns in response to disease outbreaks. As proof of concept, we applied the framework to four priority pathogens: Lassa virus, Nipah virus, MERS coronavirus, and Rift Valley virus.

Results: Annual vaccine regimen requirements for a population-wide strategy ranged from > 670,000 (95% prediction interval 0–3,630,000) regimens for Lassa virus to 1,190,000 (95% PrI 0–8,480,000) regimens for Rift Valley fever virus, while the regimens required for ring vaccination or targeting healthcare workers (HCWs) were several orders of magnitude lower (between 1/25 and 1/700) than those required by a population-wide strategy. For each pathogen and vaccination strategy, reactive vaccination typically prevented fewer than 10% of cases, because of their presently low R_0 values. Targeting HCWs had a higher per-regimen impact than population-wide vaccination.

Conclusions: Our framework provides a flexible methodology for estimating vaccine stockpile needs and the geographic distribution of demand under a range of outbreak response scenarios. Uncertainties in our model estimates highlight several knowledge gaps that need to be addressed to target vulnerable populations more accurately. These include surveillance gaps that mask the true geographic distribution of each pathogen, details of key routes of spillover from animal reservoirs to humans, and the role of human-to-human transmission outside of healthcare settings. In addition, our estimates are based on the current epidemiology of each pathogen, but pathogen evolution could alter vaccine stockpile requirements.

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Keywords: Zoonosis, Zoonotic disease, Emerging disease, Vaccine demand modeling, Vaccine stockpile, Spillover

Background

Less than 2 years ago, SARS-CoV-2 was an unknown virus circulating in a zoonotic reservoir [1]. In the time since, it has caused a pandemic resulting in more than 4.6 million deaths [2]. Theoretical work [3] predicts that frequent small-scale outbreaks in humans may provide opportunities for the selection of more transmissible variants that facilitate emergence from the original reservoir. Indeed, virological studies indicate that a sequence of mutations acquired in this manner may offer a plausible explanation for the emergence of SARS-CoV in 2003 [4]. More frequent spillovers and more human-to-human transmission ensuing from those spillovers are expected to increase the probability that adaptations such as these arise and facilitate more widespread emergence [5]. Because of this evolutionary potential, even zoonotic pathogens with limited human-to-human transmission—as defined by a basic reproduction number, R_0 , below 1—are viewed as a concern. The status quo of investing in the development of diagnostics, therapeutics, and vaccines only in reaction to emerging disease threats has made the world dangerously vulnerable to pandemics [6, 7].

To preempt future public health emergencies arising from emerging zoonotic diseases, the World Health Organization (WHO) developed a research and development blueprint for action to prevent epidemics [8]. This R&D Blueprint prioritizes and regularly updates a list of pathogens for the development of diagnostics, therapeutics, and vaccines. The Coalition for Epidemic Preparedness Innovations (CEPI) was launched in 2017 to accelerate the development of vaccines against emerging infectious diseases and to enable equitable access to these vaccines for people during outbreaks [9–11]. The first call for proposals from CEPI was on developing vaccines for Lassa virus (LASV), MERS coronavirus (MERS-CoV), and Nipah virus (NiV). Soon after, it added Rift Valley fever virus (RVFV) and chikungunya virus (CHIKV) to its portfolio. As of early 2021, CEPI was supporting the development of a total of 19 different vaccine candidates for these five diseases, in addition to other efforts related to Ebola, COVID-19, and “disease X” [12].

In anticipation of vaccine candidates for these diseases progressing through safety and efficacy trials and towards implementation, there is a need to understand future potential vaccine demand [6]. Even though these vaccines are not yet available for public health use (a NiV vaccine is currently undergoing a phase I clinical trial [13], and MERS-CoV and LASV vaccines are currently in phase

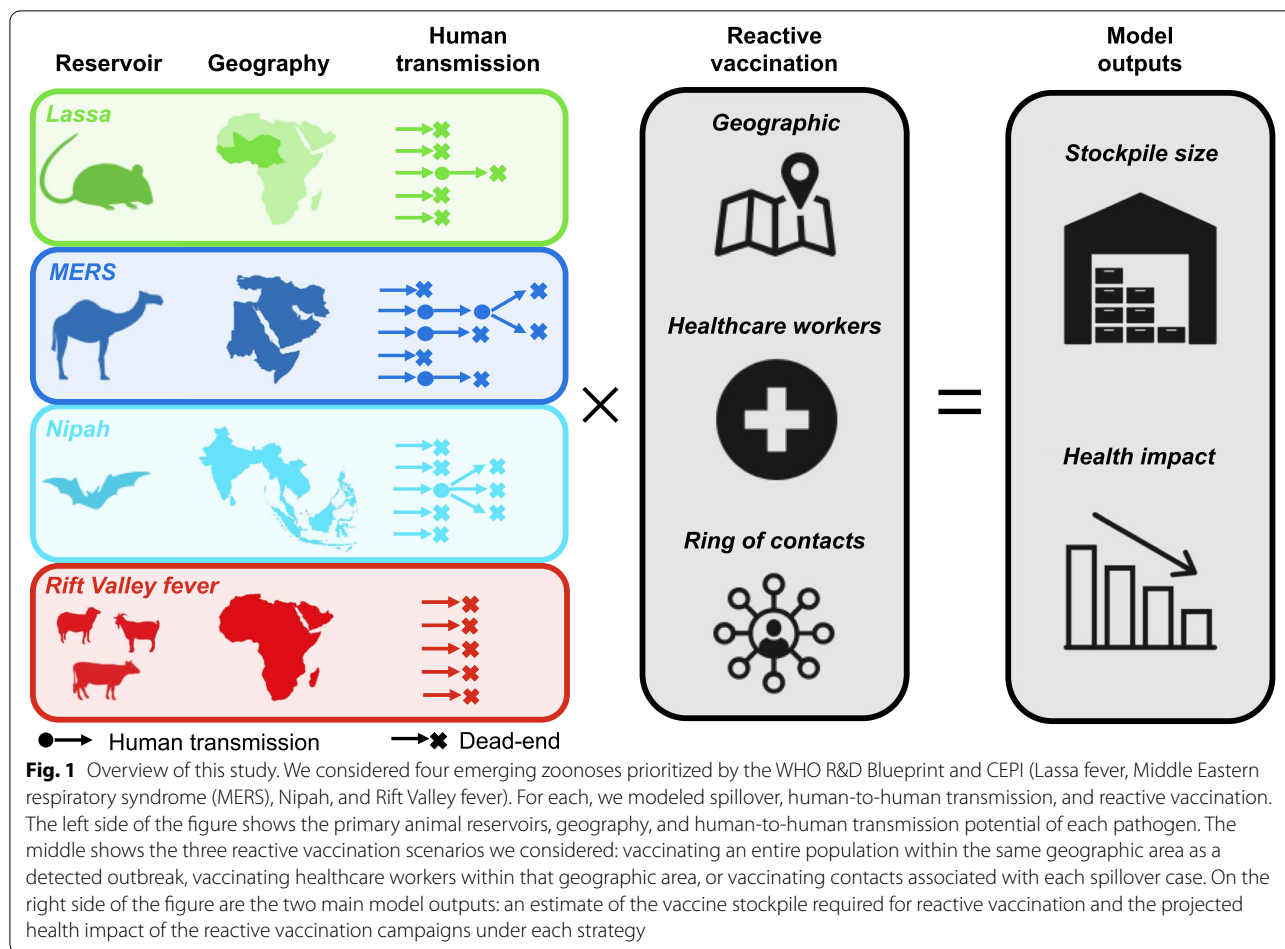
II clinical trials [14]), understanding demand at an early stage is important to inform fundraising and planning efforts in support of the manufacturing and distribution infrastructure that will be required for their implementation [7]. Following the development of a new vaccine, manufacturing capacities are typically the first limiting factor for vaccine supply, which raises allocation and prioritization decisions to protect people at higher risk of infection and clinical diseases [15, 16]. Appropriate planning of vaccine stockpiles to support vaccine demand is important to minimize the extent to which difficult decisions about vaccine prioritization must be made once a vaccine becomes available for use. At the same time, overestimating vaccine stockpile needs could result in doses expiring and resources that could have gone to other needs being wasted.

To improve capabilities to plan vaccine stockpiles for emerging zoonotic pathogens, we developed a modeling framework to quantify the vaccine stockpile size needed to meet the demand for outbreak response and applied it to LASV, MERS-CoV, NiV, and RVFV (Fig. 1). Each of these pathogens is zoonotic, with the majority of human cases believed to result from spillover transmission from non-human hosts accompanied by self-limiting, human-to-human transmission [17–20]. Our model is driven by geographically and seasonally realistic patterns of spillover for each pathogen, with each spillover event having the potential to spark an outbreak that we simulated stochastically with a branching process model. Outbreak response with reactive vaccination was triggered in our model whenever a threshold number of cases was exceeded within a certain space-time window. We quantified the number of vaccine regimens required (where the number of regimens equals the number of individuals vaccinated) under three different approaches to reactive vaccination: (1) population-wide within the same geographic area as the outbreak, (2) targeted on healthcare workers (HCWs) within that area, or (3) targeted on a ring of contacts around each index case. Using vaccines modeled after target product profiles for each pathogen [21–24], we also quantified the impact of reactive vaccination under a range of scenarios about deployment timing, coverage, per-exposure protection (PEP) from vaccination, and several epidemiological parameters.

