Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in infants: a phase 2, randomised, double-blind, active-controlled trial in Guinea and Sierra Leone

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Summary

Background This study assessed the safety and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo Ebola virus (EBOV) vaccine regimen in infants aged 4–11 months in Guinea and Sierra Leone.

Methods In this phase 2, randomised, double-blind, active-controlled trial, we randomly assigned healthy infants (1:1 in a sentinel cohort, 5:2 for the remaining infants via an interactive web response system) to receive Ad26.ZEBOV followed by MVA-BN-Filo (Ebola vaccine group) or two doses of meningococcal quadrivalent conjugate vaccine (control group) administered 56 days apart. Infants were recruited at two sites in west Africa: Conakry, Guinea, and Kambia, Sierra Leone. All infants received the meningococcal vaccine 8 months after being randomly assigned. The primary objective was safety. The secondary objective was immunogenicity, measured as EBOV glycoprotein-binding antibody concentration 21 days post-dose 2, using the Filovirus Animal Non-Clinical Group ELISA. This study is registered with ClinicalTrials.gov (NCT03929757) and the Pan African Clinical Trials Registry (PACTR201905827924069).

Findings From Aug 20 to Nov 29, 2019, 142 infants were screened and 108 were randomly assigned (Ebola vaccine n=75; control n=33). The most common solicited local adverse event was injection-site pain (Ebola vaccine 15 [20%] of 75; control four [12%] of 33). The most common solicited systemic adverse events with the Ebola vaccine were irritability (26 [35%] of 75), decreased appetite (18 [24%] of 75), pyrexia (16 [21%] of 75), and decreased activity (15 [20%] of 75). In the control group, ten (30%) of 33 had irritability, seven (21%) of 33 had decreased appetite, three (9%) of 33 had pyrexia, and five (15%) of 33 had decreased activity. The frequency of unsolicited adverse events was 83% (62 of 75 infants) in the Ebola vaccine group and 85% (28 of 33 infants) in the control group. No serious adverse events were vaccine-related. In the Ebola vaccine group, EBOV glycoprotein-binding antibody geometric mean concentrations (GMCs) at 21 days post-dose 2 were 27 700 ELISA units (EU)/mL (95% CI 20 477–37 470) in infants aged 4–8 months and 20 481 EU/mL (15 325–27 372) in infants aged 9–11 months. The responder rate was 100% (74 of 74 responded). In the control group, GMCs for both age groups were less than the lower limit of quantification and the responder rate was 3% (one of 33 responded).

Interpretation Ad26.ZEBOV and MVA-BN-Filo was well tolerated and induced strong humoral responses in infants younger than 1 year. There were no safety concerns related to vaccination.

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See **Comment** page e1672

For the French translation of the abstract see **Online** for appendix 1

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Introduction

Since the discovery of Ebola virus disease (EVD) in 1976, more than 30 outbreaks have been reported, mostly in west and central Africa, where the disease is endemic.[1–3] The two largest outbreaks occurred in west Africa in 2014–16, which led to 28 652 cases and 11 325 deaths, and in eastern Democratic Republic of the Congo and Uganda in 2018–20, which resulted in 3470 cases and 2287 deaths.[2,4] During these two outbreaks, roughly 20–30% of the cases were in children younger than 18 years.[5,6] Mortality rates in the west African outbreak were 42–63% in children younger than 18 years and 73–86% in children younger than 5 years.[7]

EVD is caused by the Ebola virus (EBOV; species Zaire ebolavirus) and is mainly transmitted by direct human-to-human contact or contact with infected bodily fluids or contaminated surfaces.[3] Young children appear to be at risk of infection through contact with household members, relatives, and other caregivers.[8] Moreover, young children have a more rapid clinical progression

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Research in context

Evidence before this study

Ebola virus disease (EVD) is a major global health problem. In the 2014–16 EVD outbreak in west Africa, nearly 20% of cases were in children younger than 15 years, and mortality rates were higher in infants and children younger than 5 years than those in older children. Currently, two Ebola vaccines have been prequalified by WHO: the replication-competent, live virus-vectored rVSVΔG-ZEBOV-GP vaccine and the replication-incompetent, heterologous, two-dose Ad26.ZEBOV and MVA-BN-Filo vaccine regimen. We searched PubMed for clinical trials published from database inception to June 9, 2022, using the search terms "Ebola virus" and "vaccine" with no language restrictions. The search yielded 51 results that were then manually screened for relevance. Among these, we identified five Ebola vaccine trials conducted in paediatric participants: two rVSVΔG-ZEBOV-GP trials conducted in participants aged 6–17 years; two Ad26.ZEBOV and MVA-BN-Filo trials conducted in participants aged 4–17 years and 1–17 years, respectively; and one trial of the ChAd3-EBO-Z investigational vaccine conducted in participants aged 1–17 years. We did not identify any Ebola vaccine studies in infant populations (younger than 1 year).

