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Safety of the rVSV ZEBOV vaccine against Ebola Zaire among frontline workers in Guinea

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ABSTRACT

Background: As part of the ring vaccination trial in Guinea, Front Line Workers were invited to participate in a sub-study to provide additional information on the immunogenicity and safety of rVSVΔG/ZEBOV-GP. Here we summarize the information on the safety follow-up.

Methods: An open-label, non-randomized, immunogenicity evaluation of one dose of rVSVΔG/ZEBOV-GP was conducted in Conakry, Guinea between March 2015 and July 2016. Front-line workers refusing vaccination were invited to participate as a control group. Participants were followed for 3 months with a subset followed-up for 6 months after vaccination. Women becoming pregnant during the follow-up were followed until pregnancy outcome. Solicited and unsolicited adverse events were monitored at each contact with participants using standardized study forms.

Results: 2016 vaccinated participants and 99 controls were included in the safety cohort. On the 3 days post-vaccination visit adverse events were very common, with over 70% of participants reporting at least one adverse event. The most frequently reported symptoms were headache, fatigue, arthralgia, subjective fever and myalgia. Among participants that completed fever diaries (n = 887), post-vaccination fever was reported by 15.22%. Comparing to the unvaccinated group, local reaction, fatigue, headache, arthralgia, myalgia and subjective fever occurring within the first 3 days post-vaccination were statistically significantly different in the vaccinated group compared to the unvaccinated. A total of 8 Serious Adverse Events were identified during follow-up. 2 SAEs were related to pregnancy.

Conclusions: Results confirm that adverse events 3 days after vaccination with the rVSV candidate vaccine are common. The occurrence of fever is of particular concern in the context of ongoing Ebola transmission. Additional studies should address important data gaps regarding the use of the vaccine in pregnancy and other vulnerable populations.

1. Introduction

The 2013–2016 outbreak of Ebola Virus Disease (EVD) in West Africa is the largest outbreak ever recorded. A total of 28,616 confirmed, probable and suspected cases of EVD and 11,310 deaths were reported in Guinea, Liberia and Sierra Leone [1]. In September 2014, the World Health Organization (WHO) convened an urgent meeting to assess the efforts underway to evaluate and produce safe and effective Ebola vaccines. The meeting concluded that phase I trials should be expedited and their results shared broadly to facilitate rapid progression to phase II. Another recommendation was that phase IIb/III studies should be conducted in parallel to phase IIa studies in Ebola affected countries, and that those studies should include frontline workers (FLW) or community members caring for Ebola patients.

As a sub-study of the ring vaccination trial [2], FLW were invited to participate in an immunogenicity and safety evaluation. This included health care workers (HCWs) working in EVD-related and other health services, members of burial teams and community outreach services. FLW are considered at greater risk of EVD infection. In the West Africa epidemic, it was estimated that HCWs had at least a 20 times higher risk of contracting EVD than non-health personnel [3]. In light of promising safety and immunogenicity data in phase I trials and the ongoing accumulation of an evidence-base from phase II trials, offering vaccine to FLW in

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the context of the response to the Ebola epidemic was considered as a means to accrue additional information while potentially protecting those at risk. Moreover, a key use of these experimental vaccines, if shown to be efficacious, will be through the vaccination of FLW working in endemic or epidemic contexts. As such, understanding of vaccine performance in this high-risk group provides essential information to inform future decision-making.

The study aimed to characterize the humoral and cellular immune response and to assess the frequency, incidence and nature of adverse events and serious adverse events (SAEs). Here, we summarize information on safety follow-up post vaccination with rVSVΔG/ZEBOV-GP amongst participants of the FLW study in Guinea.

2. Methods

2.1. Study design

This was an open-label, non-randomized, immunogenicity evaluation of one dose of rVSVΔG/ZEBOV-GP candidate vaccine. We conducted this study in the city of Conakry, and the health zones of Coyah and Forecariah between March 2015 and July 2016 when the last follow-up was completed.

