Ebola Outbreak Response with Ring Vaccination By rVSV-ZEBOV-GP, DRC

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ABSTRACT

BACKGROUND

When the 2018-20 Eastern DRC Ebola outbreak began there was no licensed vaccine, but cluster-randomized evidence from Guinea had indicated that ring vaccination around new cases (targeting contacts and contacts-of-contacts), using single-dose live-replicating rVSV-ZEBOV-GP, reduced Ebola virus disease (EVD) rates from day 10. Ring vaccination was therefore added to the standard control measures. We report EVD incidence within 0-9 days of vaccination, when little protection was expected from case isolation or ring vaccination, and later.

METHODS

1853 rings were enumerated around new cases or clusters 2-21 days after symptom onset and offered vaccination. Vaccinees were monitored until outbreak closure in mid-2020 for EVD onset.

RESULTS

Between August 8, 2018 and January 14, 2020, 265,183 individuals were vaccinated (with 102,515 monitored on days 0, 3, and 21 for safety); 463 developed EVD (386 during days 0-9 after vaccination, 35 during days 10-29, and 42 later), including 380/57,563 (0.66%) contacts and 54/136,836 (0.04%) contacts-of-contacts. The sooner control measures, including ring vaccination, began after index case onset, the sooner EVD rates fell among contacts. In each subgroup, EVD rates fell at around Day 10. Rates during days 10-29 were lower in contacts or contacts-of-contacts (32/194,019; 0.16‰) than among similarly-defined ring members in Guinea with standard control measures undertaken promptly but vaccination delayed 21 days (21/4528, 4.64‰; ratio of rates 0.04, 95%CI 0.02-0.06). No safety concerns were identified.

CONCLUSIONS

Non-randomized evidence on standard EVD control measures plus ring vaccination in Eastern DRC reinforces the randomized evidence from Guinea of vaccine efficacy against EVD onset 10 or more days after vaccination.

On August 1, 2018 the Democratic Republic of Congo (DRC) government declared an Ebola virus disease (EVD) outbreak in Eastern Congo (Kivu and Ituri provinces), which must have started some time earlier. Due to violence from armed groups and pockets of mistrust in some affected communities[1] this outbreak was difficult to control despite rapid national and international responses. It lasted for about 2 years, peaking in mid-2019 but continuing until mid-2020 (Figure 1). By the time it ended, 3470 confirmed and probable cases of EVD had been reported to the World Health Organisation (WHO), of whom 66% (2287) died of EVD.[2] This was the first Ebola outbreak in which case isolation and other methods to prevent infection were routinely accompanied by ring vaccination around new cases—ie, by vaccinating a ring around the case intended to include only the recent contacts and contacts of those contacts. Given the size of the outbreak, this provided an opportunity to assess the efficacy of isolation plus ring vaccination.

Ring vaccination had been a key component of smallpox elimination half a century earlier[3]. During the 2014-16 West African Ebola outbreak, similarities between smallpox and Ebola transmission dynamics led to immediate vs delayed ring vaccination against EVD being evaluated in a cluster-randomized trial in the West African country of Guinea. In that trial, rings were enumerated within a few days of EVD case identification and randomly allocated between single-dose vaccination immediately vs vaccination 21 days after ring enumeration. The vaccine was live replicating rVSV-ZEBOV-GP, intended to produce transient infection with a recombinant vesicular stomatitis virus (rVSV) modified to express the Zaire Ebola virus surface glycoprotein (ZEBOV-GP), thereby eliciting an antibody response against Ebola virus. As this vaccine is live, it usually causes a day or more of generally moderate symptoms of transient systemic VSV infection.

Towards the end of the Guinea outbreak, that trial provided evidence of protection against EVD onset ≥10 days post-vaccination[4,5] that led to cluster-randomization being terminated in 2015, with the few subsequent rings all being vaccinated immediately.[6] It also led the WHO to recommend in 2017 that if another EVD outbreak were to occur

before any vaccine was licensed, ring vaccination with rVSV-ZEBOV-GP should be deployed promptly under the WHO Expanded Access/Compassionate Use framework,[7] administering the vaccine with informed consent and collecting data on vaccinee characteristics and outcomes in compliance with Good Clinical Practice (GCP) guidelines.

