Ebola vaccination in the Democratic Republic of the Congo

Chad R. Wells[a,1], Abhishek Pandey[a,1], Alyssa S. Parpia[a], Meagan C. Fitzpatrick[a,b], Lauren A. Meyers[c], Burton H. Singer[d,2], and Alison P. Galvani[a]

[a]Center for Infectious Disease Modeling and Analysis, Yale School of Public Health, New Haven, CT 06520; [b]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD 21201; [c]Department of Integrative Biology, University of Texas, Austin TX, 78712; and [d]Emerging Pathogens Institute, University of Florida, Gainesville, FL 32610

Contributed by Burton H. Singer, February 1, 2019 (sent for review October 8, 2018; reviewed by Carlos Castillo-Chavez and Claudio Jose Struchiner)

Following the April 2018 reemergence of Ebola in a rural region of the Democratic Republic of the Congo (DRC), the virus spread to an urban center by early May. Within 2 wk of the first case confirmation, a vaccination campaign was initiated in which 3,017 doses were administered to contacts of cases and frontline healthcare workers. To evaluate the spatial dynamics of Ebola transmission and quantify the impact of vaccination, we developed a geographically explicit model that incorporates high-resolution data on poverty and population density. We found that while Ebola risk was concentrated around sites initially reporting infections, longer-range dissemination also posed a risk to areas with high population density and poverty. We estimate that the vaccination program contracted the geographical area at risk for Ebola by up to 70.4% and reduced the level of risk within that region by up to 70.1%. The early implementation of vaccination was critical. A delay of even 1 wk would have reduced these effects to 33.3 and 44.8%, respectively. These results underscore the importance of the rapid deployment of Ebola vaccines during emerging outbreaks to containing transmission and preventing global spread. The spatiotemporal framework developed here provides a tool for identifying high-risk regions, in which surveillance can be intensified and preemptive control can be implemented during future outbreaks.

Ebolavirus | vaccine | spatial analysis | spatial interaction model

Ebola vaccine development ramped up considerably during and following the devastating 2013–2016 West African outbreak. In addition to many animal studies (1), 44 clinical trials have been completed, with more ongoing (2). In a cohort study, recombinant vesicular stomatitis virus (rVSV)-vectored vaccine for Ebola virus disease (rVSV-ZEBOV) elicited seroconversion in 100% of participants [defined by IgG antibody titer ≥58.84 ELISA units (EU)/mL (3)]. Furthermore, the phase III trial for this vaccine conducted toward the end of the West African outbreak found no infections among the 4,539 immediately vaccinated participants and 16 infections among the 4,557 participants in the control arm (4, 5). From this study, a vaccine efficacy estimate of 100% (95% CI: 79.3–100%) was obtained (4, 5). Since the West African clinical trials, rVSV-ZEBOV was deployed for the first time during the April–July 2018 Ebola outbreak in the Democratic Republic of the Congo (DRC).

In April 2018, Ebola emerged in a rural area of the Équateur province in the DRC and then spread to a populous urban center (6), reminiscent of the devastating West African outbreak. However, relative to the West African outbreak, this recent DRC epidemic was swiftly contained after a total of 54 cases and 33 deaths (7). Upon confirming two cases on May 8, the DRC Ministry of Health declared an outbreak and initiated contact tracing. Two weeks later, on May 21, ring vaccination was initiated to protect contacts of diagnosed cases and to terminate chains of transmission (8). Through contact tracing, individuals who may have come into contact with infected individuals and the contacts of those contacts are identified. Ring vaccination involves vaccinating a primary ring of the contacts of infected individuals, as well as vaccinating the contacts of those contacts, which constitute the secondary ring. This vaccination strategy notably achieved the historic eradication of smallpox and is currently employed in response to mumps outbreaks. Ring vaccination was implemented during the final 15 mo of the 2013–2016 Ebola outbreak in Guinea both to control the epidemic and to assess the efficacy of rVSV-ZEBOV. This program identified primary and secondary contacts of 117 confirmed cases. Of these, 3,796 were immediately vaccinated, and 2,041 constituted a control group who were vaccinated after a delay of 21 d (4). There were no infections among the contacts immediately vaccinated, whereas several individuals in the delayed-vaccination control group were infected.

