Safety of MVA-BN in Healthcare Personnel, Democratic Republic of the Congo

Faisal S. Minhaj[a]*, PharmD; Anna Mandra[a]*, DVM; Béatrice U. Nguete[b], MD; Stephanie Tran[a], MPH; Jordan L. Kennedy[a], MSPH; Benjamin Monroe[a], MPH; Christine M. Hughes[a], MPH; Taina Joseph[a], MPH; Marissa K. Person[a], MSPH; Michael B. Townsend[a], PhD; Panyampalli S. Satheshkumar[a], PhD; Toutou Likafi[c], MD; Gaston Kokola[c], MD; Joelle Kabamba[d], MD; Mary G. Reynolds[a], PhD; Agam K. Rao[a], MD; Dorah Kasongo[c], MD; Patricia A. Yu[e], MPH; Yon Yu[e], PharmD; Robert Shongo Lushima[c], MD; Didine Kaba[b], MD; Brett Petersen[a], MD; Andrea M. McCollum[a], PhD

*These authors contributed equally

[a]Division of High Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, GA, USA

[b]Kinshasa School of Public Health, Democratic Republic of the Congo

[c]Ministry of Health, Kinshasa, Democratic Republic of the Congo

[d]Centers for Disease Control and Prevention, Kinshasa, Democratic Republic of the Congo

[e]Office of Readiness and Response

Corresponding author: Faisal Minhaj, rhu5@cdc.gov

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Abstract

Background: Modified vaccinia Ankara-Bavarian Nordic (MVA-BN) is a third generation, replication-deficient, smallpox and mpox vaccine prepared in liquid and lyophilized formulations. The Democratic Republic of the Congo reports the highest number of cases of clade I mpox annually.

Methods: During the summer of 2017 and 2019, 1,600 healthcare personnel were enrolled in an investigational prospective cohort study to evaluate safety of the 2-dose MVA-BN vaccine series; 1000 were administered liquid and 600 were administered reconstituted lyophilized MVA-BN. Vaccine doses were given on study days 0 and 28 and presence or absence of adverse events were evaluated at routine follow-up appointments for up to two years.

Results: There were 49% of liquid and 54% of lyophilized formulation participants who experienced at least one adverse event within 7 days. Eighteen serious adverse events, including seventeen deaths and one stillbirth, occurred within the 2-year study period; safety monitors deemed none were causally associated with vaccine administration. Fourteen pregnancies occurred within one month of vaccination, 13 gave birth to healthy infants.

Conclusions: This study adds to the growing body of literature on the safety of MVA-BN in different populations. The data from this Congolese cohort demonstrate good safety outcomes for up to two years with both liquid and lyophilized vaccine formulations. As MVA-BN vaccination campaigns are launched in endemic and surrounding countries in late 2024 as part of clade I mpox outbreak response efforts, the data from this study supporting safety of MVA-BN in an African population are crucial to build vaccine confidence.

Trial registry number: NCT02977715

Introduction:

Mpox is caused by monkeypox virus which has two clades: clade I is found in Central Africa and is historically associated with more severe disease; clade II is found in West Africa and spread globally starting in 2022. The Democratic Republic of the Congo (DRC) is endemic for clade I MPXV and continuously reports the majority of African mpox cases, predominantly occurring in forested areas of the country. Since 2023, DRC has experienced an unusual outbreak of suspected clade I MPXV affecting provinces that previously had not reported human cases; the outbreak has further spread to neighboring countries and via travel to other continents. Healthcare personnel in DRC are known to be at least 3 times

higher risk for infection than the general population.[1] This may be due to differences in healthcare personnel training, limited resources, and lack of infection prevention and control measures.

Modified vaccinia Ankara-Bavarian Nordic (MVA-BN) or JYNNEOS® is a live, third generation vaccine licensed for smallpox and mpox prevention in the United States and does not replicate in mammalian cells.[2] MVA-BN has been studied in special populations in high income countries including persons living with HIV[3], atopic dermatitis[4], and hematopoietic stem cell transplant recipients.[5] Vaccine use in these populations was safe and well tolerated in clinical studies. Additional studies evaluated cardiac safety due to other live, replicating orthopoxvirus vaccines known association with myopericarditis.[6] MVA-BN was extensively used in high income countries throughout the global mpox outbreak that started in 2022 and passive surveillance through the Vaccine Adverse Reporting System and the Vaccine Safety Datalink supported the safety of MVA-BN in broad populations in the United States, including patients with HIV.[7,8] MVA-BN is manufactured as both a liquid and as a freeze-dried frozen formulation, however only the liquid form has been used outside of clinical trials including during the clade II global outbreak. More recently it is being used in Africa in 2024-2025 to combat the clade I outbreak. The liquid formulation is easier to use once thawed as it can be drawn up directly from the vial for administration. The lyophilized formulation must be reconstituted, adding an additional preparation step, however, it has the advantage of improved stability at refrigerated temperatures (i.e., 2-8°C).

