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SUPPLEMENT ARTICLE

Monitoring Serious Adverse Events in the Sierra Leone Trial to Introduce a Vaccine Against Ebola

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The Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) was a randomized, controlled trial of rVSVΔG-ZEBOV-GP vaccine in healthcare and frontline workers during the 2014–2016 Ebola epidemic. Overall safety findings have been previously reported; there were no vaccine-related serious adverse events (SAEs). Here we describe the safety monitoring system established for STRIVE and the health conditions that resulted in reported SAEs, as well as factors affecting SAE incidence. Participants were randomized to immediate (≤7 days) or deferred (18–24 weeks later) vaccination and were monitored for safety for 6 months (immediate-vaccinated group) or until vaccination (deferred [unvaccinated] group). Once vaccinated, the latter group was termed crossover-vaccinated and monitored for 6 additional months. Of the 8577 STRIVE participants with safety follow-up data, 4172 were in the immediate-vaccinated group and 4398 were in the unvaccinated group, of whom 3787 received crossover vaccination. Overall, 143 SAEs were reported among 132 participants. Of the 143 SAEs, 130 (90.9%) resulted in hospitalization, and 24 (18.2%) participants with an SAE died. Infections were the most common SAEs; malaria was the most common single diagnosis and the most common cause of death. STRIVE built local capacity for vaccine safety monitoring in future clinical trials and research and in the national immunization program. This information about serious health conditions that resulted in hospitalization or death among a population of relatively young, healthy adults in Sierra Leone could help inform improved delivery of preventive and therapeutic health services.

Clinical Trials Registration. ClinicalTrials.gov [NCT02378753] and Pan African Clinical Trials Registry [PACTR201502001037220].

Keywords. Ebola; Ebola vaccine; serious adverse events; vaccine clinical trial

Sierra Leone was the most heavily impacted of the three West African countries during the 2014–2016 Ebola virus disease (Ebola) epidemic. After the first identified case in Sierra Leone in May 2014, the epidemic quickly spread through the country and, by September 2014, >2000 cases and 600 deaths had been reported [1]. In this setting, with a rising epidemic, the global public health community undertook unprecedented research efforts to test candidate Ebola therapeutics and vaccines [2].

The Centers for Disease Control and Prevention (CDC), in partnership with the Sierra Leone Ministry of Health and Sanitation and the College of Medicine and Allied Health Sciences (COMAHS), University of Sierra Leone, sponsored a phase 2/3 trial to assess the safety and efficacy of the rVSVΔG-ZEBOV-GP Ebola vaccine (Merck) in a high-risk adult population of healthcare and frontline Ebola response workers.

The Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) was planned and implemented under emergency conditions in a very short time frame. The main trial results are reported in this supplement: there were no cases of Ebola, so a vaccine efficacy assessment was not possible, but vaccine safety was evaluated. No vaccine-related severe adverse events (SAEs) were reported among almost 8000 vaccinated STRIVE participants, including approximately 400 participants (200 vaccinated and 200 unvaccinated) enrolled in an enhanced safety substudy in which participants were called on days 1, 3, 7, 14, and 28 to assess vaccine reactogenicity and any AEs or SAEs occurring during the first month [3]. In this article, we present a detailed description of the safety monitoring system that was established for this large clinical trial, the SAEs reported, and factors associated with reporting an SAE. Because no SAEs were vaccine related, the data provided an opportunity to describe serious health conditions and deaths that occurred in this generally healthy adult cohort in Sierra Leone.

METHODS

STRIVE Study Design, Participants, and Definitions

STRIVE was a randomized, controlled clinical trial to assess the safety and efficacy of the candidate Ebola vaccine

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(rVSVΔG-ZEBOV-GP) among adult healthcare workers and frontline Ebola response workers in Sierra Leone; no placebo was used. The trial methods have been previously described [3, 4]. In brief, the trial was conducted at 7 sites in 5 districts with high Ebola incidence. Participants who met trial criteria were randomized to receive immediate (within 7 days of enrollment) or deferred (18–24 weeks after enrollment) vaccination with a single 2×10^7 plaque-forming units dose of rVSVΔG-ZEBOV-GP vaccine. Before vaccination, the deferred vaccination group was referred to as the unvaccinated group, and after vaccination, they were referred to as the crossover-vaccinated group. Exclusion criteria included pregnancy (pregnancy testing was required for all women <50 years old), breastfeeding, and self-reported human immunodeficiency virus infection or other clinically important conditions of immunodeficiency. Participants were monitored for safety for 6 months following vaccination. Until crossover vaccination, the deferred (unvaccinated) group was also monitored from enrollment to vaccination, thereby providing contemporaneous unvaccinated-person-time on reported medical conditions for comparison to the immediate-vaccinated cohort. We analyzed SAE incidence according to the "as treated" status (see the "SAE Analysis" subsection, below), defining immediate-vaccinated participants as including both those who were randomized to the immediate group and vaccinated, as well as the few participants randomized to the deferred group who received vaccination in error before the crossover period. Similarly, we considered as unvaccinated participants those who were randomized to deferred vaccination during the period prior to crossover vaccination, as well as the small number of participants randomized to immediate vaccination who were never vaccinated.

