Efficacy and Effectiveness of an rVSV-Vectored Vaccine Expressing Ebola Surface Glycoprotein: Interim Results from the Guinea Ring Vaccination Cluster-Randomised Trial

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

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Summary

Background A recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus (rVSV-ZEBOV) is a promising Ebola vaccine candidate. We report the results of an interim analysis of a trial of rVSV-ZEBOV in Guinea, west Africa.

Methods For this open-label, cluster-randomised ring vaccination trial, suspected cases of Ebola virus disease in Basse-Guinée (Guinea, west Africa) were independently ascertained by Ebola response teams as part of a national surveillance system. After laboratory confirmation of a new case, clusters of all contacts and contacts of contacts were defined and randomly allocated 1:1 to immediate vaccination or delayed (21 days later) vaccination with rVSV-ZEBOV (one dose of 2×10^7 plaque-forming units, administered intramuscularly in the deltoid muscle). Adults (age ≥18 years) who were not pregnant or breastfeeding were eligible for vaccination. Block randomisation was used, with randomly varying blocks, stratified by location (urban *vs* rural) and size of rings (≤20 *vs* >20 individuals). The study is open label and masking of participants and field teams to the time of vaccination is not possible, but Ebola response teams and laboratory workers were unaware of allocation to immediate or delayed vaccination. Taking into account the incubation period of the virus of about 10 days, the prespecified primary outcome was laboratory-confirmed Ebola virus disease with onset of symptoms at least 10 days after randomisation. The primary analysis was per protocol and compared the incidence of Ebola virus disease in eligible and vaccinated individuals in immediate vaccination clusters with the incidence in eligible individuals in delayed vaccination clusters. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Findings Between April 1, 2015, and July 20, 2015, 90 clusters, with a total population of 7651 people were included in the planned interim analysis. 48 of these clusters (4123 people) were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 42 clusters (3528 people) were randomly assigned to delayed vaccination with rVSV-ZEBOV. In the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomisation, whereas in the delayed vaccination group there were 16 cases of Ebola virus disease from seven clusters, showing a vaccine efficacy of 100% (95% CI 74·7–100·0; p=0·0036). No new cases of Ebola virus disease were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination. At the cluster level, with the inclusion of all eligible adults, vaccine effectiveness was 75·1% (95% CI –7·1 to 94·2; p=0·1791), and 76·3% (95% CI –15·5 to 95·1; p=0·3351) with the inclusion of everyone (eligible or not eligible for vaccination). 43 serious adverse events were reported; one serious adverse event was judged to be causally related to vaccination (a febrile episode in a vaccinated participant, which resolved without sequelae). Assessment of serious adverse events is ongoing.

Interpretation The results of this interim analysis indicate that rVSV-ZEBOV might be highly efficacious and safe in preventing Ebola virus disease, and is most likely effective at the population level when delivered during an Ebola virus disease outbreak via a ring vaccination strategy.

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For the **protocol** see http://www.bmj.com/content/bmj/suppl/2015/07/27/bmj.h3740.DC1/cama026973.w1_default.pdf

See Online for appendix

Introduction

Vaccines against Ebola virus disease are an urgent international priority.[1] However, at present, no licensed vaccines are available, despite promising results for several candidate vaccines in non-human primate studies and phase 1 trials.[2–9] The recombinant, replication-competent vesicular stomatitis virus-based candidate vaccine expressing the glycoprotein of a Zaire Ebolavirus (rVSV-ZEBOV) causes a transient systemic infection after a single injection, and produces a rapid immune response against the Ebola virus surface protein.[6,7]

The *Ebola ça Suffit* ("Ebola this is enough") cluster-randomised phase 3 trial is currently underway in Guinea to assess the efficacy of the rVSV-ZEBOV candidate vaccine for the prevention of Ebola virus disease. The trial uses a novel design for recruitment and estimation of vaccine efficacy,[10] modelled on the ring vaccination approach used for smallpox eradication in the 1970s.[11] Ring vaccination is defined as the vaccination of a cluster of individuals at high risk of infection, owing to their social or geographical connection to a confirmed index case.

The pilot phase of the trial began on March 23, 2015, with the immediate vaccination of three non-randomised clusters; randomisation of clusters started on April 1, 2015. Herein, we report the interim results of this trial, describe the characteristics of the clusters and individuals enrolled in the trial, report the incidence of Ebola virus disease in the rings up to July 20, 2015, and provide preliminary estimates of vaccine safety and effectiveness.

Methods

Study design and participants

Described in detail elsewhere,[10] the ring vaccination trial is a novel cluster-randomised trial design to assess vaccine efficacy and effectiveness during outbreaks. We used an adaptive trial design with an α spending strategy to allow for interim analyses of the data. The full trial protocol can be accessed as a data supplement to a previous publication on this trial[10] and the original French version is available in the appendix.