In 2017, we initiated a study to evaluate the safety and immunogenicity of liquid and lyophilized formulations of MVA-BN within a population of healthcare personnel in Tshuapa province, DRC where clade I mpox occurs regularly (Clinicaltrials.gov registry number NCT02977715).[9] This is this first evaluation of safety of MVA-BN in a clade I endemic country where MPXV circulates naturally.

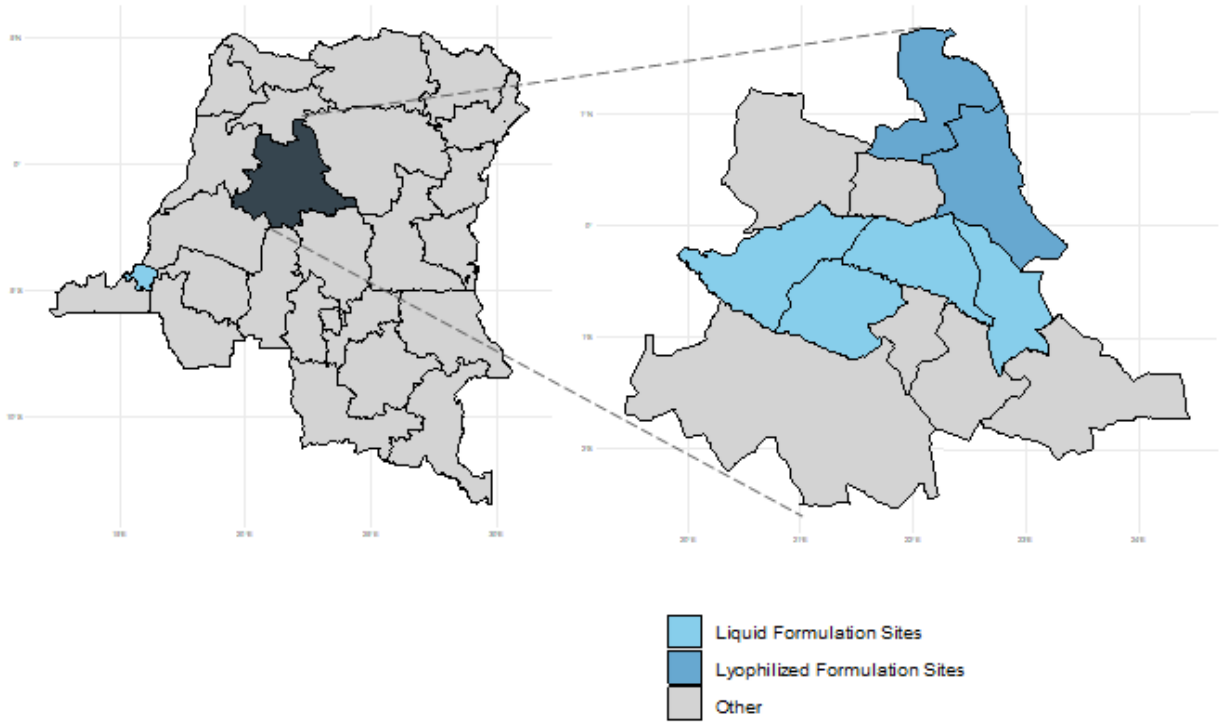
Methods and Materials:

Study design and Enrollment:

The Centers for Disease Control and Prevention (CDC), DRC Ministry of Health (MOH), and Kinshasa School of Public Health (KSPH) implemented an open-label prospective cohort study of MVA-BN in healthcare personnel at risk of mpox. The study design has been described previously and is enrolled in clinicaltrials.gov (NCT02977715).[1] Participants were followed on days 0, 14 (subset of total participants), 28, 42, 180, 365, 545, and 730. MVA-BN was administered subcutaneously as a 2-dose series on days 0 and 28 via either a liquid or lyophilized formulation; no one received a heterologous series. The liquid formulation was administered to participants from 4 health zones in Tshuapa Province and Kinshasa in 2017; and the lyophilized formulation was administered to participants in two health zones in Tshuapa

Province in 2019 (Figure 1). Participants were excluded for any of the following reasons: positive pregnancy test on the day of vaccination; previous anaphylactic reaction to a vaccine, acute illness (e.g., temperature ≥37.2 °C, self-declaration, clinician discretion); other vaccine administration in the past 28 days; involvement in a research study in the last 4 weeks; and, presence of any conditions that may have placed the participant at an unacceptable risk of injury or rendered the participant unable to meet the requirements of the protocol (e.g., lack of mental capacity to consent, inability to complete follow up).

Figure 1: Locations of study sites



The figure represents the provinces of the Democratic Republic of the Congo. Highlighted on the left are Kinshasa and Tshuapa, the primary provinces of the study. The health zones within Tshuapa province (right) and the whole province of Kinshasa (light blue on left map) are colored based on where each formulation was used.

All female study participants of potential childbearing age (<60 years) had a pregnancy test administered upon initial enrollment prior to the first and, prior to second dose administration, were advised to avoid becoming pregnant for 28 days after vaccination. Participants who reported a new pregnancy or tested positive upon a rapid pregnancy test after receipt of the first vaccine dose did not receive the second vaccine dose but were followed for all subsequent study activities.