The study included adult personnel working in health services (including Ebola treatment center, Ebola outreach and non-Ebola related health services), who provided informed consent to participate in the study and agreed to follow study procedures. Exclusion criteria included previous EVD infection or recent exposure, self-reported clinically important immunodeficiency, history of anaphylaxis to a vaccine or vaccine component, severe illness, pregnancy and fever.

At inclusion, participants received one dose of 2×10^7 plaque-forming units (PFUs) of the candidate vaccine. A study nurse or doctor administered the vaccine by intramuscular injection into the deltoid muscle, in preference of the non-dominant arm. If during the informed consent process potential participants stated that they did not wish to receive the vaccine, the doctor performing the consent offered the possibility to participate without vaccination but follow the rest of the protocol. Infection control advice was provided to all participants on the day of recruitment to ensure that precautions were adequately implemented and not altered as a result of vaccination.

Participants were requested to attend the study site on days 3, 14, 28 and 84 after inclusion. A subset of participants was also requested to attend for a follow-up visit 180 days after inclusion. Follow-up outside of scheduled visits was passive. Women becoming pregnant during the study period were referred to a dedicated clinic for antenatal care and followed-up by the study team until pregnancy outcome.

2.2. Assessment of adverse event at study visits

On immunization day, participants remained in observation 30 min after vaccination to detect and manage possible anaphylactic reactions occurring immediately after vaccination. During the follow-up visits 3 and 14 days after inclusion, a study clinician recorded temperature using an infrared thermometer and asked participants about solicited and unsolicited adverse events occurring since the previous visit. Using the study forms, the clinicians asked for the occurrence of local injection site reactions including local pain and induration, headache, fatigue, vomiting, diarrhea, muscle and articular pain, occurring since the previous visit. The date of onset of symptoms and duration were recorded. Moreover participants were asked for other symptoms occurring during the same period. For each symptom and following the subjective assessment of the participant, the clinician classified the symptom as a mild discomfort, symptom of moderate intensity without affecting daily activities or symptoms of severe intensity affecting daily activities.

SAE were assessed at each contact with participants and followed up to resolution. Following ICH guidelines [4] SAEs were defined as "any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or, is a congenital anomaly/birth defect in the offspring of a study participant".

2.3. Fever diaries and management of adverse events

On the day of inclusion, participants were requested to keep a diary to monitor fever, other symptoms and intake of medication for the first 3 days post-vaccination and were asked to bring the completed form on the first follow-up visit. On this visit, participants were given a second diary to continue recording information up to the next follow-up visit on the day 14 after vaccination. Together with the diary, participants received a thermometer and were asked to record armpit temperature twice per day, in the morning and in the evening. At the time of recording the temperature, participants also indicated if they had taken any medication.

On vaccination day, participants were reminded of the possible symptoms after vaccination and were provided with 6 tablets of Paracetamol 500 mg, 6 tablets of Ibuprofen 400 mg and a blister of 24 tablets of Artemether 20 mg/Lumefantrine 120 mg. Each participant received telephone credit and was advised to contact the study clinician on call in case of fever or other symptoms of concern to receive indications on medication intake and other recommendations. Antimalarials were included to treat participants with persistent fever. This was to reduce suspicion of EVD by treating a common disease such as malaria while avoiding malaria testing and potential exposure to EVD for health workers and unnecessary referral to the Ebola Treatment Centre for testing.

2.4. Data analysis

The first occurrence of the adverse event was specified in days after vaccination using the date of vaccination (day 0) and the date of onset of the event as recorded by a clinician. Duration was analyzed as the number of days between onset and the end of the event. For participants reporting the same event more than once, the frequency and pattern of re-occurrence were also analyzed.

Fever was defined as the endogenous elevation of at least one measured body temperature of $\geq$38 °C [5]. Readings below 35.5 °C were considered as no fever and recoded as 36 °C. Temperature measurements were analyzed in 0.5 °C increments, and as the percentage of subjects whose highest temperature fell within the increment by day.