The aim of the open-label *Ebola ça Suffit* trial is to assess whether or not one dose of rVSV-ZEBOV candidate vaccine administered by intramuscular injection to adult contacts and contacts of contacts of patients with confirmed Ebola virus disease can provide protection against the development of laboratory-confirmed Ebola virus disease. The trial is based in Basse-Guinée, a coastal area of Guinea, west Africa, that comprises the capital Conakry and eight other prefectures (for a map, see figure 1). This area was chosen because it was the only area of Guinea in which cases of Ebola virus disease were confirmed at the time of the start of the study. The Guinean national Ebola response teams report all newly confirmed cases of Ebola virus disease daily to the trial team. Suspected cases are ascertained by the national Ebola surveillance system based on reports from health-care facilities and the community, and confirmed in designated laboratories.[11] Within a few days of notification, a cluster of all contacts and contacts of contacts (including absent residents) is defined and randomly allocated to immediate or delayed vaccination.

Research in context

Evidence before this study

The ongoing outbreak of Ebola virus disease in west Africa is the largest outbreak ever recorded. As of July 19, 2015, a total of 27 705 reported confirmed, probable, and suspected cases have been reported in Guinea, Liberia, and Sierra Leone, including 11 269 reported deaths. A meeting convened by WHO in September, 2014, in Geneva, Switzerland, concluded that an urgent need exists for efficacy and safety testing of the unlicensed vaccine candidates that are currently in development and that trials of candidate Ebola virus disease vaccines should be expedited. We searched Medline and Embase from January, 1990, to July 20, 2015, for phase 3 clinical trials assessing the efficacy of Ebola vaccines, without language restrictions, using the search terms "Ebola virus", "filovirus", "prophylaxis", "vaccine", and "clinical trials" to identify any published phase 3 trial results of Ebola vaccines. The rVSV-ZEBOV vaccine has been studied in phase 1 and 2 studies, which have documented its immunogenicity and safety profile. To our knowledge, ours is the only phase 3 trial of this vaccine in west Africa that has reported results, and no trial until now has used the ring vaccination cluster-randomised design. Therefore, we could not do a detailed systematic review at this point in time.

Added value of this study

Effective vaccines against Ebola virus disease could reduce morbidity and mortality and end the devastating Ebola epidemic, which is severely affecting the health system and the populations in west Africa. Our results provide the first evidence that the rVSV-ZEBOV vaccine is efficacious in a trial setting and might be effective in real-life scenarios. These results also document the feasibility and adequacy of ring vaccination cluster trial design in an outbreak situation in a resource-poor setting and when the incidence of Ebola virus disease is low in the general population.

Implications of all the available evidence

The results of this interim analysis suggest that rVSV-ZEBOV might be highly efficacious in preventing Ebola virus disease, and most likely effective at the population level when delivered during an outbreak using a ring vaccination strategy. These data can contribute to the ongoing assessment of this vaccine and help to inform policy and regulatory decisions with regard to the Ebola vaccination strategy.

Eligible consenting adults (aged ≥18 years) are vaccinated immediately or 21 days after randomisation. Participants in all clusters have access to free medical care at a private clinic in Conakry for any acute illness during the study period. The exception is suspected Ebola virus disease, for which the participants are transferred to the nearest Ebola treatment unit as per national guidelines.

For every index case included in the study, we define contacts as individuals who, within the last 21 days, lived in the same household, were visited by the index case after the onset of symptoms, or were in close physical contact with the patient's body or body fluids, linen, or clothes.[12] Contacts of contacts include neighbours, family or extended family members living within the nearest geographical boundary of all contacts, plus household members of any high-risk contacts.[12] Local social mobilisation experts visit the area of the index case's residence and seek participants' consent for the trial team to enumerate the cluster. A written information sheet and informed consent form were used to obtain consent from all participants. If the person was illiterate, these documents were read to him or her in one of the local languages in the presence of a valid witness. To document consent, a signature or fingerprint was obtained and a literate witness also signed the form. If a participant listed in a previously defined cluster develops Ebola virus disease, they are assessed as a potential new index case, as an outcome for the trial, or both. A new cluster is defined if at least 60% of the contacts and contacts of contacts live outside the original cluster.

All individuals aged 18 years or older who live in the defined cluster are eligible for vaccination. Exclusion criteria were any history of Ebola virus disease (self-reported or laboratory-confirmed disease), women who are breastfeeding, women with a self-reported or confirmed pregnancy (women are offered, but not required to take, a pregnancy test), self-report of clinically significant immunodeficiency, history of anaphylaxis to a vaccine or vaccine component, severe illness that makes the participant bed-bound or requires admission to hospital at the time of the vaccination. Eligible individuals might not receive the vaccination because they refuse or withdraw consent, or because they are away from home at the time of vaccination.

The trial was approved by the Guinean national medicines regulatory agency (Direction Nationale de la Pharmacie et du Laboratoire) and the national ethics committee (Comité National d'Ethique pour la Recherche en Santé), and by the WHO Ethical Research Commitee, and Norwegian Regional Committees for Medical and Health Research Ethics. All participants provided written informed consent, as described earlier.

Randomisation and masking

Randomisation was done in a 1:1 ratio at the cluster level. An independent statistician not otherwise involved in the trial generated the allocation sequence.