MVA-BN is manufactured by Bavarian Nordic. The vaccine comes in single dose vials with $1X10^8$ [$TCID_{50}$] per 0.5 mL. Liquid and lyophilized formulations were used in 2017 and 2019, respectively, and the vaccine was stored, transported, and administered per manufacturer recommendations. Prior to use, the liquid formulation was thawed to room temperature, swirled for 30 seconds, and visually inspected for foreign particulate matter. The lyophilized formulation was brought to room temperature, reconstituted per manufacturer instructions, and visually inspected for foreign particulate matter. Vaccine was administered subcutaneously in the upper arm as a 2-dose series on days 0 and 28.

The protocol received human subjects' ethical and regulatory approvals from the CDC[§] and KSPH Institutional Review Boards and was authorized by the U.S. Food and Drug Administration. This study is registered in ClinicalTrials.gov under identifier NCT02977715.

Safety Data collection

Data were collected from five forms: 1) enrollment; 2) self-report of medical history; 3) visit documentation; 4) serious adverse event reporting form completed by study staff; and 5) a 7-day adverse event diary completed by the participant. The initial enrollment, self-report of medical history and visit documentation forms recorded basic demographics, medical history, vaccine administration site, lot number, and dose data. Study staff observed participants for 30 minutes after vaccination for adverse events. Nineteen local and systemic reactions were solicited and recorded on the visit documentation form as either present or absent both prior to vaccination and 30 minutes after vaccine administration. Participants were provided with an adverse event diary containing six local and 13 systemic adverse reactions to monitor for the 7 days after vaccination. Participants were given a thermometer to measure temperature and instructed to complete the form each day. Participants were asked to record if their symptoms on each day limited daily activity or required medical intervention. Although cardiac events were of particular interest, the area where this study was conducted did not allow us to perform thorough

cardiac evaluations (e.g., EKG, cardiac biomarkers). Therefore, assessment of myopericarditis was limited to reporting of chest pain symptoms in the symptom diary.

An adverse event (AE) was defined as any untoward medical occurrence associated with the use of MVA-BN, regardless of causal association with MVA-BN administration. Any AE or suspected AE was considered serious if it resulted in any of the following outcomes: death; life-threatening injury or illness; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant incapacity or a substantial disruption of the ability to conduct normal life functions; congenital abnormalities or birth defects in the offspring of the study participant; or other important medical events that may jeopardize the participant or may require intervention to prevent one of the outcomes above. AEs were graded as 1-mild, 2-moderate, or 3-serious (Supplemental Appendix S0). Any grade 3 (serious AEs) prompted investigation by a local physician and completion of the serious AE reporting form. The physician submitted the form to the principal investigators and safety monitors. A minimum of two physician safety monitors (including board-certified physicians in the United States and in DRC) independently reviewed the report and assessed the relationship between MVA-BN and the occurrence of the event.

Data were collected on paper-based study forms and entered into a secure Microsoft Access database. Any conflicts in data entry were resolved through discussion among data entry managers and study personnel.

Safety Data Analysis

RStudio version 4.0.3 was used to perform statistical analysis. All participants born in 1980 and after were considered vaccinia-naïve and those born before 1980 were conservatively considered previously immunized given routine childhood vaccination coverage with an orthopoxvirus vaccine was very high leading up to smallpox eradication in 1980. Demographic data were analyzed overall and compared by formulation. Adverse event data were analyzed and compared by formulation (overall for participants and stratified by dose) and by vaccination status stratified by formulation. Missing values were excluded in percentage calculations. Percentages were compared using chi-squared or Fisher's Exact test or by calculating odds ratios and 95% confidence intervals. P-values were considered significant at <0.05.

Results

Participant characteristics:

A total of 1600 participants were enrolled and received at least one dose of vaccine; 1000 received the liquid formulation and 600 received the lyophilized formulation. Of those administered vaccination, 1591 (99.4%) had forms returned and data available for analysis: 999 (99.9%) from the liquid formulation and 592 (98.7%) from the lyophilized formulation (Table 1). The median participant age was 45 (range 18–84) years, 68% were male, and 74% of participants considered previously vaccinated. The second vaccine dose was given to 973 (97.4%) and 570 (96.3%) participants with the liquid and lyophilized formulations, respectively. Of the 48 (3.0%) participants who did not receive the second dose, 4 (8.3%) were due to pregnancy, 8 (16.7%) due to recent tetanus vaccination, 12 (25%) due to being absent or unenrolled, and the remaining 24 (50%) were lost to follow up. Three (0.2%) additional participants were lost to follow up after the second vaccination dose.