Added value of this study

To our knowledge, EBL2005, a randomised, double-blind, active-controlled, phase 2 study, is the first trial to evaluate the safety and immunogenicity of the two-dose, heterologous Ebola virus vaccine regimen (Ad26.ZEBOV and MVA-BN-Filo) in infants aged 4–11 months, enrolled in Guinea and Sierra Leone. Infants are at risk of EVD if their primary caregivers become infected and, as a group, suffer high mortality rates (90% in infants younger than 1 year). We found that the vaccine regimen was well tolerated, and the safety profile was characterised by mild-to-moderate adverse events. There were no serious adverse events related to the vaccines. The Ad26.ZEBOV and MVA-BN-Filo vaccine regimen induced strong immune responses, measured by Ebola virus glycoprotein-binding antibody concentrations, in all infants 21 days after administration of the second dose. These humoral responses persisted for at least 12 months after the first dose.

Implications of all the available evidence

To date, no Ebola vaccine regimen has been evaluated in infants younger than 1 year. This study's results are consistent with those from previous trials of Ad26.ZEBOV and MVA-BN-Filo in older paediatric populations, which demonstrated acceptable safety and immunogenicity profiles. In 2021, the Strategic Advisory Group of Experts on Immunization to the WHO recommended the off-label use of this vaccine regimen in infants and children from birth to 17 years of age in outbreak settings. In addition to its approved use by the European Commission in children aged 1 year or older, the current study results could support the use of Ad26.ZEBOV and MVA-BN-Filo in infants aged 4–11 months.

and a higher risk of death than older children, especially those younger than 5 years.[9,10] Therefore, there is a crucial need for effective vaccines against EVD in young children.

Since the west African EVD outbreak, increased numbers of EBOV vaccine candidates have entered late-phase clinical development.[2] The live, attenuated, single-dose vaccine rVSVΔG-ZEBOV-GP (Ervebo, Merck & Co, Whitehouse Station, NJ, USA) and the heterologous, two-dose Ad26.ZEBOV and MVA-BN-Filo vaccine regimen (Zabdeno and Mvabea, Janssen Pharmaceutica, Beerse, Belgium) have been prequalified by WHO.[11–13] The rVSVΔG-ZEBOV-GP vaccine has received approval from the US Food and Drug Administration and conditional marketing authorisation from the European Medicines Agency (EMA) for use in people aged 1 year or older,[14,15] and the Ad26.ZEBOV and MVA-BN-Filo regimen was authorised under exceptional circumstances by the EMA for prophylactic use in people aged 1 year or older.[16] The favourable safety profile and induction of strong humoral immune responses by Ad26.ZEBOV and MVA-BN-Filo in children aged 1 year or older were demonstrated by Afolabi and colleagues.[17]

Since 2021, the Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the off-label use of the rVSVΔG-ZEBOV-GP vaccine and the partial off-label use of the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in an outbreak setting for infants and children from birth to 17 years and emphasised the need to collect additional safety data in these populations.[18] In this study, we report the results of the first-in-infant trial of an Ebola vaccine, which evaluated the safety and immunogenicity of the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen in infants younger than 1 year.

See Online for appendix 2

Methods

Study design

This randomised, double-blind, active-controlled, phase 2 study was performed at two clinical sites in west Africa: Conakry, Guinea, and Kambia, Sierra Leone. The protocol was approved by independent ethics committees or institutional review boards as listed in appendix 2 (p 6). Changes to the protocol made after the study began, along with rationale, are summarised in the protocol. After the main study (reported in this Article) ended, the protocol was updated to add an extension phase to offer the Ebola vaccine to the infants in the control group. The trial was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines and local regulations. The protocol can be found in appendix 2 (pp 12–88).

Participants

Eligible participants were healthy infants aged 4–11 months (ie, ≥4 months and <12 months) who had received all

routine immunisations appropriate for their age in accordance with their respective national guidelines and who had normal haemoglobin concentration, normal platelet counts, and normal white blood cell counts at screening. If laboratory screening test results were out of range and deemed clinically significant, a repeat screening test to assess eligibility was permitted once during the screening period. Main exclusion criteria comprised any history of EVD or previous exposure to EBOV, previous receipt of an Ebola vaccine or experimental Ad26-based or MVA-based candidate vaccine, previous receipt of a blood transfusion or other blood products within 8 weeks of screening, known allergy or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine products, and having been vaccinated with any live-attenuated vaccine within 30 days before the first study vaccination and with any inactivated vaccine within 15 days before the first study vaccination. The full list of inclusion and exclusion criteria is available in the protocol (appendix 2 pp 41–43) and was verified before enrolment. All parents and guardians provided written informed consent for their infant to participate. Additional details on study recruitment are provided in appendix 2 (p 6).

