Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response.

The Ebola virus disease (EVD) outbreak in North Kivu and Ituri provinces has recently shown an increase in the number of cases reported by week, after many weeks of overall decline. As of 10 April 2019, 1206 confirmed and probable cases of Ebola virus disease have been reported during this outbreak in the Democratic Republic of the Congo (DRC). There is no licensed vaccine against Ebola Virus Disease (1).

ABOUT THIS ANALYSIS

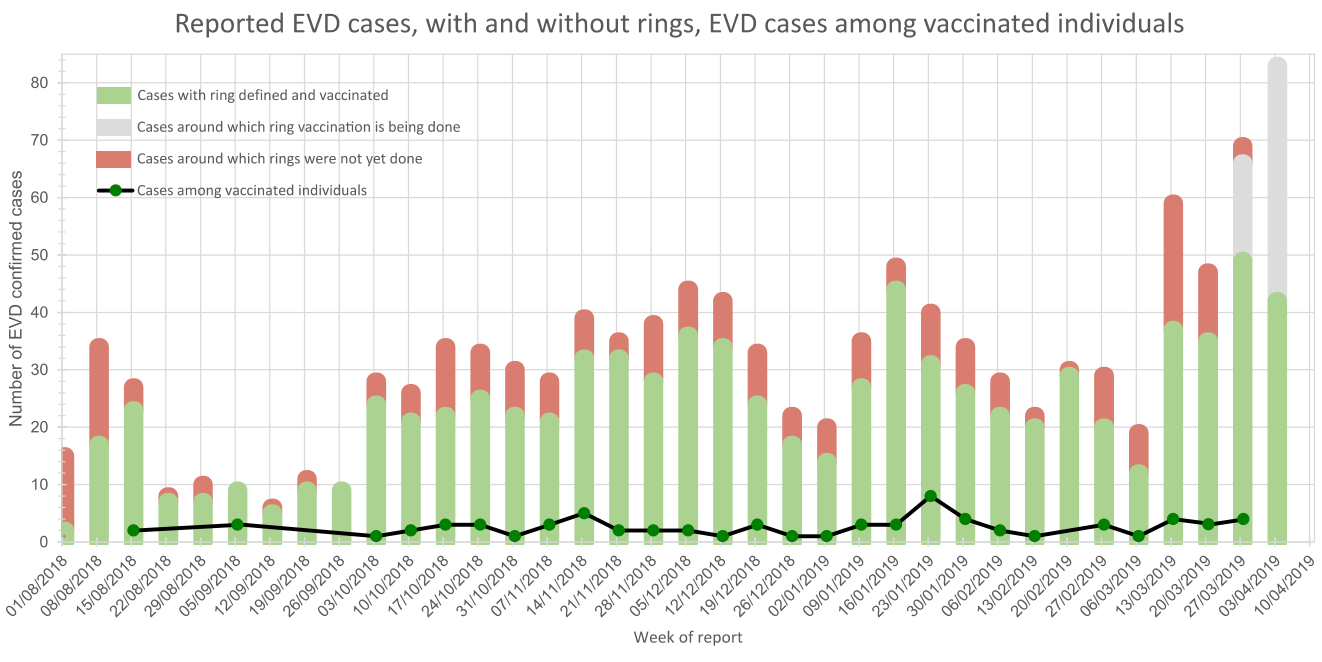
DRC's national research institute, the Institut National pour la Recherche Biomedicale (INRB) and WHO have conducted a preliminary analysis of the data being collected from the ring vaccination protocol. The analysis summarized here includes data between May 1, 2018 and March 25, 2019. This preliminary analysis was completed with the aim to better understand whether or not the rVSV-ZEBOV-GP candidate vaccine is effective and is contributing to prevent cases when delivered using the ring vaccination strategy. A more detailed analysis is being prepared and will be available in a peer-reviewed journal.

Ring vaccination using the Expanded Access/Compassionate Use protocol has been recommended by SAGE (1). It was initiated seven days after the declaration of the outbreak, on 1 August 2018, following approval by the National Regulatory Authority of DRC and the Ethics Review Committee of the Ecole de Santé Pùblique in Kinshasa.

