

Guinea – The Ebola vaccine trial and the reported interim results

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Overview

In response to the challenging circumstances, and desires to fast-track Ebola vaccine research, investigators studying rVSV-ZEBOV did not use a placebo¹-controlled trial design, which is the standard format for testing most vaccines. Instead, they used an innovative approach called “ring-vaccination”. This approach was based on working with a “ring” of people – exposed contacts – around patients with laboratory-confirmed Ebola virus disease (so-called ‘index’ cases). Such exposed persons, or ‘contacts’, were invited to participate in the study. Researchers recruited 7,651 such contacts and randomized them so that they either received i) immediate vaccination with rVSV-ZEBOV or ii) the same vaccination but delayed by 21 days. This paper refers to these two rings as the ‘immediate’ or ‘delayed’ vaccination rings, respectively.

Investigators then followed all study participants for several weeks [84 days] to monitor vaccine safety and assess whether vaccinated subjects were protected against Ebola virus disease (the primary endpoint being ‘laboratory-confirmed Ebola virus disease with onset of symptoms at least 10 days after randomization’). Based on evidence that the incubation period² of naturally developing Ebola disease is at least 10 days, the investigators discounted any cases that emerged within 10 days following vaccination under the assumption that these people were already infected when they received the vaccine and because the trial did not aim to test vaccine efficacy in people who got vaccinated after exposure. In other words, in terms of the primary analysis, these cases were not taken into account. On the other hand 4 vaccinated cases that occurred in the delayed rings were included in the primary analysis based on their occurrence after the time point of randomization and the fact that they were considered to result from an infection that took place before vaccination.

In the ‘immediate’ vaccination rings, there were no Ebola cases that emerged following 10 days after vaccination (although there were 9 cases that emerged before 10 days). In the ‘delayed’ vaccination rings there were 16 cases of Ebola after the 10 day period (and 16 before the 10 day period). On account of the fact that following 10 days, the number of cases of Ebola virus disease was so much lower (i.e., zero) in the ‘immediate’ vaccination rings, the investigators concluded the vaccine was 100% efficacious.

¹A ‘placebo’ control trial is when those vaccinated either get the test vaccine or, what is called a ‘placebo’; a placebo could be a vaccine for a completely different disease, or a formulation without antigen which, therefore, should have no effect whatsoever. The test and placebo vaccines are coded so that neither the persons being vaccinated nor the people administering the vaccines know which is which. The results of these trials are assessed (disease monitoring) by people who do not know which person received which formulation. It is only once the results are collected that the code is broken and the difference between the two groups – if any, emerges. This design avoids the well-documented possibilities of perceptions, and bias interfering with the results.

²‘Incubation period’ refers to the time from initial infection to emergence of clinical symptoms.

Concerns with the interpretation of results

There are several reasons to question the safety and 100% efficacy interpretations and even to conclude that these interpretations could be completely wrong. Overall, the fact that ***all Ebola cases in vaccinated individuals occurred within less than one week after vaccination*** combined with the fact that a ***100% efficacy*** rate was reported for this vaccine has raised skepticism of the conclusions of this study.

Concerns with the vaccine's efficacy and safety are detailed below.

Vaccine efficacy

The investigators appeared to take measures to ensure that the contacts in the 'immediate' and 'delayed' vaccination rings were broadly comparable in terms of demographics, what was known of their exposure risk, compliance with follow-up visits and implementation of nonvaccine disease control measures in the areas where they lived. However, without a placebo-controlled arm in this study, biases in terms of selecting contacts and how they are assessed and monitored could have affected results. Indeed, placebo-controlled trials have emerged as the design of choice because such biases have been historically found to have the potential to greatly influence results.

There are sound scientific arguments suggesting that the vaccine itself may have altered the incubation period for Ebola – making it shorter than normal and allowing Ebola symptoms to emerge earlier than normal (see below under 'vaccine safety'). But even if all Ebola cases considered for the primary analysis had occurred after an incubation time of at least 10 days, the natural infection rates between the 'immediate' and 'delayed' vaccination rings appeared to be very different – raising questions as to whether it was legitimate to compare data between the two types of rings³.