We followed Food and Drug Administration (FDA) standards for reportable safety events, including AEs and SAEs [5]. An AE was defined as any adverse medical condition that developed after trial enrollment, regardless of its relatedness to vaccination. An AE was considered serious (ie, an SAE) if it resulted in any of the following outcomes: (1) death, (2) a life-threatening condition, (3) inpatient hospitalization or prolongation of existing hospitalization, (4) a significant disability or incapacity (defined as a substantial disruption of the ability to conduct normal life functions), or (5) a medical condition that jeopardized the participant or required intervention to prevent one of the previously listed outcomes. For participants who reported being pregnant after enrollment, congenital abnormalities in a study participant's infant were also considered SAEs; none of these occurred, and more details of pregnancy outcomes will be reported in a separate analysis [3]. Because Ebola was the efficacy outcome of interest, it was not classified as an SAE, and admissions of study participants to an Ebola facility for evaluation were not considered SAEs unless the participant was discharged to a hospital for treatment for their medical condition or if the condition met other SAE criteria.

STRIVE Safety Procedures, Reporting, and Staff

We conducted safety monitoring from 3 participant follow-up centers that served 2–3 study sites each. STRIVE study staff in these centers recorded information on AEs and SAEs reported via active and passive surveillance (Figure 1). STRIVE safety follow-up staff included >70 surveillance monitors (mainly recently graduated nurses and pharmacists), 21 study nurses, 9 part-time study physicians, 2 part-time senior physicians (a clinical director and an assistant clinical director), and the Sierra Leone principal investigator. Additional staff from the CDC and COMAHS provided onsite assistance with safety system implementation and ongoing training of the STRIVE safety follow-up staff. Representatives from 2 US-based clinical research organizations (CROs) provided external oversight of safety monitoring, data analysis, and additional onsite technical support and training in Sierra Leone and remotely from the United States.

Following enrollment, participants were given a cellular telephone with a prepaid SIM card that provided access to a closed user group to facilitate communication among STRIVE staff and participants. Participants also provided their personal cellular telephone number and those of other contacts (eg, family members) to facilitate follow-up. Study surveillance monitors conducted active surveillance by telephoning participants monthly to ask about Ebola or any new AEs, SAEs, or pregnancies. STRIVE staff made home visits if participants could not be reached after 6 call attempts during a 3-day period. Participants who reported an AE were referred to a study nurse as described below. Passive surveillance was performed via a STRIVE telephone hotline available to participants for reporting AEs 24 hours/day. At enrollment, participants were instructed to call the hotline to report any acute medical condition and the hotline staff would immediately refer the participant to a study nurse. Once study nurses received a report of an AE via the active or passive surveillance systems, they called the participant on their cellular telephone, recorded the symptoms, assessed the participant's condition, and provided initial basic treatment advice, if indicated. Study nurses referred participants to a study physician immediately if they assessed the AE to be potentially serious or during follow-up if the AE did not resolve. Study physicians provided care at designated outpatient clinics and admitted patients, as needed, to designated hospitals contracted to provide care to STRIVE participants. Nurses and physicians actively followed up participants by telephone and in person, respectively, until improvement or resolution of symptoms or death. Medical care and medications provided to STRIVE participants by the STRIVE medical staff and in designated health facilities were free of charge throughout the study. Patients also had the option to seek care at their own expense with unaffiliated physicians and health facilities.

The STRIVE staff followed standardized operating procedures and used standardized forms to document all reported AEs and SAEs. AE reporting was initiated by surveillance monitors