The cumulative incidence rate of adverse events amongst study participants was calculated and the occurrence of events described by median, range, mean and standard deviation (SD). Occurrence of adverse events between those vaccinated and unvaccinated was compared using Fisher's exact test. Analysis was performed using Stata version 13 (Stata, College Station, TX, USA).

2.5. Ethical considerations

The study was approved by the national ethics committee in Guinea (Comité National d'Ethique pour la Recherche en Santé), the WHO Ethical Research Committee and the Médecins Sans Frontières Ethics Review Board. In additional the Guinean national medicines regulatory agency (Direction Nationale de la Pharmacie et du Laboratoire) approved the study. The study was designed and

performed in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice Guidelines established by the International Conference on Harmonization. All participants provided written informed consent to participate in the study. Participation was voluntary, confidential and there were no financial incentives. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

3. Results

A total of 2016 participants received the investigational vaccine and were included in the safety cohort. This includes a first cohort of 1172 participants and an additional 844 participants who were enrolled after publication of the interim ring vaccination trial in August 2015 but that were not included in the immunogenicity evaluation. Information from participants' diaries includes only the first cohort. A total of 99 participants did not wish to receive the vaccine, but agreed to participate in the study as a control group. Vaccinated participants had a mean age of 33.4 years (range 18–75), 75.0% (n = 1512) were males, 44.3% (n = 892) worked in EVD services (Table 1). In comparison with the vaccinated group, control were younger, more likely to be female and work in a health center (Table 1).

Safety follow-up visits on days 3 and 14 post-vaccination were completed by 2002 (99.3%) and 1957 (97.1%) of vaccinated participants, respectively. The 84 day follow-up was completed by 1895 (94.0%) of vaccinated participants. For the subset followed-up for 180 days, 90 of the 106 participants (84.9%) completed this visit (Fig. 1).

3.1. Safety follow-up visits

Overall 1506 vaccinated participants (74.7%) reported an adverse event during the 14 day post-vaccination period. Events were more often reported at the 3 day follow-up visit, with 1460 participants (72.4%) reporting an adverse event. During the 30 min post-vaccination observation period, adverse events were rare and reported in two participants. One participant had a local reaction accompanied by nausea and one participant reported vision disturbance without further detail. On day 14, 268 (13.3%) participants reported an event starting after the 3 day follow-up visit. Amongst these, 46 participants reported an adverse event for the first time. Over 40 symptoms were reported by participants. The most frequently reported symptoms were headache, fatigue, arthralgia, myalgia and subjective fever. Symptoms lasted a median of 2 days and for most disappeared within 3–4 days (Table 2). Most symptoms were mild to moderate in intensity.

As expected, the occurrence of local reaction, fatigue, headache, arthralgia, myalgia and subjective fever within the first 3 days post-vaccination was different ($p < 0.001$ for each of these variables) in the vaccinated group compared to the unvaccinated. Other symptoms and symptoms reported after the 3 days post-vaccination were not different between the vaccinated and unvaccinated groups ($p > 0.1$ for each event).

During the first 3 days post-vaccination, the most frequent combination of symptoms was fatigue and headache reported by 633 participants (31.6%). These were accompanied by arthralgia in 237 (37.4%) participants, by myalgia in 210 (33.2%) and by fever in 207 (32.7%) participants.

3.2. Fever

From participants included in the first cohort, 887 (75.7%) returned a fever diary, with 863 and 402 diaries completed on the 3 and 14 days post-vaccination visits, respectively. Within the 14 day follow-up period, 135 (15.2%) vaccinated participants reported at least one reading with temperature ≥38 °C. For most (85.2%), fever was <39 °C and maximum temperature recorded was 40 °C.

Fever was most common within 48 h following vaccination (Table 3), with 61 (7.2%) participants reporting fever within the 24 h after vaccination and with 74 (8.8%) participants reporting fever one day after vaccination. From participants who reported

Table 1
Participants' baseline characteristics, safety cohort.