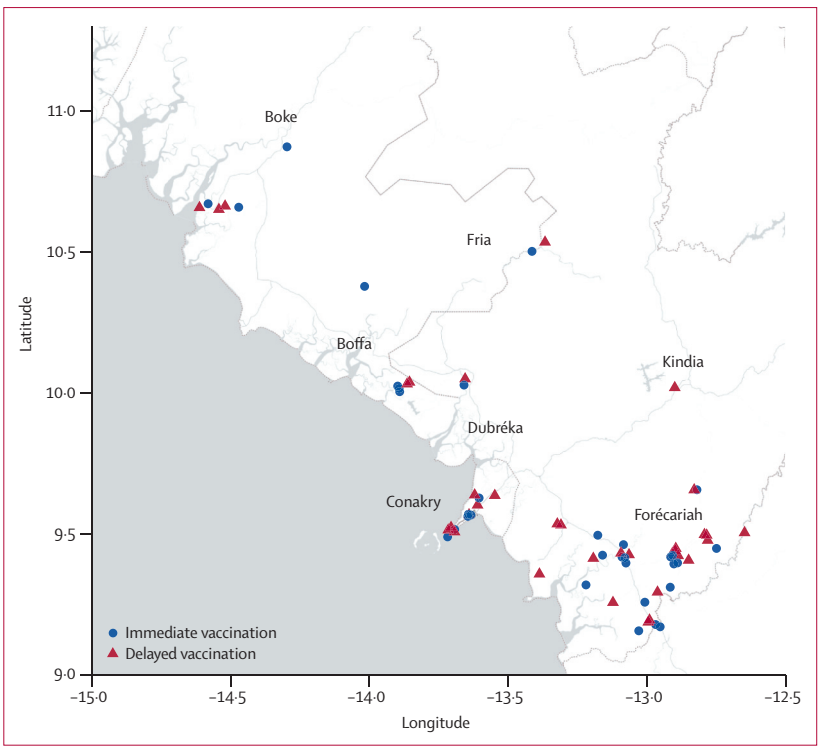

Figure 1: **Study area of *Ebola ça Suffit* cluster vaccination trial in Basse-Guinée**

Block randomisation was used with randomly varying blocks, stratified by location (urban *vs* rural) and size of rings (≤20 *vs* >20 individuals). The list of eligible participants and a preliminary eligibility assessment was done before randomisation. The randomisation list is stored in a data management system not accessible to anyone involved in the recruitment of trial participants. Allocation of a cluster was revealed only after registering the cluster in the system. Informed consent and assessment of eligibility were done after randomisation, but allocation was not disclosed to the participants until the end of the informed consent process. The study is open label, but Ebola response teams and laboratory workers are unaware of the allocation of clusters.

Procedures

One dose of 2×10^7 plaque-forming units (PFUs) of the rVSV-ZEBOV vaccine is administered intramuscularly in the deltoid muscle. It is recommended, but not required, that this injection should be administered into the non-dominant arm. To ensure that the participants in delayed clusters receive the vaccine on the designated date and, to improve compliance with follow-up, we contact the participants by telephone on the days before the scheduled visits. Merck Sharp & Dohme (Kenilworth, NJ, USA) provided the rVSV-ZEBOV vaccine used in the trial.

We observe the vaccinated volunteers for 30 min post-vaccination to record any adverse events, and visit them

at home on days 3, 14, 21, 42, 63, and 84 post-vaccination to document the potential occurrence of any serious adverse events. On days 3 and 14 post-vaccination, we obtain information about any type of adverse event from participants or next of kin, using a standardised questionnaire. We report all serious adverse events, including cases of Ebola virus disease in vaccinees to the trial's data and safety monitoring board as part of the serious adverse event reporting procedures.

The primary outcome—Ebola virus disease occurring at least 10 days after randomisation—is confirmed through detection of Ebola virus RNA by reverse-transcriptase PCR.[13] The Ebola response teams, which operate independently from the trial teams, investigate