Safety analysis:

Only four (0.2%) and one (<0.1%) of participants who received the liquid and lyophilized formulations, respectively, had any symptoms within 30 minutes of vaccine administration (Table S1). Within seven days after vaccination, participants noted similar proportions of local injection site reactions (36% and 36%) between the liquid and lyophilized formulations, respectively, but a lower proportion of systemic symptoms with the liquid (34%) compared to lyophilized (41%) formulation (Table 2). The most common injection site AEs reported included pain (24%), pruritus (13%), and edema (12%) for the liquid formulation and pain (20%), tenderness (13%), and pruritus (8.9%) for the lyophilized formulation. The most common systemic symptoms were headache (13%), fatigue (7.7%), and fever (7.5%) for the liquid formulation and headache (14%), fever (12%), and myalgia (10%) for the lyophilized formulation. Participants who received the liquid formulation had higher odds ratios for some injection site symptoms, including induration (OR 1.93 95% CI 1.26-3.04), edema (OR 1.84 95% CI 1.26-2.73), and pruritus (OR 1.54 95% CI 1.09-2.21). Participants who received the liquid formulation had lower odds ratio of any systemic symptoms (OR 0.73 95% CI 0.59-0.91), and of fever (OR 0.60 95% CI 0.42-0.86) and chills (OR 0.47 95% CI 0.30-0.74) specifically, compared to the lyophilized formulation.

Reported AEs were more frequent following dose one compared to dose two for the liquid (43% and 23%, respectively) and lyophilized (47% and 17%, respectively) vaccine products (Table 3). The liquid formulation had a higher frequency of some local injection site reactions than the lyophilized formulation. For dose 1 only, this included pruritus (9.8% vs. 5.9%, p=0.007). For dose 2 only, this included tenderness

(5.3% vs. 3.0%, p=0.042) and erythema (3.6% vs. 0.9%, p=0.002). For both dose 1 and dose 2, this included induration (7.4% vs. 4.3%, p=0.014 for dose 1 and 4.3% vs. 1.7%, p=0.007 for dose 2) and edema (9.0 vs. 5.2%, p=0.006 for dose 1 and 5.1% vs. 2.3%, p=0.008 for dose 2). The liquid formulation had a lower frequency for some systemic reactions compared to the lyophilized formulation. These included fever (4.6% vs 7.2%, p=0.026 for dose 1), chills (1.7% vs 7.1%, p<0.001 for dose 1), and myalgia (5.1% vs 9.0%, p=0.003 for dose 1). However, arm pain was reported at a higher frequency for the liquid formulation compared to the lyophilized formulation for dose 2 (1.8% vs 0.6%, p=0.049).

Most AEs were mild with either formulation. Overall, less than 5% of participants had AEs that limited activity, and less than 7% of participants had AEs requiring medical intervention, all considered a grade-2 (moderate) AE. There was a statistically significantly higher rate of medical intervention needed for participants who received dose one of the liquid formulation compared to dose two (4.5% vs 2.4%, p=0.015) however, this finding was not significant with the lyophilized formulation (3.6% vs 2.4%, p=0.091). Chest pain was reported in 3.7% vs 2.2% of participants for liquid and lyophilized formulations, respectively.

Participants who were considered previously vaccinated had a lower odds ratio of experiencing at least one symptom, regardless of formulation (OR 0.64, 95% CI 0.47-0.87 for liquid, OR 0.63, 95% CI 0.44-0.91 for lyophilized) (Table 4).

Eighteen grade 3 (serious) AEs, including seventeen deaths (rate 5.1 deaths/1,000 person-year (95% CI 1.6-10.2)) and one stillbirth were reported and investigated during the two-year study period (Table S2). Study safety monitors determined that none of the serious AEs were related to MVA-BN administration.

Pregnancies

Fourteen pregnancies occurred within 28 days of vaccine administration (Table S3). Thirteen (93%) resulted in healthy infants born at or near term (35-41 weeks) and one (7%) resulted in a stillbirth at 37 weeks gestation, reported as a serious AE, and determined by study safety monitors not to be related to MVA-BN administration.

Discussion:

This study provides data from the safety monitoring for the first field trial of MVA-BN vaccine in an endemic area of Africa. The large number of participants and duration of follow-up ensured comprehensive safety monitoring data. Among study participants, the AE frequency was 49% and 54% for liquid and lyophilized formulations, respectively. Most AEs were mild and did not require additional

212 treatment or limit activity level. Safety monitoring did not identify any serious AEs related to vaccine
213 administration.

214 Data from this study demonstrate lower rates of AEs compared to rates observed from published
215 clinical trials. Thirty-six percent of participants experienced a local vaccination site reaction for both
216 formulations and 34% and 41% of participants reported a systemic reaction with the liquid and lyophilized
217 formulations, respectively. AE rates were higher with naïve participants (58% of the liquid and 61% of the
218 lyophilized), compared to previously vaccinated participants (47% for liquid and 50% for lyophilized). In
219 comparison to the largest (n=4005) phase III clinical trials in vaccination naïve participants, the overall
220 rates of solicited local or systemic AEs were 88.6-90.6% in groups receiving MVA-BN.[10] In another study
221 with previously vaccinated participants, the rates of solicited AEs were slightly lower at 72.6-85.5% for
222 local and 33.9-43.5%, for systemic AEs.[11] AE rates reported 7 days after vaccination in a study from
223 Australia were similar to this study at 44% for local and 23% for systemic AEs.[12] However, in a study in
224 Italy, AE rates were higher, 93% with local and 48% with systemic AEs.[13]

225 There are several possible reasons for the observed decreased AE rate in our study. There may be
226 cultural differences between what would be considered an adverse reaction worth self-reporting.
227 Additionally, many diaries were not completed daily and were completed at the subsequent study visit
228 with the assistance of study staff, which may help with reporting but, also, could result in recall bias.