Participants' characteristics	All (N = 2115)		Vaccinated (N = 2016)		Non-vaccinated (N = 99)		p-value[1]
Demographic							
Age (years)	33.19	(10.42)	33.43	(10.51)	28.31	(7.04)	<0.001
Male	1574	(74.42)	1512	(75.00)	62	(62.63)	0.006
Function							
Doctor	438	(20.71)	426	(21.11)	12	(12.12)	0.031
Nurse	250	(11.82)	245	(12.14)	5	(5.05)	0.033
Auxiliary nurse	76	(3.59)	73	(3.62)	3	(3.03)	0.758
Laboratory technician	55	(2.60)	55	(2.73)	0		0.096
Cleaner	16	(0.76)	14	(0.69)	2	(2.02)	0.137
Other support personnel	158	(7.47)	157	(7.78)	1	(1.01)	0.012
Security personnel	94	(4.44)	92	(4.56)	2	(2.02)	0.231
Administrative staff	26	(1.23)	26	(1.29)	0		0.256
Surveillance team member	124	(5.86)	111	(5.50)	15	(15.15)	<0.001
Inhumation team member	184	(8.70)	153	(7.58)	31	(31.31)	<0.001
Ambulance personnel	11	(0.52)	11	(0.55	0		0.461
Other	683	(32.29)	655	(32.46)	28	(28.28)	0.382
Workplace							
Ebola Treatment Centre	408	(19.29)	408	(20.24)	0		<0.001
Ebola outreach services	685	(32.39)	484	(24.01)	19	(19.19)	0.272
Hospital	503	(23.78)	314	(15.58)	11	(11.11)	0.229
Health Centre	325	(15.37)	621	(30.80)	64	(64.65)	<0.001
Clinic	37	(1.75)	37	(1.84)	0		0.174
Other	157	(7.42)	152	(7.54)	5	(5.05)	0.356
Medical							
Temperature (°C)	36.48	(0.36)	36.43	(0.36)	36.38	(0.35)	0.021

*Data are means (SD) or numbers (%).
[1] Comparison of vaccinated versus non-vaccinated participants.