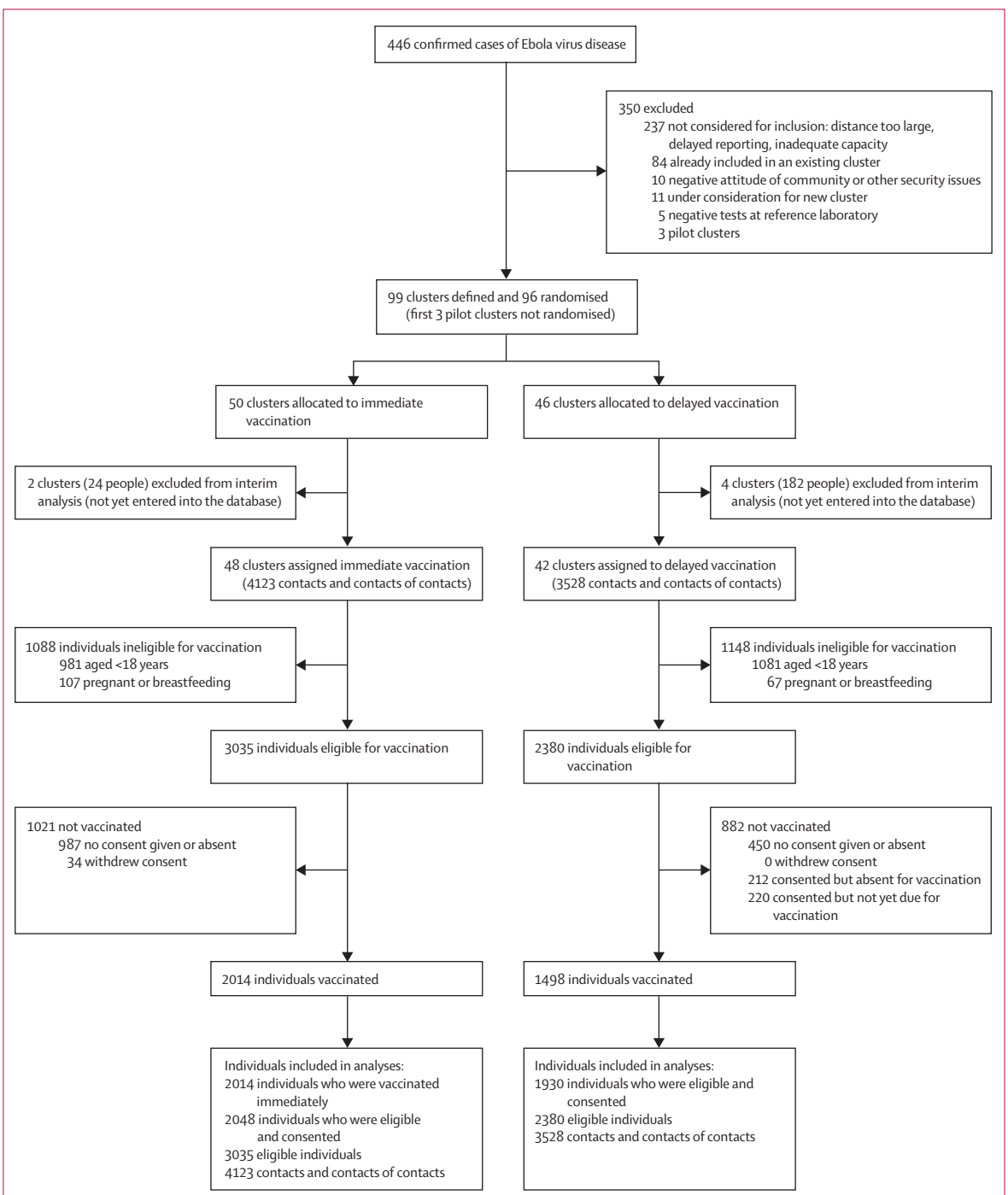

Figure 2: **Trial profile**

each suspected case and classify cases according to WHO definitions.[14] Whenever a suspected case is identified, the Ebola response team isolates and transfers the patient to the nearest Ebola treatment unit, and collects blood samples for laboratory tests in one of several designated laboratories. If the person has died, the response team collects specimens for laboratory confirmation and coordinates a safe and dignified burial. All contacts are monitored at home by members of the Ebola response team for 21 days following their last known exposure to the case, and are isolated if they become ill.[12]

Outcomes

The primary outcome is Ebola virus disease occurring at least 10 days after randomisation, confirmed through detection of Ebola virus RNA by reverse-transcriptase PCR, analysed per protocol as vaccine efficacy. Secondary outcomes were suspected and probable cases and serious adverse events occurring up to 84 days post-vaccination. Every day, the trial team reviews the data about confirmed new cases and searches the trial database, using surveillance and laboratory identification codes, name, last name, age, location, date of onset of symptoms, and date of notification to ascertain whether or not a new case qualifies as a primary outcome in a randomised cluster. We also review all available information about chains of transmission in the area of origin of the new Ebola virus disease case. The case is considered for inclusion as a new cluster.

Statistical analysis

The protocol and statistical analysis plan were approved and in place when the trial was started on April 1, 2015; amendments to the analysis plan made on May 15, 2015, modified the α spending rules to a more conservative function, and interim analysis timing (see appendix for the protocol, statistical analysis plan, and amended plan). The data and safety monitoring board reviewed interim analysis data on July 3, 2015.

Sample size calculations assumed that each cluster would contain an average of 50 consenting participants. We required 90% power to reject the null hypothesis of no vaccine efficacy, with the probability of a type I error (ie, α level) set at 5%, for a two-sided test of significance. To account for the clustering (ie, the design effect), we assumed an intra-class correlation coefficient of 0·05.[15,16] We calculated sample sizes by varying the percentage of contacts becoming infected and developing Ebola virus disease (ie, the illness rate) between 1% and 5%. We also varied the potential vaccine efficacy from 50% to 90%. For example, we found that if the vaccine efficacy was 70% and the infection rate 2%, then a total of 190 clusters would be needed. However, if the vaccine efficacy was 90%, with a 2% infection rate, then a total of 98 clusters would be needed. The trial is done in an adaptive manner, for which a two-sided, symmetric O'Brien-Fleming α spending strategy truncated at an absolute value of 3·00 is used (the O'Brien-Fleming threshold for this interim analysis was 0·0027).[17] We planned to do a single interim analysis at around 100 total clusters. No boundaries for futility were specified. The data and

