Effectiveness of Ring Vaccination as Control Strategy for Ebola Virus Disease

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Using an Ebola virus disease transmission model, we found that addition of ring vaccination at the outset of the West Africa epidemic might not have led to containment of this disease. However, in later stages of the epidemic or in outbreaks with less intense transmission or more effective control, this strategy could help eliminate the disease.

During 2014–2015, trials of candidate vaccines for Ebola virus disease (EVD) were fast tracked in response to the unprecedented EVD epidemic in West Africa (*1*). In March 2015, a phase 3 ring vaccination trial of a recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine began in Guinea (*2*). Interim trial results suggested that the vaccine could have a high level of efficacy in humans (*3*). Ring vaccination has also been used for disease control, notably in the final stages of the smallpox eradication program (*4*). Furthermore, a recent modeling study calibrated by using population-level EVD data from Sierra Leone and Liberia (*5*) suggested that ring vaccination could supplement case isolation and contact tracing in reducing transmission. However, it remains unclear whether prompt ring vaccination, as opposed to large-scale mass vaccination, could have contained the EVD epidemic in West Africa, and under what circumstances it could be effective in controlling future outbreaks.

The Study

We developed a stochastic model of EVD transmission (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/22/1/15-1410-Techapp1.pdf) using individual-level transmission data from Guinea to inform our model structure. Transmission chains during March–August 2014 suggest substantial variation in the number of secondary cases generated (*6,7*). In particular, index cases, defined as those that could not be linked to an already known transmission chain, had a reproduction number of $R_m = 7$, where m indicates missed cases and R_m denotes the average number of secondary cases generated, whereas cases within known transmission chains (w) had a reproduction number of $R_w = 0.66$ (online Technical Appendix, Figure 1).

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In the model, transmission followed a branching process (*8*), and secondary cases were generated from a negative binomial distribution to include potential for superspreading events (*6,9*). Each cluster started with an index case, which generated an average of $R_m = 7$ secondary cases. Many EVD cases reported in Guinea were not part of already known transmission chains (online Technical Appendix, Figure 2). We therefore assumed there was a probability ρ that a secondary case would missed and go on to seed an independent transmission cluster as an index case with $R_m = 7$. Otherwise, the case would remain within the known chain of transmission (with probability $1 – \rho$); these cases would then generate an average of $R_w = 0.66$ secondary cases. The simulated outbreaks ended when, by chance, no secondary cases were generated by active cases. Distributions of incubation period, duration of infectiousness, and time to reporting were obtained from reported values for Guinea in 2014 (*10*). Model simulations produced similar patterns to those observed in 2014 (Figure 1). When half of the cases were missed, the overall reproduction number, defined as the mean number of secondary cases generated across all infectious persons, was ≈1.5, which was similar to values observed in early 2014 in West Africa (*11*) and in the initial stages of other outbreaks (online Technical Appendix Table 1).

We simulated ring vaccination by using a protocol similar to that used in Guinea trial (*3*). We defined a ring as all persons who could potentially form part of the known chain of transmission (i.e., traceable contacts of infected persons within a transmission cluster and their contacts). Once the index case was reported, we assumed it took 2 days to vaccinate a ring and that protective immunity developed 7 days after vaccination. In the model, we assumed that vaccine efficacy was 80% and that 70% of the ring received vaccination (online Technical Appendix). The reproduction number within a ring was therefore reduced by a factor of $1 –(0.8 \times 0.7) = 0.44$ once the vaccine became effective (online Technical Appendix Figure 3).

To estimate the effect of ring vaccination, we simulated multiple outbreaks and calculated the proportion of these outbreaks that became large (i.e., >500 clusters). We found that if more than a few cases were missed, large outbreaks could occur under ring vaccination (Figure 2, panel A). This event could occur because missed cases, which had a higher reproduction number, would not be inside the ring when vaccination was introduced. Although ring vaccination failed to contain the outbreak in this scenario, it still reduced disease transmission (online Technical Appendix