Further, the number of vaccinees who ended up with Ebola (regardless of whether they were from 'immediate' or 'delayed' rings) appears to be identical⁴ to the number of Ebola cases in *nonvaccinated subjects matching the same trial profile (i.e. all individuals who were eligible and provided consent, but were not vaccinated)*.

Even if one were to accept the claim of 100% efficacy, that would mean that protective immunity would

³The rVSV-ZEBOV vaccine has been shown to take a full week before providing full protective immunity in nonhuman primates (A. Marzi et al.; published online 6 August 2015; <http://www.sciencemag.org/content/early/recent>). It is not unreasonable to postulate that a similar lag time would also be observed in humans upon administration of the very same rVSV-ZEBOV vaccine according to a comparable pre-exposure vaccination scenario. Hence, the observed absence of cases between day 10 and day 17 in the immediate vaccination rings would lead one to conclude that none of the vaccinees got infected during the first week after vaccination whereas 7 nonvaccinated subjects included in the primary analysis were diagnosed with Ebola over the same period of time (i.e., between day 10 and day 17: see fig. 3A). Such discrepancy in infection rates would further question the validity of the comparison of cases between the immediate and delayed rings that were considered for the primary analysis (primary EP: Onset of disease symptoms at least 10 days after randomization)

⁴i.e., $9 + 4 = 6 + (11-4) = 13$; see table 2, first two columns of the paper which published the results.

have been induced by the vaccine within just a few days following vaccination⁵ – this is at a point in time much too early for functional antibodies to be generated. Protective immune responses that are specifically tailored to prevent infectious diseases take longer to generate⁶. In addition, a fast onset of protective immune responses as suggested by the results of the current study has only been proven to occur upon *pre-exposure* vaccination with VSV-based Ebola vaccine (VSV-ZEBOV) but nothing is known about the effect of the vaccine when administered during the incubation time of Ebola virus (i.e., upon *post-exposure* vaccination)⁷.

In any case, one concludes that even in the unlikely event that the claims for efficacy were eventually proven to be true, this result would have to be due to some non-specific response – a tonic of some sort for people’s immune systems, which occurred very fast and happened to be beneficial in fending off an imminent Ebola infection (vaccine experts may call this an ‘adjuvant’ effect). If this occurred, then a vaccine of this type could only be used to control Ebola in known contacts but not in health care and front line workers - as is currently envisaged - for the study did not provide any evidence of durable immunity against future infection.

Furthermore, the reported evidence of high vaccine effectiveness in the ring vaccination trial was concluded based on the comparison between cases in immediate vaccination rings and delayed vaccination rings with the inclusion of *all eligible* adults. A such comparison is biased by the outcome of the primary analysis⁸ (efficacy) and, therefore, does not allow to suggest protection against transmission through some sort of herd immunity.

Vaccine safety

All 9 cases of Ebola in the ‘immediate’ vaccination rings occurred within the first 10 days after the vaccine was administered (in actual fact, all occurred within just 6 days). Since the incubation period for Ebola virus disease is typically longer than 10 days, the investigators concluded that these 9 cases had been infected prior to vaccination and, therefore, decided to exclude them from the primary analysis.

This decision seems to have introduced a serious bias since: i) it is difficult to imagine that all of these 9

⁵This can reasonably be concluded based on the fact that i) The incubation time for the disease was assumed to be at least 10 days and ii) All nonvaccinated cases included in the primary analysis occurred between day 10 and day 21 post randomisation whereas no single case was observed in vaccinated individuals followed over the very same window. In other words: in order for a vaccinee not to develop Ebola disease between d10 and d21, the vaccine should have exerted its protective effect within the first 12 days after vaccination (d21 – 10 = 11)

⁶Vaccine immunology. , Pages 14-32, Claire-Anne Siegrist in: Vaccines, by Stanley Plotkin, Walter Orenstein, Paul Offit, 2013

⁷Marzi et al.; VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain; Science 349, 739 (2015): 739-742