No EVD vaccine had yet been licensed when the Eastern DRC Ebola outbreak was declared on August 1, 2018, but the WHO and the DRC National Institute of Biomedical Research (INRB) obtained regulatory and ethical approval and initiated ring vaccination within a week of the outbreak declaration, using a study protocol previously developed by the WHO Research and Development Blueprint[8]. As all rings were vaccinated immediately, with no randomized comparator group, no precisely unbiased assessment of efficacy was expected. As this 2018-20 outbreak persisted so long, some 200,000 members of almost 2000 rings were vaccinated and followed for EVD onset (more than 20 times as many vaccinees as in the Guinea study). Hence, the DRC findings for EVD incidence 0-9 and ≥10 days post-vaccination are assessable. This report describes these findings and compares them with the findings in the Guinea trial in the similarly-defined rings that were enumerated but randomly allocated not to be vaccinated until 21 days later. The DRC rings and Guinea rings were monitored until the outbreaks ended, with any surviving cases diagnosed before or after ring formation removed (avoiding further transmission) to evaluation and treatment centers.

METHODS

The designs and methods of Ebola virus ring vaccination studies have been described previously.[4-6,8] After the surveillance teams identified a new case, usually days after symptom onset, and isolated any contacts of this and any other cases nearby, field teams enumerated as ring members all who had recently been contacts or contacts of such contacts. Vaccination was with one dose of rVSV-ZEBOV, an attenuated, genetically engineered, replication-competent live vaccine.

Ring formation took place from August 8, 2018 to January 14, 2020. The protocol was amended twice following recommendations of the WHO Strategic Advisory Group of Experts on immunization (SAGE). On June 13, 2019 it was amended to adjust the vaccine dose from 50 million to 25 million plaque-forming units (PFUs), and to expand eligibility to include women in the second and third trimester of pregnancy, lactating women, and infants 6-11 months of age. Women in the first trimester and younger infants were not included. After that date, safety visits were only to infants and pregnant women; for all others the safety visits at 3 days and 21 days post-vaccination were discontinued. At the same time, eligibility for vaccination was extended to allow others living near a case to be vaccinated as ring members if they asked because they could potentially be involved in the tertiary generation of cases (to create a barrier around the contacts of contacts in affected areas and increase community acceptance), but these third-level contacts do not contribute to the analyses of EVD incidence in contacts or contacts of contacts. In December 2019 ring definition continued but all safety visits were discontinued, as safety information from over 100,000 vaccinees had already been collected, but pregnancy outcomes continued to be monitored throughout the study. Full study details can be found in the protocol and SAP at nejm.org.

PROCEDURES

For each confirmed case with onset <21 days previously, community agreement with ring vaccination was sought. This was generally provided, after which the vaccination team visited (sometimes discovering additional cases still within 21 days of ring formation) and the community collaborated in rapidly enumerating a ring, seeking to include all who had within the past 21 days been a contact of any of these cases (before or after symptom onset) or a contact of such a contact. Contacts were defined as any person having been exposed to a confirmed case of EVD less than 21 days before their identification (i.e. slept in the same household; direct physical contact when alive or dead, direct physical contact with the dead case at the funeral, touched his/her blood or body fluids during the illness; touched his/her clothes or linen; or a baby been breastfed by an EVD case). The contacts of a contact included neighbors, family, or extended family members living within the nearest geographical boundary of all contacts, plus household members of any high-risk contacts. Where health-care workers or front-line

workers are known contacts or contacts of contacts, they were included in ring vaccination. Even if some did not live near any of the cases they were still included in the ring (as satellites). In addition, health-care workers or front-line workers in an affected community who were not contacts or contacts of contacts were offered vaccination and recorded as not ring members.