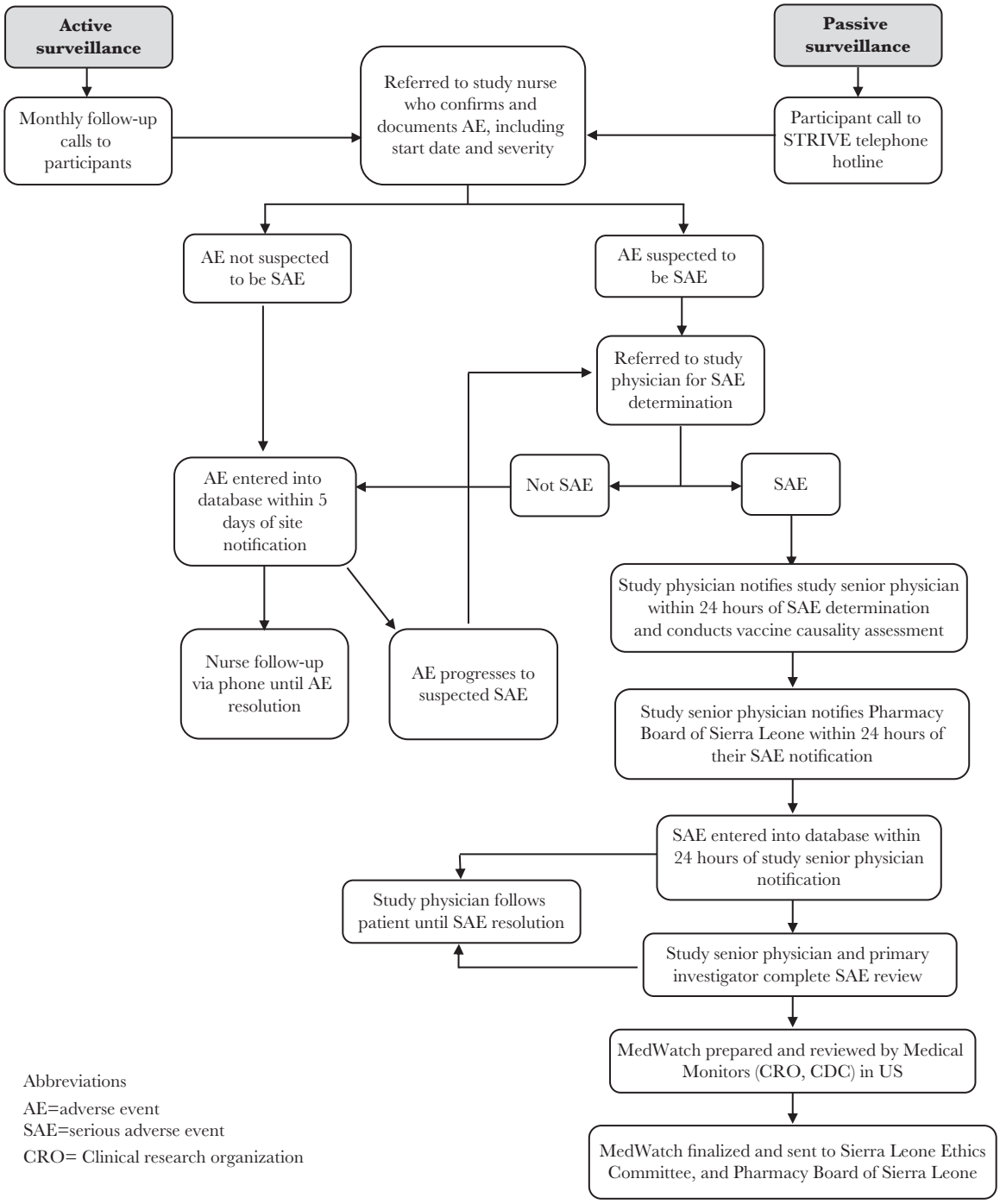

Figure 1. Safety reporting for adverse events (AEs) and serious AEs (SAEs) in the Sierra Leone Trial to Introduce a Vaccine Against Ebola.

if the event was reported during a monthly call and by study nurses if it was relayed through the hotline. Nurses reviewed and confirmed all AE reports, regardless of how the AE was initially reported, including start and end dates and AE severity (Figure 1). For any AE suspected to be an SAE, study physicians reviewed and determined whether the AE met SAE criteria, after evaluating the participant and/or reviewing clinic, hospital, or other participant records. If the participant sought medical care at unaffiliated healthcare facilities, the STRIVE study physician also reviewed medical records from that facility and, when feasible, discussed the case with the managing physician. The study physician reviewed and confirmed the start date of SAEs (which were determined by the nursing staff during initial AE reporting) and determined the end date for SAEs. The SAEs were assessed for causality (vaccine related or not related) in accordance with FDA guidance [3, 5]. The study physician who completed the SAE determination also completed the SAE reporting form. One of the 2 STRIVE senior physicians reviewed

the SAE reporting form, including evaluation of vaccine causality. The assessment was then reviewed by the local principal investigator, with a final review by the US-based medical monitor. For SAEs that resulted in death, permissions were sought for a formal autopsy. Otherwise, verbal autopsies were conducted using a modified World Health Organization verbal autopsy tool [6]. Information gathered during the autopsy was used to update the cause of death as appropriate. If a participant experienced multiple interrelated SAEs (eg, malaria, seizures, and aspiration pneumonia during a single hospitalization), the study physicians made a single unifying SAE diagnosis (eg, cerebral malaria) and documented all related complications—in this example, seizures and aspiration pneumonia—on the SAE reporting form. A participant could contribute >1 SAE to the analysis if they had SAEs that were distinct in time and/or nature.

All AE data were entered into a database in Sierra Leone and reviewed in real time by one of the CROs, who coded the diagnoses by using the *Medical Dictionary for Regulatory Activities, Version 19.0* (MedDRA) [7]. A MedWatch report (a standardized form available from the FDA that can be used for clinical trial SAE reporting) was completed for each SAE; reviewed by CDC's medical monitor for SAE criteria, severity, and causality assessment; and submitted to the Sierra Leone Ethics and Scientific Review Committee (SLESRC) and Pharmacy Board of Sierra Leone (PBSL) for review [5]. STRIVE safety data were reviewed by an independent data and safety monitoring board.