Within each country, infants were stratified by age group (≥4 to ≤8 months and >8 to <12 months) to support balanced inclusion of younger and older infants in each vaccine group. Enrolment started with vaccination of a sentinel cohort of 16 infants before exposing the remainder of the infants to the study vaccines.

Randomisation and masking

Infants were randomly assigned (1:1 for the 16 sentinel infants and 5:2 for the remaining infants) to receive either the two-dose Ad26.ZEBOV and MVA-BN-Filo vaccine regimen (Ebola vaccine group) or a WHO-prequalified meningococcal group A, C, W135, and Y conjugate vaccine (MenACWY) active control (control group). MenACWY was chosen as the control instead of placebo to offer clinical benefit to participants in the control group.

Randomisation was done centrally using randomly permuted blocks, with a block size of four for the sentinel cohort and seven for the remainder of the infants (schedule prepared before the study by the study sponsor or under the sponsor's supervision), and stratified by country and age group. This was achieved via an interactive web response system provided by Signant Health (Blue Bell, PA, USA). Study infants, their parents and guardians, and all study team members (except for an unmasked team, which included an independent study intervention monitor and pharmacist or other qualified pharmacy staff members who prepared the vaccines at each site) were masked to study vaccine allocation. All dispensing syringes containing the vaccine allocated to each infant contained the same volume and were taped by the unmasked team to conceal the colour of the liquid inside. Additional details on randomisation and masking are described in appendix 2 (p 6).

Enrolment started with vaccination of the sentinel cohort. First, eight sentinel infants were randomly assigned 1:1 to receive the Ebola vaccine or control vaccine. In the absence of safety concerns, another eight infants (randomly assigned 1:1) were enrolled to complete the sentinel cohort of 16 infants. When the last infant in the sentinel cohort completed the 7 days post-vaccination safety visit, an independent data monitoring committee (IDMC) reviewed all available data and recommended continuing vaccination of the remaining infants. At 56 days post-dose 1, the sentinel cohort was given post-dose 2 and the IDMC repeated the safety review process. This IDMC was instituted before study commencement and periodically reviewed safety data to ensure progressive safety of the infants.

Procedures

Infants in the Ebola vaccine group received Ad26.ZEBOV (5×10^{10} viral particles) on day 1 of the first dose, followed by MVA-BN-Filo (1×10^{8} infectious units) on day 57. Ad26.ZEBOV is a monovalent, replication-incompetent, Ad26 vector-based vaccine encoding the Zaire EBOV Mayinga glycoprotein, and MVA-BN-Filo is a multivalent, recombinant, non-replicating, modified vaccinia virus Ankara strain (Bavarian Nordic, Kvistgård, Denmark) encoding the Zaire EBOV glycoprotein, Sudan virus Gulu variant glycoprotein, Marburg virus Musoke glycoprotein, and Taï Forest virus nucleoprotein. Those in the control group received MenACWY on days 1 and 57. In keeping with the recommended immunisation regimen for this meningococcal vaccine, all infants received a dose of MenACWY at the 6-month post-dose 2 visit (day 237 [ie, during their second year of age]). Following randomisation and first vaccination (day 1) infants were followed up for a year through seven follow-up visits (day 8+1 day, day 29±7 days, day 57±7 days, day 64+1 day, day 78±7 days, day 237±30 days, and day 365±30 days) onsite.

Details on vaccine preparation and reconstitution are provided in appendix 2 (p 7). A masked vaccinator administered the first vaccination as a 0·5 mL intramuscular injection into the anterolateral thigh. The second vaccination was administered into the opposite thigh from the first vaccination, if possible. After each vaccination, infants were directly observed for 30 min at the trial site for the presence of any acute reactions, or longer if deemed necessary by the investigator. Upon discharge from the site, parents and guardians were provided with and trained to use a thermometer, a ruler (to measure local injection-site reactions), and a diary (to record body temperature and solicited local [at the injection site] and systemic symptoms). During the first 7 days after each vaccination, a trained field assistant visited infants daily at their home to collect data on local and systemic adverse events using the purpose-designed diary card. Infants came to the site 7 days after the first and second vaccinations (days 8 and 64), where the diary was reviewed. From day 8 until day 57 and from day 64 until the end of

follow-up, adverse events were captured by onsite study physicians using a standardised case report form. Unsolicited adverse events were reported from the first vaccination until 28 days after dose 1 (day 29) and from the second vaccination until 28 days after dose 2 (day 85). Serious adverse events were continuously reported until 6 months after the second dose, except for those related to study procedures, which were reported until the end of the study. Details on safety monitoring and adverse event grading are described in appendix 2 (p 6). A list of contraindications to dose 2 is provided in the protocol.

Venous blood samples (1·0 mL) for laboratory safety assessments were collected at the screening visit and on day 57, immediately before vaccination. Venous blood samples (2·0–2·5 mL) for the determination of immune responses were collected at screening and on days 78 and 365.