Following oral explanation, written individual informed consent (in local languages) was obtained from each individual in the ring, or from a parent or guardian. Those who consented were vaccinated immediately and offered antipyretics to prevent mistaken suspicion of EVD arising from the symptoms of systemic infection that are routinely to be expected for some days after receiving this live vaccine. The vaccine was stored and transported at -80 to -60ºC, then maintained at +2 to +8ºC for up to 14 days. There was to be safety follow-up after 30 minutes, and, until June 12, 2019, safety visits at 3 days and 21 days post-vaccination. After that date, safety visits were only to infants and pregnant women, but pregnancy outcomes were monitored.[9] Individuals with adverse events recorded were followed until recovery or resolution. EVD incidence in vaccinees was sought at the safety visits but was monitored in the entire outbreak-affected area by linkage to Ebola Treatment Unit records and to the national EVD surveillance system that systematically covered the whole area until the outbreak ended in mid-2020, with laboratory confirmation by INRB-designated laboratories. Data collection on smart devices used the OpenDataKitCollect app,[10] recording GPS locations of cases and vaccinees. When checked, all forms were asymmetrically encrypted in the field using a 2048-bit openSSL key.

OUTCOMES

All vaccinees were monitored for EVD onset, as was the whole population of the outbreak-affected region, until the end of the outbreak on June 25, 2020, 6 weeks after the last case recovered. Longer-term monitoring was through EVD treatment centre records and the national EVD surveillance system, which covered the whole area systematically until the outbreak ended. The main outcome in the present report is confirmed EVD onset, analysed by time since vaccination. The 3-day and 21-day safety visits and the pregnancy outcomes are also reported.

STATISTICAL ANALYSIS

The single anonymized dataset used for analyses combined detailed, consistent information from several de-identified sources on each vaccinee. During this process, central checks led to about 3% of individual records being eliminated as blank, duplicate or incomplete (for reasons unrelated to outcome), 4% being manually reformatted (chiefly regularizing date or text formats or correcting the positions of variables), and 0.01% having implausible ring membership codes corrected. After this, the dataset appeared to be of high quality, despite the difficult field circumstances under which it had been collected and checked.

EVD onset rates are tabulated separately for days 0-9, 10-29 and 30+ after vaccination (with the breakpoints at days 10 and 30 chosen empirically from the data). Tabular analyses of EVD rates against time since the last case onset before ring formation assess the relevance of the delay until intervention (by isolation of all cases and ring vaccination) to the delay until EVD rates fell in contacts. Kaplan-Meier methods display cumulative EVD incidence to day 60 in various subgroups. Cox regression, sometimes with various adjustments, yields EVD incidence rate ratios (RRs). (As there was no censoring during the post-vaccination month when almost all EVD incidence occurred, this is approximately equivalent to logistic regression on the overall risk in the first month, regardless of whether hazard ratios vary with time.)

There was no prior statistical analysis plan for the analyses of this non-randomised study and the 95% confidence intervals (CIs) are not adjusted for multiplicity, and cannot be used directly to infer vaccine efficacy or effectiveness. Analyses used SAS (version 9.4) and R (version 4.3.3).

OVERSIGHT AND FUNDING

DRC ethical approvals were by the Ministry of Health (regulatory) and Kinshasa School of Public Health (ethics). An independent Data and Safety Monitoring Board (DSMB) reviewed the protocol and assessed any reports of serious adverse events. The study accorded with Good Clinical Practice and Helsinki Declaration principles. All authors vouch for the accuracy and completeness of data, statistical analyses presented. The

vaccine was donated to WHO by Merck. Funders were non-commercial and had no influence on study design, conduct, analyses, reporting or journal submission.

RESULTS

In the 2018-20 outbreak in Eastern DRC, ring vaccination was implemented over a wide area (Figure 1). The population of about 3 million had for many years suffered from severe insecurity, civil conflicts and armed groups, and insecurity hampered access to some EVD-affected communities. Of 3470 cases of EVD reported, 3323 were lab-confirmed. No ring could be formed around 145/3323 (4.4%) because of security issues (24 cases) or community reticence (121 cases). The remainder were either cases in existing ring members or cases around which the 1853 rings got formed (some around >1 case). 303,171 consented and were vaccinated, including 265,183 with 30-minute follow-up sought and with linkage to subsequent EVD incidence (Figure S0). Of these 265,183, 57,563 were contacts, 136,836 were contacts of a contact (the two main populations analysed in this report), 11,923 were tertiary contacts (contacts of a contact of a contact, none of whom developed EVD after day 0), and.58,861 were healthcare or frontline workers who were not ring members (Table S1).