229 Most participants (98.6%) from this study population live and work in Tshuapa Province where MPXV
230 is endemic.[14,15] Although most of the population (74%) in this study were born before 1980 and were likely
231 previously vaccinated for smallpox, many remain at risk due to the nature of their work; 47% reported
232 having an exposure to someone with mpox previously and 38% reporting caring for someone with mpox
233 in the past. Study participants were expected to have a relatively higher level of baseline exposure to
234 OPXV then populations used during the clinical trials in Europe and the United States.[1] Studies in the
235 United States and in Europe have suggested that vaccinia naïve populations may experience higher rates
236 of AEs.[10,13,16] We similarly found that vaccinia naïve (i.e., previously unvaccinated) individuals had 1.56-
237 1.58 greater odds ratio of experiencing at least one AE.

238 Seventeen deaths were identified during the study period, the US and DRC-based study physician
239 safety monitors determined these deaths were unrelated to vaccine administration. The annual crude
240 death rate in DRC is 9.9 deaths/1,000 persons based on 2017 estimates.[17] By comparison, the annual
241 death rate among the study participants was lower than the overall country estimates at 5.1 deaths/1,000
242 persons (95% CI 1.6-10.2). The number of deaths seen in participants is not unexpected for this
243 population.

The results of this study need to be interpreted considering some limitations. The symptoms in the AE diary were self-reported and were not clinically evaluated or measured individually in terms of severity. Each symptom was asked about separately, then participants were collectively asked about limitations in activity and if medical interventions were required. There may be some residual confounding associated with adverse event rates given most patients in the previously vaccinated group were older. Secondly, access to healthcare and treatment in Tshuapa is limited. Study physicians were limited by the quality of health records and access to imaging and laboratory diagnostics to determine diagnoses when investigating SAEs. Thirdly, there were a small number of pregnant people in this study and results should be interpreted cautiously. Finally, no active surveillance for myopericarditis was conducted, such as, ECG or serial troponin levels. Therefore, participants experiencing chest pain could not be thoroughly evaluated for myopericarditis.

Conclusions

This study adds to the growing body of literature on the safety of MVA-BN in different populations. The data from the Congolese healthcare personnel cohort demonstrate good and similar safety outcomes for up to two years with both liquid and lyophilized vaccine product. The increased stability of the lyophilized formulation may help reach communities with storage and transportation challenges. Given the increase in clade I mpox and spread to surrounding countries, these data provide reassurance of the safety of this vaccine in endemic regions. As MVA-BN vaccination campaigns are launched in endemic and surrounding countries in late 2024, the data from this study supporting safety of MVA-BN in an African population are crucial to build vaccine confidence. However, continued pharmacovigilance is necessary to capture any AEs once larger populations are vaccinated.

[§]See 45 C.F.R. part 46; 21 C.F.R. part 5

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Tables

Table 1. Demographic information of study participants

Characteristic	Liquid N = 999[1]	Lyophilized N = 592[1]	Overall N = 1,591[1]	p-value[2]
Sex				0.2
Female	312 (31)	201 (34)	513 (32)	
Male	687 (69)	387 (66)	1,074 (68)	
Unknown[3]	0	4	4	
Age				**<0.001**
18-29	71 (7.1)	89 (15)	160 (10)	
30-39	238 (24)	128 (22)	366 (23)	
40-49	301 (30)	155 (26)	456 (29)	
50-59	254 (25)	151 (26)	405 (25)	
60-69	109 (11)	58 (9.8)	167 (10)	
70+	20 (2.0)	11 (1.9)	31 (1.9)	
Unknown[3]	6	0	6	
Previously Vaccinated[4]	781 (78)	389 (66)	1,170 (74)	**<0.001**
Unknown[3]	6	0	6	
History of mpox	48 (4.8)	24 (4.1)	72 (4.5)	0.5
Unknown[3]	1	1	2	

Characteristic	Liquid N = 999[1]	Lyophilized N = 592[1]	Overall N = 1,591[1]	p-value[2]
Contact with someone with mpox	442 (44)	301 (51)	743 (47)	**0.011**
Unknown[3]	1	0	1	
Cared for a patient with mpox	389 (39)	209 (35)	598 (38)	0.2
Unknown[3]	2	3	5	
Occupation				**<0.001**
Doctor	26 (2.6%)	7 (1.2%)	33 (2.1%)	
Patient Care Assistant	226 (23%)	121 (21%)	347 (22%)	
Hygienist	68 (6.8%)	50 (8.4%)	118 (7.4%)	
Laboratory technician	33 (3.4%)	7 (1.2%)	40 (2.5%)	
Midwife	137 (14%)	80 (14%)	217 (14%)	
Nurse	457 (46%)	238 (40%)	695 (44%)	
Other	37 (3.8%)	85 (14%)	122 (7.8%)	
Unknown[3]	15	4	19	
Facility				**<0.001**
Hospital	246 (26%)	146 (25%)	392 (25%)	
Health post	284 (30%)	97 (16%)	381 (25%)	