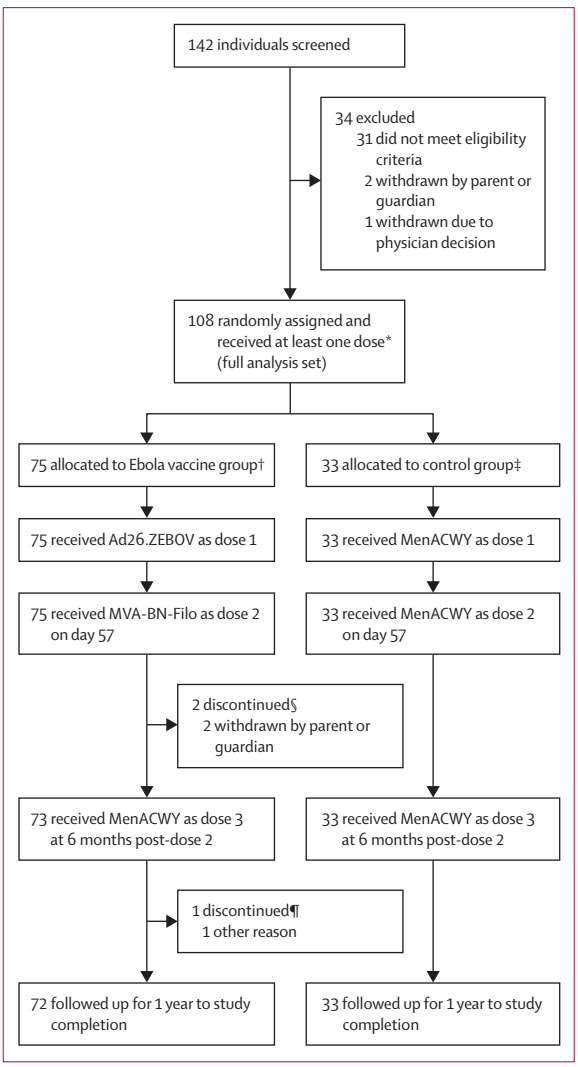

Figure 1: **Trial profile**
MenACWY=meningococcal group A, C, W135, and Y conjugate vaccine. *Includes the 16 infants in the sentinel cohort. †43 infants were in the 4–8 months subgroup and 32 were in the 9–11 months subgroup. ‡19 infants were in the 4–8 months subgroup and 14 were in the 9–11 months subgroup. §Both infants were in the 4–8 months subgroup. ¶This infant was in the 4–8 months subgroup and did not complete all study evaluations due to travel to another country.

EBOV glycoprotein-specific binding antibody responses were measured by the EBOV glycoprotein Filovirus Animal Non-Clinical Group (FANG) ELISA (Q² Solutions, San Juan Capistrano, CA, USA) at baseline (screening visit), 21 days post-dose 2 (day 78), and 12 months post-dose 1 (day 365). The presence of neutralising antibodies against the adenovirus vector was measured at baseline using an Ad26 virus neutralisation assay (VNA; Janssen Clinical Immunology Laboratory, Leiden, Netherlands).

Outcomes

The primary objective was safety and reactogenicity, measured as the occurrence of solicited local and systemic adverse events during a 7-day follow-up period after each vaccination, unsolicited adverse events during a 28-day follow-up period after each vaccination, and any serious adverse events until 6 months post-dose 2 and serious adverse events related to study intervention until the end of the study. The reactogenicity of the study vaccines (defined as solicited local and systemic adverse events that are common and known to occur after vaccination) was assessed by investigators masked to allocation. The secondary objective was immunogenicity, measured by the EBOV glycoprotein-specific binding antibody response using FANG ELISA at 21 days post-dose 2.

The exploratory objectives included measurements of EBOV glycoprotein-specific binding antibody response using FANG ELISA at baseline and 12 months post-dose 1, and neutralising antibody response to the adenovirus vector using Ad26 VNA at baseline.

Safety blood tests were performed at the local laboratories using the same reference ranges. For vaccine safety, adverse event grading was performed locally by site investigators according to the same grading scale for consistency. Seriousness and causality assessments of adverse events were done by local site investigators according to the protocol. For vaccine immunogenicity, all samples were tested centrally.

Statistical analysis

The sample size was not based on formal hypothesis testing considerations. Active control recipients were included for masking and safety analyses and provided control samples for immunological testing. The target overall size of 107 infants (73 to receive Ebola vaccine and 34 to receive control vaccine) was expanded the safety and immunogenicity database for the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen to infants. Although mild-to-moderate vaccine reactions were expected, adverse events that might preclude administration of the second dose or lead to study pause or more serious events that would limit the product development were not anticipated. If 73 infants were vaccinated with Ad26.

ZEBOV and MVA-BN-Filo, we calculated that the observation of no such reactions would be associated with a 95% confidence that the true rate is less than 4·0%.