Among the contacts or contacts of a contact there were 434 cases of EVD (0.2 per ring), almost all within days 0-9 (380 cases) or 10-29 (32 cases). There were 22 cases after day 29 during an average of 170 more days of follow-up. EVD incidence was higher in those enumerated as contacts (6.6 per 1000, 380/57,563) than as contacts of a contact (0.4 per 1000, 54/136,836), especially during days 0-9, when the rate ratio was 0.04 (95% CI 0.03-0.06); Figure 2 plots risks only to day 60. Among the contacts, EVD incidence was highest during the first week after vaccination (when little vaccine effect was expected), then decreased during the second week. It was lower during the third week and declined further after the third week (Figure 2). Among the contacts of a contact, EVD incidence was lower but also decreased substantially during the second week.

The sooner after index case onset intervention took place (with case isolation and ring vaccination), the sooner a decrease in EVD onset rates occurred. Table 1 relates EVD onset rates in vaccinated contacts not to time since vaccination, as in all other analyses, but to time since index case onset. Two similar-sized groups of contacts are compared, those vaccinated within 8 days of index case onset (median 6 days, N=31,027) and those vaccinated later (median 12 days, N=26,536). During the period <12 days after index case onset no comparison between these groups can be made, and ≥24 days after index case onset both groups were at such low risk that again no comparison could be made. But, during the periods 12-17 and, particularly, 18-23 days after index case onset the incidence rate was lower in the earlier-intervention than in the later-intervention group, with 68 vs 103 cases arising during days 12-17 after index case onset (RR=0.55, CI 0.40-0.76) and 2 vs 53 arising during days 18-23 (RR=0.03, CI 0.01-0.11). Table S2 subdivides time more finely than Table 1 and suggests about 95% (CI 89-98%) effectiveness of the intervention against EVD onset 12 or more days after case-contact vaccination.

Table 2 subdivides the EVD risks among contacts during days 0-9, 10-29 and 30+ after vaccination by sex, age, pregnancy, index-case vaccination status, and the date ring vaccination began; web-figures S1-S5 give Kaplan-Meier graphs of the same findings EVD risks among contacts were lower in males than females (ratio 0.64, 95% CI 0.51-0.79), lower in children than adults, intermediate in pregnant women between men and non-pregnant women, and lower if the index case was a vaccinee (ratio 0.43, 0.29-0.65). Within each subgroup there was a decrease in EVD incidence about 10 days after vaccination that persisted. The vaccine dose was reduced on June 13, 2019, and this date, together with dates 3 months before and after it, defined 4 recruitment phases. Although there was no change in vaccine dose between phases 1 and 2, EVD risks during days 0-9 (before vaccination would have offered much protection) increased over time from 2.8‰ in phase 1 to 6.3‰ in phase 2 and 9.0‰ in phases 3 and 4.

Vaccinated health-care or front-line workers within rings had 30-day EVD risk 1.9‰ (22/11,835), similar to the risk of 2.0‰ (364/182,564) in other ring members. After day 30 they had risks of 0.4‰ (22/11,835) as against 0.1‰ (17/182,564) in other ring members. Vaccinated health-care workers or front-line workers not in rings had 30-day EVD risks of 0.1‰ (8/58,861) plus risks of 0.3‰ (20/58,861) after day 30 (table S1, figure S7).

Among vaccinees (contacts, contacts of a contact and health-care workers or front-line workers, time to EVD onset after vaccination was associated with decreasing risk of death. Among combined the case-fatality rates were, respectively, 26% (99/385), 14% (5/35) and 5% (2/42) for cases with EVD onset 0-9, 10-29 and ≥30 days after vaccination (figure S8). The overall case-fatality rate among vaccinees was 23% (106/462), as against 75% (2271/3008) among other cases in this outbreak.

Review of adverse event reports attributed (by the investigator) none to vaccination (Tables S3-S4). Table S5 describes the symptoms reported at the routine safety interviews 30 minutes, 3 days and 21 days after vaccination (excluding any symptoms of EVD in those who developed it). Almost all who had a 3-day or 21-day safety interview had received a vaccine dose of 50 million plaque-forming units, as when this dose was halved in June 2019 these safety interviews ended (except for infants and pregnant women). No definite side-effects were seen, apart from the mild symptoms (mainly headache, myalgia or arthralgia) to be expected by day 3 from infection by this live vaccine, no definite side-effect was seen. Those with such symptoms appeared to have somewhat lower EVD onset rates subsequently, but this was based on only small numbers of cases (Table S6).