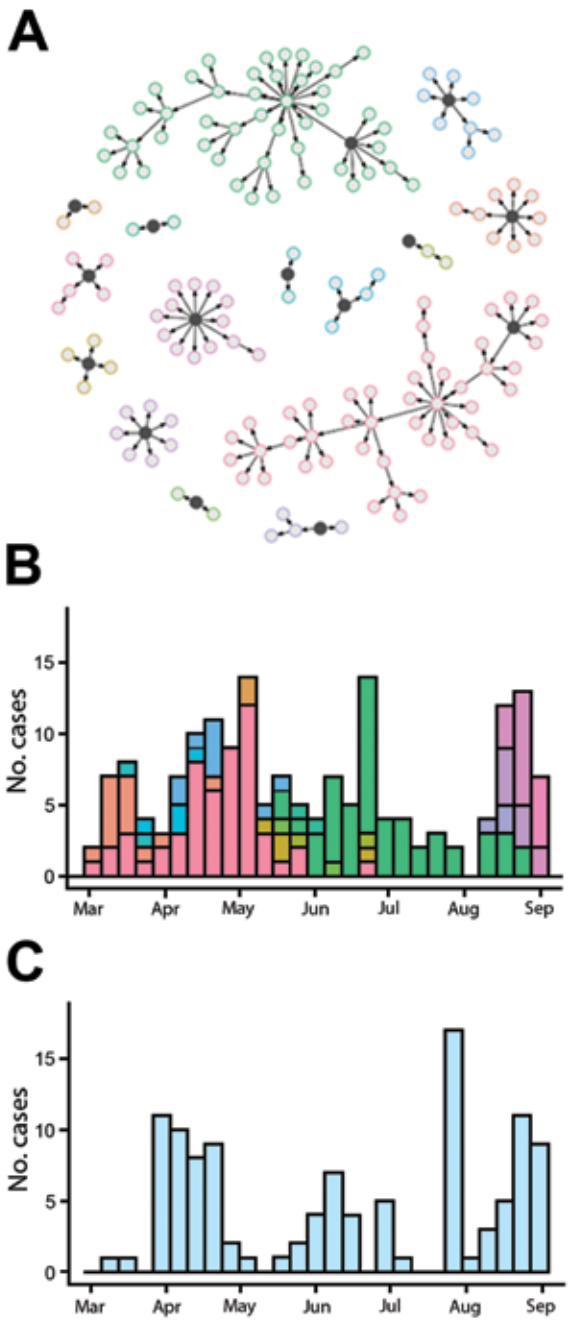

Figure 1. Outbreak dynamics in a model of transmission of Ebola virus disease. A) Chains of transmission generated in a simulated outbreak starting with 2 infected persons on March 1, 2014. Black circles indicate the index case within each cluster, and arrows indicate routes of transmission. Within each cluster, we assumed that there was a 15% probability that a secondary case would be missed and would instead seed a new cluster (these missed links are not shown). B) New cases per week, by date of symptom onset, for the chains of transmission shown in panel A. Colors of clusters in panel A match colors of bars in panel B. C) Observed weekly confirmed and probable cases reported in Conakry Prefecture, Guinea, during March–September 2014. Data were obtained from the Guinea Ministry of Health and World Health Organization Situation Reports (*11*).

Figure 4). We also considered the effect of preemptive mass vaccination, which reduced the reproduction number for all cases by a factor of 0.44, regardless of whether cases were in the cluster or missed. This strategy was more effective in containing outbreaks, even if many cases were missed (Figure 2, panel A). Similar qualitative patterns were observed when vaccine efficacy was 95% (online Technical Appendix Figure 5).

In the later stages of the EVD epidemic in West Africa, behavior changes and improved control measures led to less transmission from burials and in hospital settings than in early 2014 (*12*). Similar reductions were observed in other Ebola outbreaks (e.g., in 1976 in Yambuku, Zaire) (*13*). We therefore also explored a partial control scenario. We omitted index cases in the 2014 Guinea transmission chains that were involved in funeral or hospital transmission, which resulted in $R_m = 2.5$ for missed cases (online Technical Appendix Figure 6). We also assumed a shorter duration of infectiousness and time to reporting on the basis of data for 2015 (*3,10*) (online Technical Appendix Table 2).

In this partial control scenario, outbreaks could be controlled with ring vaccination, even if 40% of cases were missed (Figure 2, panel B). Our results suggest that ring vaccination could substantially reduce the potential size and duration of outbreaks if other control measures are also in place (Table). We also estimated how many vaccine doses would be required for ring vaccination (online Technical Appendix); in the partial control scenario, several thousand doses might be needed (online Technical Appendix Table 3). We could not estimate doses required for mass vaccination, and thus could not perform an economic analysis of different strategies, because this would depend on the potential for long-distance transmission events and populations in different areas. However, implementing mass vaccination for even a single district in West Africa could require >100,000 doses.

Our analysis has some limitations. In the early 2014 transmission scenario, we assumed that missed cases had a much higher reproduction number than cases within clusters. However, if an effective vaccine became available, persons at risk might be more likely to engage with public health efforts. The high reproduction number for index cases might also be caused in part by ascertainment bias: cases that generate many secondary infections are more likely to be designated as index cases. We also assumed that mass vaccination would target 70% of the population at random; in practice, there could be clustering effects. Furthermore, we assumed that chains of transmission were independent and that the reproduction number remained unchanged over time. In reality, missed cases might have shared contacts and behavior might change during outbreak, which could reduce transmission. Our estimates are therefore likely to represent a reasonable worst-case scenario.