No formal statistical testing of safety data was planned. Safety data were analysed descriptively per intervention group. Data from both countries were pooled for analysis. The study data are presented per age subgroup (≥4 to ≤8 months and >8 to <12 months) as well as pooled. All statistical analyses were done using SAS (version 9.4).

Infants were analysed according to the actual intervention received. The full analysis set includes infants vaccinated with one dose or more. The per-protocol immunogenicity population includes all randomly assigned and vaccinated infants for whom immunogenicity data were available, excluding infants with major protocol deviations expected to impact the immunogenicity outcomes.

Baseline characteristics are presented with summary statistics per vaccine intervention group. Binding antibody responses against EBOV glycoprotein are shown as geometric mean concentrations (GMCs) with 95% CIs, and responder rates. All values less than the lower limit of quantification (LLOQ) were imputed with half of the corresponding LLOQ, and values above the upper limit of quantification (ULOQ) were imputed with the ULOQ. Responder rates with exact 95% Clopper-Pearson CIs are also shown. Responders were defined as those with either a negative ELISA result at baseline and a positive post-baseline value greater than 2·5 times the LLOQ, or a positive result at baseline with a post-baseline value greater than a 2·5-fold increase from the baseline value. Neutralising antibody activity is shown as geometric mean titres (GMTs).

This study is registered with ClinicalTrials.gov (NCT03929757) and the Pan African Clinical Trials Registry (PACTR201905827924069).

Role of the funding source

The Innovative Medicines Initiative had no role in the study design, data collection, analysis, interpretation, or writing of the report. Janssen Vaccines & Prevention, the study sponsor, had a role in the study design, data collection, analysis, interpretation, and writing of the report.

Results

The EBL2005 study started recruiting infants on Aug 20, 2019, and enrolment was completed on Nov 29, 2019. The database cutoff for the current analysis was on Dec 8, 2020. The total number of infants screened and included, and the reasons for exclusion, are presented in figure 1. The demographic and baseline characteristics of the study infants by age subgroup are summarised in table 1. Of the 108 randomly assigned infants in the full analysis set, 62 (57%) were aged 4–8 months and 46 (43%) were aged 9–11 months; 55 (51%) were enrolled in Sierra Leone and 53 (49%) were enrolled in Guinea. Infants in the Ebola vaccine and control groups were generally similar and comparable in age, sex, weight, and height. In the control group, when stratified by age, there were more boys than girls in the 4–8 months subgroup (14 [74%] of 19 infants were boys and five [26%] were girls); however, this was not expected to affect the study results.

Overall, all 108 randomly assigned infants received the study vaccine, with 75 (69%) allocated to the Ebola vaccine group and 33 (31%) allocated to the control group. The sentinel cohort of the first 16 infants was vaccinated in Sierra Leone. In the Ebola vaccine group, all 75 infants received the complete Ebola vaccine regimen, Ad26.ZEBOV as dose 1 and MVA-BN-Filo as dose 2; 73 of these infants also received MenACWY as dose 3 at 6 months post-dose 2 according to the protocol and 72 completed 1 year of follow-up until study completion. The three missing infants for MenACWY vaccination or at 1 year were in the 4–8 months subgroup and their participation was discontinued due to parent or guardian withdrawal or their unavailability due to travel. In the control group, all 33 infants received three doses of MenACWY and completed the study. Overall, 105 (97%) of 108 infants completed the study.

The safety and reactogenicity assessments were performed on 108 vaccinated infants in the full analysis set. The Ebola vaccine regimen was well tolerated. There were no safety concerns related to vaccination. The reactogenicity profile comprised mild-to-moderate adverse events (grade 1 or 2). Overall, 50 (67%) of

	Ebola vaccine group			Control group			Total (N=108)
	Age 4–8 months (n=43)	Age 9–11 months (n=32)	Age 4–11 months pooled (n=75)	Age 4–8 months (n=19)	Age 9–11 months (n=14)	Age 4–11 months pooled (n=33)	
Age at random assignment, months	6 (5–7)	10 (10–11)	7 (5–10)	5 (4–6)	10 (10–11)	7 (5–10)	7 (5–10)
Sex							
Female	19 (44%)	18 (56%)	37 (49%)	5 (26%)	8 (57%)	13 (39%)	50 (46%)
Male	24 (56%)	14 (44%)	38 (51%)	14 (74%)	6 (43%)	20 (61%)	58 (54%)
Weight, kg	7·1 (6·7–7·8)	8·5 (7·7–9·4)	7·6 (7·0–8·5)	7·8 (7·1–8·4)	8·5 (7·3–8·8)	8·0 (7·2–8·6)	7·7 (7·1–8·5)
Height, cm	66 (64–67)	73 (72–74)	67 (65–72)	66 (64–68)	72 (71–73)	69 (66–72)	68 (66–72)

*Data are presented as median (IQR) or n (%).