	Immediate vaccination (n=48)	Delayed vaccination (n=42)
Index cases used to define clusters		
Age of index case, years	35·0 (20·1–40·0)	37·5 (25·0–50·0)
Women	26/48 (54%)	25/42 (60%)
Time from onset of symptoms to reporting of case by Ebola response team, days	3·9 (2·6)	4·3 (2·3)
Randomly allocated clusters		
Total number of people in cluster	80 (58–100)	74 (60–95)
Clusters located in rural areas	37/48 (77%)	32/42 (76%)
Clusters with ≥20 participants eligible and consenting in the clusters	44/48 (92%)	37/42 (88%)
Age of eligible participants, years	40·0 (26·5–50·0)	37·0 (29·0–55·0)
Compliance with follow-up visits for safety monitoring among eligible participants		
Day 3	1803/2014 (90%)	1384/1498 (92%)
Day 14	1657/1834 (90%)*	1326/1471 (90%)
Day 21	1562/1731 (90%)†	1306/1441 (91%)
Day 42	1212/1342 (90%)	930/1017 (91%)
Day 63	779/875 (89%)	308/397 (78%)
Day 84	313/345 (91%)	..

Data are median (IQR), n/N (%), or mean (SD). *The day 14 follow-up visit was not done in two clusters (121 vaccinees) because of public security issues. †The day 21 follow-up visit was not done in one cluster (31 vaccinees) because of public security issues.

Table 1: **Characteristics of index cases, rings, and compliance with follow-up visits for safety monitoring**

	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (–7·1 to 94·2)	76·3% (–15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

Table 2: **Calculations of vaccine efficacy and vaccine effectiveness based on different study populations**