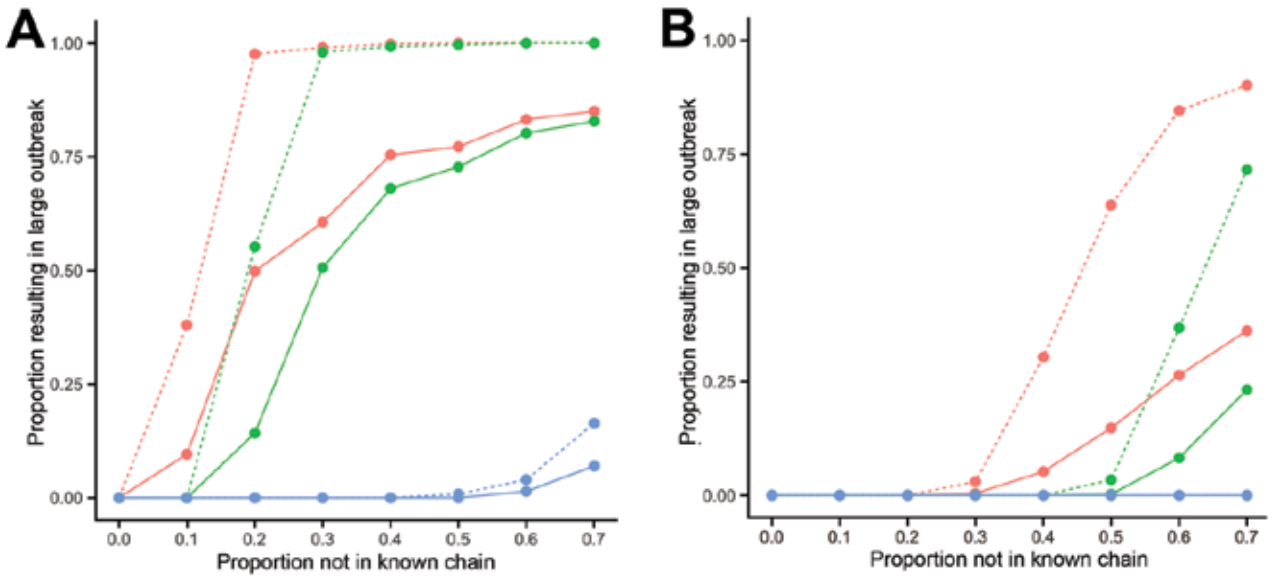

Figure 2. Effectiveness of vaccination strategies for Ebola virus disease under different transmission scenarios. A) Proportion of simulations that led to a large outbreak (defined as >500 clusters) in the early 2014 Guinea transmission scenario. Red lines indicate no vaccination, green lines indicate ring vaccination, blue lines indicate mass vaccination; solid lines indicate outbreaks that started with 1 index case, and dashed lines indicate outbreaks that started with 5 index cases. We simulated 1,000 outbreaks and calculated the proportion that resulted in >500 clusters. When the space between the red and green lines is large, the model suggests that ring vaccination would provide substantial additional value over standard public health control measures alone. B) Proportion of simulations that led to a large outbreak in partial control scenario.

Conclusions

Ring vaccination enhances standard public health measures of contact tracing, isolation, and community engagement (*14*) and could be effective when such measures are in place. However, if standard measures are not working because many cases are not in known transmission chains, as in West Africa in early 2014, ring vaccination might be insufficient to contain the outbreak. If an EVD vaccine is shown to be efficacious, our results suggest that mass vaccination, or hybrid strategies involving mass and ring vaccinations, might need to be considered alongside ring vaccination when planning for future outbreaks.

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Table. Estimated total cases and outbreak duration in partial control scenario with 5 index cases initially by using the model of Ebola virus transmission*

Probability of case missed	No vaccination	Ring vaccination	Mass vaccination
Median no. cases (95% CI)			
10%	42 (14–235)	30 (13–79)	13 (7–60)
20%	63 (15–551)	39 (14–131)	13 (7–57)
30%	104 (17–2,660)	53 (15–229)	13 (6–48)
40%	296 (20–2,410)	78 (18–452)	13 (6–46)
Duration of outbreak, d (95% CI)			
10%	87 (28–278)	62 (26–145)	41 (12–139)
20%	123 (33–480)	83 (31–214)	43 (11–149)
30%	185 (43–1,020)	110 (36–319)	47 (11–142)
40%	364 (51–1,150)	149 (45–486)	47 (9–147)

*Model assumes 80% vaccine efficacy.

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Technical Appendix

Transmission Model

In the model, transmission followed a branching process, and secondary cases were generated from a negative binomial distribution (*1*,*2*). We estimated the reproduction number for missed cases, R_m, and for cases within a cluster, R_w, by fitting negative binomial distributions (*3*) to data on chains of transmission in Conakry, Guinea, during March–August 2014 (*4*). The distribution of secondary cases in this dataset was enumerated by Althaus (*1*). Our maximum likelihood estimates were $R_m = 7$ and $R_w = 0.66$ (Technical Appendix Figure 1, panels A, B). We also obtained estimates of the dispersion parameters (Technical Appendix Table 1), which suggested that transmission from cases within clusters was highly overdispersed (k = 0.19). This estimate indicated that although R_w was small, there was still potential for superspreading events within each cluster. As a validation, we also analyzed published data on a transmission chain in Liberia, which occurred during December 2014–March 2015 (*14*). The results were similar: the index case had $R_m = 5$ and the secondary cases generated by nonindex cases had $R_w = 0.76$ and $k = 0.82$ (Technical Appendix Figure 1, panel C).

In our transmission model, each cluster started with an index case, which generated secondary cases from the fitted negative binomial distribution with average R_m. We assumed there was a probability $1 - \rho$ that each secondary case would remain within the known chain of transmission; these cases would then generate an average of R_w secondary cases. If a case was missed (with probability ρ), it went on to seed a new cluster as an index case with reproduction number R_m. The simulated outbreaks came to an end when no secondary cases were generated by the currently active cases.

In the Conakry transmission scenario, we assumed that incubation period, duration of infectiousness, and time from onset to notification were gamma distributed, and had a mean and

SD as in the World Health organization patient database for Guinea (*5*). The duration of infectiousness was equal to the time from onset to death (6.4 days).