The uncertainties inherent in the spatiotemporal dissemination of infectious diseases present an obstacle to containment strategies. Risk maps can inform targeting and prioritization of limited resources. While population density (9, 10), poverty (11), and human mobility (12, 13) have been shown to exacerbate Ebola transmission, their combined impact on the geospatial spread of Ebola is not yet understood.

Here, we develop a framework that integrates a data-driven gravity model (13) with population density, poverty, and geographic distance, which we calibrated to spatial Ebola incidence data from the 2018 Équateur outbreak before the initiation of the vaccination campaign. We use this high-resolution modeling framework to evaluate the spatiotemporal evolution of Ebola risk in the DRC and assess the effectiveness of the recent vaccination efforts. Our results suggest that the outbreak would have likely spread further had vaccination rollout been delayed even 1 wk.

Significance

Using a spatial model that incorporates human mobility, poverty, and population density, we assessed the effectiveness of the vaccination program that was implemented during the 2018 Ebola outbreak in the Democratic Republic of the Congo. Our results demonstrate that even modest delays in initiating vaccination would have markedly eroded the impact of the program. The methodology we present has applicability for identifying areas at risk during outbreaks of other emerging and reemerging diseases, which is imperative for swift control.

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[1]C.R.W. and A.P. contributed equally to this work.

[2]To whom correspondence should be addressed. Email: bhsinger@epi.ufl.edu.

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The modeling framework that we develop here to combine the contributions of poverty, human mobility, and population density on the severity and geographic scope of disease spread could be applied to other outbreaks of directly transmitted zoonotic diseases. Assessing the spatial distribution of risk for a disease following emergence or reemergence would facilitate the geographic targeting of control measures, such as vaccination, movement restrictions, and public education efforts.

Results

We estimated the geographic distribution of Ebola risk at a spatial grid unit resolution of one arcminute (1.85×1.85 km^2) over the 4 wk following the initiation of the vaccination program on May 21, 2018. To assess risk, probabilities of an Ebola infection over a 4 wk time period were calculated for each of the 219,152 spatial units that constitute the northwestern part of the DRC. From the model fitting (*Methods*), we obtain the background probability of an infection in the absence of any symptomatic cases (P_0 calculated in *SI Appendix*, Eq. **S14**). We classified an area as "at risk" if the infection probability within the area exceeded P_0 and at "high risk" if this infection probability exceeded 0.05. We used a maximum likelihood approach to fit the model to spatial prevalence data from April 5 to May 10. We then validated our spatiotemporal projections from May 11 to May 20 (*SI Appendix*, Fig. S1). Comparison of our spatiotemporal projections with the timing and location of cases arising after May 10 demonstrated a good fit (*SI Appendix*, Fig. S1). For the remaining analyses, we use a model fit to the epidemiological data from April 5 to May 20. In the base case, we considered a vaccine efficacy of 100%, the estimate from phase III clinical

