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Authors' reply

We thank Yanyu Zhang and colleagues for their interest in the methods of Ebola Ça suffit ring vaccination trial in Guinea[1,2] and for their words of encouragement.

In our article published in the British Medical Journal,[1] we specified that the primary analysis in a ring vaccination trial estimates vaccine efficacy against Ebola virus disease. Vaccine efficacy is defined as VE=1−è, where è=ë1/ë0 is the hazard ratio of ë1 (the hazard of Ebola virus disease for eligible and vaccinated individuals in a ring who receive immediate vaccination) and ë0 (the hazard of Ebola virus disease for eligible individuals in a ring who receive delayed vaccination before individuals in the ring are vaccinated). To capture events that can be used for the estimation of vaccine efficacy, the analysis period is shifted to the right 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. This estimate of vaccine efficacy is what was reported in the interim analysis.[1,2] We acknowledge that the depiction of this delay in figure 2 of our methods article[1] could potentially lend itself to some misinterpretation by the reader, if considered in isolation, but we argue that the narrative in both of our publications provides welldefined descriptions of the methods and definitions used.

Therefore, our primary analysis 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 secondary analyses compared the incidence in eligible and consenting individuals, eligible individuals, and all individuals. The first two analyses estimate vaccine efficacy, the latter two, overall vaccine effectiveness in different populations.[3,4] A total of 90 clusters were included in the planned interim analysis of this cluster randomised trial: 48 clusters were assigned to immediate vaccination with the rVSVZEBOV Ebola vaccine and 42 clusters were assigned to delayed vaccination with rVSV-ZEBOV. In the immediate vaccination group, no cases of Ebola virus disease were noted with symptom onset at least 10 days after randomisation, whereas in the delayed vaccination group there were 16 cases from seven clusters. The estimated vaccine efficacy was, therefore, 100% (95% CI 74·7–100·0; p=0·0036). As per the statistical α-spending rules defined a priori, the p value needed to declare success on this reported interim analysis was 0·0027.[2] As we previously suggested, vaccination can reduce the risk of disease not only in people who were vaccinated but also indirectly to the unvaccinated population of the cluster. Such an effect was also evident in this interim analysis, as measured by overall vaccine effectiveness, but this finding was not statistically significant.[2]

The full data for primary and secondary outcomes of efficacy, effectiveness, and safety will be shown in a future report once follow-up is completed for all participants in the trial.

ME, WJE, and CHW have acted as unpaid advisers 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. CHW has acted as an unpaid adviser to the EBOVAC trial, for which CHW reports travel and accommodation paid for by the EBOVAC consortium to attend a meeting. All other authors declare no competing interests.

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