In the partial control scenario, we assumed that this was equal to the time from onset to hospitalization (5.3 days) because of the increased proportion of cases that would have been isolated. Note that these parameters do not affect the number of secondary cases generated by an infectious person (which is specified by R_m and R_w), but do affect the duration of the outbreak. The incubation period remained unchanged, but the average time from onset to reporting decreased 3.6 days, as reported in the 2015 Guinea ring vaccination trial (*15*). The proportion of cases in known chains during this period is shown in Technical Appendix Figure 2. The model was implemented in R version 3.1.3 (*17*).

Comparison of Overall Reproduction Numbers in Simulated and Real Outbreaks

To compare our 2 simulated scenarios with transmission dynamics in real Ebola virus disease outbreaks, we calculated the overall reproduction number in outbreak simulations. This number was defined as the mean number of secondary cases generated across all infectious persons. For example, in the transmission chain shown in Figure 1, the overall reproduction number R = 0.88. The mean overall reproduction number for the scenarios shown in Figure 2 are shown in Technical Appendix Figure 4. As the reproduction number approaches the critical value of 1 in Technical Appendix Figure 4, on average transmission will become self-sustaining in the model, and thus the probability of observing a large outbreak increases substantially in Figure 2.

When 20%–70% of cases are missed in the model, the overall reproduction number for the Conakry scenario ranges between 1 and 2 if outbreaks start with a single initial case in the absence of vaccination (Technical Appendix Figure 4, panel A). This finding is consistent with estimates of the reproduction number for the West Africa epidemic in early 2014, and with estimates of the community reproduction number from the early period of other outbreaks (Technical Appendix Table 1). Detailed transmission chain data are not available for historical outbreaks, and thus scenarios we consider might not exhibit the same individual variation in secondary transmission (as specified by the dispersion parameter *k*). However, the similarity in overall reproduction number suggests that the average transmission dynamics are comparable.

However, the crucial difference between pre-2013 outbreaks and the situation in West Africa during 2013–2015 is that previously the overall reproduction number decreased substantially within weeks rather than over months or years. Thus, our partial control scenario, in which the mean overall reproduction number is >1 even without vaccination (Technical Appendix Figure 4, panel B) is likely to be more representative of the transmission patterns typically faced during earlier EVD outbreaks.

Ring Vaccination

During the 2015 Guinea recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine trial, ring vaccination was implemented by vaccinating all named contacts of confirmed index case-patients, as well as other persons who would have been at risk because of their connections to the case-patient; for example, the village of the case-patient, or household contacts of a named high-risk contact that lived far from the case-patient (*15*). In the model, we therefore assumed that a randomly sampled proportion of all persons who could form part of the transmission cluster (i.e., were not missed) would be vaccinated.

Once the index case was reported, which depended on the time from onset to reporting, it took 2 days for persons to be vaccinated. We assumed that the vaccine became effective after an additional 7 days because interim results suggested that no infections were observed in vaccinated persons in the Guinea ring vaccination trial after $\geq$6 days (*15*). We also assumed an efficacy of 80%, which is toward the lower end of the range given in the interim results from the Guinea trial (*15*). As a sensitivity analysis, we repeated our simulations assuming an efficacy of 95% (Technical Appendix Figure 5).

In the trial, 5,415 (71%) of 7,651 contacts were >18 years of age and not pregnant or breastfeeding, and thus were eligible for vaccination. Overall, 52% were eligible and consented. Because vaccination will in the future likely be expanded to younger age groups, in the model, we therefore assumed that a uniformly random sample of 70% of the cluster received the vaccine. The reproduction number within a cluster was therefore reduced by a factor $(1 – 0.8 \times 0.7) = 0.44$ once the vaccine became effective. Thus, the reproduction number was equal to R_w before vaccine becomes effective and $R_v = 0.44\ R_w$ afterwards.

We also estimated how many vaccine doses would be required to conduct out such ring vaccination. On the basis of the number of persons vaccinated in each cluster in the Guinea

recombinant vesicular stomatitis virus–Zaire Ebola virus vaccine trial (*15*), we specified the vaccination ring size to be normally distributed with a mean size of 80 persons and an SD of 20, with each new transmission cluster requiring this number of persons to be vaccinated. In the partial control scenario, several thousand doses may therefore be required to implement ring vaccination (Technical Appendix Tables 2, 3).

Mass Vaccination

To introduce mass vaccination in the model, we assumed that 70% of all persons in at-risk areas were vaccinated; efficacy = 80% (sensitivity analysis with 95% efficacy is shown in Technical Appendix Figure 4). This assumption suggests the proportion of the population who were susceptible to infection was reduced by a factor of 0.44, regardless of whether they were in the cluster or missed. In our branching process model, this assumption was implemented by reducing R_m and R_w by a factor of 0.44. When there is 1 initial case, our framework is equivalent to the assumption that mass vaccination was performed preemptively before that specific outbreak began. When there are several initial cases, we are making the assumption that large-scale mass vaccination was conducted in the short period between the first case being reported and the start point of the simulation, by which multiple initial cases were infected.