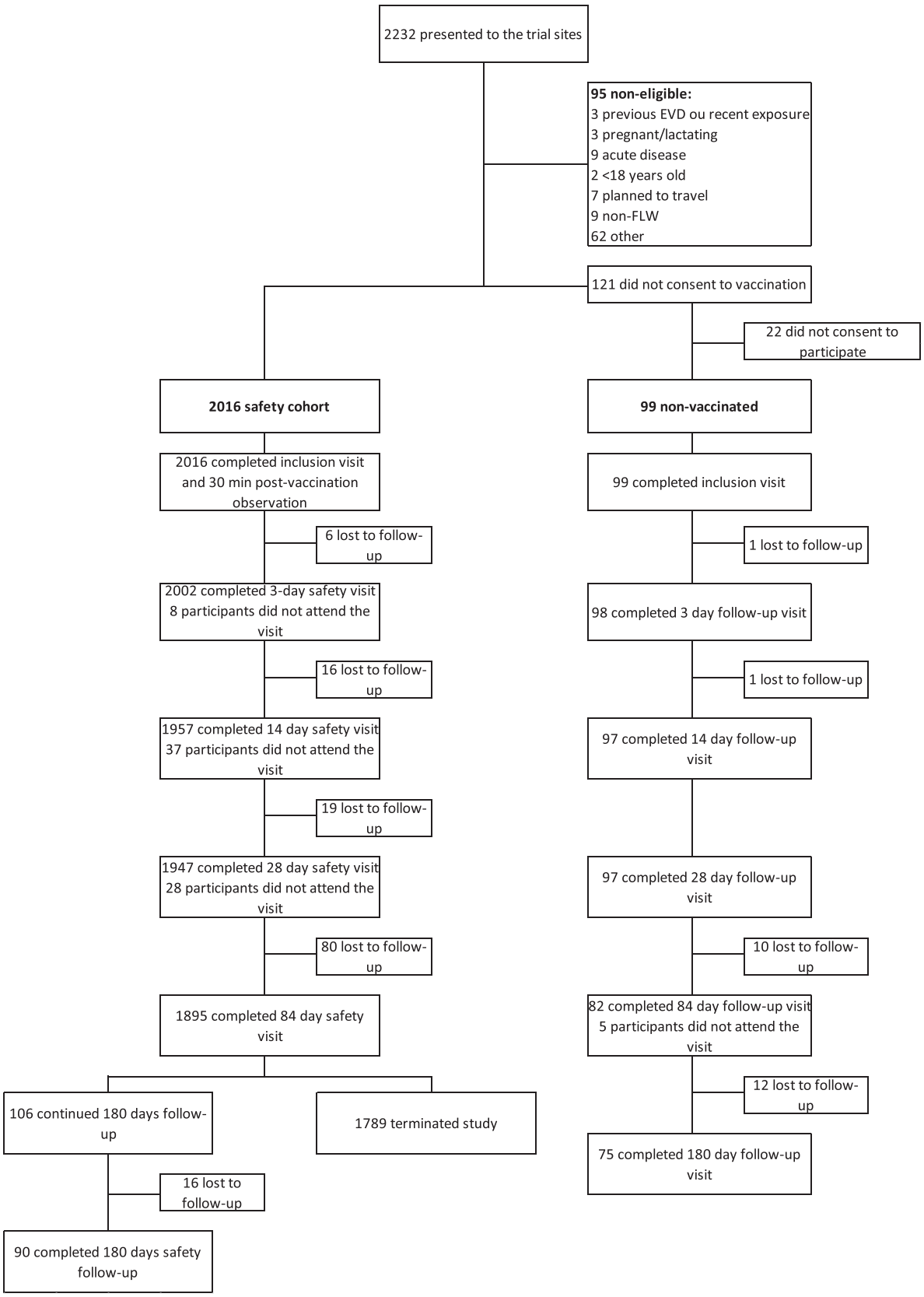

Fig. 1. Participants' flowchart.

fever, 103 (76.3%) reported fever on one day only. However, 32 (23.7%) participants reported fever on more than one day, with 20 participants reporting fever on 2 days, 10 on 3 days and 2 on 4 days. Consecutive days with fever were more often in the first 3 days following vaccination when 20 (62.5%) of the 32 participants had 2 or 3 days with temperature $\geq$38 °C.

Table 2
Total new events, first appearance and duration of the most frequently reported symptoms.

Symptom	Total	Within 24 h	1st day	2nd day	3rd to 6th day	7th to 14th day	Duration (days)		
	N (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Median	Min	Max
Headache	1049 (52.03)	378 (18.88)	574 (28.67)	51 (2.55)	15 (0.77)	31 (1.58)	2	0	35
Fatigue	921(45.68)	278 (13.89)	526 (26.27)	71 (3.55)	11 (0.56)	35 (1.79)	2	0	22
Arthralgia	501 (24.85)	135 (6.74)	282 (14.09)	47 (2.35)	12 (0.61)	25 (1.28)	2	0	22
Myalgia	491(24.36)	154 (7.69)	276 (13.79)	34 (1.70)	9 (0.46)	18 (0.92)	2	0	14
Fever/fever sensation*	482(23.91)	467 (23.33)			15 (0.77)		–		
Local reaction	234 (11.61)	131(6.54)	87 (4.35)	14 (0.70)	1 (0.05)	2 (0.10)	2	1	14
Vertigo*	79 (3.92)	65 (3.25)			14 (0.72)		–		
Back pain*	65 (3.22)	58 (2.90)			8 (0.41)		–		
Abdominal pain*	60 (2.98)	36 (1.80)			24 (1.23)		–		
Diarrhea*	48 (2.38)	6 (0.30)	17 (0.85)	10 (0.50)	5 (0.26)	10 (0.51)	1	1	11
Nausea	45 (2.23)	34 (1.70)			11 (0.56)		–		
Vomiting	38 (1.88)	7 (0.35)	17 (0.85)	7 (0.35)	3 (0.15)	4 (0.20)	1	0	2
Other	637 (31.60)	184 (9.19)	388 (19.38)	58 (2.90)	6 (0.31)	1 (0.05)	2	0	22

N = 2002 for within 24 h, 1st and 2nd day post-vaccination and 1957 for 3rd to 6th and 7th to 14th day post-vaccination.
* Unsolicited symptoms; start day and duration included in "other".