DISCUSSION

The protective effects of ring vaccination, case isolation and other infection control measures could not be reliably separated within the present dataset, as there was no randomly allocated unvaccinated comparator group. In 2015, however, during the West

African outbreak (Figure 1A) a cluster-randomized trial had been undertaken in Guinea of immediate vs deferred ring vaccination.[4-6] In that trial, rings had been formed, cases isolated and other control measures taken as in the 2018-20 DRC outbreak, but half the rings in Guinea had been randomly allocated to be controls, with ring vaccination delayed until day 21. Comparison of the pattern of EVD incidence during days 0-29 in Guinea control ring members who were to be vaccinated on day 21 versus Guinea ring members vaccinated on day 0 and DRC contacts or contacts of contacts vaccinated on day 0 (Figure 3) can help separate the effect of vaccination itself from any effects of before or after day 0 of vaccinee selection, case isolation, or other measures. Among those in Guinea vaccinated on day 21, EVD incidence was higher both during days 0-9 and during days 10-29. In contrast, both in Guinea and in the DRC, those vaccinated on day 0 had a decrease in EVD incidence at about day 10, with low rates during days 10-29 that suggest vaccine efficacy in this period. Comparing EVD onset rates during days 0-9, the similarity between vaccinees and non-vaccinees in Guinea means that the lower rates in the DRC do not imply vaccine efficacy during this earlier period.

Isolation of cases, other EVD control measures, and ring vaccination with single-dose live rVSV-ZEBOV vaccine can alter the course of outbreaks of the Zaire species of Ebola virus. About nine days after intervention with ring vaccination and other protective measures the incidence of EVD started to decrease substantially, and after several days few further cases arose. Moreover, the sooner after index case onset these interventions occurred the sooner the incidence of EVD in contacts decreased. The association of the timing of the decrease in EVD incidence among contacts of those receiving the intervention package provides evidence that this set of interventions was protective, but does not separate the protective effects of vaccination and the other measures. Evidence that ring vaccination with rVSV-ZEBOV enhances the protective effect of the other measures is provided by comparison of the vaccinees in Eastern DRC rings with the control rings in the 2015 Guinea cluster-randomized trial, in which vaccination was deferred for 21 days but the procedures for ring formation and measures other than vaccination were similar to those in the DRC. Moreover,

symptoms at the day 3 follow-up consistent with systemic vaccine infection were associated with a somewhat lower subsequent incidence of EVD.

Vaccine efficacy may be stronger against fatal than against non-fatal EVD, as a retrospective cohort analysis of patients hospitalized during the 2018-20 outbreak reported lower case-fatality in vaccinees than in others.[13] The present study, with more detailed vaccination records, supports the lower case-fatality rate of vaccinees and shows case-fatality is even lower for cases arising ≥10 days after vaccination. Also in the hospitalised cases, a randomized trial showed that case-fatality could be reduced by appropriate monoclonal antibodies.[14] This enhances the plausibility of vaccination protecting against EVD onset and reducing case-fatality if, despite vaccination, EVD does occur.

Children were vaccinated throughout the study, and the latter part of the study included infants more than 6 months old, lactating women and women in the second or third trimester of pregnancy. Although the present study did not involve a placebo-controlled comparison, no serious side-effects were apparent. The rVSV-ZEBOV-GP vaccine used in this outbreak is now pre-qualified by the WHO and approved in the EU, US, and several African countries.

The key need in an outbreak is rapid, reliable identification of cases and vaccination of contacts. The results from this study suggest vaccination of the contacts of a contact is less important, for although more numerous they are at much lower risk. Among vaccinees, the healthcare workers and front-line workers who were not contacts or contacts of a contact were at even lower short-term risk than the contacts of a contact and would be at still lower long-term risk in an outbreak that is controlled more quickly than the West African or Eastern DRC outbreaks. The third-level contacts vaccinated were at very low risk. Integration of research into the 2018-20 DRC outbreak response identified effective treatments for hospitalised patients and has facilitated further assessment of vaccine safety and efficacy, while helping control disease transmission.