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Technical Appendix Table 1. Estimates of overall community reproduction number in historical Ebola outbreaks and in early stages of the 2013–20515 Ebola virus disease epidemic in West Africa

Location	Date	Reproduction no.	Reference
Yambuku, Zaire	1976	1.34	(*6*)
Kikwit, Zaire	1995	1.83	(*7*)
		3.65	(*8*)
		2.7	(*9*)
Uganda	2000–2001	1.34	(*7*)
		1.79	(*8*)
		2.7	(*9*)
Guinea	2014 Mar–Aug	1.5	(*10*)
	2014 Mar–Aug	≈1	(*11*)
	2014 Jul–Sep	1.71	(*5*)
	2014 Jul–Oct	1.2–1.7	(*12*)
Sierra Leone	2014 Mar–Aug	2.5	(*10*)
	2014 Jun–Jul	1.4	(*11*)
	2014 Jul–Sep	2.02	(*5*)
	2014 Jul–Oct	1.3–1.5	(*12,13*)
Liberia	2014 Mar–Aug	1.59	(*10*)
	2014 Jun–Jul	1.7	(*11*)
	2014 Jul–Sep	1.83	(*5*)

Technical Appendix Table 2. Parameters used in the model for the 2 transmission scenarios for Ebola virus disease*

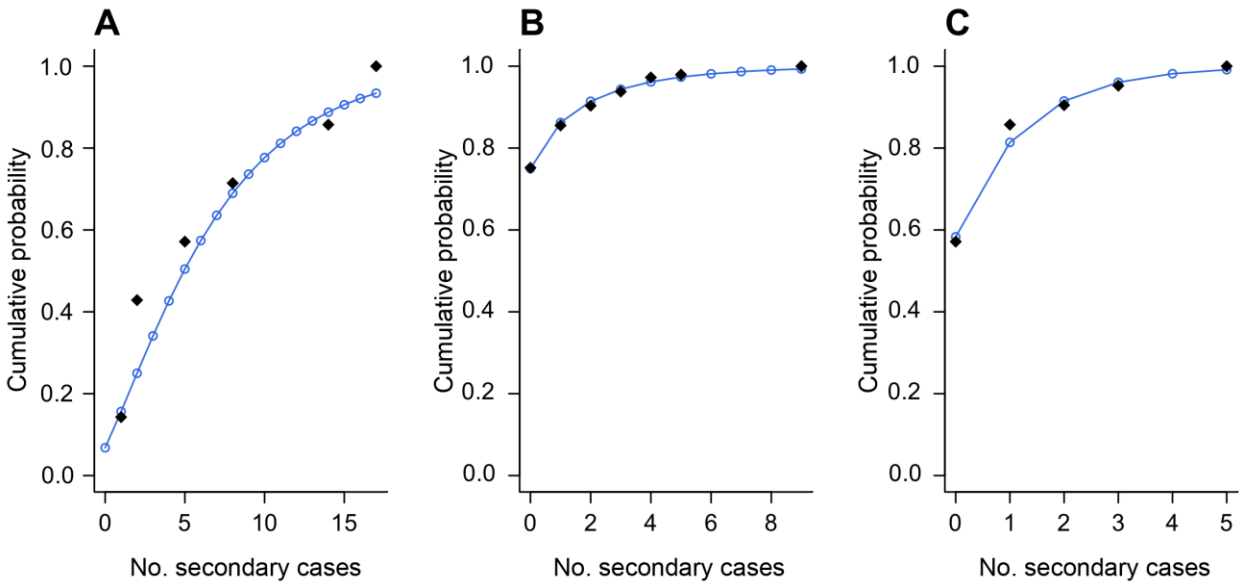
Parameter	Guinea, early 2014	Partial control
Reproduction no. for index cases, R_m	7 (k = 1.6)	2.5 (k = ∞)
Reproduction no. for secondary cases within cluster, R_w	0.66 (k = 0.19)	0.66 (k = 0.19)
Incubation period, d, mean ± SD	9.1 ± 7.3	9.1 ± 7.3
Time from onset to reporting, d, mean ± SD	7.5 ± 10.4	3.9 ± 2.6
Duration of infectiousness, d, mean ± SD	6.4 ± 5.3	5.3 ± 4.3
Proportion of persons within a cluster who are vaccinated, %	70	70
Vaccine efficacy, %	80–95	80–95
Vaccination ring size, mean ± SD	80 ± 20	80 ± 20

*The fitted dispersion parameter *k* for the negative binomial distributions is given along with reproduction numbers. We assumed that incubation period, time from onset to reporting, and duration of infectiousness followed a gamma distribution.

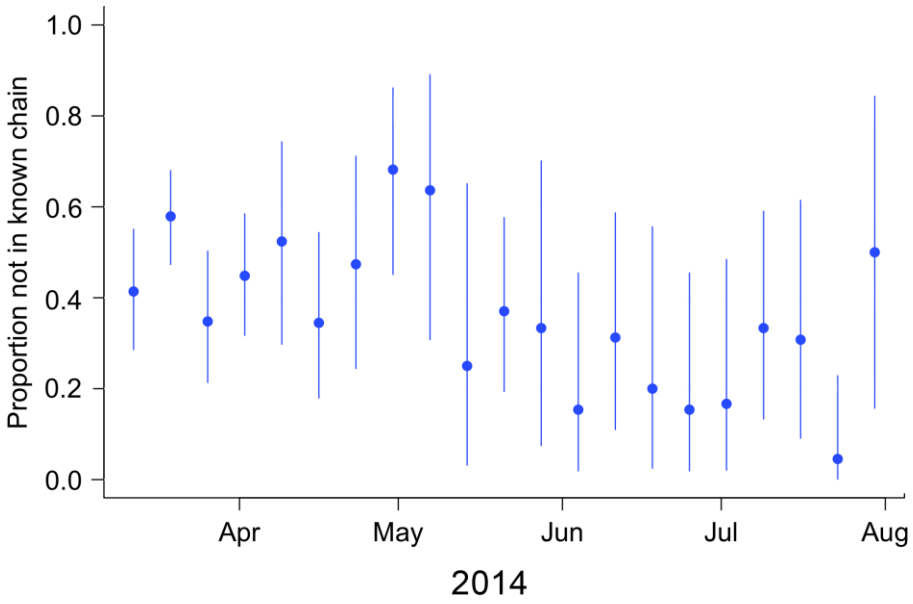
Technical Appendix Table 3. Estimate doses required for elimination of Ebola virus disease with a ring vaccination strategy in the partial control scenario*