Characteristic	Liquid N = 999[1]	Lyophilized N = 592[1]	Overall N = 1,591[1]	p-value[2]
Health center	388 (40%)	301 (51%)	689 (44%)	
Other	44 (4.6%)	45 (7.6%)	89 (5.7%)	other
Unknown[3]	37	3	40	
Health Zone				N/A
Kinshasa	23 (2.3%)	-	23 (1.4%)	
Boende	305 (30.5%)	-	305 (19.2%)	
Wema	251 (25.1%)	-	251 (15.8%)	
Bokungu	257 (25.7%)	-	257 (16.2%)	
Mondombe	164 (16.4%)	-	164 (10.3%)	
Djolu	-	365 (61.7%)	365 (22.9%)	
Lingomo	-	218 (36.8%)	218 (13.7%)	
Unknown[3]	-	9 (1.5%)	9 (0.6%)	

[1]n (%)

[2]Pearson's chi-square

[3]Unknown values not included in percentage calculations

[4]Individuals born before 1980 were classified as previously vaccinated.

338 Table 2. Number of participants that reported adverse events in the 7 days following vaccination by

339 formulation[1]

340

	Symptom	Liquid N = 995[2]	Lyophilized N = 586[2]	Odds Ratio	95% CI[3]
Overall	Any symptom	488 / 995 (49%)	315 / 586 (54%)	0.83	0.67, 1.02
	Any injection site	356 / 995 (36%)	213 / 586 (36%)	0.98	0.78, 1.21
	Any systemic	335 / 995 (34%)	240 / 586 (41%)	**0.73**	**0.59, 0.91**
Injection Site	Pain	241 / 995 (24%)	120 / 586 (20%)	1.24	0.96, 1.60
Symptoms	Tender	114 / 995 (11%)	79 / 586 (13%)	0.83	0.60, 1.14
	Erythema	77 / 995 (7.7%)	30 / 586 (5.1%)	1.55	0.99, 2.49
	Induration	97 / 995 (9.7%)	31 / 586 (5.3%)	**1.93**	**1.26, 3.04**
	Edema	121 / 995 (12%)	41 / 586 (7.0%)	**1.84**	**1.26, 2.73**
	Pruritus	130 / 995 (13%)	52 / 586 (8.9%)	**1.54**	**1.09, 2.21**
Systemic	Fever	75 / 995 (7.5%)	70 / 586 (12%)	**0.60**	**0.42, 0.86**
Symptoms	Chills	42 / 995 (4.2%)	50 / 586 (8.5%)	**0.47**	**0.30, 0.74**
	Sweating	72 / 995 (7.2%)	31 / 586 (5.3%)	1.40	0.89, 2.23
	Nausea	30 / 995 (3.0%)	24 / 586 (4.1%)	0.73	0.41, 1.32
	Fatigue	77 / 995 (7.7%)	40 / 586 (6.8%)	1.14	0.76, 1.75
	Myalgia	72 / 995 (7.2%)	59 / 586 (10%)	0.70	0.48, 1.02
	Arthralgia	55 / 995 (5.5%)	32 / 586 (5.5%)	1.01	0.63, 1.64
	Headache	126 / 995 (13%)	84 / 586 (14%)	0.87	0.64, 1.18
	Dizziness	44 / 995 (4.4%)	16 / 586 (2.7%)	1.65	0.90, 3.16
	Chest pain	37 / 995 (3.7%)	13 / 586 (2.2%)	1.70	0.88, 3.52

	Symptom	Liquid N = 995[2]	Lyophilized N = 586[2]	Odds Ratio	95% CI[3]
	Shortness of breath	14 / 995 (1.4%)	9 / 586 (1.5%)	0.91	0.37, 2.41
	Arm pain	40 / 995 (4.0%)	15 / 586 (2.6%)	1.59	0.85, 3.14
	Arm swelling	32 / 995 (3.2%)	24 / 586 (4.1%)	0.78	0.44, 1.40
	Other	20 / 995 (2.0%)	12 / 586 (2.0%)	0.98	0.45, 2.22
Severity	Limit activity	35 / 995 (3.5%)	24 / 583 (4.1%)	0.85	0.49, 1.51
	Medical intervention	60 / 995 (6.0%)	32 / 582 (5.5%)	1.10	0.70, 1.77

[1]A participant was reported as having an adverse event if they recorded one after any doses of the primary series. They were only reported as not having an adverse event if they did not report any after both doses. The lyophilized formulation group is the reference for comparison.