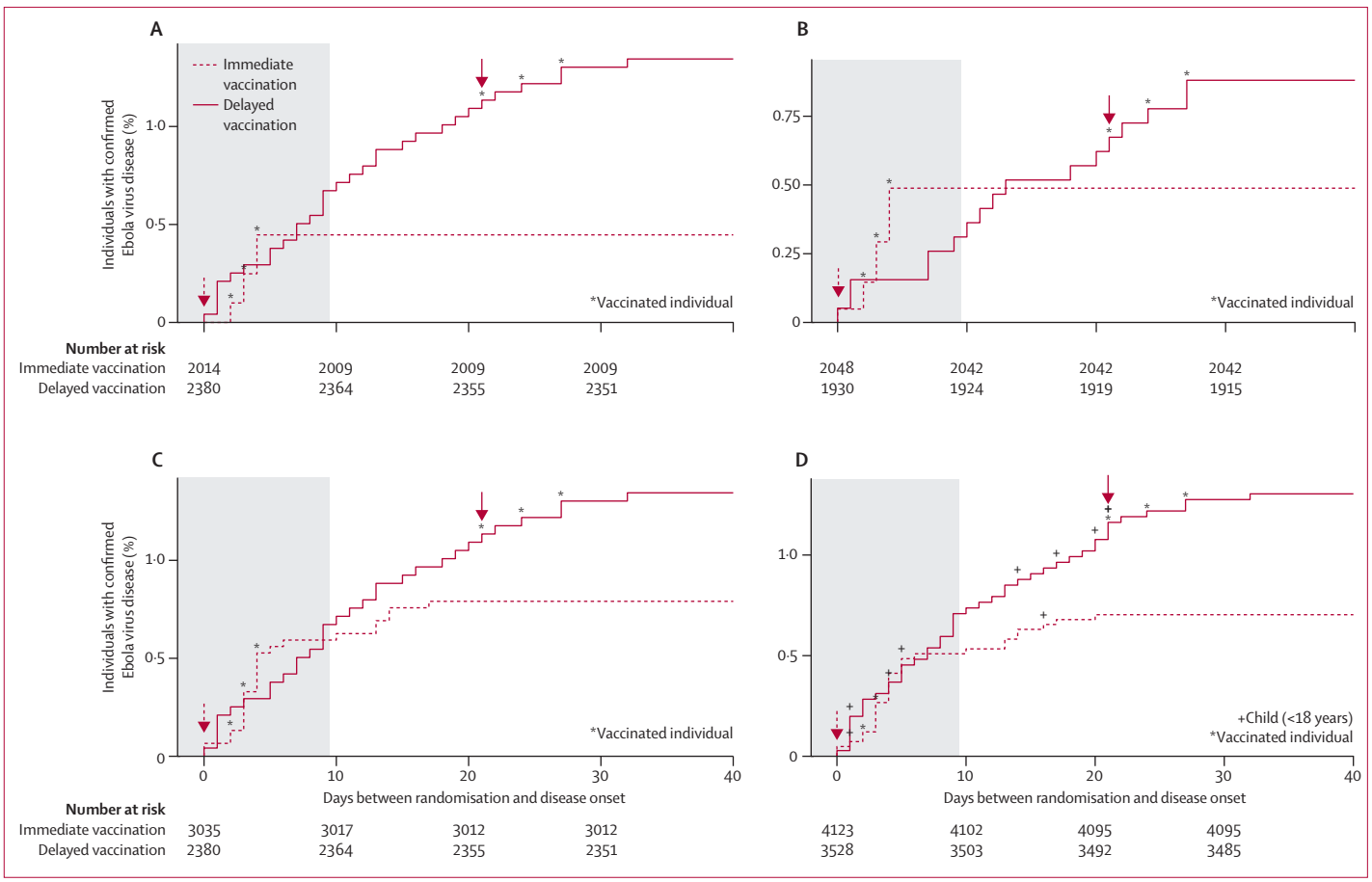

Figure 3: **Kaplan-Meier plots of the cumulative incidence of confirmed Ebola virus disease in different study populations**
(A) All vaccinated individuals assigned to immediate vaccination versus all eligible individuals assigned to delayed vaccination (primary analysis). (B) All eligible and consenting individuals. (C) All eligible individuals. (D) All individuals. Arrows indicate immediate (day 0) and delayed (day 21) vaccination. The shaded area shows the period excluded from analyses.

safety monitoring board can decide whether to continue or stop the trial, according to success, failure, or insufficient evidence.

A priori, we defined a delay of 10 days in the primary analysis to account for the incubation period of Ebola and the unknown time for the vaccine to develop protective immunity. Analyses of vaccine efficacy were therefore restricted to events occurring 10 days or more after randomisation. The primary analysis, as defined in a previous publication on this trial,[10] compared the incidence of Ebola virus disease in eligible and vaccinated individuals in immediate vaccination clusters with the incidence in eligible individuals in delayed vaccination clusters. Additional analyses compared the incidence in eligible and consenting individuals, eligible individuals, and all individuals. The first two analyses estimate vaccine efficacy, the latter two, vaccine effectiveness in different populations.[18]

In case of zero cases of Ebola virus disease occurring (ie, vaccine efficacy 100%) a 95% CI was derived by fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy. For comparisons in which events were reported in both groups, a Cox proportional hazards model was fitted using a cluster-level frailty term to adjust for clustering within rings.[10,19] We used a Fisher's exact test to compare the proportions of clusters with at least one event across the two trial groups. All analyses were done in R, version 3.2.0.[20]

This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Role of the funding source

The funders had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

This interim analysis includes clusters randomly assigned from April 1, 2015, up until July 20, 2015. Between these dates, 90 clusters were included, with a

total population of 7651 participants (figure 2). 48 clusters (4123 people) were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 42 clusters (3528 people) were randomly assigned to delayed vaccination (21 days later). A total of 75 laboratory-confirmed cases of Ebola virus disease were identified in the 90 randomised clusters during the study period, of whom 33 patients died. The case-fatality rate was 52% (15/29) in the immediate vaccination rings and 39% (18/46) in the delayed vaccination rings.

At baseline, the two groups were similar in terms of characteristics of the index cases (age, sex, and delay between onset of symptoms and reporting of case by Ebola response teams) and the location and size of the clusters (table 1). The median age of the eligible and consenting adults was similar (table 1). The median number of people in each cluster was similar: 80 (IQR 58–100) in the immediate clusters and 74 (60–95) in the delayed clusters. Immediate and delayed clusters were similar in terms of the number of clusters with at least 20 participants and the mean age of the eligible and consenting participants (table 1). Rates of participant compliance to follow-up safety visits were roughly 90% for all visits in both immediate and delayed vaccination clusters.

In the 48 immediate vaccination clusters, 3035 (74%) of 4123 contacts and contacts of contacts were eligible for vaccination and 2014 (49%) were vaccinated. In the 42 delayed vaccination clusters 2380 (67%) of 3528 contacts and contacts of contacts were eligible for vaccination and 1498 (42%) were vaccinated (figure 2).

In our primary analysis, we compared the incidence of Ebola virus disease in all vaccinated individuals from the immediate vaccination group with all eligible individuals in the delayed vaccination group (table 2). At 10 days or more post-randomisation, no cases of Ebola virus disease occurred in the immediately vaccinated participants compared with 16 confirmed cases in eligible individuals in the delayed vaccination group. These 16 cases were from seven delayed vaccination rings, in three different prefectures. The estimated vaccine efficacy was 100% (95% CI 74·7–100·0). According to Fisher's exact test comparing the proportions of clusters with one or more eligible case, the p value was 0·0036 and did not cross the interim analysis threshold of p=0·0027. Figure 3A shows the cumulative incidence of Ebola virus disease in the two groups.

In a comparison of eligible and consenting individuals, the analysis of vaccine efficacy is based on zero cases of Ebola virus disease at 10 days or more post-randomisation in the immediate vaccination group and 11 confirmed cases in the delayed vaccination group, for an estimated vaccine efficacy of 100% (95% CI 70·8–100·0) and a p value of 0·0194 (table 2, figure 3B). When the analysis is expanded to all eligible people, six cases of Ebola virus disease occurred in three clusters in the immediate vaccination group versus 16 cases in seven clusters in the delayed vaccination group (table 2, figure 3C). Notably, all the cases in the immediate vaccination group occurred in unvaccinated individuals. The estimate of vaccine effectiveness in eligible people is 75·1% (95% CI –7·1 to 94·2; p=0·1791). Finally, if we include all contacts and contacts of contacts, the comparison is between eight confirmed cases of Ebola virus disease from four clusters (all in unvaccinated individuals) in the immediate vaccination group and 21 cases from seven clusters in the delayed group. The estimated vaccine efficacy in all members of the 90 clusters is 76·3% (95% CI –15·5 to 95·1, p=0·3351; table 2, figure 3D).