Probability of case missed	No. doses required (95% CI)
10%	382 (175–822)
20%	533 (216–1,440)
30%	774 (265–2,900)
40%	1,220 (329–6,760)

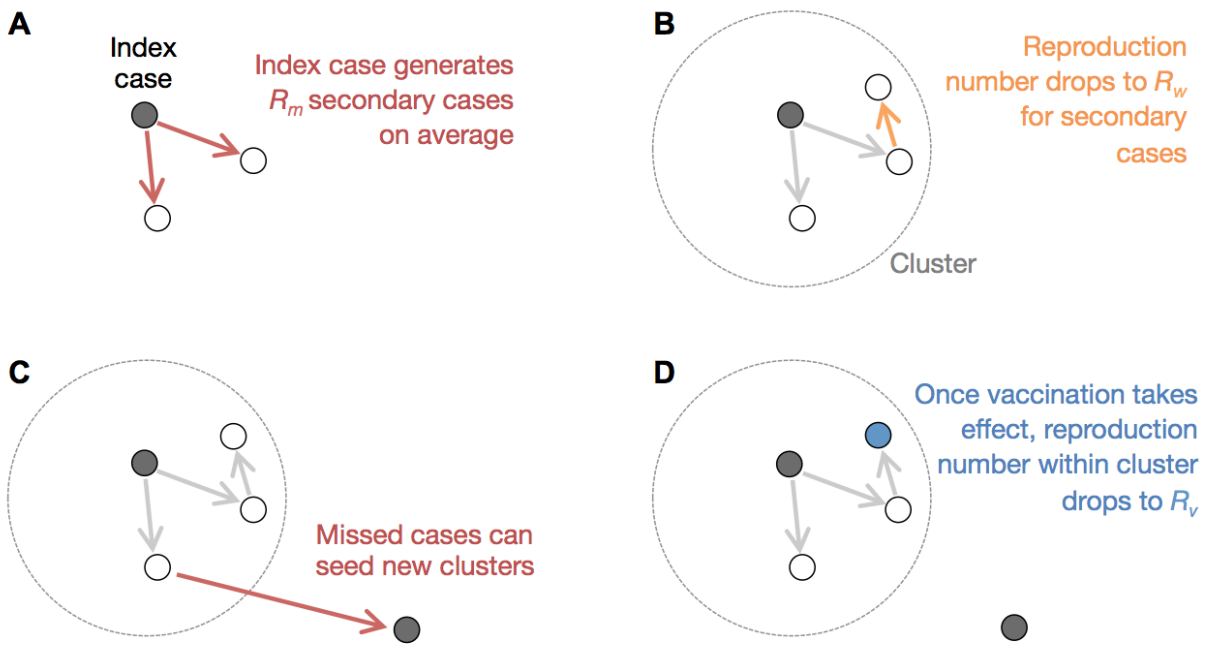
*Outbreaks started with 5 index cases and 80% vaccine efficacy.



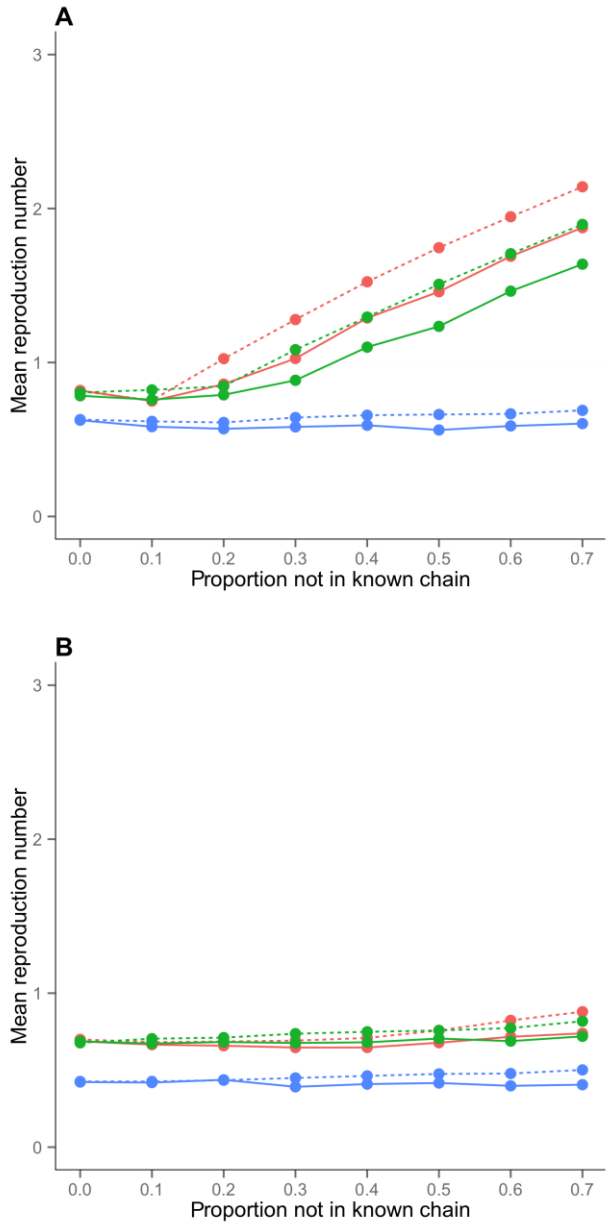
Technical Appendix Figure 1. Fitted distributions of reproduction numbers for effectiveness of ring vaccination as control strategy for Ebola virus disease. A) Cumulative distribution of secondary cases generated by index cases in transmission chains in Conakry, Guinea, March–August 2014 (*4*). Blue line indicates fitted negative binomial distribution, blue circles indicate values of the distribution at integer intervals, and black diamonds indicate data. B) Secondary cases generated by cases within clusters in Conakry. C) Secondary cases generated by nonindex cases in Liberia cluster.