Methods

Study overview

We considered four emerging zoonoses prioritized by the WHO R&D Blueprint and CEPI. For each, we



modeled spillover, human-to-human transmission, and reactive vaccination. We quantified the vaccine stockpile necessary to meet the demands of reactive vaccination under three scenarios: vaccinating an entire population within the same geographic area as a detected outbreak, vaccinating healthcare workers within that geographic area, or vaccinating contacts associated with each spillover case. Lassa fever is caused by LASV, a virus that circulates in rodents in West Africa and has resulted in thousands of cases and deaths in recent years [25, 26]. Nipah is caused by NiV, a virus that circulates in fruit bats that can be found throughout tropical and subtropical Asia [27, 28], but documented spillover to humans has been mainly limited to India, Bangladesh, and Malaysia [20, 29, 30]. Middle Eastern respiratory syndrome is caused by MERS-CoV, a coronavirus that probably originated in bats [31] and is known to circulate among domestic camel populations in the Middle East and parts of eastern and northern Africa, resulting in spillover from camels to humans [32–34]. Human-to-human transmission has been reported in nosocomial settings for three of these pathogens [20, 35, 36],

although only MERS was reported in large hospital outbreaks [36, 37]. The evidence for community transmission of these viruses is more limited [19, 20, 34]. Rift Valley fever is caused by RVFV, a mosquito-transmitted virus infecting ruminant livestock species in Africa, the Arabian Peninsula, and the Indian Ocean islands [38–40]. RVF outbreaks have been associated with heavy rainfall in eastern and southern Africa [41, 42], but transmission can also occur outside of these epizootic events [17]. Humans can be infected via direct contact with infected animals or via mosquito bites but are believed to be dead-end hosts [43].

Epidemiological data

For each of the pathogens, we collated epidemiological data through the end of 2020 from multiple sources, including WHO outbreak reports (e.g., [44]), ProMED reports [45], country-level reports [46, 47], and a literature search. A detailed overview of the source of epidemiological data for each pathogen can be found in Additional file 1: Table S1.

Spillover simulation

Given extensive spatial heterogeneity of incidence, we collated epidemiological data at the first administrative level (adm1) in each country—e.g., province or state—within the study region for each pathogen. Epidemiological data availability below the adm1 level was too sparse to attempt a finer-scale analysis of spillover rates. The primary epidemiological data used to inform spillover rates was the annual incidence of reported cases of each pathogen at the adm1 level (Additional file 1: Table S1). Where possible, case data was categorized into cases of documented or suspected human-to-human transmission, documented or suspected spillover cases, and cases of unknown origin. The geographic coverage of our analysis for each pathogen was determined by the geographic distribution of spillover cases in the literature. All countries with at least one documented spillover case were included in our analysis. We excluded countries with imported cases but no spillover from a zoonotic source (e.g., South Korea for MERS-CoV).

Spillover rates were estimated using a generalized linear mixed model (GLMM) with a zero-inflated negative binomial distribution to capture overdispersion in the annual distribution of spillover cases within an adm1. Spillover cases were defined as documented spillover cases, suspected spillover cases, or cases of unknown origin, thereby excluding any cases of documented or suspected human-to-human transmission. Year, country, and adm1 were treated as random effects, with the adm1 variable nested within the country variable. Year was also included as a random effect for the zero-inflated portion of the model. Model fitting was conducted using the glmmTMB package in R [48]. This default model did not converge for NiV; therefore, for NiV, we used the GLMM model without the random effect by year in the zero-inflated portion of the model to enable convergence. Then, for each pathogen, we simulated annual spillover cases for each year and adm1 by taking draws (1000 replicates) from a zero-inflated negative binomial distribution using the estimated parameters from the appropriate GLMM fit. We randomly sampled 1000 of these simulated spillovers from the last 5 years as inputs to the outbreak simulation model so that the simulated spillovers would reflect recent spillover rates.

To account for the seasonality of spillover, we fitted a beta distribution to the timing of spillover cases within a year (daily for MERS, weekly for Lassa fever, monthly for Nipah and RVF) and simulated the timing of each spillover case as a random draw from that distribution (Table 1). To account for spatial clustering of cases below the adm1 level, we associated each simulated case with a catchment area. We did so according to the probabilities proportional to the catchment area population.

Table 1 Overview of the parameter estimates. Incubation period and infectious period are defined in units of days, and parameters for seasonality refer to the week of the year. Numbers in parentheses for R_0 represent the 95% confidence intervals. SD standard deviation

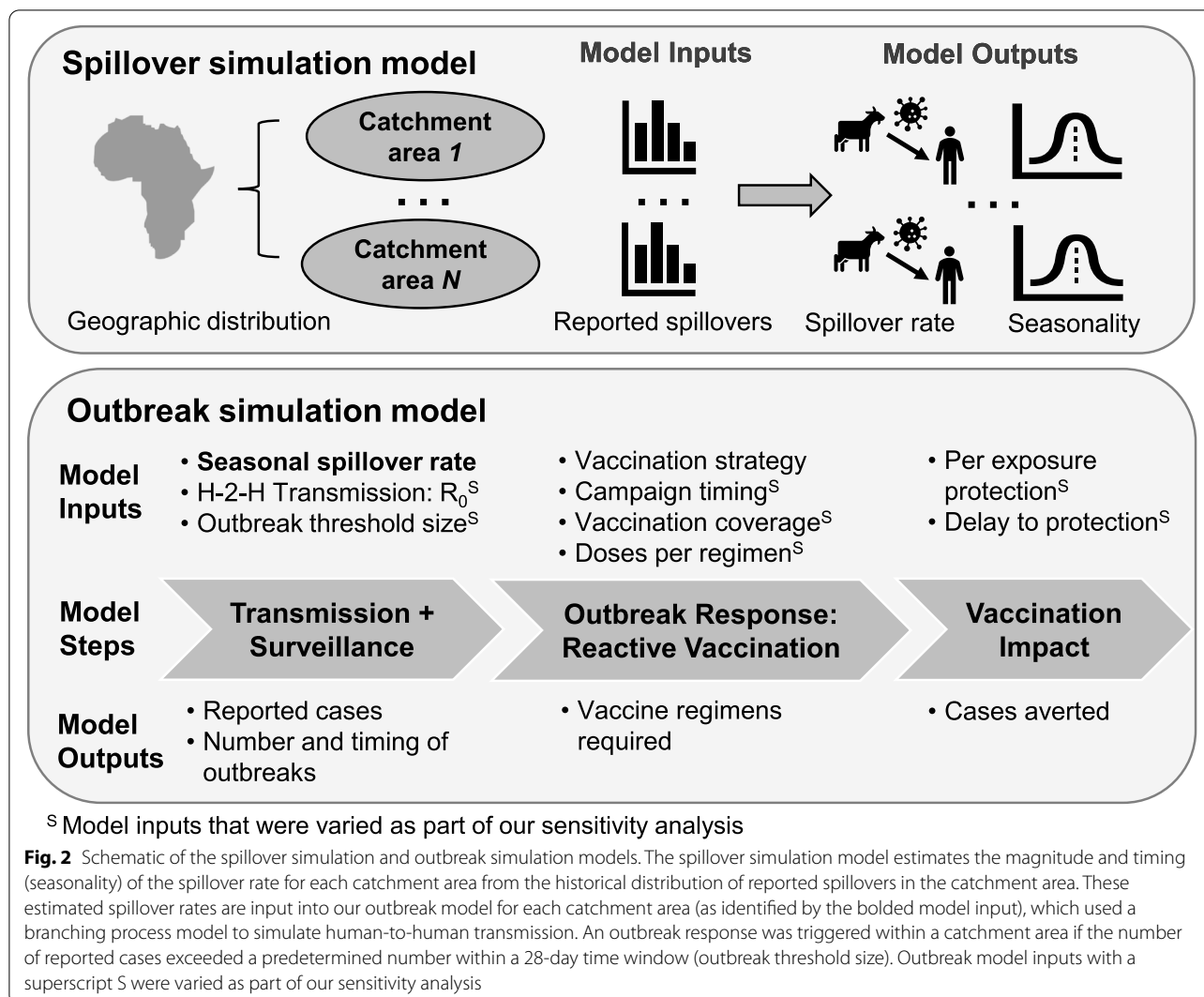
Parameter	LASV	MERS-CoV	NiV	RVFV
Seasonality				
Peak (weeks)	31.1	23.3	27.3	23.2
SD (weeks)	6.2	13.6	6.4	12.7
Incubation period				
Mean (days)	12.05	5.56	9.87	2.88
SD (days)	3.62	0.77	0.84	1.95
Infectious period				
Mean (days)	11.31	13.5	6.49	7 ^a
SD (days)	8.29	2.61	0.26	–
R_0				
Mean	0.063 (0.05, 0.08)	0.58 (0.31, 0.99)	0.325 (0.21, 0.52)	0 (0.01)
Dispersion	–	1.42	0.048	–

^a Fixed value used for sensitivity analysis only

Catchment areas were defined by the second administrative level (adm2) or hospitals aggregated within 10 km for the first administrative (adm1) areas that did not have an adm2 level. These catchment areas, therefore, represent areas where individuals would be expected to seek care and have their diagnosis reported, and the aggregation of hospitals within a 10-km area assumes that individuals who seek treatment for the relatively severe symptoms of these diseases do so at larger hospitals. Hospital location data for sub-Saharan Africa used in the analysis of LASV was obtained from [49], and hospital location data outside of sub-Saharan Africa was obtained from Healthsites.io [50]. The primary set of findings we reported are based on a set of 1570 catchment areas for LASV, 767 for MERS-CoV, 5076 for NiV, and 2126 for RVFV, which differ because of the different geography of each pathogen. We examined the sensitivity of our results to the definition of a catchment area by rerunning the analyses with either adm1 catchment areas or all hospitals within an adm1 as distinct catchment areas. The results of these analyses are presented in the supplement (Additional file 1: SI Text).