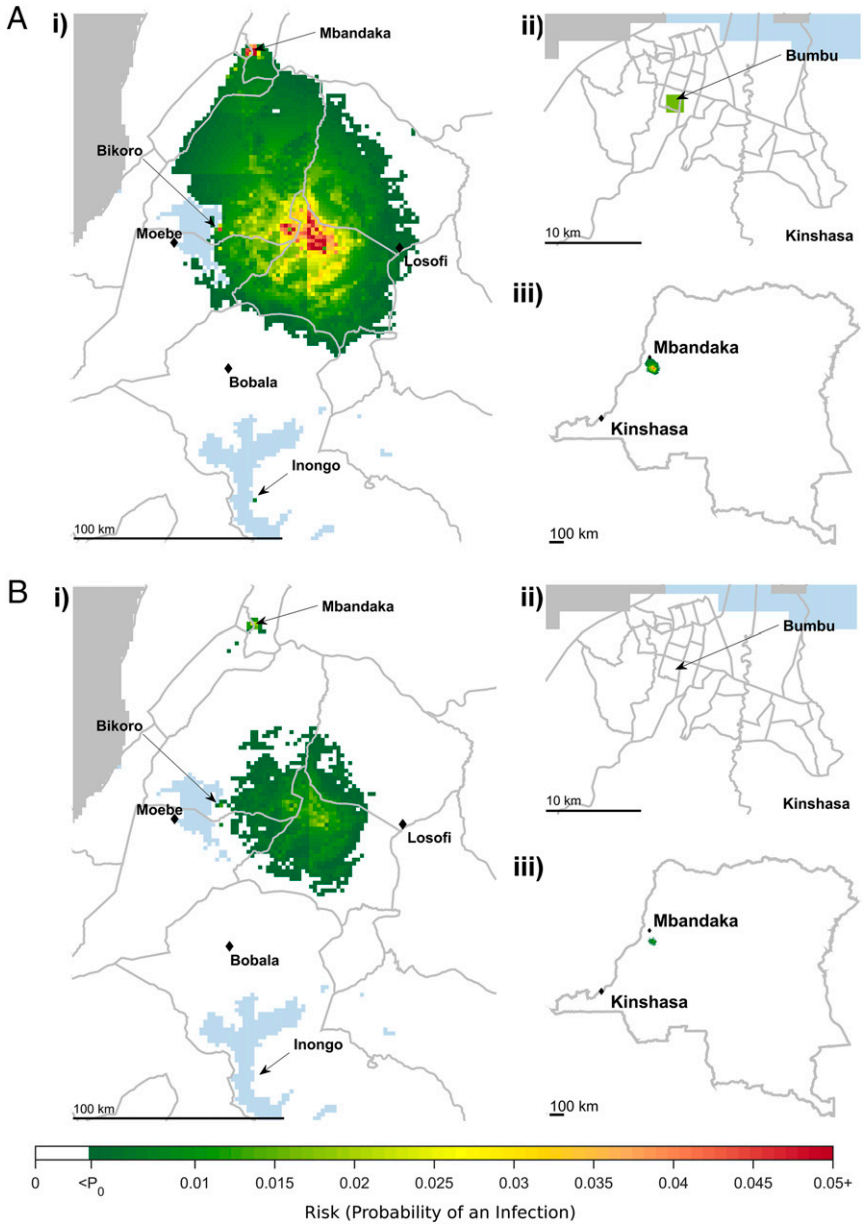

Fig. 1. The spatial risk of Ebola in the DRC evaluated with and without implementation of the ring vaccination program. The risk of Ebola between May 21 and June 17, 2018 at a one arcminute resolution of 1.85×1.85 km^2 in the DRC, (*A*) if no vaccination was implemented and (*B*) with vaccination initiated May 21, 2018. In the DRC, we highlight the area at risk in (*i*) the Équateur Province and (*ii*) Bumbu, a health zone in Kinshasa (capital), as well as in (*iii*) in northwestern DRC relative to the country as a whole. Gray lines indicate health zone borders.

trials, but also evaluated efficacy across the empirical 95% confidence interval from 79.3 to 100% (4, 5).