Table 1: **Demographic and baseline characteristics of study infants (full analysis set)***

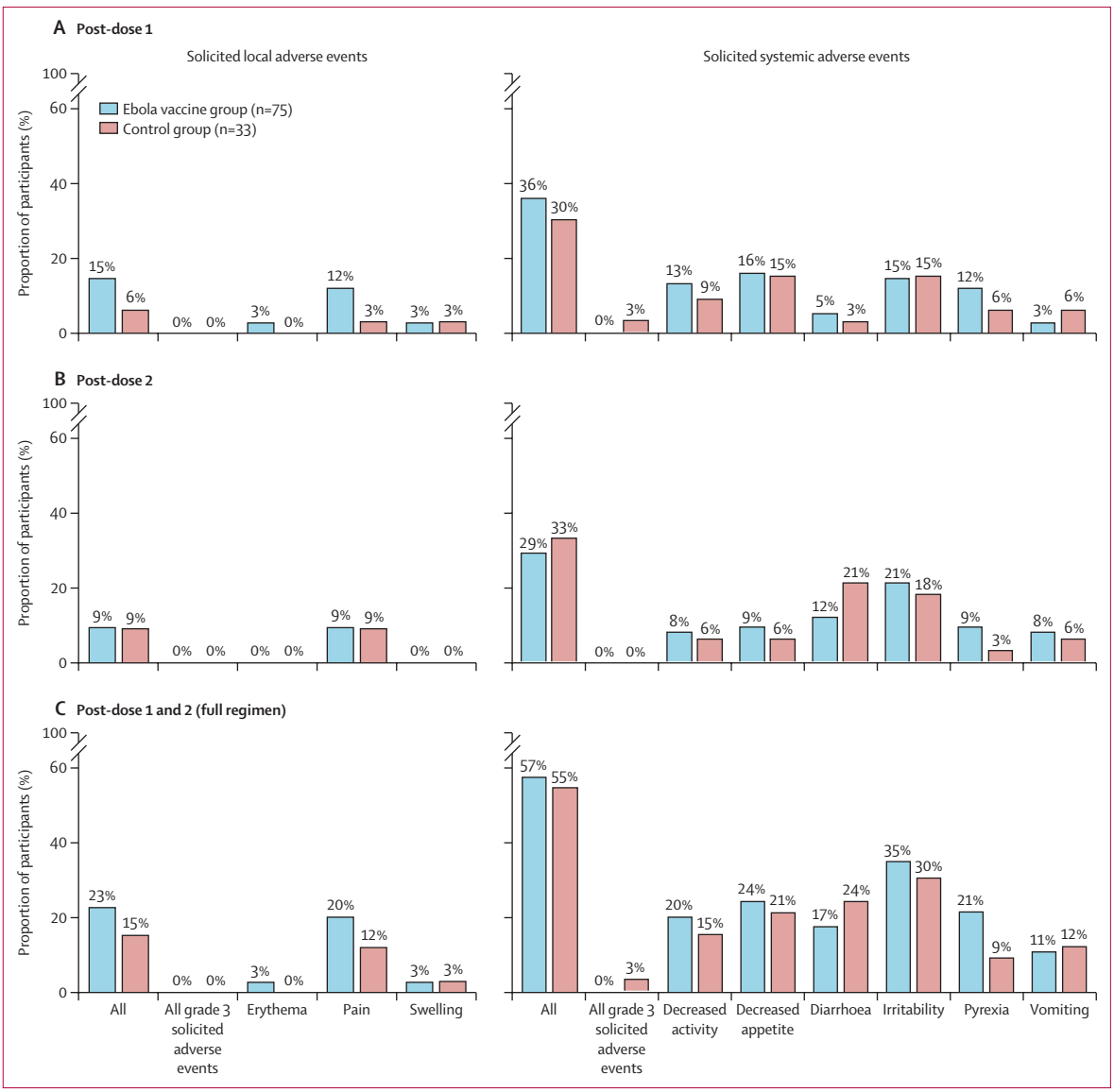

Figure 2: **Solicited local and systemic adverse events after vaccination among infants overall**
For the Ebola vaccine group, dose 1 was Ad26.ZEBOV and dose 2 was MVA-BN-Filo. For the control group, dose 1 was MenACWY and dose 2 was MenACWY. Solicited local and systemic adverse events were collected daily for 7 days after dose 1 and dose 2 vaccinations and are reported post-dose 1 (A), post-dose 2 (B), and post-dose 1 and 2 (C; full regimen) among infants overall (aged 4–11 months pooled). Data labels above each bar are rounded to the nearest whole number. MenACWY=meningococcal group A, C, W135, and Y conjugate vaccine.