Outbreak simulation

To simulate incidence attributable to human-to-human transmission, we considered each spillover case as a potential index case for an outbreak. A schematic overview of both the spillover and outbreak simulation models, including outbreak response, is provided in Fig. 2. Human-to-human transmission was simulated



stochastically using a branching process model. For each primary case, a certain number of secondary cases was drawn either from a Poisson distribution (for Lassa fever and RVF) with $\lambda = R_0$ or from a negative binomial distribution (for MERS and Nipah) with $\mu = R_0$ and a dispersion parameter, k . A Poisson distribution was used for Lassa fever and RVF, because both have an estimated $R_0 < 0.1$ and no available estimate of overdispersion. We used a negative binomial distribution for MERS and Nipah, because secondary cases for these diseases are known to be overdispersed, with a majority of human-to-human transmission arising from a small minority of primary cases [18, 20].

We estimated R_0 and variability therein differently for each pathogen. For LASV, we estimated an R_0 for nosocomial transmission by fitting a simple branching process model to observed outbreak sizes from [51] using the optimize function in R and assuming a Poisson offspring

distribution [52]. The resulting estimate of R_0 for LASV was 0.063 (95% confidence interval [CI] 0.05–0.08) (Table 1). For MERS-CoV, we compiled estimates of R_0 from multiple studies analyzing data from MERS outbreaks [18, 53–57] and described variability in those estimates with a gamma distribution, which resulted in a median R_0 of 0.583 (90% CI 0.31–0.99). The dispersion parameter estimate, $k = 0.26$, for MERS-CoV was obtained from [57]. For NiV, we estimated R_0 and its variability from detailed epidemiological investigations of Nipah outbreaks in Bangladesh that estimated person-to-person chains of NiV transmission [58]. Using data from these studies on the number of secondary infections per primary infection and the size of each transmission cluster, we obtained maximum likelihood estimates of R_0 (0.33, 95% CI 0.21–0.52) and k (0.048, 95% CI 0.031–0.074), which were consistent with a branching process with a negative binomial offspring distribution. For

RVFV, we assumed $R_0 = 0$ and considered $R_0 = 0.01$ for sensitivity analysis only, as no human-to-human transmission has been definitively documented to date [43].

The timing of incubation and infectious periods were then simulated subsequently based on gamma distributions of those periods that we estimated by fitting a model to reconcile variability in previously published estimates (Table 1). As no human-to-human transmission is known for RVFV, we assumed for the sensitivity analysis a fixed duration for the infectious period of 7 days that is consistent with the duration of detectable viremia after the onset of symptoms [59]. For all pathogens, the infection date of secondary cases was simulated as a draw from a uniform distribution over the infectious period of the primary case. Each secondary case was assigned to the same catchment area as the associated index case. A detailed overview of the source for each parameter of each pathogen can be found in Additional file 1: Table S1.

Vaccine campaign simulation

Three different reactive vaccination strategies were evaluated: (1) vaccinating a portion of the general population in a given catchment area, (2) specifically targeting the HCWs in that catchment area, or (3) adopting a ring vaccination strategy where the local population surrounding each index case are targeted for vaccination. These strategies were chosen as they represent three of the most frequently deployed outbreak response strategies. For each strategy, baseline vaccination campaign parameter values (and parameter ranges for the sensitivity analysis) were based on vaccine target product profiles for each pathogen [21–24] or chosen in consultation with CEPI and subject-matter experts for each pathogen (Table 2).

To estimate the impact of vaccination, we simulated each outbreak response relative to a counterfactual simulation in which there was no outbreak response. Vaccination impact was defined as the number of cases averted via vaccination and calculated by taking the difference between the number of cases in the vaccination and no-vaccination scenarios. In our baseline scenario, an outbreak response within a single catchment area was triggered once ten cases of Lassa fever and MERS or three cases of Nipah and RVF were detected within a 4-week window (Table 2). These outbreak response thresholds were chosen through discussion with CEPI and pathogen experts and do not necessarily match the different outbreak definitions currently used by WHO or individual countries. The vaccination start date was calculated by adding a delay to the outbreak response date. To simplify vaccine uptake in our model, we assumed that each target population was immunized on a single day. Multi-day vaccination campaigns would likely reduce the impact of outbreak response relative to our estimates,

Table 2 Overview of the simulation scenarios. Parameter values for the baseline reactive vaccination scenario for each pathogen. Outbreak response threshold cases and threshold window refer to the number of cases that need to occur within a certain time window to trigger an outbreak response. Parameter values in parentheses are alternative values used as a part of the sensitivity analysis

Parameter	LASV, MERS-CoV	NiV, RVFV
Outbreak response		
Threshold cases	10 (5)	3 (1, 5)
Threshold window	28 days	28 days
Delay	28 days (7, 120)	28 days (7, 120)
Vaccination		
Coverage HCW ^a	70% (80, 50, 90)	
Coverage population	70% (20, 50, 90)	
Delay between doses	28 days	
Regimens per index case (ring vaccination only)	90	
Per-exposure protection (PEP)		
Single dose	70% (50%, 90%)	
Two doses, 1st	35% (25%, 45%)	
Two doses, 2nd	70% (50%, 90%)	
Delay	7 days (14)	

^a Excluded for RVFV as no nosocomial transmission has been documented

but this impact would be less severe than a comparable delay in protection following vaccination because at least a portion of the population would be protected at the beginning of the campaign. Therefore, our analysis of the sensitivity of vaccination impact to a delay in protection following vaccination could be considered an upper bound on the sensitivity to extending the vaccine administration period for a given round of vaccination. In the case of a 2-dose vaccine, an additional delay of 28 days was assumed between the administration of the first and second doses.

For the general population vaccination strategy, HCWs were treated as part of the general population and were vaccinated with the same probability as the general population. For the HCW vaccination strategy, non-HCWs were not vaccinated, except for a hybrid strategy tested as part of our sensitivity analysis, where 20% of the general population was vaccinated versus 80% of HCWs (Table 2). For the ring vaccination strategy, we calculated the number of index cases that would arise after the reactive vaccination campaign had started and assumed that 90 vaccine regimens would be needed to vaccinate a ring of individuals around each index case based on estimates from ring vaccination campaigns during recent Ebola and cholera outbreaks [60, 61]. For the ring vaccination strategy, we only estimated the number of vaccine regimens that would be required and did not attempt to estimate

the impact of vaccination on cases averted, because our model was designed to simulate a single vaccine campaign and not the periodic deployment as required by a ring vaccination strategy.

Once a vaccination campaign was completed and the delay between vaccination and protective immunity had elapsed, vaccination in the general population removed spillover cases with a probability equal to vaccination coverage in the general population multiplied by per-exposure protection (PEP). The PEP of the vaccine can therefore be viewed as a reduction in the per-exposure risk of symptomatic infection. Although we did not make an assumption regarding the ability of a vaccine to prevent asymptomatic infections, because we assume that only symptomatic cases are infectious, the PEP could be seen as equivalent to a per-exposure probability of sterilizing immunity from an epidemiological perspective. Vaccination of the general population also removed patient-to-HCW nosocomial cases with a probability equal to vaccination coverage in HCWs multiplied by PEP. Vaccination of HCWs had no impact on spillover cases, but it removed nosocomial cases with a probability equal to vaccination coverage in HCWs multiplied by PEP. PEP depended on whether a sufficient amount of time since vaccination had elapsed and, in the event of a two-dose vaccine, whether an individual had received one dose or two doses at the time of exposure (Table 2). Cases downstream in a transmission chain from a case averted by vaccination were also averted.

Vaccine demand calculation

To quantify the number of regimens required to meet the demands of a given outbreak response strategy, we estimated the number of healthcare workers and the overall population associated with each catchment area where an outbreak occurred. The overall population per catchment area was estimated based on WorldPop data from 2015 [62]. For healthcare workers, we took the national-level numbers of healthcare workers and distributed them proportional to the population associated with each catchment area [63].

Graphical user interface

A generalized implementation of the model is provided as a graphical user interface (GUI) at <http://eidvaccine.demand.crc.nd.edu>. In the generalized implementation, a few adjustments were made to allow for a more flexible application of the model and to make computing time more acceptable for an interactive web tool. First, annual spillovers are drawn from a negative binomial distribution and then distributed across the catchment areas with a multinomial distribution proportional to the probability that spillovers occur in these catchment

areas. Second, the population in the catchment areas was defined by a negative binomial distribution so that specific geographies did not need to be reproduced. The default parameters for the GUI of each pathogen were obtained by fitting the corresponding distribution function to the estimated spillover and population data from this study. The source code for the GUI is provided at https://github.com/lerch-a/CEPI_VaccineCampaignGUI.