Spatial Spread. We estimated that 10,661 km^2 would have been at risk for Ebola infection between May 21 and June 17, 2018, if a vaccination program had not been administered (Fig. 1). We found that risk was predominantly governed by proximity to the outbreak origin and human mobility, a function of the population size and distance between spatial units, with an exacerbating impact of poverty. Over 48 km^2 of the area surrounding the initial sites of infection was at high risk (Fig. 1). Approximately 95% of the area at risk was located within a 84.4 km radius of the outbreak origin near the market town of Bikoro (Fig. 1). Beyond the local region, the risk was high in Mbandaka, a populous city and the provincial capital located 77 km from Bikoro, where two major waterways merge. Although the outbreak originated in rural Équateur, the high risk in Mbandaka is attributable to human movement toward urban centers. At lower but still significant risk was Inongo, a relatively populous town 134 km from Bikoro. Poverty plays a role in exacerbating risk as far out as the capital Kinshasa. Specifically, although Kinshasa is 512 km from Bikoro, the risk in its most densely populated and impoverished municipality was over 2.5 times higher than in Inongo.

In the DRC, public health policies, including contact tracing and vaccination, are administered at the level of the health zone. Cases were reported only in the health zones of Bikoro, Iboko, and Wangata. Without vaccination, more than 87% of area within Bikoro and Iboko, as well as 44% of the area in Wangata, would have been at risk (Fig. 2). The pattern was different for locations at high risk: Wangata had the greatest percentage of its area at high risk (5.6%). However, in terms of absolute area at high risk, Wangata only has 3.4 km^2 at high risk, whereas 27.5 km^2 of Iboko and 10.3 km^2 of Bikoro are predicted to be at high risk. The area at highest risk within Iboko was located near the border of Iboko and Bikoro, only 2.4 km^2 from the concentration of cases and risk in Bikoro.

In the six health zones neighboring those with cases reported before May 20, the area at risk ranged from 1.8% in Inongo to 52% in Ingende, the latter of which borders both Bikoro and Iboko (Fig. 2). Beyond the neighboring health zones, the Bumbu health zone located in the DRC capital of Kinshasa, 11 health zones away from the affected health zones, was predicted to be at moderate risk. Kinshasa is a transportation hub that draws people from all over the country, and Bumbu is the most densely populated of its health zones.

Impact of Vaccination. We found that the ring vaccination program initiated on May 21 reduced the area at risk by 70.4% and diminished the level of risk by 70.1% (Fig. 1 *A* and *B*). The radius of the area that accounts for 95% of the risk around Bikoro contracted from 84.4 km (Fig. 1 *A*, *i*) to 66.0 km (Fig. 1 *B*, *i*). Further from the outbreak origin, the ring vaccination program was also projected to reduce risk in populous urban centers. For example, vaccination was projected to decrease the likelihood of an Ebola infection in Mbandaka city by 54.2%, in the town of Inongo by 76.8%, and in Kinshasa by 85.4% over the course of a month.

At the health zone level, vaccination contracts the area that is classified as at-risk (Fig. 2). For example, the area at risk in Iboko, Bikoro, and Wangata, the health zones in which cases were reported, was reduced by 47.8, 78.4, and 37.5%, respectively. In the health zones of Inongo, Bumbo, and Pendjua, vaccination resolved the risk that had been present in the absence of vaccination. Vaccination also shifted the distribution of the level of risk in health zones previously identified as at-risk to an overall lower level of risk. The ring vaccination program eliminated high-risk areas. Among the six health zones neighboring the health zones that reported cases before May 11, slightly over 10 km^2 of Mbandaka and of Ingende remained at moderate risk following vaccination (Fig. 2).

In practice, not all contacts and healthcare workers at risk for Ebola infection are eligible for vaccination due to pregnancy, breastfeeding, comorbidities, and/or young age (4). Further, it is likely that some eligible contacts may not consent to receiving the vaccine. Thus, we estimated the impact of implementing a vaccination campaign with reduced coverage such that only 52% of contacts were vaccinated, as occurred in the phase III trial of the administered vaccine (4). At this lower coverage, the overall area at risk was reduced by 53.8%, and the level of risk in this area was reduced by 58.9%, compared with 70.4% reduction in area and 70.1% reduction in level of risk when all contacts were vaccinated.