SAE Analysis

We report the analysis of safety data according to "as treated" status, rather than randomized status. We excluded participants if they did not have at least 1 safety follow-up. We described SAEs by demographic variables and by MedDRA system organ classes (SOCs) and preferred terms (PT). We present SAEs as incidence rates per 100 person-years, and to evaluate differences in SAE incidence by vaccination status, we compared SAEs between the immediate-vaccinated and unvaccinated groups. Associations were considered significant if the P value was $< .05$. We constructed univariate and multivariate Poisson regression models to assess factors associated with reported incidence of SAEs. For all models, we examined the following candidate predictors: enrollment month, study site, age, sex, ethnicity, occupation, facility type, and education level. Incidence ratios and 95% confidence intervals (CIs) are presented for each level of a predictor as compared to its reference group. Incidence ratios presented in a multivariable model are adjusted for the other predictors in the model.

Ethical Approvals

The STRIVE protocol received ethical and regulatory approvals from the SLESRC, CDC Institutional Review Board, PBSL, and FDA; the study was conducted according to good clinical practice guidelines; and all participants provided written informed consent.

RESULTS

Of the 8651 participants enrolled and randomized in STRIVE, 8577 were followed up for safety, including 4172 in the immediate-vaccinated group and 4398 in the unvaccinated group. There were 3787 participants in the unvaccinated group who received crossover vaccination, including 7 participants who contributed safety data only during their crossover period. The median age of the participants was 32 years (range, 22–56 years), 56.1% were male, and almost 75% were nurses and frontline response workers. On enrollment, most of the participants worked in Ebola facilities or hospitals. Demographic characteristics were similar for the immediate-vaccinated and the unvaccinated participants [3].

Overall, 132 participants reported SAEs: 54 (1.3%) were in the immediate-vaccinated group (median follow-up, 180 days), 32 (0.7%) were in the unvaccinated group (median follow-up, 150 days), and 47 (1.2%) were in the crossover-vaccinated group (median follow-up, 180 days; Table 1). These 132 participants reported 143 SAEs; 121 reported 1 SAE, and 11 reported 2 SAEs (6 were in the immediate-vaccinated group, 4 were in the crossover-vaccinated group; the final participant reported 1 SAE while in the unvaccinated group and 1 while in the crossover-vaccinated group). A total of 130 of 143 SAEs (90.9%), which occurred in 121 of 132 participants (91.6%), resulted in hospitalization. Death occurred in 24 of 132 participants (18.2%) with an SAE during the safety follow-up period of up to 6 months. The median age of those reporting SAEs was 32 years (interquartile range, 26–40 years), similar to the study population as a whole, and demographic characteristics were similar across the immediate-vaccinated and unvaccinated groups (Table 1).

The incidence of reported SAEs was higher among immediate-vaccinated participants than among unvaccinated participants (2.97 cases/100 person-years [95% CI, 2.26, 3.82] vs 1.94 cases/100 person-years [95% CI, 1.33, 2.72]; $P = .046$; Table 2). This largely reflects a higher reported SAE incidence during the first month among immediate-vaccinated participants (6.72 cases/100 person-years [95% CI, 4.26, 10.08] vs 2.22 cases/100 person-years [95% CI, 0.96, 4.36]; $P = .004$), as well as a higher, though less significant, SAE incidence during the third month among immediate-vaccinated participants ($P = .012$).

Among immediate-vaccinated participants, the most common SAEs as defined by MedDRA SOC were "infections and infestations," followed by "gastrointestinal disorders" (Table 2). Malaria was the most common PT reported under "infections and infestations," and hernia and peptic ulcer disease (PUD) were the most common PTs reported under "gastrointestinal disorders" (Supplementary Table 1). Among unvaccinated participants, "injury, poisoning, and procedural complications" was the most common SAE SOC group, followed by "infections and infestations" (Table 2). For "injury, poisoning,

Table 1. Baseline Demographic Characteristics of Participants in the Sierra Leone Trial to Introduce a Vaccine Against Ebola Who Reported a Serious Adverse Event, by Vaccination Status