Results

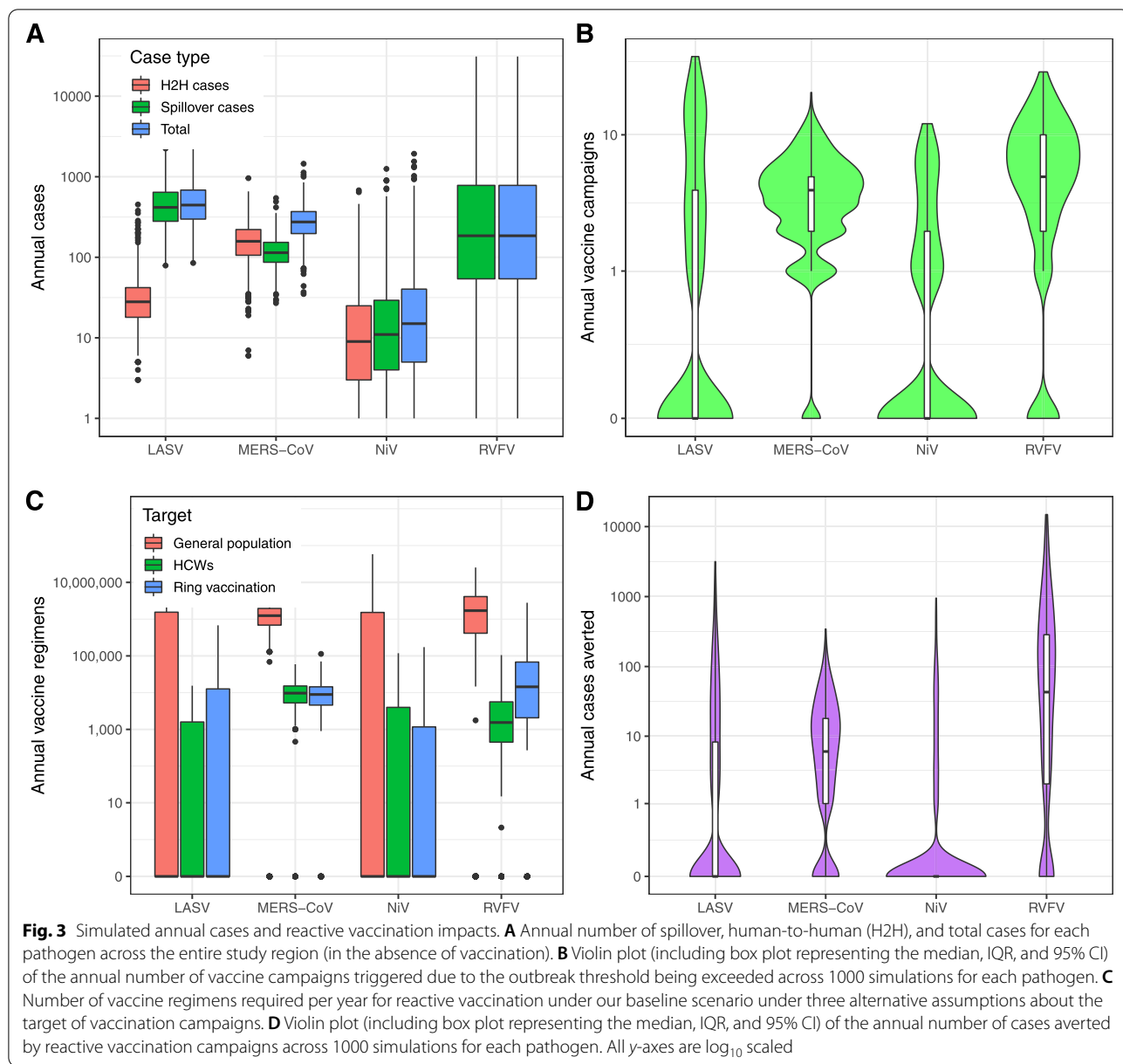
Spillover cases and human-to-human transmission

The median annual number of spillover cases was 6 (95% prediction interval 0–190) for Nipah, 114 (95% PrI 48–266) for MERS, 185 (95% PrI 8–13,134) for RVF, and 417 (95% PrI 142–1837) for Lassa fever (Fig. 3A). Simulated variability in the annual number of spillover cases matched the cumulative distribution of observed spillover cases for each pathogen (Additional file 1: Figs. S1B–S4B). Spillover rates for each pathogen varied both seasonally (Additional file 1: Figs. S1A–S4A) and geographically (Fig. 4A). Spillover cases of Lassa fever were concentrated in Sierra Leone, Liberia, and Nigeria, although a few spillover cases occurred in other western African countries. Spillover of RVF to humans was widespread in South Africa, Madagascar, eastern Africa, and the Arabian Peninsula, with frequent spillover cases occurring in several western and northern African countries as well. The majority of MERS spillover cases occurred in Saudi Arabia, and the majority of Nipah spillover cases occurred in Bangladesh, with additional spillover events in India and Malaysia.

The number of cases arising from human-to-human transmission depended on both the spillover rate and R_0 (Fig. 3A). Under our default parameter assumptions, there was no human-to-human RVFV transmission, but in the absence of vaccination, the median annual number of human-to-human cases following spillover was 2 (95% PrI 0–82) for Nipah, 29 (95% PrI 11–143) for Lassa fever, and 161 (95% PrI 46–407) for MERS (see Fig. 5 for an example of the transmission chains for one catchment area).

Estimates of vaccine demand

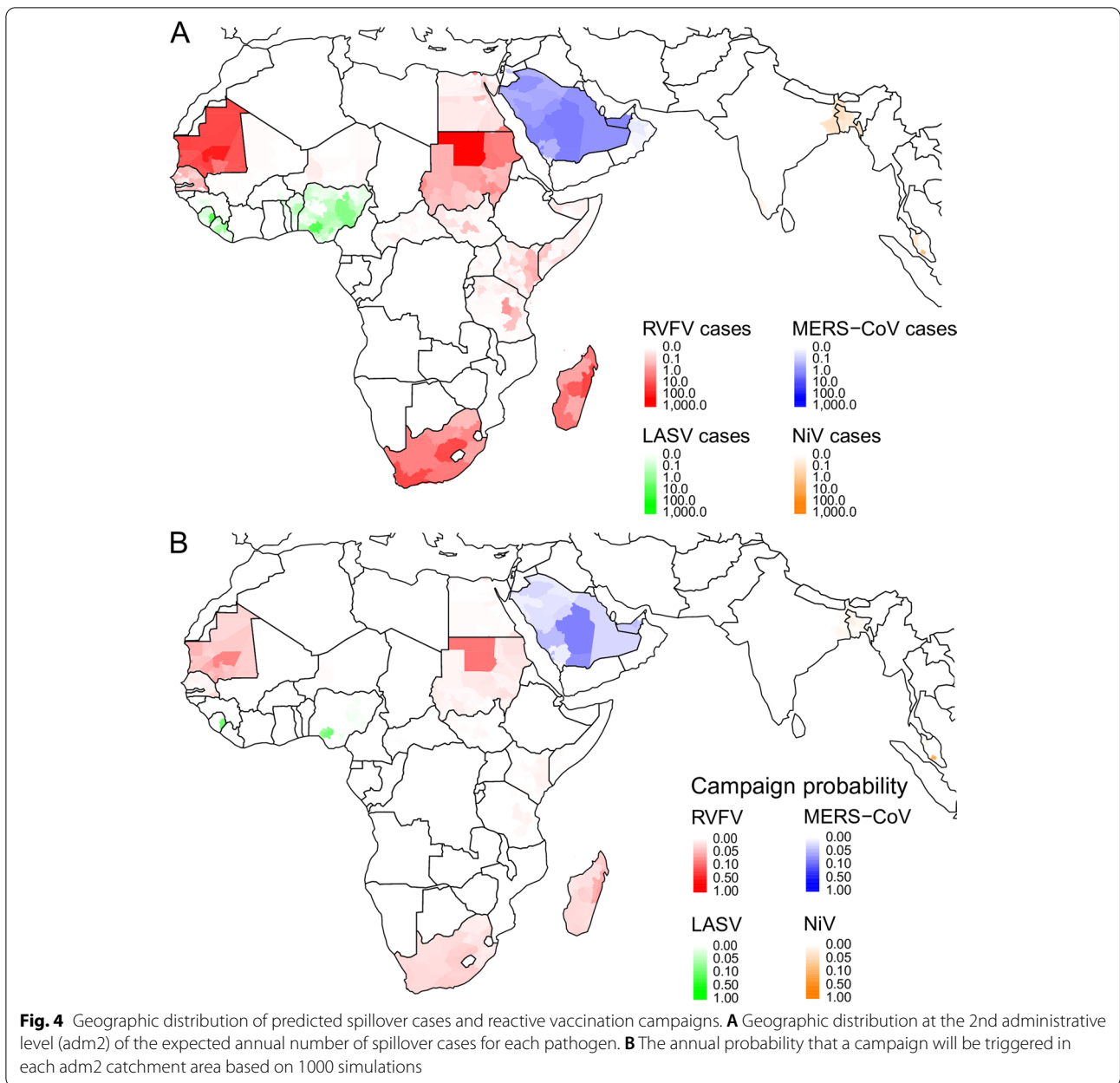
In our analysis, a median of 0 (95% PrI 0–8) Nipah reactive vaccination campaigns were triggered annually, compared to 4 (95% PrI 0–11) MERS campaigns, 5 (95% PrI 0–20) RVF campaigns, and 0 (95% PrI 0–20) Lassa fever campaigns (Fig. 3B). The locations of reactive vaccination campaigns broadly followed the geographic distribution of spillovers for each pathogen, although Lassa fever spillovers in Guinea, Benin, Togo, and western Nigeria were rarely reported frequently enough to trigger a response in our simulations (Fig. 4B). The number of



reactive vaccination campaigns that were triggered, and the timing of those campaigns, was strongly influenced by the seasonal pattern of pathogen spillover (Additional file 1: Figs. S1-S4).