To determine the impact of vaccine efficacy on the effectiveness on the program, we considered the variation in efficacy across the 95% confidence interval of the clinical trial, which ranged from 79.3 to 100.0% (4). Compared with a 100% efficacious vaccine, a

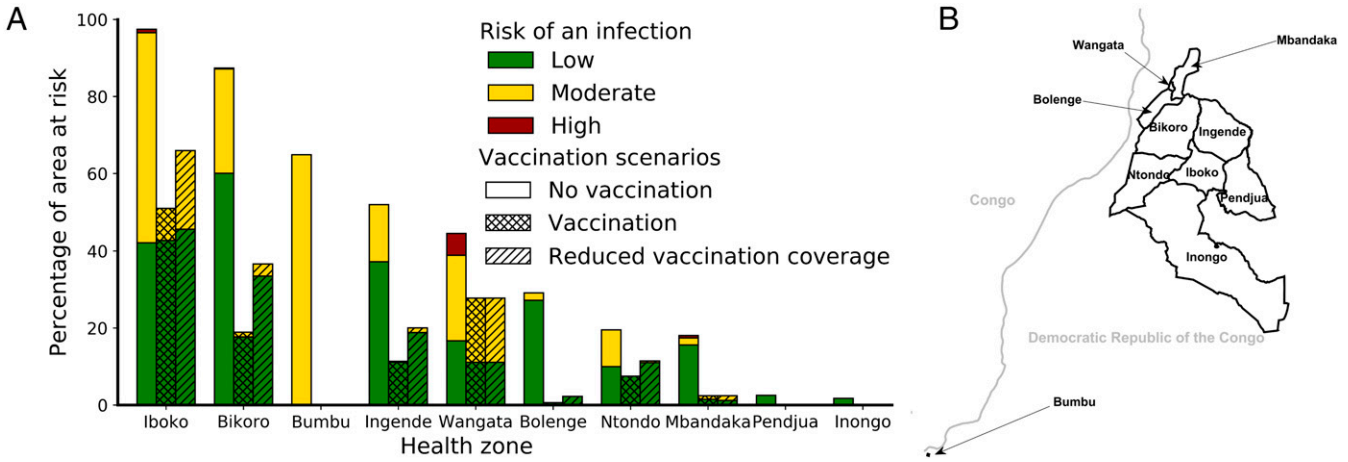

Fig. 2. (*A*) The percentage of area at risk in the health zone relative to the size of the health zone under scenarios of no vaccination, vaccination of all contacts (cross-hatches), and vaccination of only 52% of contacts (hatches) between May 21 and June 17, 2018. We categorized risk of an Ebola infection as high, moderate, and low if the probability of an infection was greater than 0.05, between 0.01 and 0.05, and between P_0 and 0.01, respectively. Within the area at risk, we determined the proportion of the area at high risk (red), moderate risk (yellow), and low risk (green). (*B*) The locations of health zones at risk are highlighted by the black lines in the map, and the border between the DRC and the Congo is indicated by the gray line.

vaccine with a 79.3% efficacy achieves 7.7% less contraction of the geographical area at risk and 4.7% smaller reduction in the overall level of risk (*SI Appendix*, Fig. S2 and Table S2).

It is likely that some participants of the vaccination campaign had already been exposed to Ebola and developed natural protection before vaccination. A metaanalysis of serological studies from previous Ebola outbreaks provided an upper bound of 27.1% for the percentage of seropositive contacts among all infectious cases and their contacts (14) (*Methods* and *SI Appendix*). Therefore, we compared geographic spread and level of risk in scenarios that incorporate both this preexisting immunity as well as the lower bound of vaccine efficacy. We found that the area and level of risk were reduced by 19 and 12.7% less, respectively, compared with the base case (*SI Appendix*, Fig. S2 and Table S2).