It is feasible to implement ring vaccination in an outbreak setting, integrating this with traditional Ebola control measures. Ring vaccination is effective, operationally efficient, and dose-sparing in comparison with population vaccination and is practicable for teams operating in insecure contexts. Under the name “surveillance-containment” it was a key component of achieving smallpox eradication, and there are substantial similarities between Ebola and smallpox transmission dynamics.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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~~**Data sharing**~~

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Figure 1. Ring vaccination sites, Guinea 2015 and DRC 2018-20
A) Locations of rings of vaccinees around 47 index cases in Guinea and 1853 in DRC
B) Weekly laboratory-confirmed EVD cases and probable EVD cases in DRC outbreak

Figure 2. EVD risks in the rings formed around index cases and then vaccinated, comparing the contacts of the index case versus the contacts of a contact

Figure 3. Non-randomised comparison between the timing of the main decrease in EVD onset in DRC rings (2018-20) and in Guinea vaccination rings (2015)
EVD onset in contacts or contacts of a contact in rings formed around index cases, by days since vaccination in DRC or days since ring formation in Guinea. In both populations similar methods were used to form rings, isolate cases, protect against spread, and monitor EVD onset in ring members. Analyses in Guinea censor at day 30 any still not vaccinated.

Table 1. EVD onsets in vaccinated contacts, by days from index case EVD onset until vaccination, and by days from index case onset until EVD onset in vaccinee

N = number of vaccinated contacts, n = number of vaccinated contacts developing EVD

Days* from index case EVD onset until EVD onset in vaccinee	Days from index case EVD onset until vaccination				EVD onset rate ratio (RR), comparing contacts vaccinated 0-8 vs 9+ days after index case onset	
	0-8 (median 6) N=31,027		9+ (median 12) N=26,536			
	n	‰	n	‰	Days since vaccination	RR (95% CI)
0-11*	138	4.45	-**	-	-	-
12-17	68	2.19	103	3.88	6-11 vs 0-5	0.55 (0.40-0.76)
18-23	2	0.06	53	2.00	12-17 vs 6-11	0.03 (0.01-0.11)
24-29	4	0.13	3	0.11		
30-59	0	0.00	2	0.08		
60+	3	0.10	4	0.15		

* Defined as days since vaccination plus median (either 6 or 12 days) from index case EVD onset until vaccination. If ring formation found >1 case the most recent was the index case, but all case-contacts were to be vaccinated.

** EVD in vaccinated contacts is counted only from the day of vaccination.

Table 2. Number of EVD onsets among vaccinated contacts by vaccinee characteristics and by days since vaccination, and 10-day risk of EVD onset

	Number of contacts vaccinated	EVD onsets by days since vaccination			
		Days 0-9	10-day risk (‰)	Days 10-29	Days 30+
Type of contact					
High risk	47904	316	6.6	20	8
Low risk	9659	31	3.2	4	1
Age (years)					
0 *	290	1	3.4	0	0
1-9	10595	25	2.4	4	1
10-17	9663	27	2.8	0	1
18-49	31118	235	7.6	10	7
≥ 50	5897	59	10.0	10	0
Sex					
Male	29979	141	4.7	12	4
Female	27584	206	7.5	12	5
Parturition (from 2019/ 06/ 13)					
Male, age 14-49 *	6324	49	7.7	4	1
Pregnant or lactating *	1882	21	11.2	1	0
Other female, age 14-49 *	4488	69	15.4	2	0
Status of index case					
Vaccinated (mostly recently)	7540	26	3.4	0	0
Unvaccinated	50023	321	6.4	24	9
Date ring vaccination began					
2018/ 08/ 08 – 2019/ 03/ 12 †	21523	61	2.8	5	7
2019/ 03/ 13 – 2019/ 06/ 12 †	14544	92	6.3	6	1
2019/ 06/ 13 – 2019/ 09/ 12	17169	155	9.0	7	1
2019/ 09/ 13 – 2020/ 01/ 14	4327	39	9.0	6	0

* Restricted to those vaccinated from June 13, 2019, when infants and pregnant or lactating women became eligible.

† Dose: 50 million plaque-forming units until June 12, 2019, then 25 million PFUs; regulatory licensure is of 20 million PFUs.