Ebola ça suffit

Ebola vaccine
Phase 3 trial, Guinea
on behalf of Ebola ça suffit: Ring vaccination trial Consortium
A. Ring vaccination trial
B. Interim results
C. Results implications
How was Smallpox eradicated?

The weekly and monthly surveillance bulletins informed the teams about the areas where Smallpox cases have been identified.

This precise information provided clear data on progress towards the zero cases objective.

In 1969, a Programme of surveillance and containment was initiated in Brazil in an State of 7 million population. After identifying each case and vaccinating each person around the case, smallpox transmission was stopped after only 50,000 people were vaccinated!

Brazil had the last case of Smallpox in 1971.
RESEARCH METHODS & REPORTING

The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola

OPEN ACCESS

Ebola ça suffit ring vaccination trial consortium
Trial objectives

Primary outcome

Vaccine efficacy against confirmed EVD

Secondary outcomes

Vaccine effectiveness (indirect and overall) in preventing confirmed EVD
Vaccine efficacy against death from confirmed EVD
Vaccine efficacy against probable and suspected EVD
Vaccine safety by assessing serious adverse events
The **INCLUSION** criterion is:

- Individuals aged 18 years or older who live in the defined vaccination ring.

The **EXCLUSION** criterion are:

- History of EVD (self-report or laboratory confirmed).
- Pregnancy (verbal report) or breast-feeding. Women are offered, but not required to take, a pregnancy test.
- Self-report of clinically important immunodeficiency condition, e.g. HIV/AIDS.
- History of anaphylaxis to a vaccine or vaccine component
- Severe illness that makes the person bed-bound or requiring hospitalisation at the time of the vaccination.
# Trial Sample Size Calculation

## Number of Rings per Arm

We assume 50 people per ring and an intraclass correlation of 0.05 for variation in incidence between rings, increase sample size by a design effect of 3.45

<table>
<thead>
<tr>
<th>Vaccine efficacy</th>
<th>Ring attack rate in before vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>50%</td>
<td>432</td>
</tr>
<tr>
<td>70%</td>
<td>191</td>
</tr>
<tr>
<td>90%</td>
<td>98</td>
</tr>
</tbody>
</table>
Important intervals to consider
The unknown time for the vaccine to develop protective immunity.
To capture endpoints that can be used for the estimation of vaccine efficacy, the analysis period is shifted in time.

This delay incorporates time for vaccinated individuals to develop protective immunity and for disease incubation, as symptom onset times are observed in the trial rather than the infection times.
Schematic presentation of the design of a ring vaccination trial

1. Newly laboratory confirmed case
2. Rapid definition of socio-geographical ring (based on place of residence of new case and contacts)
3. Random allocation of ring
   - Immediate vaccination
   - Delayed vaccination
4. Follow-up for outcomes
   - Follow-up for outcomes
5. Comparisons

![Pie charts showing efficacy and effectiveness with categories: Eligible, vaccinated, Eligible, not vaccinated, Not eligible, not vaccinated]
What is a vaccination ring?

Contacts and contacts of contacts

INDEX CASE
Lab confirmed EVD case

close contact with patient body or body fluids, linen, or clothes

household members of high risk contacts

lived in the same household

extended family

neighbours

visited the symptomatic patient
In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case.
Clinical Monitors

AARSH uses experienced monitors from Africa (which facilitates working in the field)

AARSH monitored the MenAfriVac® (Group A meningococcal conjugate) trials that resulted in licensure, WHO prequalification and GAVI support for that vaccine

A CVD-Mali monitor makes supplemental visits
Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, MD, Prof Ira M Longini, PhD, Prof Matthias Egger, MD, Natalie E Dean, PhD, Prof W John Edmunds, PhD, Anton Camacho, PhD, Miles W Carroll, PhD, Moussa Doumbia, MD, Bertrand Draguez, MD, Sophie Duraffourg, PhD, Godwin Enwere, FWACP, Rebecca Grais, PhD, Stephan Gunther, MD, Stefanie Hossmann, MSc, Prof Mandy Kader Kondé, PhD, Souleymane Kone, MSc, Eeva Kuismaa, PhD, Prof Myron M Levine, MD, Sema Mandal, MD, Gunnstein Norheim, PhD, Ximena Riveros, BSc, Aboubacar Soumah, MD, Sven Trelle, MD, Andrea S Vicari, PhD, Conall H Watson, MFPH, Sakoba Kéita, MD, Dr Marie Paule Kiery, PhD††, Prof John-Arne Rättingen, MD†

† These authors contributed equally

Published Online: 03 August 2015
446 confirmed cases of Ebola virus disease

350 excluded
- 237 not considered for inclusion: distance too large, delayed reporting, inadequate capacity
- 84 already included in an existing cluster
- 10 negative attitude of community or other security issues
- 11 under consideration for new cluster
- 5 negative tests at reference laboratory
- 3 pilot clusters