For all four pathogens, there was a wide range in the number of vaccine regimens required in a typical year due to the dependence of vaccine demand on the spatiotemporal clustering of spillover cases required to trigger an outbreak response. The largest annual vaccine demand was for RVFV, with a median of 1,191,741 (95% PrI 0–8,480,275) vaccine regimens required to target the general population under our baseline outbreak response scenario (Fig. 3C). The median annual number

of vaccine regimens for MERS-CoV was 870,045 (95% PrI 0–2,843,407). The median annual number of vaccine regimens needed for NiV and LASV was zero, implying that an outbreak response was triggered less than 50% of the time. However, the mean annual number of vaccine regimens was 673,167 (95% PrI 0–3,629,052) for LASV and 1,450,177 (95% PrI 0–12,240,814) for NiV (Fig. 3C). The number of vaccine regimens required to conduct a ring vaccination strategy or to cover healthcare workers as a part of an outbreak response was typically several orders of magnitude (between 1/25 and 1/700) lower than the number required to cover the general population (Fig. 3C). The median annual number of MERS-CoV

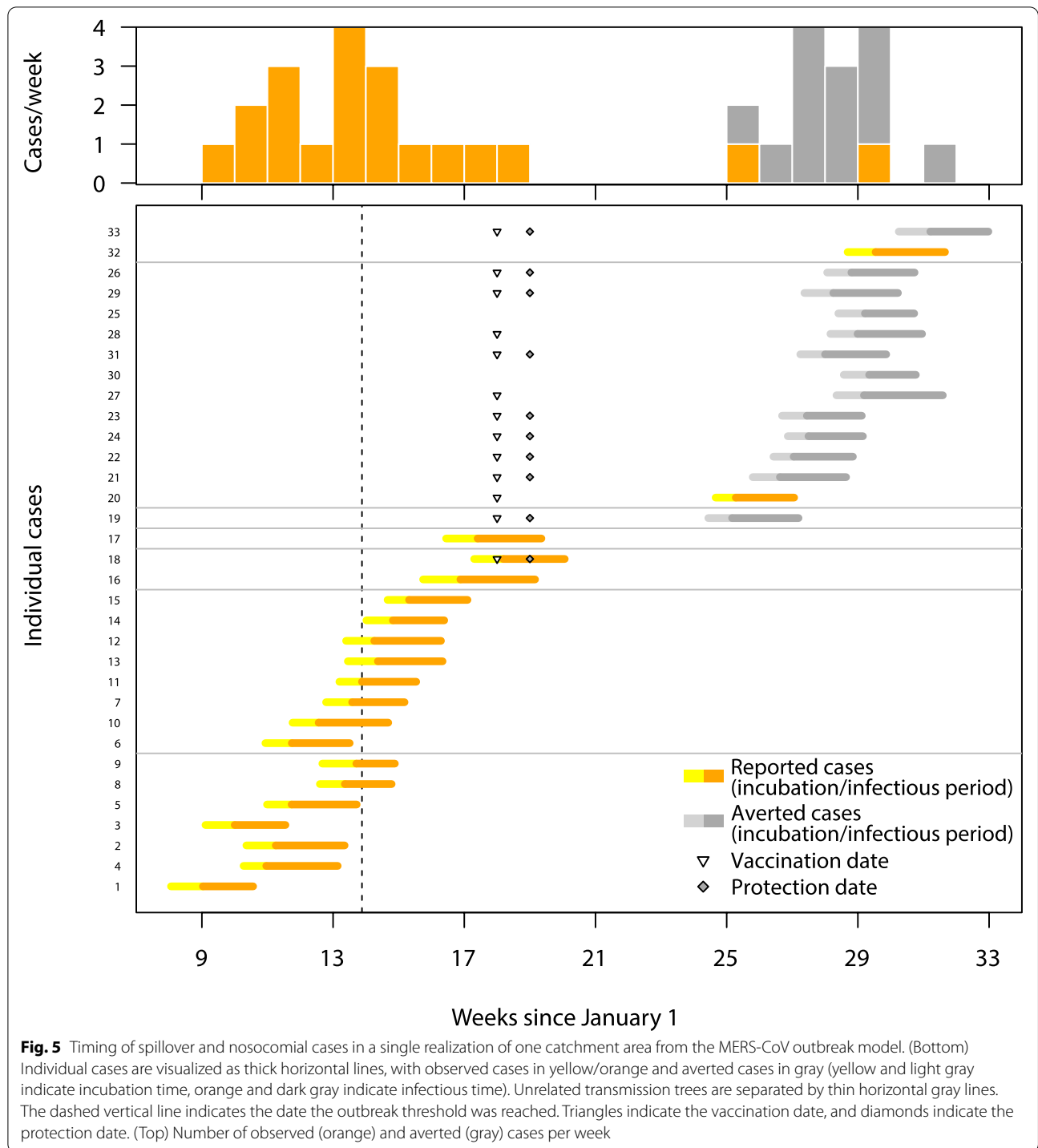


vaccine regimens required to cover healthcare workers was 6786 (95% PrI 0–22,086). A median of 1540 (95% PrI 0–62,320) vaccine regimens were needed among health-care/veterinary workers annually for RVFV outbreak response, 0 (mean 1144; 95% PrI 0–6485) were required for LASV, and 0 (mean 2330; 95% PrI 0–15,833) for NiV. The median annual number of vaccine regimens required for ring vaccination was 4860 (95% PrI 0–21,429) for MERS-CoV, 12,150 (95% PrI 0–1,175,758) for RVFV, 0 (mean 13,774; 95% PrI 0–108,056) for LASV, and 0 (mean 2605; 95% PrI 0–21,641) for NiV. The median size of a single reactive vaccination campaign targeting

the general population was 153,773 (95% PrI 47,723–485,034) for LASV, 156,634 (95% PrI 1478–1,162,080) for RVFV, 275,471 (95% PrI 90,171–358,259) for MERS-CoV, and 460,408 (95% PrI 32,633–5,098,459) for NiV (the sizes of single HCW vaccination campaigns are included in Additional file 1: Table S2).

Impact of outbreak response

The estimated impact of reactive vaccination as an outbreak response tool was generally low for all four pathogens. Vaccinating 70% of the general population in response to an outbreak with a single-dose vaccine



prevented an annual median of 43 (95% PrI 0–5853) RVF cases, 6 (95% PrI 0–83) MERS cases, 0 (95% PrI 0–90) Nipah cases, and 0 (95% PrI 0–357) cases of Lassa fever (Fig. 3D). These vaccine impacts correspond to 0.69 (95% PrI 0–2.92) cases averted per 100,000 vaccine regimens administered for MERS, 3.61 (95% PrI 0–69.02) for

RVF, 0 (95% PrI 0–9.84) for Lassa fever, and 0 (95% PrI 0–0.74) for Nipah. Vaccinating only healthcare workers typically had a smaller total impact than vaccinating the general population at the same coverage level, because there was no protection against spillover in the general population, but a larger per-regimen impact due

to the lower number of regimens is required. Vaccinating 70% of HCWs prevented an annual median of 4 (95% PrI 0–77) MERS cases, corresponding to 58.9 (95% PrI 0–348.6) cases averted per 100,000 vaccine regimens in HCWs. Vaccinating HCWs averted a median of 0 (95% PrI 0–46) Lassa fever cases and 0 (95% PrI 0–48) Nipah cases, corresponding to 0 (95% PrI 0–710.4) and 0 (95% PrI 0–303.5) cases averted per 100,000 HCW vaccine regimens, respectively (we did not explore vaccinating HCWs against RVFV due to the lack of any documented nosocomial transmission).

Sensitivity analysis

The number of total cases increased with higher R_0 values for each pathogen, with the largest sensitivity observed for MERS-CoV, because its higher value of R_0 was close to one (Additional file 1: Fig. S16). There was also a large increase in the number of vaccine regimens required to vaccinate either the general population or HCWs for MERS-CoV at the higher R_0 value, but the impact of R_0 on the required number of vaccine regimens was minimal for the other pathogens (Additional file 1: Figs. S17–S18). As a result, there were minimal differences in the impact of vaccination under higher or lower R_0 values for LASV, NiV, or RVFV (Additional file 1: Figs. S19–S22). Vaccination averted both a greater magnitude and a higher fraction of MERS cases as R_0 increased (Additional file 1: Figs. S19–S20). In addition, the number of MERS cases averted per vaccine regimen administered to the general population or to HCWs also increased as R_0 increased (Additional file 1: Figs. S21–S22).