75 infants in the Ebola vaccine group and 19 (58%) of 33 in the control group experienced one solicited adverse event or more. The most common solicited local adverse event was injection-site pain, which occurred in 15 (20%) of 75 infants in the Ebola vaccine group and in four (12%) of 33 in the control group. The most common solicited systemic adverse events in the Ebola vaccine group were irritability (26 [35%] of 75), decreased appetite (18 [24%] of 75), pyrexia (16 [21%] of 75), and decreased activity (15 [20%] of 75). In the control group, these solicited systemic adverse events were recorded in ten (30%) of 33 infants for irritability, seven (21%) of 33 for decreased appetite, three (9%) of 33 for pyrexia, and five (15%) of 33 for decreased activity. A detailed breakdown of the solicited local and systemic adverse events observed after dose 1, dose 2, and the full regimen for the overall study population is presented in figure 2 and in different age subgroups in appendix 2 (pp 8–9). In the Ebola vaccine group, a greater proportion of infants experienced solicited adverse events (34 [45%] of 75), solicited systemic adverse events (27 [36%] of 75), and solicited local adverse events (11 [15%] of 75) after dose 1 (Ad26.ZEBOV) administration compared with dose 2 (MVA-BN-Filo) administration (25 [33%] of 75 for solicited adverse events,

22 [29%] of 75 for solicited systemic adverse events, and seven [9%] of 75 for solicited local adverse events).

Within 7 days of administration of either dose, there were no grade 3 solicited adverse events in the Ebola vaccine group and one grade 3 adverse event of pyrexia in the control group. According to the protocol, all solicited local adverse events were considered vaccine-related. 20 (27%) of 75 infants in the Ebola vaccine group and five (15%) of 33 in the control group experienced at least one solicited systemic adverse event that was considered related to the study vaccine.

In the Ebola vaccine group, 62 (83%) of 75 infants experienced at least one unsolicited adverse event within 28 days of vaccination (46 [61%] of 75 after Ad26.ZEBOV and 43 [57%] of 75 after MVA-BN-Filo). At least one unsolicited adverse event within 28 days of vaccination occurred in 28 (85%) of 33 infants in the control group (22 [67%] of 33 post-dose 1 and 24 [73%] of 33 post-dose 2). The most commonly observed (occurring in ≥15%) unsolicited adverse events in the Ebola vaccine group were respiratory tract infection (15 [20%] of 75), malaria (13 [17%] of 75), and nasopharyngitis (13 [17%] of 75). Rhinitis occurred in ten (13%) of 75 infants, bronchitis in nine (12%) of 75 infants, and upper respiratory tract infection in eight (11%) of 75 infants in the Ebola vaccine group. In the control group, the most common unsolicited adverse events (occurring in ≥15%) were respiratory tract infection (nine [27%] of 33), malaria (nine [27%] of 33), bronchitis (seven [21%] of 33), nasopharyngitis (six [18%] of 33), upper respiratory tract infection (six [18%] of 33), and rhinitis (five [15%] of 33). All unsolicited adverse events in both groups were mild or moderate in severity (grade 1 or 2) and none were attributed to the study vaccines.

There were 25 serious adverse events involving 14 (13%) of 108 infants. 18 serious adverse events occurred in the Ebola vaccine group and seven in the control group. A similar proportion of infants in the two groups reported at least one serious adverse event: ten (13%) of 75 infants in the Ebola vaccine group and four (12%) of 33 in the control group. Most serious adverse events were infections or infestations (appendix 2 p 10) and most were moderate in severity (ie, grade 2). In the Ebola vaccine group, three serious adverse events in two infants in the 4–8 months subgroup were severe (grade 3; two malaria and one anaemia). In the control group, two serious adverse events in one infant in the 4–8 months subgroup were severe (grade 3; hypovolaemic shock and malaria). None of the serious adverse events were vaccine-related. There was no discernible pattern observed for the occurrence of serious adverse events in Guinea contrasted with Sierra Leone (appendix 2 p 10). No deaths were observed during the study period.

Regarding vital signs, physical examinations, and other observations, there were no clinically significant findings related to the safety of the Ebola vaccine regimen. There were 11 clinically significant abnormal laboratory values

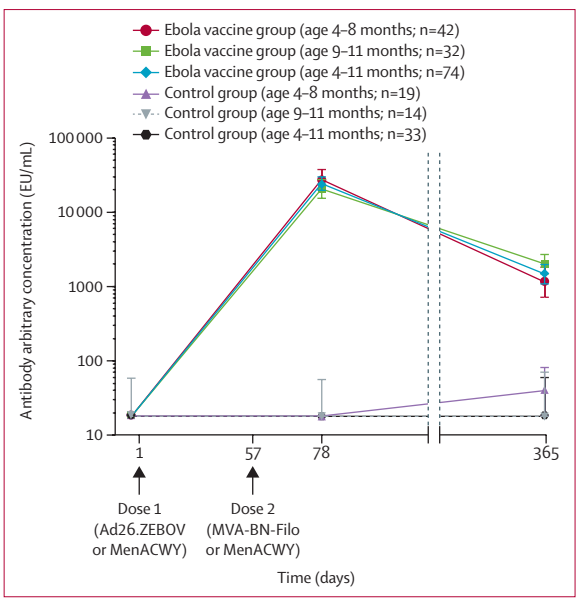

Figure 3: **EBOV glycoprotein-specific binding antibody concentrations over time**