96 clusters randomised

50 clusters allocated to immediate vaccination

2 clusters (24 people) excluded from interim analysis (not yet entered into the database)

48 clusters immediate
4123 contacts + contacts of contacts

1081 individuals ineligible for vaccination
- 981 aged <18 years
- 107 pregnant or breastfeeding

3035 individuals eligible for vaccination

1021 not vaccinated
- 987 no consent given or absent
- 34 withdrew consent

2014 individuals vaccinated

 Individuals included in analyses:
- 2014 individuals who were vaccinated immediately
- 2048 individuals who were eligible and consented
- 3035 eligible individuals
- 4123 contacts and contacts of contacts

46 clusters allocated to delayed vaccination

4 clusters (182 people) excluded from interim analysis (not yet entered into the database)

42 clusters immediate
3528 contacts + contacts of contacts

1148 individuals ineligible for vaccination
- 1081 aged <18 years
- 67 pregnant or breastfeeding

2380 individuals eligible for vaccination

882 not vaccinated
- 450 no consent given or absent
- 0 withdrew consent
- 212 consented but absent for vaccination
- 220 consented but not yet due for vaccination

1498 individuals vaccinated

 Individuals included in analyses:
- 1930 individuals who were eligible and consented
- 2380 eligible individuals
- 3528 contacts and contacts of contacts
Location of the rings
<table>
<thead>
<tr>
<th>Index cases used to define clusters</th>
<th>Immediate vaccination (n=48)</th>
<th>Delayed vaccination (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of index case, years</td>
<td>35.0 (30.1-40.0)</td>
<td>37.5 (35.0-50.0)</td>
</tr>
<tr>
<td>Women</td>
<td>26/48 (54%)</td>
<td>25/42 (60%)</td>
</tr>
<tr>
<td>Time from onset of symptoms to reporting of case by Ebola response team, days</td>
<td>3.9 (2.6)</td>
<td>4.3 (2.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomly allocated clusters</th>
<th></th>
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<tbody>
<tr>
<td>Total number of people in cluster</td>
<td>80 (58-100)</td>
<td>74 (60-95)</td>
</tr>
<tr>
<td>Clusters located in rural areas</td>
<td>37/48 (77%)</td>
<td>32/42 (76%)</td>
</tr>
<tr>
<td>Clusters with ≥20 participants eligible and consenting in the clusters</td>
<td>44/48 (92%)</td>
<td>37/42 (88%)</td>
</tr>
<tr>
<td>Age of eligible participants, years</td>
<td>40.0 (26.5-50.0)</td>
<td>37.0 (29.0-55.0)</td>
</tr>
<tr>
<td>Day</td>
<td>Compliance</td>
<td>N/Total (%)</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>3</td>
<td>1803/2014</td>
<td>(90%)</td>
</tr>
<tr>
<td>14</td>
<td>1657/1834</td>
<td>(90%)</td>
</tr>
<tr>
<td>21</td>
<td>1563/1731</td>
<td>(90%)</td>
</tr>
<tr>
<td>42</td>
<td>1213/1342</td>
<td>(90%)</td>
</tr>
<tr>
<td>63</td>
<td>779/875</td>
<td>(89%)</td>
</tr>
<tr>
<td>84</td>
<td>313/345</td>
<td>(91%)</td>
</tr>
</tbody>
</table>
The primary analysis compared the incidence of EVD in eligible and vaccinated individuals in immediate vaccination rings with the incidence in eligible individuals in delayed vaccination rings.

Additional analyses compared the incidence in eligible and consenting individuals, eligible individuals, and all individuals.
All vaccinated individuals assigned to immediate vaccination versus all eligible individuals assigned to delayed vaccination

<table>
<thead>
<tr>
<th>Number of individuals (clusters)</th>
</tr>
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<tbody>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>Delayed</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Number of cases at &lt;10 days (affected clusters)</th>
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</thead>
<tbody>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>Delayed</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of cases at ≥10 days (affected clusters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
</tr>
<tr>
<td>Delayed</td>
</tr>
</tbody>
</table>

Vaccine efficacy/effectiveness‡ (%; 95% CI) 100% (74.7 to 100)

p value§ 0.0036

†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6.
All vaccinated adults assigned to immediate vaccination versus all eligible individuals assigned to delayed vaccination

†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6
All eligible and consenting adults

†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6
†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6
All individuals