Timing of Vaccine Implementation. The swift deployment of vaccination was instrumental to both controlling the epidemic within infected sites as well as its spread to other regions. If the ring vaccination campaign had been delayed by 1 wk from May 21 to May 28, the reduction in risk area was projected to have fallen from 70.4 to 33.3%, relative to no vaccination (Fig. 3). A vaccination program implemented 2 wk later, on June 4, would have only achieved a 12.0% contraction of risk area. Vaccination implementation delays had a comparable effect on the reduction in level of risk. Specifically, 1- and 2-wk delays resulted in the reduction in risk falling from 70.1 to 44.8 and 20.5%, respectively (Fig. 3).

Discussion

As food insecurity and deforestation have expanded wildlife habitat encroachment, Ebola has been emerging with increasing frequency (15–17). In the DRC alone, five outbreaks have been reported over the last 6 y (18). Fortunately, pharmaceutical innovations have provided new tools with which to curtail transmission. Phase III clinical trials during the final phase of the 2013–2016 Ebola outbreak in Guinea estimated a vaccine efficacy of 100% (95% CI: 79.3–100%) for rVSV-ZEBOV (4, 5). In recent outbreaks, the manufacturer donated doses which were swiftly administered by local health zones.

To examine the risk of Ebola introduction into new regions and the impact of vaccination on the geographic distribution of cases, we developed a framework that combines a spatial gravity model with socioeconomic, population density, and geographic distance covariates. We fit the model to geographically explicit incidence data before the rollout of the vaccination campaign. We then projected the geographical distribution of risk with and without the rollout of the campaign. Although the projections indicated that most risk would remain concentrated in Bikoro and Iboko, highly populous and impoverished areas from which and to which there is significant mobility were also at risk. Most precariously, we found that a municipality within capital Kinshasa would have been at considerable risk in the absence of vaccination. Given daily domestic, international, and transcontinental air travel to and from Kinshasa, emergence in Kinshasa would pose a significant global health threat.

Our projections over the 4 wk following initiation of the vaccination program showed that both the area and the level at risk had been substantially diminished by the program. The health zone with highest risk, albeit substantially reduced by vaccination, was Iboko. Consistent with these projections, after deployment of rVSV-ZEBOV during the 2018 DRC outbreak, confirmed cases occurred only in the Iboko health zone (19, 20). Our results are also consistent with the unfolding Ebola outbreak in North Kivu, DRC. Vaccination efforts there have been impeded by armed conflict, and the outbreak has continued, with 81 casualties thus far (21). Concordantly, we found that imperfect or delayed coverage, whether due to vaccine refusal or civil unrest, can appreciably erode the effectiveness of vaccination to control the outbreak. These results also underscore the importance of thorough and rapid contact tracing as well as high vaccine uptake.

As the confidence interval of the estimated vaccine efficacy during the phase III trials of rVSV-ZEBOV ranged from 79.3 to 100% (4, 5), we examined the effect of reduced vaccine efficacy on vaccination campaign impact. In addition, some contacts may have naturally acquired immunity through Ebola exposure even before vaccination, yet there is an absence of data on this measure in Équateur. Furthermore, due to the prioritization of resources for vaccination, treatment, and case isolation there is broadly a deficiency in data on immunity in the early stages of Ebola outbreaks. The logistical challenges in reaching contacts of cases during an outbreak further limit the accuracy of such serological studies. For example, in the North Kivu outbreak that began in 2018, nearly half of those diagnosed with Ebola were not in known chains of transmission in February 2019 due to ongoing conflict (22). Thus, we used a metaanalysis of several Ebola outbreak studies as a conservative estimate of the underlying level of immunity. Even combining a conservative vaccine efficacy and the upper bound of prior immunity, the vaccine campaign still reduced