Lowering the outbreak threshold (from 10 to 5 cases within a 28-day window for MERS-CoV and LASV, and from 3 to 1 case for NiV and RVFV) increased both the number of vaccine regimens needed for outbreak response and the number of cases averted. With the lower outbreak threshold, the projected demand for MERS-CoV vaccine regimens was 2,351,059 (95% PrI 492,028–5,872,847), a 170% increase, while the median number of cases averted was 19 (95% PrI 0–162), a 217% increase compared to the baseline. The required number of vaccine regimens for RVFV increased to 4,793,351 (95% PrI 659,297–14,157,197), a 302% increase, while the median number of RVF cases averted was 66 (95% PrI 0–6066), a 53% increase. The median number of vaccine regimens for LASV increased from 0 to 756,273 (95% PrI 0–6,644,995), and the median number of Lassa fever cases averted increased from 0 to 15 (95% PrI 0–534). The median number of vaccine regimens for NiV increased from 0 to 3,501,587 (95% PrI 0–54,814,275), but the median number of cases averted remained 0 (95% PrI 0–119). When the outbreak threshold was increased to 5 cases for RVE, the required number of vaccine regimens

decreased by 50% to 594,894 (95% PrI 0–7,493,183). The number of RVF cases averted via vaccination decreased to 26 (95% PrI 0–5735), which was 41% fewer cases averted compared with an outbreak threshold of 3 cases.

Decreasing the time delay between the outbreak threshold being reached and the start of the vaccination campaign tended to increase the number of cases averted, while increasing the delay reduced the number of cases averted (Fig. 6). For MERS-CoV, reducing the time delay from 28 to 7 days increased the median number of cases averted from 6 (95% PrI 0–83) to 14 (95% PrI 0–112), while increasing the delay to 120 days reduced the number of cases averted to 0 (95% PrI 0–38).

Increasing or decreasing the percentage of the population that was targeted during reactive vaccination campaigns also led to corresponding increases or decreases in the number of cases averted (Fig. 6). For example, if only 50%, rather than 70%, of the population was vaccinated for MERS-CoV, the median number of cases averted declined from 6 (95% PrI 0–83) to 4 (95% PrI 0–72). In contrast, if vaccination coverage was increased to 90%, then 7 (95% PrI 0–93) MERS cases were averted. The number of MERS cases averted per 100,000 vaccine regimens administered decreased from 0.69 (95% PrI 0–2.92) at 70% coverage to 0.64 (95% PrI 0–3.55) at 50% coverage and 0.63 (95% PrI 0–2.54) at 90% coverage. The sensitivity of the impact of outbreak response to other campaign parameters considered in our model, including per-exposure protection, time to protection following vaccination, vaccination coverage levels in HCWs, and one-dose vs. two-dose vaccines, is provided in Fig. 6. The sensitivity analyses for the other pathogens (NiV, LASV, and RVFV) and for different catchment levels are provided in the supplement (Additional file 1: SI Text). In general, the number of cases averted was highest when the spatial scale for vaccine response (catchment area) was at the first administrative level, but the per-regimen vaccination impact was higher for the smaller catchment areas (second administrative level or hospital-based catchment areas), because fewer vaccine regimens were required per campaign in those areas (Additional file 1: Figs. S33–S34).

Discussion

Model performance

Our spillover simulation model estimates closely matched the average annual reported number of spillover cases for each pathogen, as well as the observed interannual variability in the number of spillover cases that have occurred in the past few decades. The simulation results also captured the geographic distribution and seasonality of spillover cases for each pathogen. The magnitude, spatial distribution, and timing of spillover rates are the main

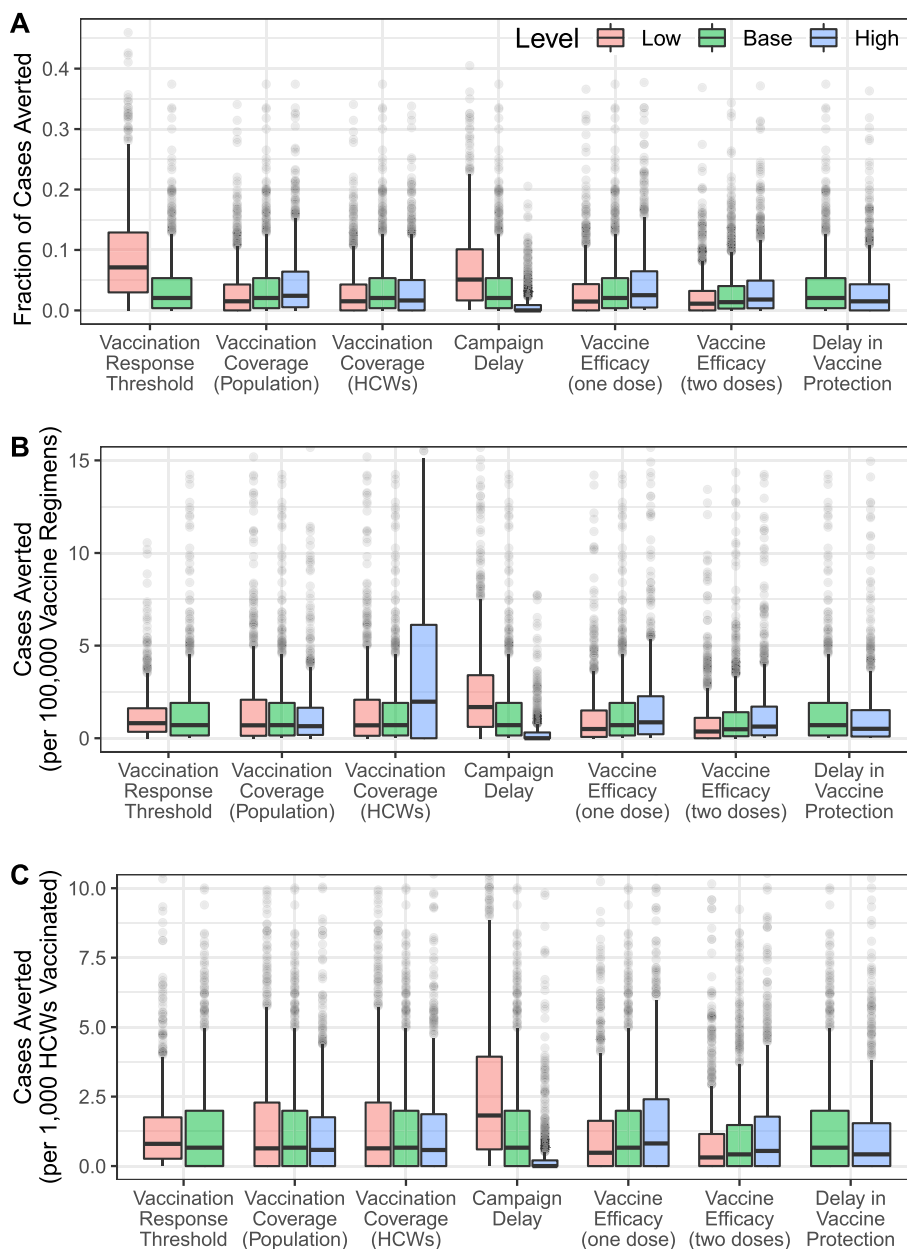


Fig. 6 Vaccine impact sensitivity analysis for MERS-CoV. Sensitivity of vaccination impact for MERS-CoV to variation in different campaign parameters expressed as **A** fraction of cases averted, **B** cases averted per 100,000 vaccinated in the general population, and **C** cases averted per 1000 health care workers (HCWs) vaccinated

determinants of how frequently an outbreak response threshold will be triggered and therefore the size of the vaccine stockpile needed for outbreak response. Although these patterns could shift to some degree in the future, our model represents what we know about them presently. In addition to influencing stockpile size, these three factors (the magnitude, spatial distribution, and timing of spillover rates) are also relevant for logistical

considerations such as the geographic location(s) of the stockpile and the necessary stockpile replenishment rate [64].

Stockpile estimates

The estimated number of vaccine regimens needed to reach vaccination coverage targets in the general population varied considerably across the four pathogens

examined. For both LASV and NiV, the median was zero, indicating that reactive vaccination campaigns would not be triggered more than 50% of the time. In contrast, the median numbers of vaccine regimens needed for MERS-CoV and RVFV were 870,000 and 1,190,000, respectively. However, the 95% prediction intervals for all four pathogens were wide due to spatial and temporal heterogeneity in spillover rates and overdispersion in outbreak sizes resulting from human-to-human transmission. For all four pathogens, the vaccine regimens needed to target HCWs were several orders of magnitude lower than needed to target the general population.