[2]n / N (%)

[3]CI = Confidence Interval

346 Table 3. Frequency of reported adverse events in the 7 days following vaccination with MVA-BN by dose

347 and formulation

		Dose 1			Dose 2		
	Symptom	**Liquid N = 983[1]**	**Lyophilized N = 580[1]**	**p-value[2]**	**Liquid N = 948[1]**	**Lyophilized N = 533[1]**	**p-value[2]**
Overall	Any symptom	422 (43%)	273 (47%)	0.11	215 (23%)	92 (17%)	**0.014**
	Any injection site	292 (30%)	180 (31%)	0.6	141 (15%)	69 (13%)	0.3
	Any systemic	269 (27%)	195 (34%)	**0.009**	138 (15%)	68 (13%)	0.3
Injection Site Symptoms	Pain	187 (19%)	96 (17%)	0.2	88 (9.3%)	41 (7.7%)	0.3
	Tender	85 (8.6%)	67 (12%)	0.061	50 (5.3%)	16 (3.0%)	**0.042**
	Erythema	55 (5.6%)	26 (4.5%)	0.3	34 (3.6%)	5 (0.9%)	**0.002**
	Induration	73 (7.4%)	25 (4.3%)	**0.014**	41 (4.3%)	9 (1.7%)	**0.007**
	Edema	88 (9.0%)	30 (5.2%)	**0.006**	48 (5.1%)	12 (2.3%)	**0.008**
	Pruritus	96 (9.8%)	34 (5.9%)	**0.007**	52 (5.5%)	21 (3.9%)	0.2
Systemic Symptoms	Fever	45 (4.6%)	42 (7.2%)	**0.026**	36 (3.8%)	31 (5.8%)	0.073
	Chills	17 (1.7%)	41 (7.1%)	**<0.001**	28 (3.0%)	12 (2.3%)	0.4

		Dose 1			Dose 2		
	Symptom	**Liquid N = 983[1]**	**Lyophilized N = 580[1]**	**p-value[2]**	**Liquid N = 948[1]**	**Lyophilized N = 533[1]**	**p-value[2]**
	Sweating	56 (5.7%)	26 (4.5%)	0.3	22 (2.3%)	5 (0.9%)	0.056
	Nausea	21 (2.1%)	15 (2.6%)	0.6	15 (1.6%)	10 (1.9%)	0.7
	Fatigue	59 (6.0%)	34 (5.9%)	>0.9	25 (2.6%)	8 (1.5%)	0.2
	Myalgia	50 (5.1%)	52 (9.0%)	**0.003**	28 (3.0%)	11 (2.1%)	0.3
	Arthralgia	39 (4.0%)	25 (4.3%)	0.7	19 (2.0%)	7 (1.3%)	0.3
	Headache	95 (9.7%)	69 (12%)	0.2	46 (4.9%)	23 (4.3%)	0.6
	Dizziness	33 (3.4%)	12 (2.1%)	0.14	13 (1.4%)	3 (0.6%)	0.15
	Chest pain	23 (2.3%)	9 (1.6%)	0.3	18 (1.9%)	4 (0.8%)	0.080
	Shortness of breathing	9 (0.9%)	7 (1.2%)	0.6	5 (0.5%)	3 (0.6%)	>0.9
	Arm pain	27 (2.7%)	12 (2.1%)	0.4	17 (1.8%)	3 (0.6%)	**0.049**
	Arm swelling	24 (2.4%)	20 (3.4%)	0.2	9 (0.9%)	4 (0.8%)	0.8
	Other	12 (1.2%)	12 (2.1%)	0.2	9 (0.9%)	0 (0%)	**0.031**
Severity	Limit activity	23 (2.3%)	15 (2.6%)[§]	0.7	12 (1.3%)	10 (1.9%)	0.4
	Medical intervention	44 (4.5%)	21 (3.6%)[¶]	0.4	23 (2.4%)	13 (2.4%)	>0.9

*n (%), Missing forms or those lost to follow up were excluded

†Pearson's Chi-squared or Fisher's Exact test

§3 had missing values and were excluded from the percent calculations (i.e., N=577)

¶4 had missing values and were excluded from the percent calculation (i.e., N=576)

352 Table 4: Frequencies and Odds Ratios of adverse events by vaccination status[1] stratified by formulation in the 7 days following vaccination

	Liquid Formulation				Lyophilized Formulation			
Characteristic	**Previously Vaccinated N = 773[2]**	**Vaccinia Naïve N = 222[2]**	**Odds Ratio**	**95% CI[3]**	**Previously Vaccinated N = 385[2]**	**Vaccinia Naïve N = 201[2]**	**Odds Ratio**	**95% CI[3]**
Overall								
Any Symptom	360 / 773 (47%)	128 / 222 (58%)	**0.64**	**0.47, 0.87**	192 / 385 (50%)	123 / 201 (61%)	**0.63**	**0.44, 0.91**
Any Injection Symptom	254 / 773 (33%)	102 / 222 (46%)	**0.58**	**0.42, 0.79**	123 / 385 (32%)	90 / 201 (45%)	**0.58**	**0.40, 0.84**
Any Systemic Symptom	246 / 773 (32%)	89 / 222 (40%)	**0.70**	**0.51, 0.96**	148 / 385 (38%)	92 / 201 (46%)	0.74	0.52, 1.06
Injection Site Symptoms								
Pain	164 / 773 (21%)	77 / 222 (35%)	**0.51**	**0.36, 0.71**	72 / 385 (19%)	48 / 201 (24%)	0.73	0.48, 1.14
Tender	75 / 773 (9.7%)	39 / 222 (18%)	**0.50**	**0.33, 0.79**	46 / 385 (12%)	33 / 201 (16%)	0.69	0.42, 1.16
Erythema	53 / 773 (6.9%)	24 / 222 (11%)	0.61	0.36, 1.06	17 / 385 (4.4%)	13 / 201 (6.5%)	0.67	0.30, 1.53
Induration	66 / 773 (8.5%)	31 / 222 (14%)	**0.58**	**0.36, 0.94**	14 / 385 (3.6%)	17 / 201 (8.5%)	**0.41**	**0.18, 0.90**
Edema	87 / 773 (11%)	34 / 222 (15%)	0.70	0.45, 1.11	19 / 385 (4.9%)	22 / 201 (11%)	**0.42**	**0.21, 0.84**