Characteristic	Immediate Vaccinated (n = 54)	Unvaccinated (n = 32)	Crossover Vaccinated (n = 47)	Overall (n = 132)
Enrollment site, district				
COMAHS Library, Western Rural	12 (22.2)	1 (3.1)	3 (6.4)	16 (12.1)
Connaught Hospital, Western Urban	12 (22.2)	14 (43.8)	14 (29.8)	39 (29.5)
Port Loko Government Hospital, Port Loko	9 (16.7)	6 (18.8)	11 (23.4)	26 (19.7)
Saint John of God Hospital–Lunsar, Port Loko	3 (5.6)	2 (6.3)	9 (19.1)	14 (10.6)
Saint John of God Health Center–Kaffu Bullom, Port Loko	2 (3.7)	1 (3.1)	1 (2.1)	4 (3.0)
Holy Spirit Hospital–Makeni, Bombali	14 (25.9)	6 (18.8)	3 (6.4)	23 (17.4)
Magburaka Government Hospital, Tonkolili	2 (3.7)	2 (6.3)	6 (12.8)	10 (7.6)
Age, y	30 (25–36)	32 (27–39)	34 (26–45)	32 (26–40)
Sex				
Male	30 (55.6)	17 (53.1)	28 (59.6)	74 (56.1)
Female	24 (44.4)	15 (46.9)	19 (40.4)	58 (43.9)
Primary occupation				
Nurse[a]	16 (29.6)	13 (40.6)	11 (23.4)	40 (30.3)
Allied health professional[b]	2 (3.7)	1 (3.1)	0	3 (2.3)
Physician	0	1 (3.1)	0	1 (0.8)
Pharmacist	0	0	1 (2.1)	1 (0.8)
Community health worker	0	0	2 (4.3)	2 (1.5)
Laboratory worker	0	0	3 (6.4)	3 (2.3)
Frontline worker	28 (51.9)	13 (40.6)	17 (36.2)	58 (43.9)
Surveillance worker	5 (9.3)	1 (3.1)	1 (2.1)	7 (5.3)
Other/not reported	3 (5.6)	3 (9.4)	1 (2.1)	7 (5.3)
Work site				
Not currently working in a health facility	0	0	11 (23.4)	10 (7.6)
Ebola facility	18 (33.3)	8 (25.0)	10 (21.3)	36 (27.3)
Hospital	23 (42.6)	17 (53.1)	18 (38.3)	58 (43.9)
Clinic setting	9 (16.7)	6 (18.8)	8 (17.0)	23 (17.4)
Other/not reported	4 (7.4)	1 (3.1)	11 (23.4)	15 (11.4)
Education level				
None	5 (9.3)	3 (9.4)	6 (12.8)	14 (10.6)
Primary	4 (7.4)	2 (6.3)	2 (4.3)	8 (6.1)
Secondary	23 (42.6)	10 (31.3)	25 (53.2)	57 (43.2)
Tertiary	21 (38.9)	16 (50.0)	12 (25.5)	49 (37.1)
Other/not reported	1 (1.9)	1 (3.1)	2 (4.3)	4 (3.0)

Data are no. or no. (%) of participants with an SAE or median value (interquartile range).

Abbreviation: COMAHS, College of Medicine and Allied Health Sciences, University of Sierra Leone.

[a]Includes nurse, nurse aide, maternal-child health aide, nursing student, midwife, community health nurse, and vaccinator.

[b]Includes physiotherapist, dental, medical counselor, and nutritionist.

and procedural complications," although the most commonly reported PTs were head injury and joint dislocation (both 0.12 cases/100 person-years), those related to fracture (MedDRA PT codes clavicle fracture, femur fracture, foot fracture, and tibia fracture) had a combined incidence of 0.23 cases/100 person-years and accounted for almost half of the conditions in this SOC. Similar to vaccinated participants, malaria was the most common PT reported under "infections and infestations" among unvaccinated participants. Compared with unvaccinated participants, the immediate-vaccinated group had higher incidence of "infections and infestations" (1.14 cases/100 person-years [95% CI, 0.72, 1.71] vs 0.41 cases/100 person-years [95% CI, 0.17, 0.85]; $P = .011$) and a lower incidence of "injury, poisoning, and procedural complications" (0.15 cases/100 person-years [95% CI, 0.03, 0.43] vs 0.53 cases/100 person-years, [95% CI, 0.24, 1.00]; $P = .039$).

In the crossover-vaccinated group, both the overall SAE incidence and the pattern of SAEs were similar to the immediate-vaccinated group. "Infections and infestations" was the most common MedDRA SOC category, followed by "gastrointestinal disorders." Malaria and gastroenteritis were the most common PT terms in these 2 SOC categories, respectively (Table 2 and Supplementary Table 1).

Comparison of immediate-vaccinated with unvaccinated participants revealed that being vaccinated (incidence rate, 1.53 [95% CI, 1.00, 2.33]; $P = .048$) was significantly associated with

Table 2. Serious Adverse Event (SAE) Incidence Among Participants in the Sierra Leone Trial to Introduce a Vaccine Against Ebola, by Vaccination Status