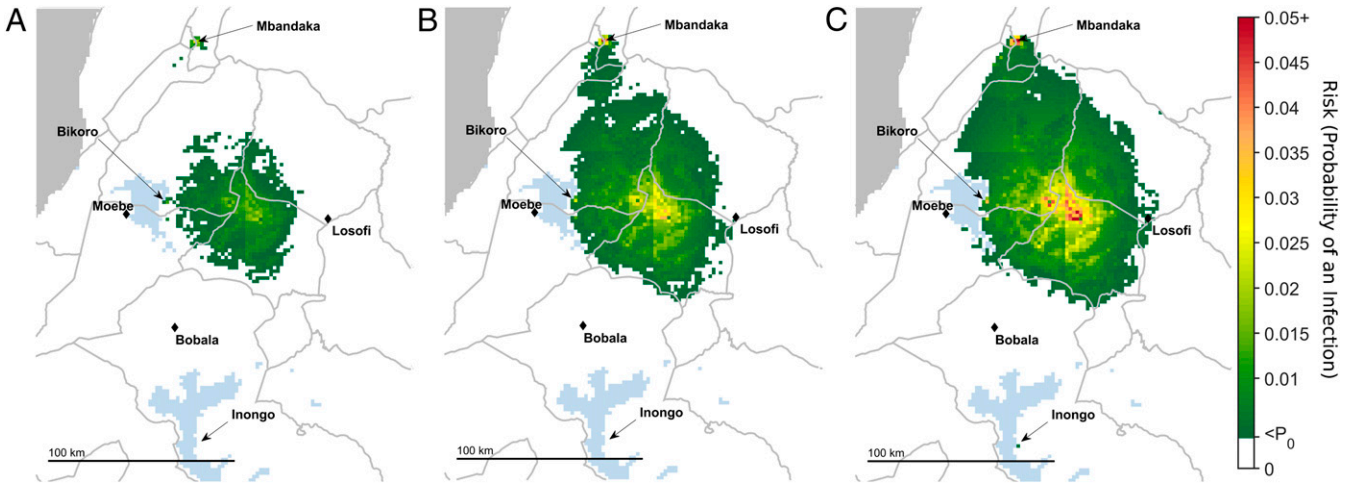

Fig. 3. The impact of delaying vaccination on the spatial distribution of risk. The risk at a one- arcminute resolution, ~1.85 × 1.85 km^2, in the DRC between May 21 and June 17, 2018 when vaccination is initiated on (*A*) May 21, (*B*) May 28, or (*C*) June 4, 2018. Gray lines indicate health zone borders.

both geographical spread and risk by over 50%, compared with projections without any vaccine deployment.

While most Ebola outbreaks have occurred in rural regions (23), human movement disseminated Ebola to multiple urban centers in the West African outbreak and presented a major challenge for disease control (12, 24, 25). Even if an urban center is relatively distant from a rural origin of an outbreak, it may still be at risk due to the counterbalancing draw of human movement. For example, an early confirmed case was reported in Mbandaka city, a highly populated provincial capital about 85 km away from the original case in Bikoro (26). Our model predicted similarly elevated risk for an impoverished municipality in the metropolis of Kinshasa, despite a distance of over 500 km from Bikoro.

Vaccination is synergistic with a suite of complementary interventions to prevent Ebola transmission, including barrier protection and hygienic burial protocols. Contact tracing and case isolation are critical components of Ebola management (27, 28), and, moreover, the success of ring vaccination is itself dependent on efficient contact tracing (29). In the absence of vaccination, our framework can nonetheless be applied to identify efficient targets for heightened surveillance and nonpharmaceutical precautions in sites not yet affected but at high risk.

Our model accounts for human mobility, poverty, and population density and can be applied both to understand past outbreaks and predict high-risk areas during active outbreaks. Incorporating these drivers of Ebola spread improves identification of areas at highest risk of disease compared with assumptions of homogeneity. Our approach is applicable to future outbreaks of Ebola or other diseases with similar routes of transmission in the DRC and beyond. The framework is also amenable to the addition of other covariates pertinent to the specific disease and setting, provided that geographically explicit data are available. High-resolution data enabled us to capture disease transmission and forecast spatiotemporal dissemination at a granular geographical scale. In future outbreaks, our model can be updated in real time to monitor control efforts and optimization resource allocation to locations at greatest risk. Even in advance of observed cases in high-risk areas, preventive efforts such as surveillance and vaccination of healthcare workers can be undertaken (30). Such measures can limit the potential of long-range spread and prevent the disease from becoming established in densely populated areas where it can perpetuate and spark outbreaks in other locations.