Table 3 provides additional information about the distribution of confirmed cases of Ebola virus disease in vaccinated and unvaccinated individuals in the immediate and delayed vaccination rings.

The data about the secondary outcomes for efficacy and effectiveness and safety are not included in this Article and will be part of a future report once follow-up is completed for all participants and analyses have been done. The information regarding serious adverse events reported so far is included in the appendix. As of July 20, 2015, a total of 43 serious adverse events had been documented among eligible and consenting trial participants, including 27 confirmed cases of Ebola virus disease (see appendix).

	Eligible adults allocated immediate vaccination		All eligible adults allocated to delayed vaccination (n=2380)	Ineligible (not vaccinated; age <18 years, pregnant, or lactating)	
	Vaccinated immediately (n=2014)	Never vaccinated (n=1021)		Allocated to immediate vaccination (n=1088)	Allocated to delayed vaccination (n=1148)
Allocated delay (42 clusters)					
Cluster D1	..	..	6	..	1
Cluster D2	..	..	3	..	4
Cluster D3	..	..	2	..	0
Cluster D4	..	..	2	..	0
Cluster D5	..	..	1	..	0
Cluster D6	..	..	1	..	0
Cluster D7	..	..	1	..	0
35 clusters with 0 cases	..	..	..	..	..
Allocated immediate (48 clusters)					
Cluster I1	0	3	..	1	..
Cluster I2	0	2	..	0	..
Cluster I3	0	1	..	0	..
Cluster I4	0	0	..	1	..
44 clusters with 0 cases	..	..	..	..	..
Total	0/2014 (0·0%)	6/1021 (0·6%)	16/2380 (0·7%)	2/1088 (0·2%)	5/1148 (0·4%)

Table 3: **Distribution of confirmed Ebola virus disease cases in vaccinated and unvaccinated individuals in immediate and delayed clusters**

Apart from Ebola virus disease, the three most common serious adverse events were suspected, unconfirmed Ebola virus disease (three cases), episodes of febrile illness (three cases), and road traffic accidents (three cases). 16 deaths occurred: 15 from Ebola virus disease and one from cardiac arrest. The initial causality assessment indicated that only one serious adverse event, an episode of febrile illness, in a male participant who recovered without sequelae was related to vaccination. Assessment of serious adverse events is ongoing.

Discussion

The interim results of the *Ebola ça Suffit* ring vaccination trial suggest that the efficacy of a single injection of rVSV-ZEBOV to prevent Ebola virus disease might be high, that protection can be established quickly, and that the vaccine might be effective at the population level when delivered by ring vaccination. As expected, Ebola virus disease typically occurred in local outbreaks, based on close-contact, person-to-person transmission.

The primary analysis of vaccine efficacy compared adults who were eligible and vaccinated in the immediate vaccination group with eligible adults in the delayed vaccination group. Eligible adults allocated to the immediate group who declined vaccination were therefore excluded from the primary analysis, whereas those from the delayed group who refused vaccination were included. Selection bias could have been introduced but was unlikely because the risk of Ebola virus disease was similar in the two groups in the first days after randomisation, and similar from day 10 onwards in eligible adults not vaccinated in the immediate group and eligible adults in the delayed group (table 2). Furthermore, when we restrict the comparison to eligible and consenting individuals, the estimated vaccine efficacy was identical to the estimate from the primary analysis (100%).

Additional evidence supports the conclusion that the rVSV-ZEBOV vaccine is efficacious and effective. Although the primary analysis considered only events prevented in the vaccinated participants from the immediate vaccination group, we recorded the same preventive effect in those individuals who were vaccinated in the delayed clusters. Indeed, no vaccinee developed symptoms more than 6 days after vaccination, irrespective of whether vaccination was immediate or delayed. This finding was also the case for the three immediate vaccination rings enrolled in the pilot phase of the trial, which were not randomised and therefore not included in the analysis reported here. Vaccination can reduce the risk of disease not only in people who were vaccinated but also indirectly in the unvaccinated population of the cluster. Such an effect was also evident in this interim analysis, but it was not statistically significant.

The rVSV-ZEBOV vaccine has been assessed in eight phase 1 studies in Europe, Africa, and North America;[6,7] a large phase 2 study (the PREVAIL study, NCT02344407) in Liberia; and an ongoing phase 3 study in Sierra Leone (the STRIVE study, NCT02378753) and more than 9000 volunteers have received this vaccine so far (Feinberg M, Merck Sharp & Dohme [known as Merck in the USA], Kenilworth, NJ, USA, personal communication). The phase 1 trials in healthy volunteers were done to test the safety and immunogenicity of the rVSV-ZEBOV vaccine and to inform dose selection.[6,7] These studies showed that the vaccine was immunogenic, with higher titres of neutralising antibodies produced at higher vaccine doses,[7] but the glycoprotein antibody titres were measured only at baseline and at 28 days post-vaccination. Although no data are yet available for the time needed for the vaccine to induce protective immunity, our results suggest that this might happen quickly, within a few days or a week. In the phase 1 trials, viraemia was transiently recorded in nearly all volunteers at the dose used in Guinea, but it was no longer detectable by day 8 in most of these individuals.