Table 3
Participants with fever by time interval.

Vaccinated	n/N	%	Median	Range	Mean	SD
Day 0	61/852	7.16	36.7	35.5–40	36.8	0.7
Day 1	74/843	8.78	36.8	35.5–39.7	36.9	0.52
Day 2	15/813	1.85	36.6	35.5–40	36.7	0.51
Days 3–6	11/751	1.46	36.5	35.5–38.9	36.6	0.51
Days 7–14	13/394	3.30	36.7	35.6–39.8	36.8	0.59

N represents participants with at least one temperature reading per day recorded in the fever diary.

A total of 423 (47.7%) participants reported having taken medication within the 14 days post-vaccination period, with 412 (47.5%) participants reporting taking medication in the first three days after vaccination and 66 (7.4%) reporting medication intake after the 3th day post-vaccination. The majority of participants, 422 (47.6%) took an antipyretic, with 278 (20.1%) taking a combination of paracetamol and ibuprofen and 122 (13.8%) taking paracetamol only. Some participants, 129 (14.5%) took an antipyretic combined with an antimalarial.

3.3. Serious adverse events

A total of 8 SAEs were detected amongst participants (Table 4). These occurred between 2 and 250 days after vaccination with a mean of 46.5 days (median = 15 days). The majority of SAEs were due to traffic accidents. There was also a cerebrovascular accident and an acute peritonitis occurring 16 and 13 days after vaccination, respectively. Two SAEs were related to pregnancy.

3.4. Pregnancy outcomes

A total of 11 women and 12 pregnancies were followed-up. Pregnancies were identified with a mean of 99.5 days (14.2 weeks) after vaccination (range = 14–160 days). Amongst the 12 pregnancies, there were 10 childbirths, 1 miscarriage and 1 stillbirth (Table 5). The childbirths, occurred at on average 40 weeks of gestation. There were no congenital malformations. Women giving childbirth were vaccinated between 0 and 68 days after their last menstrual cycle (mean = 50.1 days). The miscarriage occurred at

Table 5
Follow-up of pregnancies.

Age (years)	Days from last menstruation to vaccination	Gestational age at outcome	Pregnancy outcomes
31	0	40	Childbirth - Normal delivery
31	2	41	Childbirth - Normal delivery
30	3	41	Childbirth - Caesarian section
25	5	40	Childbirth - Normal delivery
24	34	40	Childbirth - Caesarian section
30	51	40	Childbirth - Normal delivery
29	61	38	Childbirth - Normal delivery
25	68	39	Childbirth - Normal delivery
25	83	40	Childbirth - Normal delivery
24	−34	5	Miscarriage
	68	40	Childbirth - Normal delivery
21	−37	41	Stillbirth

Table 4
Serious adverse events.

Age	Sex	Days after vaccination	SAE type	Outcome
49	F	16	Cerebrovascular accident	Resolved, with sequela
40	M	2	Traumatic brain injury after traffic accident	Died
26	M	29	Deep wound left hand, contusion of the right shoulder and knee after traffic accident	Resolved
42	M	44	Dislocated right shoulder after traffic accident	Resolved
37	M	4	Traumatic brain injury after traffic accident	Resolved
24	F	14	Spontaneous miscarriage	Resolved
42	M	13	Acute peritonitis	Resolved
21	F	252	Normal delivery of a stillborn baby	Stillbirth

5 weeks of gestation in a woman vaccinated 34 days after her last menstruation. She became pregnant 4 months later and gave birth to a healthy baby. The stillbirth occurred at term in a woman vaccinated 37 days after her last menstruation. This participant had a second stillbirth two years prior. At inclusion, these two participants were not identified as being pregnant.