Methods

To evaluate the spread of Ebola in the Équateur province of the DRC, we developed a spatial logistic model that includes a gravity model (31, 32), with distance (33), purchasing power parity (34, 35), and population density (36) as covariates (*SI Appendix*). Our analysis is performed at the resolution of one arcminute, which generates 219,152 spatial grid units of ~1.85 × 1.85 km^2. The probability of an infection in a unit on a given day depends on the infection status of all grid units in northwestern DRC, as well as the aforementioned covariates. The impact of grid units on each other diminishes over geographic distance, such that probabilities of transmission approach negligibility beyond the Équateur province.

The number and location of Ebola cases over time were compiled from reports by the World Health Organization (21, 37). Our model was fit to this data spanning from April 5, the retrospectively determined start of the index infection, to May 20, 2018, the day before ring vaccination was initiated (6). Given that the duration of infectiousness was not available for individual cases, we sampled a duration for each case from a negative binomial distribution with a mean of 7.5 d and a SD of 6.8 d (38). A binomial likelihood was used to estimate the coefficients of the model covariates. Human mobility between each of these grid units is captured by a combination of the distance metric and a gravity model. We used purchasing power parity as a measure of poverty, which is known to exacerbate Ebola transmission (11). The geographical distribution of risk from May 21 to June 17 was evaluated in terms of the probability of at least one Ebola case within a specified grid unit. Risk of an Ebola infection was categorized as high, moderate, and low if the probability of an infection was greater than 0.05, between 0.01 and 0.05, and between P_0 and 0.01, respectively. The threshold P_0 was determined by the intercept of our logistic model (*SI Appendix*).

We quantified the effectiveness of vaccinating primary and secondary contacts by comparing the risk to each spatial unit with and without vaccine deployment. The number of primary and secondary contacts were sampled using a distribution of cluster size from rVSV-ZEBOV ring vaccination trial (*SI Appendix, Vaccination*). Consistent with the clinical trial results, vaccine efficacy of rVSV-ZEBOV was assumed to be 100% in the base case. Additionally, an efficacy of 79.3% was incorporated into scenario analyses, corresponding to the lower bound of the empirical 95% confidence interval (4, 5). The ring vaccination program was assumed to reduce the probability of an infection proportional to the vaccination coverage, which was based on the ratio of administered doses to the number of primary and secondary contacts of each case (21) (*SI Appendix, Vaccination*). For example, by May 30, an estimated 17% of the contacts had been vaccinated, and by June 17, 83% of the contacts had been vaccinated.

Further, we quantified the impact of preexisting immunity in the population on the effectiveness of the vaccination campaign. During this outbreak, no data on the immune status of individuals before vaccination were available; however, a metaanalysis of studies on Ebola case contacts found that 27.1% of all seropositive contacts were asymptomatic (14). As seronegative contacts were excluded in calculating this estimate, 27.1% represents an upper bound for preexisting immunity among contacts (*SI Appendix*). Applying this upper bound, we compared the impact of the vaccination campaign with and without the presence of preexisting immunity.

We also evaluated the impact of two challenges that may arise during vaccination campaigns: reduced coverage and delayed implementation. Specifically, we considered a 48% reduction in coverage (52% of contacts vaccinated), which corresponded with the percentage of identified contacts in the ring vaccination trial who were not able to be vaccinated due to either ineligibility criteria, such as pregnancy and young age, or refusal (4). We also assessed the impact of 1 and 2 wk delays in ring vaccination rollout on the effectiveness of the campaign to reduce the geographic distribution and magnitude of risk. See *SI Appendix* for equations and more model details.

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