The ring vaccination cohort protocol in the DRC is based on previous experiences in West Africa (2, 3, 4, 5). It is a remarkable example of South to South collaboration, where 45 trained Guinean and Niger researchers have coordinated the field implementation under the leadership of a senior Congolese researcher. Leveraging their experience in clinical trials in West Africa, the Guinean teams have also contributed to train nearly 300 Congolese colleagues. Combining this level of collaboration with the ring vaccination strategy and the rVSV-ZEBOV-GP vaccine should contribute to bringing the current Ebola outbreak in the DRC to an end, and to controlling future outbreaks as effectively and rapidly as possible. Figure 2 summarizes the actions implemented in the field by the ring vaccination teams.

From August 1, 2018 to March 25, 2019, 951 confirmed and probable cases of Ebola virus disease were reported during the analysis period. The ring vaccination research teams were able to define 679 rings and enumerate contacts and contacts of contacts around 776 cases. In addition, 28,888 health care workers/ front line workers (HCWs/FLWs) were vaccinated. Due to security reasons and lack of consent from communities, it was not possible to define rings around 175 (18%) of the cases of Ebola virus disease occurring during this period (figure 1). In all 100,754 contacts and contacts of contacts were listed and 91,492 eligible individuals who provided informed consent were vaccinated (90.8% of all enumerated contacts and contacts of contacts were vaccinated in the defined rings).

Figure 1: Number of confirmed EVD cases by the national surveillance system of DRC, number of cases included in the ring vaccination and, number of cases among vaccinated individuals.



The characteristics of the Ebola cases around who a ring was defined (index cases) are described in Table 1. Women represented 53% of the index cases. Mean time from symptom onset in index cases to ring definition and vaccination was 7 days. Rings had a median of 104 people. Seventy-three per cent of the people at risk included in the rings were defined as contacts of contacts. High risk contacts accounted for 9% of the members of the rings. Women represented 42% of the people included in the rings.

Compliance with scheduled follow-up visits for safety monitoring on Days 3 and 21 post vaccination for all rings was more than 90%.

Table 1. Baseline characteristics of index cases and rings (August 1, 2018 to March 25, 2019).

Index cases used to define rings$^{\Phi}$	
Age in years	28 (16 - 38)
Women	350/658 (53%)
Time from symptom onset to confirmation of the index case of EVD	6 (3 - 8)
Time from symptom onset to start of ring vaccination	7 (3 - 10)
Rings characteristics	
Number of people in ring	104 (59 - 157)
Number of people in healthcare workers clusters	123 (68 - 252)
Number of people in targeted geographic areas	440 (320 - 559)
Number of people vaccinated	93965
Age in years	28 (17 - 40)
Women	39651 (42%)
No detailed contact information (no consent)	2449 (3%)
Contact of contact	68279 (73%)
Contact	22298 (24%)
High-risk contact	8123 (9%)

Data are median (25th quartile - 75th quartile) or n/N (%).

Φ *Reporting of EVD cases is independent of participation in the expanded access/compassionate use protocol is done independently by the national surveillance system).*

Seventy-one cases of Ebola occurred among the 93,965 people at risk vaccinated in 679 rings (Table 2). Conversely, during the same period, 880 cases occurred among individuals at risk of Ebola who were not vaccinated. Of the, 71 Ebola cases occurring among vaccinated individuals, 15 cases had onset of symptoms 10 days or more days post- vaccination (this is the time after which vaccinees are assumed to be protected) and 57 cases had onset of symptoms 0-9 days post vaccination (it is assumed that during this period the vaccinees are not protected or partially protected).

Moreover, only 8.8% (60/679) of the vaccinated rings reported Ebola cases, and only 2.2% (15/679) reported Ebola cases 10 days or more after vaccination. The majority of cases among vaccinated people (76%, 54/71) occurred among high risk contacts. Only 2 out of 68,279 vaccinated contacts of contacts developed Ebola. This indicates that the ring vaccination has an effect in preventing tertiary generation of cases. The estimated Ebola attack rate for vaccinated individuals was about 0.017%, compared with an estimated 0.656 %in unvaccinated individuals. This yields an estimated vaccine efficacy of 97.5%, 95% CI [95.8 – 98.5%].