8* vs 21†

†Four cases were vaccinated and developed symptoms on day 0, 2, 6, 6.
<table>
<thead>
<tr>
<th></th>
<th>All vaccinated in immediate versus all eligible in delayed (primary analysis)</th>
<th>All eligible and consented</th>
<th>All eligible (eligible adults, contacts and contacts of contacts)</th>
<th>All (all contacts and contacts of contacts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of individuals (clusters)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>2014 (48)</td>
<td>2048 (48)</td>
<td>3035 (48)</td>
<td>4123 (48)</td>
</tr>
<tr>
<td>Delayed</td>
<td>2380 (42)</td>
<td>1930 (42)</td>
<td>2380 (42)</td>
<td>3528 (42)</td>
</tr>
<tr>
<td><strong>Number of cases at &lt;10 days (affected clusters)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>9 (4)</td>
<td>10 (5)</td>
<td>18 (9)</td>
<td>21 (9)</td>
</tr>
<tr>
<td>Delayed</td>
<td>16 (12)</td>
<td>6 (5)</td>
<td>16 (12)</td>
<td>25 (13)</td>
</tr>
<tr>
<td><strong>Number of cases at ≥10 days (affected clusters)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6* (3)</td>
<td>8* (4)</td>
</tr>
<tr>
<td>Delayed</td>
<td>16† (7)</td>
<td>11† (5)</td>
<td>16† (7)</td>
<td>21† (7)</td>
</tr>
<tr>
<td>Vaccine efficacy/effectiveness† (%; 95% CI)</td>
<td>100% (74.7 to 100)</td>
<td>100% (70.8 to 100)</td>
<td>75.1% (-7.1 to 94.2)</td>
<td>76.3% (-15.5 to 95.1)</td>
</tr>
<tr>
<td>p value§</td>
<td>0.0036</td>
<td>0.0194</td>
<td>0.1791</td>
<td>0.3351</td>
</tr>
</tbody>
</table>

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6,
As of July 20, 2015

a total of **43 SAEs** had been documented among eligible and consenting trial participants, including **27 confirmed EVD cases**.

Apart from EVD, the three most common SAEs were suspected, unconfirmed EVD (3 cases), episodes of febrile illness (3 cases) and road traffic accidents (3 cases)
There were 16 deaths, 15 from EVD and one from cardiac arrest.

The initial causality assessment indicated that only one SAE - an episode of febrile illness, in a male who recovered without sequelae - was classified related to vaccination.

Assessment of SAEs is ongoing.
Of the 2,014 contacts and contacts of contacts (of 48 people infected with Ebola) who received the vaccine immediately, **none** developed Ebola after a 10-day window.

Of the 2,380 contacts and contacts of contacts (from 42 people infected with Ebola) in the delayed group, **16** developed Ebola after a 10-day window.
Additional evidence

In the three immediate vaccination rings enrolled in the pilot phase of the trial, no vaccinee developed Ebola.
These results suggest that the experimental vaccine against Ebola (rVSV-ZEBOV) is able to protect immunized individuals (after a delay of about 10 days, as hypothesized).

To date, the vaccine proved effective in all vaccinees.
Next steps
The candidate vaccine used in the ring vaccination trial in Guinea (and soon in Sierra Leone) is an experimental product, non licensed and that should therefore not be used outside a clinical trial context.

In the ring vaccination trial, WHO - as the Sponsor - has acquired the legal responsibility to ensure that the candidate vaccine is used only and strictly as per the trial protocol
Next steps

1. The Phase III trial is continuing, but randomisation stopped on 26 July, 2015 to allow for all adults in the newly-defined rings to receive the vaccine immediately, and to gather more conclusive evidence on effectiveness of the vaccine and of the ring vaccination strategy.

http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/
In addition, an amendment to extend the age group for adolescents and children has been submitted.

http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/
The Guinean regulatory authority, the national Ethics Committee of Guinea, and the WHO Ethics Committee have approved:

• the continuation of the trial,
• stopping randomisation and
• the inclusion of younger age groups
Next steps

2. MSF and WHO are filing an official request for amendment of the 'front-line workers' study protocol in order to vaccinate 2,000 additional front-line workers and increase the amount of information available on the safety of the vaccine rVSV-ZEBOV.

http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/
1200 front-line workers who were to be enrolled in an ancillary study to assess safety and immunogenicity, all have received the vaccine.
Next steps

3. The government of Sierra Leone has officially requested WHO for an extension of the ring vaccination trial to Sierra Leone.

Preparations are well advanced.

http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/
Next steps

4. Merck, Sharp & Dohme, the manufacturer of the vaccine, is making every effort to produce enough vaccine in the coming months, but rVSV-EBOV stocks are limited in the short term. WHO is providing evidence of efficacy to support the manufacturer initiating procedures towards licensing of the vaccine.

http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/
“…..encourage Merck to submit promptly a request to FDA and EMA for the authorisation of de vaccine for mass use .....”

Monsieur Kenneth FRAZIER, 
Président Directeur Général 
des Laboratoires Merck Sharpe and Dohme, 
2000 Galloping Hill Road 
Kenilworth, NJ 07033 
Etats-Unis d’Amérique
Acknowledgments

We thank the people in Basse-Guinée for their participation, and all the field, laboratory, and data management staff who worked extremely hard and under difficult conditions to successfully implement this study.
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