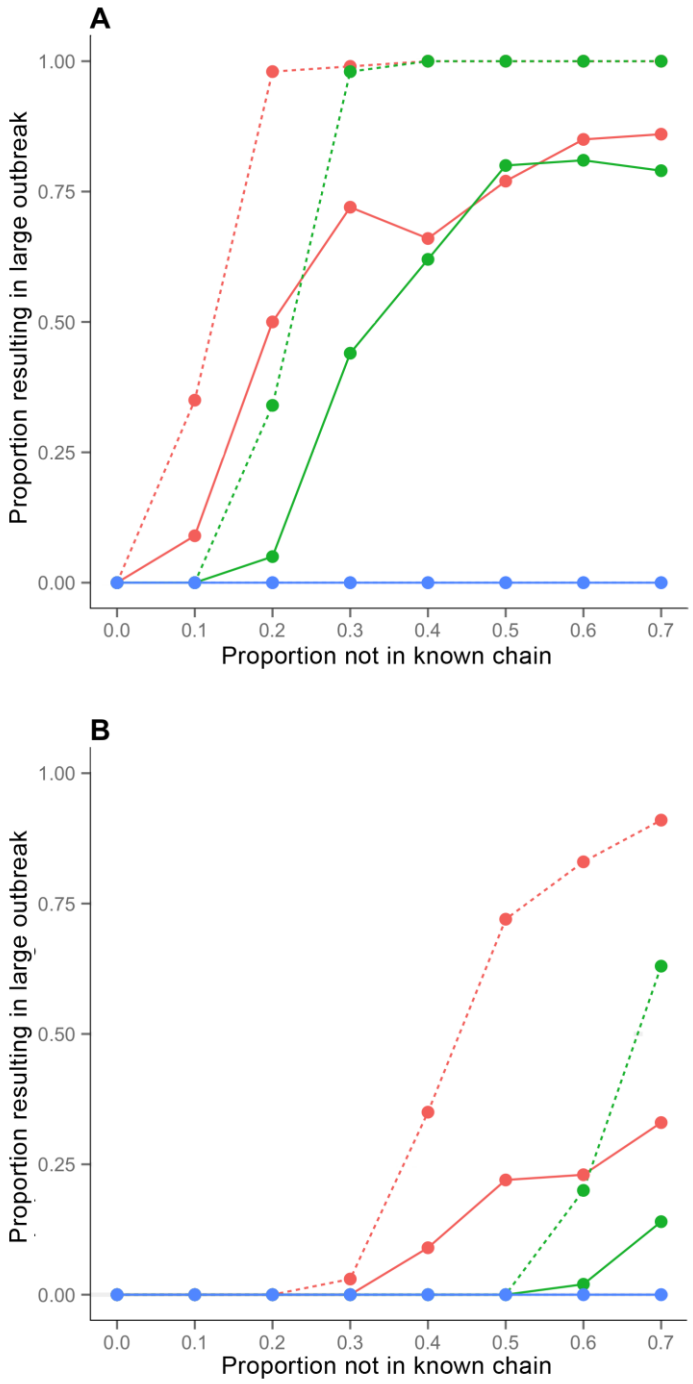
Technical Appendix Figure 2. Proportion of weekly new cases of Ebola virus disease in Guinea in 2015 that were not a known contact of an existing case, and were not part of an existing transmission chain. Points show expected proportion, and lines show 95% binomial CIs. Data were obtained from the World Health Organization (*16*).



Technical Appendix Figure 3. Model schematic for effectiveness of ring vaccination as control strategy for Ebola virus disease. A) Index cases generate an average of R_m secondary cases. B) Secondary cases within cluster have a lower reproduction number (R_w). C) There is a probability ρ that a secondary case will be missed and go on to seed a new transmission cluster. D) Once vaccination takes effect, the reproduction number for cases within the cluster decreases to R_v.