We were unable to estimate the number of unvaccinated health care workers/front line workers in the affected area, but we were able to estimate the vaccine efficacy using the Poisson approximation to the binomial distribution. We used this to calculate the approximate confidence intervals. The estimated vaccine efficacy for those with onset of illness 10 day or more post vaccination is 97.5% , 95% CI [92.4 – 99.1] and for those with EVD regardless of timing of onset of illness is 88.1%, 95% CI [79.9 -92.9].

Notably, there were 9 deaths among 56 cases with onset of symptoms 0-9 days after vaccination (who are assumed to be only partially protected by vaccination) and, no deaths among people where the illness onset occurred ten day more after they were vaccinated (who are assumed to be protected by vaccination) so the CFR in this group was 0 and estimated vaccine efficacy is 100% , lower 95% confidence limit 90.3%.

Table 2: Distribution of all confirmed EVD cases among all eligible, consented, and vaccinated people at risk

	Confirmed EVD cases among all eligible, consented and, vaccinated people at risk		
	Onset of symptoms <10 days after vaccination	Onset of symptoms ≥10 days after vaccination	All cases among vaccinated people
Number of EVD cases (rings with EVD cases)	56 (45)	15 (15)	71 (60)
Type of contact with index case			
Contact of contact	5	2	7
Non high-risk contact	1	0	1
High-risk contact [δ]	48	6	54
Healthcare worker	2	7	9
Clinical Outcome			
Death (rings with EVD cases)	9 (9)	0 (0)	9 (9)
Alive	39	15	54
Illness ongoing [λ]	8	0	8

[δ] This also includes health care workers / front line workers enrolled as part of community rings

[π] CT value available for 50 EVD cases (37 before 10 days, 13 after 10 days)

[λ] As of March 25, 8 vaccinated individuals who became cases are still under treatment at ETUs. Among them, 0 case developed EVD 10 or more days after vaccination.

Key public health messages arising from this information

1. These early results confirm previous observations of high efficacy of rVSV-ZEBOV-GP Ebola vaccine against disease (2, 3). We note that this is an observational study with the inherent methodological limitations. The ring vaccination strategy works because of the rapid protection after single dose, and high coverage achieved in the rings (91%).
2. No deaths were reported among vaccinees who developed Ebola with onset 10 or more days after vaccination. Moreover, the overall case fatality rate was reduced among all vaccinees who developed Ebola. Therefore, there is high vaccine efficacy against death.
3. Vaccination of HCWs/FLWs in the affected areas have provided information on the efficacy of this vaccine in preventing disease and death due to Ebola among HCWs/FLWs.
4. The ring vaccination strategy is a highly efficient delivery strategy for Ebola vaccines during outbreaks. Only 2 contacts of contacts developed EVD suggesting ring vaccination is effective in preventing tertiary generation of cases. This concept, which is based on smallpox eradication strategies (7), considers the fact that Ebola transmits mainly through human-to-human contact, has a relatively long serial interval (i.e., 2 weeks), and that the people at risk of contracting the disease can be identified (contacts and contacts of contacts). It is also efficient for teams operating in an insecure context and is a dose sparing vaccination strategy.
5. Integration of research into the outbreak response has facilitated the further assessment of this candidate Ebola vaccine, while contributing to the control of the outbreak. It is feasible to rapidly and effectively implement ring vaccination using a yet to be licensed Ebola vaccine in an outbreak setting and, to integrate this innovative strategy with the more traditional Ebola control measures. The fact that a protocol was available and trained teams and equipment could be promptly deployed meant that ring vaccination was initiated only 7 days after the declaration of the outbreak.

Why are these data critical for the response to this outbreak?

This evidence is critical to the control of the current outbreak because it provides evidence on the role that ring vaccination with rVSV-ZEBOV-GP can play in an outbreak when implemented with the other key Ebola control measures. We can communicate to the communities at risk of Ebola and the outbreak responders the follwoing:

1. There is increasing evidence on the efficacy of this vaccine and therefore it is critical to offer this vaccine to all people at risk of Ebola (contacts and contacts of contacts).
2. Even those people at risk already infected at the time of vaccination may have greater chances of survival. This is a particularly important finding if we consider that there are no licensed treatments for Ebola, although investigational therapeutics are being used.
3. Emerging data on disease on health care workers reiterates the importance to vaccinate those in affected areas.

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