These results indicate that the size of the vaccine stockpile needed to meet annual reactive vaccination demands will depend on the pathogen's epidemiology, the vaccine coverage strategy, and the specific demands of a sustainable manufacturing strategy. In addition to the median or mean annual vaccine demand, our estimates also provide an estimate of the inter-annual variability in vaccine demand and the potential magnitude of vaccine demand in low-frequency, but high-demand years. For example, the 75th or 90th percentile of our estimates corresponds to the level of demand experienced once every 4 or 10 years, on average. The desired size of a vaccine stockpile will likely depend not only on the average annual vaccine demand, but also on the stockpile capacity needed to adequately handle the unpredictability in the timing, frequency, geography, and magnitude of outbreaks. These questions will depend on sustainable vaccine manufacturing capacity, the geographic distribution of both this manufacturing capacity and the stockpile, and vaccine shelf life. A graphical user interface is available at <http://eidvaccinedemand.crc.nd.edu> to facilitate interactive exploration of these dependencies.

Our vaccine demand estimates indicate that the biggest determinant of the size of the reactive vaccine stockpile needs was the vaccination strategy: targeting the general population, only HCWs, or ring vaccination. For pathogens that primarily cause nosocomial outbreaks (e.g., LASV), vaccinating HCWs can protect high-risk individuals. In our analysis, this strategy had a larger impact in terms of cases averted per vaccine regimen than vaccinating the general population. The impact of vaccinating HCWs will be highest when spillovers are highly spatially clustered because vaccination campaigns are more likely to be triggered in high-spillover catchment areas, thereby protecting HCWs against nosocomial transmission in areas where vaccination has already occurred earlier in the transmission season but where the spillover risk may remain high. A ring vaccination strategy would also require significantly fewer regimens than a general vaccination strategy. We estimated that the vaccine demand under a ring vaccination strategy would be similar to the

demand under a HCW vaccination strategy for LASV, NiV, and MERS-CoV and moderately higher than the HCW vaccination strategy for RVFV. Another strategy to reduce the number of vaccine regimens needed per reactive campaign that we did not consider in our analysis would be to target high-risk sub-populations instead of the whole population of a catchment area. In the case of RVFV, this would be animal workers like butchers, veterinarians, and farmers who are at the highest risk of infection [65–67]. For MERS-CoV, camel workers have a higher risk of infection than the general population [33]. For LASV, rural populations within a catchment area are assumed to have a higher risk than urban populations (but see Chika-Igwenyi et al. [68], where > 50% of patients in one outbreak were urban residents). For NiV, rural populations and people drinking raw date palm sap could be targeted for vaccination [69, 70].

In addition to providing an estimate of vaccine stockpile size, our modeling approach also provides an estimate of where the stockpile will most frequently need to be deployed. An understanding of the geographical distribution of vaccine demand is critical for sustainable manufacturing and timely response to outbreaks [71–73]. Knowledge of vaccine needs by geographic area is essential so that the stockpile(s) can be strategically positioned for rapid deployment following the triggering of an outbreak response. Vaccine demand in a given area will be a function of the probability of an outbreak response being triggered and the size of the target population. Because we used a sliding time window for the outbreak threshold, the probability of a reactive vaccination campaign being triggered will also depend on the seasonality of spillover. Spillover cases that are highly seasonal will be more likely to trigger a response than spillovers that occur sporadically throughout the year. Highly seasonal spillover rates also increase the importance of the rapid deployment of reactive vaccination campaigns, because the shorter duration of the transmission season increases the likelihood that any delays would cause campaigns to occur only after seasonal spillover transmission has declined.

The size of the outbreak response catchment areas (our baseline catchment area at the 2nd administrative level vs. 1st administrative units or individual hospitals within each 1st administrative unit) also had a large impact on the frequency and timing of outbreak response. First-level administrative catchment areas triggered more outbreak responses and also have larger population sizes and would therefore require a larger vaccine stockpile. However, this result assumes that the outbreak threshold (number of cases needed to trigger a reactive vaccination campaign) is the same regardless of the size of the catchment area. Adjusting the threshold size based on the

geographic extent or population size of the catchment areas would alter the stockpile requirements and could be one approach to aligning expected stockpile demands with manufacturing capacity. The expected number of regimens needed for adm1 catchment areas might also be an overestimate if only certain regions in an adm1 are at risk. Therefore, another approach that could balance the advantage of expanded adm1 catchment surveillance areas against the larger stockpile requirements would be to monitor spillover cases at the adm1 level, but limit reactive vaccination to the adm2 regions within the adm1 catchment area where spillover cases were observed.

Vaccination impact

Our results indicate that reactive vaccination strategies for preventing the transmission of zoonotic pathogens with $R_0 < 1$ tend to have limited impacts. For each of the four pathogens we considered, reactive vaccination of the general population averted fewer than 100 cases per year on average and required more than 10,000 vaccine regimens per case averted. The largest impact (as measured by total cases averted or fraction of cases averted) was achieved for RVFV, which was the only pathogen where $> 5\%$ of total cases were averted via reactive vaccination under our default assumptions. On a cases-averted per regimen basis, vaccinating HCWs was more effective than vaccinating the general population for each of the pathogens with at least some human-to-human transmission in nosocomial settings (LASV, MERS-CoV, and NiV), suggesting that targeting this group may be a viable strategy for reducing the spread of zoonotic pathogens that are capable of nosocomial transmission.

Under our baseline reactive vaccination scenario, vaccination averted a higher proportion of RVF cases than cases of the other three diseases, even though we assumed that there was no human-to-human RVFV transmission. The higher impact of reactive vaccination for RVFV was the result of two factors. First, our default threshold to trigger an RVFV vaccination campaign was three cases (compared to 10 cases within a 28-day window for LASV or MERS-CoV), which led to more RVFV campaigns being triggered than for the other diseases. Second, RVFV spillovers are highly clustered in space and time, so additional spillover cases were often concentrated in catchment areas where previous spillovers during the transmission season had already triggered a reactive vaccination campaign. Although the lower threshold led to more vaccine regimens being required for RVFV than for the other pathogens, the per regimen impact of reactive vaccination was still highest for RVFV. These results highlight the importance of understanding the underlying epidemiology of zoonotic pathogens when assessing the feasibility of a reactive vaccination strategy.

The spatial and temporal heterogeneity in spillover patterns will be a primary factor determining the potential impact of reactive vaccination for pathogens where cases primarily occur via zoonotic spillover rather than human-to-human transmission. With a sensitive case threshold for triggering a vaccination campaign, and a relatively quick response time (28 days), our results indicate that $\sim 25\%$ of RVF cases could be averted. However, if the response time is slower (120 days), fewer than 5% of RVF cases would be averted via reactive vaccination. This highlights the importance of rapid response and vaccine deployment to the success of reactive campaigns when spillover is seasonal.

After RVFV, the impact of vaccination was modestly higher for the pathogen (MERS-CoV) with the highest R_0 (baseline $R_0 = 0.58$), indicating that rapid deployment of a reactive vaccination campaign can avert a fraction of cases for pathogens capable of at least some sustained human-to-human transmission. However, even for MERS-CoV, fewer than 10% of annual cases were averted by reactive vaccination, even under our most optimistic scenario with a minimal delay. This was partly because a significant fraction of cases were spillover cases in geographic areas where no vaccination campaign was triggered, and partially because reactive vaccination often did not occur rapidly enough to avert a significant proportion of cases resulting from secondary human-to-human transmission. The one scenario where reactive vaccination had a large impact on MERS-CoV transmission was with a higher R_0 value of 0.99. In this case, 84.0% (95% PrI 10.7–97.5%) of MERS cases could be averted under our baseline reactive vaccination scenario, compared to only 2.1% (95% PrI 0–18.2%) of cases averted with the default $R_0 = 0.58$. This result highlights the increased potential impact of a reactive vaccination strategy as R_0 approaches or exceeds one and self-sustaining human-to-human transmission chains that lead to larger outbreaks become more likely.

Reactive vs. prophylactic vaccination

Delays between the triggering of the outbreak threshold and vaccine administration limit the impact of reactive vaccination. In most simulated outbreaks, the outbreak died out before the vaccination was administered due to the low R_0 . In light of this, prophylactic immunization of HCWs or people at high risk could have a larger impact than reactive vaccination. However, a potentially important aspect that was not considered in our study was the impact that reactive vaccination campaigns in 1 year had on protection in subsequent year(s). Depending on the duration of vaccine-derived immunity, the number of cases averted in subsequent years could be substantial, particularly if the geographic clustering of spillovers

is fairly consistent from year to year. For example, in the past few years, some catchment areas in Nigeria have experienced outbreaks of Lassa fever multiple years in a row [19, 26]. As an extension of our work, the number of averted cases in the years following a reactive vaccination campaign could be estimated based on the spillover rate, the probability of an outbreak, and the durability of vaccine-derived immunity.

Limitations

We have attempted to estimate vaccine stockpile needs and identify the most important determinants of success for reactive vaccination of zoonotic emerging pathogens by modeling several vaccination strategies and exploring the sensitivity of our results to different aspects of pathogen natural history and vaccine deployment. However, there are some limitations to our approach that could affect these estimates. We briefly mention the main limitations here and include an expanded discussion of these limitations in Additional file 1: SI Text.