4. Discussion

Similarly to previous studies [6–9], safety data collected here shows that rVSV vaccine is generally well-tolerated, with frequently reported, but mild to moderate intensity symptoms that disappear within few days.

In this study, the detection of fever, as a temperature recording, was limited to participants' reports and varied from 15% with a temperature reading $\geq$38 °C to 24% participants reporting subjective fever. These proportions are similar to those reported in the phase 1 trials using the 2×10^7 PFU dose [10,11,12] and the phase 2 conducted in Liberia [13]. Vaccine-associated fever has also been reported as one of the predominant AE in trials using chimpanzee and human adenovirus vectored vaccines, with at least 25% having fever or feverishness in several trials [13–17].

Fever, is of particular concern in the context of an Ebola outbreak, particularly where those vaccinated are contacts and at risk personnel, and fever could indicate an active infection. In this study, a risk assessment was conducted for each participant before inclusion to determine potential exposure to the Ebola virus in the previous 21 days. Moreover, participants were provided with medication and were advised to contact the on-call clinician in case of symptoms. Following the study's standard operating procedure for the management of fever, study clinicians advised participants to take medication or referred for EVD testing.

Here, none of the participants were considered as having had a recent exposure at inclusion and there were no referrals for EVD testing. Management of fever in future uses of this vaccine in areas where there is ongoing Ebola transmission would require specific protocols to differentiate between adverse events following vaccination and suspicion of Ebola. Additional information also needs to be collected to incorporate this vaccine into other personal protection protocols for healthcare and frontline workers. As we learn more about this vaccine and its performance, information about vaccine protection will provide important information about how interaction with potentially exposed and infected individuals may change for frontline and healthcare workers.

Although the number of pregnant women follow-up in this study is low, we observed that fetal exposure to rVSV led to a negative outcome. Some live vaccines can pass the placental barrier to the fetus, posing a theoretical risk [18]. Vaccines such as measles, rubella, mumps, oral polio vaccine and yellow fever are considered safe or have very low risk when administered during pregnancy. Despite this, some of these are still not recommended during pregnancy as a precautionary measure [18]. Due to the ethical issues related to potential harm to the mother and the fetus, prelicensing clinical trials usually exclude pregnant women, limiting the information available and recommendation. However, EVD infection in pregnancy is associated with a high rate of obstetric complications and poor maternal and perinatal outcomes, including spontaneous abortion, pre-term birth, fetal death and maternal and neonatal death [19]. Moreover, Ebola infection in pregnancy poses additional challenges to health services and puts health workers at risk [20,21]. In this situation, finding a preventive strategy to protect women and potentially the unborn child is essential. It is therefore critical to collect more information on the safety of the rVSV candidate vaccine among pregnant women to guide future recommendations.

5. Conclusion

This study provides additional information on adverse events following rVSV vaccination, with almost 75% of participants reporting adverse events. Events were most often reported in the first 3 days following vaccination and generally disappeared within 3–4 days. Amongst the FLW who participated in this study the most frequently reported symptoms were headache, fatigue, arthralgia, fever (subjective and objective) and myalgia. Amongst participants that kept a fever diary, temperature readings above 38 °C were recorded for 15% of participants. Fever was generally <39 °C and most frequent within the first two days after vaccination. Few SAEs were reported over the follow-up period. It is important to note that although this study was not designed to detect potentially rare events, this study provides additional information on use of rVSV in FLWs.

This study highlights the need to continue collecting safety information, particularly amongst pregnant women and other vulnerable populations excluded from the study, such as children. Additional studies should take into account the special considerations of including these populations and address the important data gaps to guide decision-making for eventual implementation.

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Author's Contributions

Initial analysis and interpretation of the data was done by AJG, JPJ, YB and RFG. The manuscript was drafted by AJG and RFG. All authors were involved in the revision of the manuscript for intellectual content and approved the final version.

Conflict of interest

The authors declare no competing interests.

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