Variable	Incidence, SAEs/100 Person-Years (95% CI)			
	Immediate Vaccinated (n = 4172; 2022 y)	Unvaccinated (n = 4398; 1703 y)	Crossover Vaccinated (n = 3787; 1832 y)	*P*[a]
SAE				
Any	2.97 (2.26–3.82)	1.94 (1.33–2.72)	2.73 (2.03–3.60)	.046
During mo 1	6.72 (4.26–10.08)	2.22 (.96–4.36)	3.54 (1.77–6.34)	.004
During mo 2	1.17 (.32–2.99)	1.39 (.45–3.24)	1.94 (.71–4.22)	.80
During mo 3	4.10 (2.24–6.89)	1.12 (.31–2.87)	1.62 (.53–3.79)	.012
During mo 4	2.06 (.83–4.25)	2.34 (1.01–4.62)	2.29 (.92–4.71)	.81
During mo 5	1.19 (.32–3.04)	2.58 (.95–5.62)	3.62 (1.81–6.48)	.22
During mo 6	2.50 (1.08–4.93)	3.91 (.47–14.13)	3.39 (1.63–6.23)	.59
SAE-defining criteria				
Death	0.40 (.17–.78)	0.35 (.13–0.77)	0.55 (.26–1.00)	.83
Life-threatening	0.10 (.01–.36)	0.18 (.04–0.51)	0.16 (.03–.48)	.52
Hospitalization	2.57 (1.92–3.37)	1.88 (1.29–2.65)	2.51 (1.84–3.35)	.16
Prolongation of hospitalization	0.10 (.01–.36)	…	…	.12
Significant disability or incapacity	0.05 (.00–.28)	0.23 (.06–.60)	0.16 (.03–.48)	.12
Medical event defined as SAE but did not meet above criteria	0.15 (.03–.43)	…	…	.06
MedDRA system organ class				
Blood and lymphatic system disorders	0.15 (.03–.43)	0.12 (.01–.42)	…	.80
Cardiac disorders	…	…	0.05 (.00–.30)	
Eye disorders	…	…	0.05 (.00–.30)	
Gastrointestinal disorders	0.69 (.38–1.16)	0.29 (.10–.69)	0.55 (.26–1.00)	.08
General disorders and administration site conditions	0.10 (.01–.36)	0.06 (.00–.33)	0.11 (.01–.39)	.66
Hepatobiliary disorders	…	…	0.05 (.00–.30)	
Infections and infestations	1.14 (.72–1.71)	0.41 (.17–.85)	1.04 (.62–1.62)	.011
Injury, poisoning, and procedural complications	0.15 (.03–.43)	0.53 (.24–1.00)	0.33 (.12–.71)	.039
Metabolism and nutrition disorders	0.05 (.00–.28)	0.06 (.00–.33)	…	.90
Neoplasms benign, malignant, and unspecified (including cysts/polyps)	0.15 (.03–.43)	0.35 (.13–.77)	0.05 (.00–.30)	.21
Nervous system disorders	0.15 (.03–.43)	0.06 (.00–.33)	0.16 (.03–.48)	.39
Pregnancy, puerperium, and perinatal conditions	0.05 (.00–.28)	…	…	.27
Psychiatric disorders	0.05 (.00–.28)	…	0.05 (.00–.30)	.27
Renal and urinary disorders	…	0.06 (.00–.33)	0.05 (.00–.30)	.21
Reproductive system and breast disorders	0.10 (.01–.36)	…	0.11 (.01–.39)	.12
Respiratory, thoracic, and mediastinal disorders	0.05 (.00–.28)	…	0.05 (.00–.30)	.27
Vascular disorders	0.15 (.03–.43)	…	0.05 (.00–.30)	.06

Abbreviation: MeDRA, *Medical Dictionary for Regulatory Activities, Version 19.0.*

[a]For comparison of the incidence between participants in the immediate-vaccinated and unvaccinated groups. *P* values <.05 are given to 3 decimal places.

reporting an SAE. Enrollment site ($P = .014$) was also significantly associated with reporting an SAE, with a higher incidence of SAEs reported among participants enrolled at 2 (Port Loko District and Makeni District) of the 6 rural sites as compared to the 1 urban site (Western Area Urban; Table 4). Age and sex were not associated with SAE incidence.

During STRIVE, no participants developed or died from Ebola. Of the 24 deaths that occurred during safety follow-up, 8 occurred among immediate-vaccinated participants, and 6 occurred among unvaccinated participants; an additional 10 deaths occurred in the crossover-vaccinated group (Table 3). We found no significant difference in mortality rates between immediate-vaccinated and unvaccinated participants (Table 2). By SOC, the most common cause of death was "infections and infestations" (5 cases), including 2 deaths from malaria, followed by "gastrointestinal disorders" (3 cases; Table 3). Other causes of death included injuries (2 cases), cancers (2 cases), and myocardial infarction, cerebrovascular accident, and hemorrhagic stroke (1 case each). Four deaths (3 in the immediate-vaccinated group and 1 in the crossover-vaccinated group) could not be attributed to a cause, owing to the paucity of data surrounding the circumstances of death.