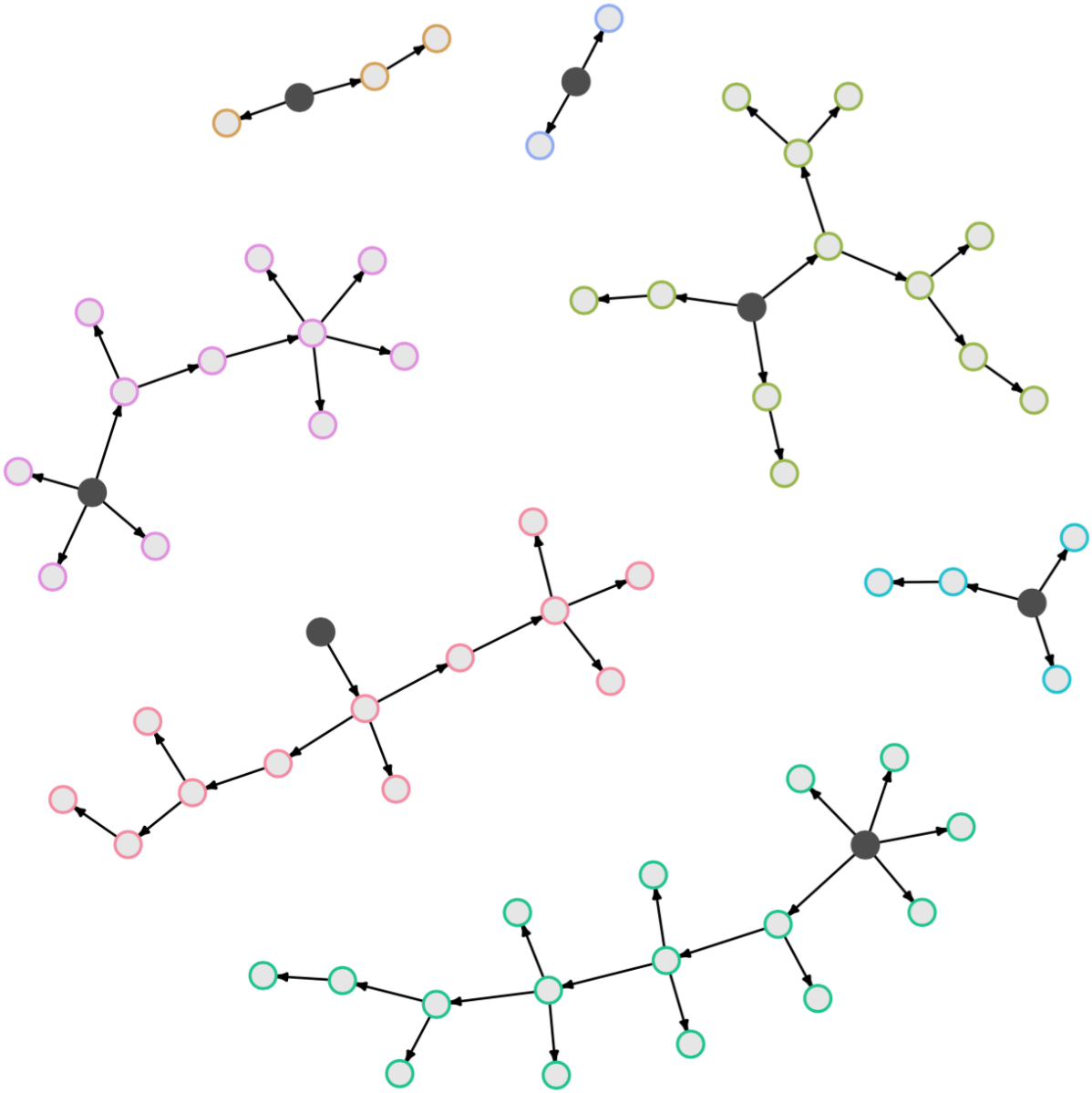


Technical Appendix Figure 4. Overall reproduction number in different scenarios for effectiveness of ring vaccination as control strategy for Ebola virus disease. A) Mean overall reproduction number across 1,000 simulated outbreaks in the Conakry, Guinea, transmission scenario. Red lines indicate no vaccination, green lines indicate ring vaccination, blue lines indicate mass vaccination, solid lines indicate outbreaks that started with 1 index case, and dashed lines indicate outbreaks that started with 5 index cases. Vaccine has 80% efficacy in the model. B) Mean reproduction number in the partial control scenario.



Technical Appendix Figure 5. Effectiveness of vaccination strategies under different transmission scenarios, when vaccine has 95% efficacy, as control strategy for Ebola virus disease. A) Proportion of simulations that led to a large outbreak (defined as >500 clusters) in the Conakry, Guinea, transmission scenario. Red lines indicate no vaccination, green lines indicate ring vaccination, blue lines indicate mass vaccination, solid lines indicate outbreaks that started with 1 index case, and dashed lines indicate outbreaks that started with 5 index cases. We simulated 1,000 outbreaks and calculated the proportion

that resulted in >500 clusters. When the space between the red and green lines is large, it suggests that ring vaccination would provide substantial additional value over standard public health control measures alone. B) Proportion of simulations that led to a large outbreak in the partial control scenario.



Technical Appendix Figure 6. Chains of transmission of Ebola virus disease generated in a simulated outbreak starting with 2 infected persons under the partial control scenario. Black points indicate the index case within each cluster, and arrows indicate routes of transmission. Within each cluster, we assumed there was a 15% probability that a secondary case would not be included in the existing chain, and would instead seed a new cluster (these missed links are not shown).