⁸The reported rate of vaccine effectiveness has been strongly influenced by the number of cases in individuals from the immediate and delayed vaccination rings included in the primary analysis

cases would have been infected even prior to the onset of symptoms in the index case⁹ ; but more compellingly, ii) ALL of the Ebola cases that were diagnosed in vaccinees occurred shortly (i.e., within max 6 days) after vaccination regardless of whether the vaccination was immediate or delayed. This observation is strongly supportive of the scientific plausibility that inflammation inherently associated with vaccination with a live replicating vaccine is likely to enhance the life-threatening immune inflammatory events known to be triggered by Ebola virus¹⁰ . In other words, those who got Ebola within 10 days of vaccination could have had earlier and more severe symptoms due to interference of the vaccine with the early, inflammatory stage of their immune response to the virus. If this were true, one might expect a greater proportion of deaths in these cases. In order to assess this possibility, WHO has been asked for data on the case fatality rate of Ebola cases that occurred in the vaccinated compared to the nonvaccinated rings but this information has not yet become available. The study reports 15 deaths resulting from Ebola disease and there is a sound scientific rationale to believe that a significant number of these deaths may have occurred in vaccinated cases¹¹ .

In general, the safety claims reported on this and other vaccines usually refer to assessments of non-exposed individuals who received vaccination. However, as stated above, the possibility of a live replicating vaccine virus accelerating the onset of disease, especially of Ebola disease, in those who have been exposed shortly before vaccination has not been examined. The seriousness of overlooking and cross-checking this possibility should be obvious: The use of the vaccine is being discussed for ring vaccination as a response to outbreaks and to curtail infection. Assuming the worst-case scenario, (which is the responsible approach for scientists to consider and denounce), ring vaccination with live virus vaccines, for example rVSV-ZEBOV, could dramatically increase the probability of a lethal outcome in people who get vaccinated while already incubating the disease.

⁹All vaccinated cases in the immediate vaccination rings taken into account for the primary analysis occurred within 5 days post vaccination (see fig. 3); in order for these cases to 'comply' with an incubation time of at least 10 days, their exposure should have occurred at least 5 days prior to randomization, i.e., even before the onset of symptoms in the index cases

¹⁰There is a high likelihood that given the ring vaccination approach chosen for the Guinea trial, several contact subjects got their shot after having been exposed already to Ebola virus (randomization and hence, vaccination of contacts did not occur before several days elapsed after onset of symptoms in the index case; see table 1). It seems, therefore, that there could be a potential risk that - in subjects who got exposed prior to vaccination - vaccine-mediated inflammatory cytokine cascades did enhance the cytokine storm triggered by Ebola virus (EBOV) during incubation of the disease (A. Marzi et al. recently reported on the capacity of both EBOV and rVSV-ZEBOV to induce inflammatory cytokines; published online 6 August 2015; <http://www.sciencemag.org/content/early/recent>).

¹¹As stated on p. 7, the overall case fatality rate (CFR) in cases of the delayed vaccination rings is 39% as compared to 52% in all subjects of the immediate vaccination rings. In the delayed rings 4 out of 46 cases had been vaccinated (developing disease within less than 1 week after vaccination) whereas in the immediate rings 20 out of 29 cases had not been vaccinated (see table 2). It can, therefore, not be ruled out that the difference in CFR between the vaccinated cases and nonvaccinated cases considered for the primary analysis was statistically significant and much higher than 13% (i.e., 52% - 39%).

The proposed way forward

Safety first!

As a first step, WHO should be made to disclose the case fatality rates (CFRs) in vaccinated as compared to nonvaccinated Ebola cases from the trial. This is essential as a first step to investigate whether the vaccine may cause a safety issue when used under a ring vaccination scenario. CFRs would ideally be shared with the broader scientific community and especially with policy and decision makers engaged in the fight against Ebola.

In the meantime, all Global Health agencies involved in the Ebola response should address some key outstanding questions on the trial as listed below (the most urgent to solicit responses from are asterixed).

Re: METHODOLOGY

- Why were vaccination cases compared to cases in people who were only eligible instead of to cases in people who were not only eligible but had also given their consent?
- Have body fluids been taken from exposed but asymptomatic people to assess whether EBOV could be detected?
- Have antibody titers been measured? Could any antibodies be detected?
- Have systemic pro-inflammatory cytokines been measured in serum from vaccinated and nonvaccinated cases?