DISCUSSION

STRIVE provides data on SAEs from almost 8000 adult recipients of rVSVΔG-ZEBOV-GP Ebola vaccine. As previously

Table 3. Description of Deaths Among Participants in the Sierra Leone Trial to Introduce a Vaccine Against Ebola, by MedDRA System Organ Class and Preferred Term

Variable	Immediate Vaccinated, No.[a] (n = 4172)	Unvaccinated, No. (n = 4398)	Crossover Vaccinated, No.[b] (n = 3787)
Blood and lymphatic system disorders			
Sickle cell anemia with crisis	0	1	0
Cardiac disorders			
Myocardial infarction	0	0	1
Gastrointestinal disorders			
Acute abdomen	1	0	0
Pancreatitis	1	0	0
Peptic ulcer perforation	0	1	0
General disorders not otherwise classified			
Drowning	0	0	1
Electrocution	1	0	0
Hepatobiliary disorders			
Hepatic cirrhosis	0	0	1
Infectious and infestations			
HIV wasting syndrome	1	0	0
Malaria	1	0	1
Pulmonary tuberculosis	0	1	0
Pyonephrosis	0	0	1
Injury, poisoning, and procedural complications			
Skeletal injury	0	0	1
Spinal cord injury	0	0	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Hepatocellular carcinoma	0	1	0
Nasopharyngeal cancer	0	1	0
Nervous system disorders			
Cerebrovascular accident	0	0	1
Hemorrhagic stroke	0	0	1
Renal and urinary disorders			
Renal failure	0	1	0
Unknown			
Unknown	3	0	1
Total	8	6	10

Abbreviation: HIV, human immunodeficiency virus.

[a]The median number of days from vaccination to death was 98 (range, 63–179 days).

[b]The median number of days from vaccination to death was 114 (range, 18–203 days).

reported, our comprehensive safety monitoring identified no vaccine-related SAEs [3]. These findings are consistent with other trials using this vaccine; although acute reactogenicity has been commonly reported, reports of vaccine-related SAEs have been rare among the >20 000 persons vaccinated [8–13]

The discrepancy we noted in reported SAE rates between the immediate-vaccinated and unvaccinated participants in STRIVE in the first month following enrollment and vaccination has been previously discussed and may reflect the reporting bias inherent to unblinded trials, with vaccinated participants having more concern that new health events could be associated with the vaccine in the immediate postvaccination period [3]. The higher rate of SAEs among vaccinated participants was also apparent in the third month after vaccination and, combined with the first month findings, resulted in a higher rate for the entire follow-up period.

Our study design, which involved use of a contemporaneously enrolled control group, was important in view of the dynamics of the Ebola epidemic and the seasonality of febrile illnesses including malaria. Additionally, our person-time analysis allowed direct comparison of SAE rates in the vaccinated and unvaccinated groups across their entire follow-up periods, which differed in length by 30 days, owing to the study design [4]. The finding that some rural enrollment sites had a higher reported SAE incidence may reflect differences in serious health conditions in different areas of Sierra Leone or differential changes in health-seeking behavior during STRIVE across enrollment sites. The mortality rate among STRIVE participants (4.31 cases per 1000) was somewhat lower than the 2013 mortality rates in Sierra Leone (5.62 cases per 1000 females aged 15–49 and 4.97 cases per 1000 males aged 15–49) [14], which may reflect the higher education level and health status of our

Table 4. Poisson Regression Analysis of Predictors of Reporting Severe Adverse Events Among Participants in the Sierra Leone Trial to Introduce a Vaccine Against Ebola

Variables	*P*[a]	Incidence Ratio (95% CI)
Vaccination group (vs unvaccinated)	.048	
Vaccinated		1.53 (1.00–2.33)
Enrollment month (vs Apr)	.34	
August		0.88 (.30–2.58)
July		0.50 (.19–1.32)
June		0.68 (.35–1.31)
May		0.56 (.31–1.02)
Site, district (vs Connaught Hospital, Western Urban)	.014	
COMAHS Library, Western Rural		0.78 (.36–1.69)
Port Loko Government Hospital, Port Loko		2.60 (1.32–5.11)
Saint John of God Hospital–Lunsar, Port Loko		1.82 (.64–5.18)
Saint John of God Health Center–Kaffu Bullom, Port Loko		1.89 (.62–5.73)
Holy Spirit Hospital, Bombali		2.01 (1.03–3.92)
Magburaka Government Hospital, Tonkolili		0.74 (.24–2.27)
Age, tertiled (vs 18.0–27.5 y)	.58	
27.5–35.4 y		1.01 (.61–1.68)
35.5–79.5 y		0.79 (.46–1.36)
Sex	.29	
Female (vs male)		1.34 (.79–2.28)
Occupation (vs frontline worker)	.12	
Nurse		0.80 (.39–1.63)
Allied health professional		2.10 (.71–6.22)
Physician, pharmacist, community health worker, laboratory worker		0.16 (.02–1.23)
Surveillance worker		1.27 (.52–3.08)
Other/not reported		1.16 (.48–2.83)
Work site (vs hospital)	.38	
Ebola treatment facility		0.69 (.39–1.20)
Clinic setting		0.66 (.35–1.24)
Other/not reported		0.61 (.23–1.62)
Education level (vs tertiary)	.44	
None		0.93 (.40–2.19)
Secondary		0.81 (.48–1.39)
Primary		1.07 (.41–2.76)
Other/not reported		4.23 (.97–18.54)

Abbreviations: CI, confidence interval; COMAHS, College of Medicine and Allied Health Sciences, University of Sierra Leone.