First, there is a relatively poor understanding of the epidemiology of most emerging zoonotic pathogens, and data that could be used to try and elucidate the most important aspects of their epidemiology is limited [74]. In this study, we collated epidemiological data and parameter estimates from a variety of published sources and also consulted pathogen-specific experts, but, inevitably, our approach was limited by current knowledge. Second, because the modeling framework is intended to be applicable to a range of emerging zoonotic pathogens, it cannot incorporate all of the specific epidemiological details that might affect the vaccine demand or impact on a particular pathogen. Our focus was on the key aspects of epidemiology and outbreak response that influence sustainable manufacturing needs, vaccine stockpile requirements, and the impact of the outbreak response. As a result, we also did not consider other potential control strategies beyond reactive vaccination in humans that might be relevant for some zoonotic pathogens, such as the use of a camel-targeted vaccine for MERS-CoV, a livestock-targeted vaccine(s) for RVFV, or vector control efforts for RVFV. In some settings, these alternative strategies might be more effective than reactively vaccinating the human population, or these additional control measures could be conducted in coordination with a reactive vaccination campaign. Third, we only considered reported cases when estimating pathogen spillover rates, because undiagnosed or unreported infections would not trigger an outbreak response, which could bias the geographic distribution of vaccine demand away from areas with limited disease surveillance systems. This decision was made to ensure that our framework could

be implemented with existing data only and therefore could be applied to other pathogens in a straightforward manner.

Fourth, because the extent of community transmission for each of the study pathogens is poorly understood, we assumed that human-to-human transmission was limited to nosocomial settings, which could result in an underestimate of vaccine demand. However, our modeling framework could be used to explicitly represent community transmission dynamics, and for pathogens with $R_0 \ll 1$, as was largely the case in this study, the limited size of the modeled transmission chains would be similar in either a community or hospital setting since we did not restrict the potential number of contacts per index case. Our outbreak model did not incorporate population density, which could also be relevant in communal settings and would likely become increasingly important as R_0 approaches or exceeds 1. However, our model implicitly incorporates the effect of population size on outbreak probability through its influence on the estimated number of spillover cases in a catchment area. Fifth, we also assumed that all nosocomial transmission was from patients to HCWs or between HCWs, and that there was no patient-to-patient or HCW-to-patient transmission. Therefore, our estimates of the impact of vaccinating HCWs represent an upper bound on the effectiveness of this strategy, as instances of patient-to-patient transmission would not be prevented via this strategy. Sixth, another simplifying assumption of our model is that cases in one catchment area do not lead to transmission or an outbreak outside of that catchment area. However, our model already implicitly incorporates the possibility of spread between catchment areas, and although our model does not predict spillover cases occurring outside of each pathogen's currently documented geographic distribution, the reactive vaccination strategies we examined should also be applicable for responding to imported cases and their associated outbreaks. Seventh, we assumed that vaccinated individuals who were successfully protected from symptomatic infection were not capable of infecting other individuals. However, if the vaccine was less effective at preventing asymptomatic infection, and these asymptomatic individuals were still capable of transmitting the pathogen, the impact of vaccination could be smaller than we have estimated. Finally, we did not consider any targeted vaccination strategies beyond ring vaccination or targeting healthcare workers to limit nosocomial outbreaks.

Conclusions

To inform the development of sustainable vaccine manufacturing processes for emerging pathogens, we developed a modeling framework to estimate the necessary

reactive vaccine stockpile size for emerging zoonotic pathogens. Our framework provides a flexible methodology for estimating vaccine stockpile needs for outbreak response and for exploring the impact of epidemiology and vaccination strategies on outcomes that have important logistical implications for sustainable vaccine manufacturing, such as the geographic distribution of demand or the required stockpile replenishment rate. However, our model showed that the impact of reactive vaccination for the four pathogens that we explored was minimal, preventing fewer than 10% of human cases under most scenarios with their current epidemiology. However, all these pathogens are closely monitored for their outbreak potential, and control measures are needed. Targeting populations at higher risk of infection, such as HCWs, had a higher per-regimen impact than population-wide vaccination in outbreak control situations. Our results highlight the need for a more thorough epidemiological understanding of these, and other, emerging zoonotic pathogens. Improved pathogen surveillance and case detection are also essential for improving the model and our estimates of vaccine demand. Further work exploring additional scenarios, such as the possibility of targeting certain high-risk populations or the potential uses of vaccines for outbreak prevention rather than just outbreak response, is also needed to improve the potential impacts of vaccination.

Abbreviations

adm1: First administrative level; adm2: Second administrative level; CEPI: Coalition for Epidemic Preparedness Innovations; CHIKV: Chikungunya virus; GLMM: Generalized linear mixed model; H2H: Human-to-human; HCW: Healthcare worker; LASV: Lassa virus; MERS-CoV: Middle Eastern respiratory syndrome coronavirus; NiV: Nipah virus; PEP: Vaccine per-exposure protection; RVFV: Rift Valley fever virus; WHO: World Health Organization.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12916-022-02405-1>.

Additional file 1: Table S1. Overview of data references. **Table S2.** Sizes of single reactive vaccination campaigns targeting the general population or healthcare workers (HCWs). **SI Text.** Sensitivity analysis and extended model limitations. **Fig. S1.** Spillover and reactive vaccination patterns for Lassa fever virus (LASV). **Fig. S2.** Spillover and reactive vaccination patterns for Middle Eastern respiratory virus (MERS-CoV). **Fig. S3.** Spillover and reactive vaccination patterns for Nipah virus (NiV). **Fig. S4.** Spillover and reactive vaccination patterns for Rift Valley fever virus (RVFV). **Fig. S5.** Vaccine regimens required for Lassa fever virus (LASV). **Fig. S6.** Vaccine regimens required for Middle Eastern respiratory virus (MERS-CoV). **Fig. S7.** Vaccine regimens required for Nipah virus (NiV). **Fig. S8.** Vaccine regimens required for Rift Valley fever virus (RVFV). **Fig. S9.** Vaccine regimens required to vaccinate healthcare workers for Lassa fever virus (LASV). **Fig. S10.** Vaccine regimens required to vaccinate healthcare workers for Middle Eastern respiratory virus (MERS-CoV). **Fig. S11.** Vaccine regimens required to vaccinate healthcare workers for Nipah virus (NiV). **Fig. S12.** Vaccine regimens required to vaccinate veterinarians for Rift Valley fever virus (RVFV). **Fig. S13.** Vaccination impact sensitivity analysis for LASV. **Fig. S14.** Vaccination impact sensitivity analysis for NiV. **Fig. S15.** Vaccination

impact sensitivity analysis for RVFV. **Fig. S16.** Number of cases under different R_0 assumptions. **Fig. S17.** Number of vaccine regimens required under different R_0 assumptions. **Fig. S18.** Number of vaccine regimens required for healthcare workers (HCWs) under different R_0 assumptions. **Fig. S19.** Number of cases averted by vaccinating the general population under different R_0 assumptions. **Fig. S20.** Fraction of cases averted by vaccinating the general population under different R_0 assumptions. **Fig. S21.** Number of cases averted per vaccine regimen administered to the general population under different R_0 assumptions. **Fig. S22.** Number of cases averted per vaccine regimen administered to healthcare workers (HCWs) under different R_0 assumptions. **Fig. S23.** Spillover and reactive vaccination patterns for Lassa fever virus (LASV) within adm1 catchment areas. **Fig. S24.** Spillover and reactive vaccination patterns for Middle Eastern respiratory virus (MERS-CoV) within adm1 catchment areas. **Fig. S25.** Spillover and reactive vaccination patterns for Nipah virus (NiV) within adm1 catchment areas. **Fig. S26.** Spillover and reactive vaccination patterns for Rift Valley fever virus (RVFV) within adm1 catchment areas. **Fig. S27.** Spillover and reactive vaccination patterns for Lassa fever virus (LASV) within adm1 hospital catchment areas. **Fig. S28.** Spillover and reactive vaccination patterns for Middle Eastern respiratory virus (MERS-CoV) within adm1 hospital catchment areas. **Fig. S29.** Spillover and reactive vaccination patterns for Nipah virus (NiV) within adm1 hospital catchment areas. **Fig. S30.** Spillover and reactive vaccination patterns for Rift Valley fever virus (RVFV) within adm1 hospital catchment areas. **Fig. S31.** Geographic distribution of spillover cases and reactive vaccination campaigns for adm1 catchment areas. **Fig. S32.** Geographic distribution of spillover cases and reactive vaccination campaigns for adm1 hospital catchment areas. **Fig. S33.** Annual cases and reactive vaccination impacts for adm1 catchment areas. **Fig. S34.** Annual cases and reactive vaccination impacts for adm1 hospital-based catchment areas.

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Authors' contributions

SMM and TAP conceived the research. SMM, TAP, MLJ, AAB, MB, and GAVM contributed to the study design. SMM and AL led the writing. AL, ASS, GMB, ME, CSH, KK, KS, and MW prepared the data sets. SMM, AL, TAP, QATB, GMB, QMT, JHH, ASS, ME, CSH, KK, KS, and MW contributed to the code development. SMM, AL, TAP, QATB, and GMB performed the analyses. All authors provided critical feedback on the revisions of the manuscript and read and approved the final manuscript.

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Availability of data and materials

The data sets collated and analyzed during the current study, along with all of the code to replicate the analysis, are available in the following GitHub repository: <https://github.com/lerch-a/VaccineCampaign>.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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