Re: SAFETY

- *- How can it be explained that all Ebola cases in vaccinated people occurred within just a few days after vaccination?
- *- Could the vaccine have accelerated the emergence of Ebola in contacts infected with EBOV before vaccination? Could the vaccine have had a detrimental effect on the development of the disease?
- *- Did people who were vaccinated and contracted the disease die more frequently than those who were not vaccinated but got Ebola?
- *- Has the impact of post-exposure vaccination with this vaccine ever been tested in a relevant animal model?

Re: EFFICACY

- *- Was protection due to antibodies, and if not, what was the presumed mechanism of protection?
- *- How is the immune response underlying the reported efficacy/ protection going to be measured to monitor the durability of protection over time?
- Was the reported efficacy due to protection provided by the VSV vector of the vaccine only or by the combined effect thereof with the inserted glycoprotein from Ebola? Have any animal experiments been conducted to verify whether the live VSV vector (i.e., without Ebola protein insert) could provide protection in its own right?
- *- Is there any evidence in humans or in nonhuman primate models that the reported type of protection/ efficacy could extend beyond the short window of observation considered for the primary endpoint?

Re: FUTURE PLANS

- * - Given the unknown effect of the vaccine when administered during Ebola virus incubation and the fast onset of disease in vaccinated cases, are plans to continue to enroll and vaccinate health care workers and front line workers in clinical trials - especially in the course of a still ongoing epidemic – not premature and potentially hazardous? In the event that answers to the safety and efficacy questions do not exist or are not forthcoming, should any further considerations to vaccinate people with the rVSV-ZEBOV vaccine not be put on hold until data from additional experiments in nonhuman primates¹²

become available? Could such studies be designed such as to include ensuring that the vaccine does not accelerate the emergence of disease in those vaccinated after recently having been exposed to Ebola?

- * - Without knowing how long immunity lasts, there is no sound rationale for using any vaccine in a prophylactic setting and, therefore, no justification for vaccinating healthy people considered at risk of exposure in case of a future outbreak (e.g., HCWs and FLWs) for this could needlessly result in healthy people putting themselves in harms way. While adequate post-exposure vaccination with the VSV-ZEBOV vaccine seems to be able to protect nonhuman primates against Ebola disease, the observed protection has been associated with innate, i.e. short-lived, immunity¹³. *So, wouldn't the next logical step be to conduct additional studies in this model to further examine the immunological basis of the observed protection and how long it lasts?*
- * - Given the waning epidemic, wouldn't it be wise to go back to the drawing board and generate more data in meaningful animal models (using natural routes of infectious challenge in natural host-pathogen models such as nonhuman primates) to ensure that only Ebola candidate vaccines proven to be safe and efficacious in relevant preclinical settings be introduced into rationally designed, state-of-the-art clinical trials?

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Conclusion

In the event that answers to the above-listed safety and efficacy questions do not exist or are not forthcoming, the comparison between case fatality rates in vaccinated as compared to nonvaccinated cases included in the primary analysis remains our single best chance for further investigating whether ring vaccination with rVSV-ZEBOV in particular, and live viruses in general, is likely to result into exacerbation of Ebola disease in previously exposed contacts.

¹² Using nonhuman primates as a highly relevant animal model, a simple experiment could be conducted, whereby a batch of macaques are infected with Ebola prior to vaccinating half of them to evaluate the impact of the vaccine on disease progression. In the event that the vaccine is shown to be safe (i.e., does not accelerate the development of disease), this experiment would at the same time enable to evaluate vaccine efficacy in a post-exposure vaccination setting. A similar setting whereby monkeys are challenged with a lethal dose of infectious Ebola virus shortly after they have been vaccinated has already been tested. Both scenarios seem relevant to mimicking vaccination of contacts who are subject to ring vaccination. In case of pre-exposure vaccination, full protection could only be induced provided infectious exposure occurred at least one week after VSV-ZEBOV vaccination.

¹³ Marzi et al.; VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain; Science 349, 739 (2015): 739-742