We took several measures to reduce the risk of bias in the *Ebola ça Suffit* cluster-randomised trial.[21] The randomisation of rings is done by an investigator based at the data centre in Conakry who is not involved in the field implementation of the trial. Any selection bias caused by subversion of randomisation is therefore unlikely.[22] The list of contacts and contacts of contacts (including contacts who happen to be absent) is completed before randomisation, and informed consent from participants is obtained post-randomisation. Separate teams are responsible for defining the clusters, obtaining informed consent and assessing patient eligibility, and for the actual vaccination process. Participants are informed about their group allocation only after they have given informed consent. The stratified randomisation procedures produce well-balanced groups and it seems unlikely that important imbalances exist in unmeasured variables strongly related to the risk of Ebola virus infection. The study is open label and masking of participants and field teams to the time of vaccination is not possible. However, the Ebola response teams and laboratory staff responsible for case ascertainment and laboratory confirmation are unaware of study participation or allocation of cases. Therefore, differential bias in the ascertainment of the outcomes is unlikely. So far, no cluster attrition has occurred and differential attrition with respect to characteristics associated with the risk of Ebola virus disease is unlikely. Cluster attrition would only affect our efficacy estimates if participants who are lost to follow-up later go on to develop Ebola virus disease, and these cases are not included in analyses. Since reporting of cases is very complete, this situation is not thought to be a likely source of bias.[15] Finally, much care is taken to ensure that the communicable disease control measures other than immediate or deferred ring vaccination are identical in the two groups.

We believe that the results from the *Ebola ça Suffit* ring vaccination trial are also likely to be externally valid and applicable to other regions of Guinea and to Sierra Leone and Liberia, the other two countries in west Africa most severely affected by the ongoing epidemic. Indeed, the

epidemiology and risk factors for Ebola virus transmission are consistent across countries.[23,24]

Our trial serves as a proof of concept for a novel ring vaccination cluster-randomised trial design.[10] This trial design is logistically feasible, even in resource-poor settings and in a crisis situation. The approach is successful when the incidence of Ebola virus disease is low in the general population and new cases are concentrated in family and community contacts. We are collecting detailed epidemiological and phylogenetic information to study transmission within the trial clusters. Ring vaccination therefore also bears great promise as a strategy for Ebola virus disease containment and elimination.

In the past few weeks, the number of new clusters that could be defined according to the present trial protocol has been reduced, since the number of new Ebola virus disease cases diagnosed per week in Guinea has fallen[25] and many of the adult contacts of the new Ebola virus disease cases are already part of defined clusters. The data and safety monitoring board has advised that the trial should be continued to expand the evidence on vaccine effectiveness and safety, but that randomisation should be stopped and we should continue with immediate vaccination of new clusters. As of July 24, 2015, approval from the national regulatory authority of Guinea and from relevant ethics review committees has been granted to implement this recommendation. The continued enrolment, immediate vaccination, and follow-up of clusters will generate additional data about the effectiveness of ring vaccination to protect communities through herd immunity, and will hopefully help to stop Ebola virus disease transmission in Guinea.

Contributors

IML, ME, AMH-R, WJE, CHW, MPK, and J-AR conceived and designed the trial; ME, AMH-R, IML, CHW, J-AR, AC, WJE, SM, GE, XR, ASV, SH, ST, and GN contributed to the protocol and design of the study. J-AR, MPK, MKK, AMH-R, BD, RG, and GN provided management and oversight of the trial as members of the study steering group. AMH-R coordinated the study design process and implementation of the trial on behalf of the study steering group. MD, MKK, and AS were co-principal investigators of this trial. AMH-R, MPK, SKé, MML, MD, MKK and AS, ASV, XR, GE, SH, ST, SKo, CHW, SM, and GN contributed to the field implementation of the trial. MWC, SD, SG, and EK supported the laboratory testing and validation of endpoints. IML, NED, and ME wrote the statistical analysis plan. IML and NED did the statistical analyses. ME, IML, NED, AMH-R, WJE, J-AR, and MPK contributed to the preparation of the report. All authors critically reviewed and approved the final version.

Declaration of interests

ME, WJE, AC, and CHW have acted as unpaid advisors to WHO on Ebola vaccination and report travel and accommodation paid for by WHO to attend meetings. WJE is a co-investigator on the European Commission Innovative Medicines Initiative-funded EBOVAC trial of the Johnson & Johnson prime-boost Ebola vaccine candidate, for which he has received a grant from the European Commission Innovative Medicines Initiative, and his partner is an epidemiologist at GlaxoSmithKline, in a role unrelated to the company's development of an Ebola vaccine. AC and CHW have acted as unpaid advisors to the EBOVAC trial, for which CHW reports travel and accommodation paid for by the EBOVAC consortium to attend a meeting. AC has received non-financial support from Janssen outside the submitted work. SG has received grants from the European Commission during the conduct of the study. ST has received grants from Research Council of Norway, during the conduct of the study. The other authors declare no competing interests.

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