	Liquid Formulation				Lyophilized Formulation			
Characteristic	**Previously Vaccinated N = 773[2]**	**Vaccinia Naïve N = 222[2]**	**Odds Ratio**	**95% CI[3]**	**Previously Vaccinated N = 385[2]**	**Vaccinia Naïve N = 201[2]**	**Odds Ratio**	**95% CI[3]**
Pruritus	97 / 773 (13%)	33 / 222 (15%)	0.82	0.53, 1.30	32 / 385 (8.3%)	20 / 201 (10.0%)	0.82	0.44, 1.56
Systemic Symptoms								
Fever	50 / 773 (6.5%)	25 / 222 (11%)	**0.55**	**0.32, 0.94**	51 / 385 (13%)	19 / 201 (9.5%)	1.46	0.82, 2.71
Chills	22 / 773 (2.8%)	20 / 222 (9.0%)	**0.30**	**0.15, 0.58**	32 / 385 (8.3%)	18 / 201 (9.0%)	0.92	0.49, 1.79
Sweating	52 / 773 (6.7%)	20 / 222 (9.0%)	0.73	0.42, 1.32	17 / 385 (4.4%)	14 / 201 (7.0%)	0.62	0.28, 1.39
Nausea	19 / 773 (2.5%)	11 / 222 (5.0%)	0.48	0.21, 1.14	12 / 385 (3.1%)	12 / 201 (6.0%)	0.51	0.20, 1.26
Fatigue	49 / 773 (6.3%)	28 / 222 (13%)	**0.47**	**0.28, 0.80**	24 / 385 (6.2%)	16 / 201 (8.0%)	0.77	0.38, 1.59
Myalgia	49 / 773 (6.3%)	23 / 222 (10%)	0.59	0.34, 1.03	30 / 385 (7.8%)	29 / 201 (14%)	**0.50**	**0.28, 0.90**
Arthralgia	37 / 773 (4.8%)	18 / 222 (8.1%)	0.57	0.31, 1.09	21 / 385 (5.5%)	11 / 201 (5.5%)	1.00	0.45, 2.34
Headache	86 / 773 (11%)	40 / 222 (18%)	**0.57**	**0.37, 0.88**	47 / 385 (12%)	37 / 201 (18%)	0.62	0.38, 1.02
Dizziness	38 / 773 (4.9%)	6 / 222 (2.7%)	1.86	0.77, 5.46	11 / 385 (2.9%)	5 / 201 (2.5%)	1.15	0.36, 4.29
Chest pain	24 / 773 (3.1%)	13 / 222 (5.9%)	0.52	0.25, 1.12	6 / 385 (1.6%)	7 / 201 (3.5%)	0.44	0.12, 1.55
Shortness of breath	12 / 773 (1.6%)	2 / 222 (0.9%)	1.73	0.38, 16.1	4 / 385 (1.0%)	5 / 201 (2.5%)	0.41	0.08, 1.94

Characteristic	Liquid Formulation				Lyophilized Formulation			
	Previously Vaccinated N = 773[2]	Vaccinia Naïve N = 222[2]	Odds Ratio	95% CI[3]	Previously Vaccinated N = 385[2]	Vaccinia Naïve N = 201[2]	Odds Ratio	95% CI[3]
Arm pain	24 / 773 (3.1%)	16 / 222 (7.2%)	**0.41**	**0.21, 0.85**	8 / 385 (2.1%)	7 / 201 (3.5%)	0.59	0.18, 1.94
Arm swelling	23 / 773 (3.0%)	9 / 222 (4.1%)	0.73	0.32, 1.81	7 / 385 (1.8%)	17 / 201 (8.5%)	**0.20**	**0.07, 0.52**
Other	14 / 773 (1.8%)	6 / 222 (2.7%)	0.66	0.24, 2.14	6 / 385 (1.6%)	6 / 201 (3.0%)	0.52	0.14, 1.95
Severity								
Limit activity	26 / 773 (3.4%)	9 / 222 (4.1%)	0.82	0.37, 2.03	14 / 384 (3.6%)	10 / 199 (5.0%)	0.72	0.29, 1.84
Medical intervention	40 / 773 (5.2%)	20 / 222 (9.0%)	0.55	0.31, 1.02	20 / 383 (5.2%)	12 / 199 (6.0%)	0.86	0.39, 1.97

[1]Previously Vaccinated defined as those born prior to 1980

[2]n / N (%)

[3]CI = Confidence Interval