[a] *P* values <.05 are given to 3 decimal places.

study population, especially the healthcare workers, compared with the population as a whole, as well as the free medical care provided to study participants.

The SAEs reported among the STRIVE participants provide a snapshot of the serious health conditions being diagnosed and deaths occurring among a relatively young, generally healthy adult cohort in Sierra Leone. The finding that treatable infections, most often malaria, were the most common causes of serious morbidity and death in this population suggests that, for adults, improvements are needed in access to quality care, including diagnostic capability and medications, as well as education, to prevent these conditions and encourage early presentation for medical care and treatment. However, owing to limited laboratory diagnostic capacity in Sierra Leone, the accuracy of these infectious diagnoses is unknown. In the case of malaria, study physicians made the diagnosis on the basis of the presence of any malaria parasites on peripheral blood smear or positive rapid diagnostic test, or signs and symptoms consistent with malaria in the absence of a diagnostic test. If the malaria diagnoses are accurate, our data are consistent with recent data showing that infections, malaria in particular, are responsible for a high burden of disease and hospitalizations among Sierra Leonean adults and highlight the high morbidity associated with this preventable and treatable disease [15–17]. The clinical pattern of reported medical conditions that resulted in SAEs in STRIVE was similar to that reported in the Ebola vaccine trial in Liberia in which malaria accounted for 70% of the reported SAEs through 12 months of follow-up but did not result in any deaths [9].

In our trial population, hernias—mostly inguinal—were the most commonly reported gastrointestinal disorders. Although strangulated or obstructed hernias clearly required urgent medical care, the availability of free care for participants during the trial may have encouraged them to report preexisting hernias as new events to get them repaired. PUD was also reported quite frequently, but these diagnoses were not confirmed by endoscopy or other imaging study. Further studies are needed to determine the true incidence of PUD and whether other conditions are being misdiagnosed as PUD.

One of STRIVE's major accomplishments was the development and implementation of an effective Good Clinical Practice–compliant clinical trial safety monitoring system in Sierra Leone. Prior to STRIVE, the country had little experience in research or clinical trials and limited infrastructure to support vaccine safety reporting, even for routine immunizations [18]. We trained approximately 100 local staff members in vaccine safety monitoring. We conducted focused initial trainings for STRIVE safety monitoring staff on the trial's standardized operating procedures and clinical trial procedures and continued reinforcing these concepts through repeated trainings at least monthly. We held weekly staff meetings to identify and resolve issues related to data collection and logistical challenges. These meetings also ensured consistent communication and coordination among safety monitoring staff, study physicians and nurses, COMAHS, and CRO staff, as well as consistency of implementation across all the follow-up sites [19]. Study physicians met on at least a quarterly basis and benefited from remote and interactive tele-learning sessions with the safety-monitoring CRO.

Our safety results must be interpreted in light of the limitations of the data. We conducted monthly follow-up primarily by telephone rather than in person because this was the only feasible method for a trial of this size. In addition, we were unable to delineate what proportion of SAEs were reported through active versus passive surveillance, which would have helped us

to better understand which monitoring system was more effective at capturing SAEs. Study physicians had to make presumptive clinical diagnoses for many SAEs because of the limited availability of laboratory and radiographic services, especially in rural areas. Particularly for participants who died outside the hospital, verbal autopsies rarely improved the cause-of-death determination; formal autopsies would have provided information that was more accurate and reliable. Unfortunately, we were unable to obtain permission for any autopsies, for a variety of reasons, including a government rule during the Ebola epidemic mandating that bodies be buried within 24 hours of collecting a postmortem swab specimen to screen for Ebola, Muslim religious requirements for burial within 24 hours after death, and limited familiarity with autopsies, which are infrequently performed in Sierra Leone.

In summary, under challenging conditions imposed by the Ebola epidemic, we successfully built local capacity among locally trained staff members for effectively implementing safety monitoring for a clinical trial in a resource-limited country. This increased capacity can be leveraged to conduct other scientific research and clinical trials in Sierra Leone, to monitor safety following use of Ebola vaccine in an outbreak response, and to enhance capacity for vaccine safety monitoring for the Expanded Program on Immunization [18, 20]. The cellular telephone–based safety monitoring system was effective for a trial of this size conducted over a wide geographic area and in a country with very limited resources in the midst of an Ebola epidemic. The reported SAEs among almost 8000 vaccinated STRIVE participants, none of which were vaccine related, provide insight on the serious health conditions that resulted in hospitalization or death in a population of relatively young, healthy adults in Sierra Leone that could help inform improved delivery of preventive and therapeutic health services.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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