GMCs of EBOV glycoprotein-binding antibodies in the Ebola vaccine group infants and the control group infants. Two participants in the 4–8 months subgroup of the Ebola vaccine group did not have available immunogenicity data at the day 365 timepoint. EBOV=Ebola virus. EU=ELISA unit. GMC=geometric mean concentration. MenACWY=meningococcal group A, C, W135, and Y conjugate vaccine.

in eight (7%) of 108 infants, four in each group (described in appendix 2 p 7).

The immunogenicity assessment was performed on 107 vaccinated infants in the per-protocol immunogenicity population. One infant in the full analysis set was excluded due to protocol deviation (venous blood sampling for immunogenicity assessment was not done per protocol schedule or was inconsistent with protocol design). At baseline, before the first vaccination, four (4%) of 107 infants had a positive sample (three infants in the Ebola vaccine group and one in the control group). The baseline GMC of the anti-EBOV glycoprotein-binding antibody response was less than the LLOQ in both the Ebola vaccine and control groups (figure 3, table 2). At day 78, the responder rate was 100% (74 of 74 infants) in the Ebola vaccine group. In Ebola vaccine recipients, the GMC was 27700 ELISA units (EU)/mL (95% CI 20477–37470) in the 4–8 months subgroup and 20481 EU/mL (15325–27372) in the 9–11 months subgroup. At day 365, the binding antibody GMC had decreased to 1144 EU/mL (714–1833) in the 4–8 months subgroup and 2000 EU/mL (1472–2717) in the 9–11 months subgroup. Ebola-specific IgG antibodies persisted for 1 year or more in 37 (93%) of 40 infants in the 4–8 months subgroup and in 32 (100%) of 32 in the 9–11 months subgroup. In the control group, GMCs for both the 4–8 months and 9–11 months subgroups were less than the LLOQ at both post-baseline timepoints, except for the 4–8 months subgroup at day 365, at which time the GMC

	Ebola vaccine group			Control group		
	Age 4–8 months	Age 9–11 months	Age 4–11 months pooled	Age 4–8 months	Age 9–11 months	Age 4–11 months pooled
Baseline						
Number of infants*	42	32	74	19	14	33
GMC (95% CI), EU/mL	<LLOQ (<LLOQ to <LLOQ)	<LLOQ (–)	<LLOQ (<LLOQ to <LLOQ)	<LLOQ (–)	<LLOQ (<LLOQ to 59)	<LLOQ (<LLOQ to <LLOQ)
Day 78 (21 days post-dose 2)						
Number of infants*	42	32	74	19	14	33
GMC (95% CI), EU/mL	27 700 (20 477 to 37 470)	20 481 (15 325 to 27 372)	24 309 (19 695 to 30 005)	<LLOQ (<LLOQ to <LLOQ)	<LLOQ (<LLOQ to 56)	<LLOQ (<LLOQ to <LLOQ)
Responders† (%; 95% CI)	42/42 (100%; 92 to 100)	32/32 (100%; 89 to 100)	74/74 (100%; 95 to 100)	1/19 (5%; 0 to 26)	0/14 (0%; 0 to 23)	1/33 (3%; 0 to 16)
Day 365 (12 months post-dose 1)						
Number of infants*	40	32	72	19	14	33
GMC (95% CI), EU/mL	1144 (714 to 1833)	2000 (1472 to 2717)	1466 (1090 to 1971)	40 (<LLOQ to 82)	<LLOQ (<LLOQ to 70)	<LLOQ (<LLOQ to 60)
Responders† (%; 95% CI)	37/40 (93%; 80 to 98)	32/32 (100%; 89 to 100)	69/72 (96%; 88 to 99)	4/19 (21%; 6 to 46)	1/14 (7%; 0 to 34)	5/33 (15%; 5 to 32)

EU=enzyme-linked immunosorbent assay unit. GMC=geometric mean concentration. LLOQ=lower limit of quantification. *Refers to the number of infants with data at that timepoint. †Expressed as n/N (%; 95% CI), in which n is the number of responders at that timepoint and N is the total number of infants with data at baseline and at that timepoint. An infant was considered a responder if they had either a negative ELISA result at baseline and a positive post-baseline value greater than 2·5 times the LLOQ, or a positive result at baseline with a post-baseline value greater than a 2·5-fold increase from the baseline value.

Table 2: **Ebola virus glycoprotein-specific binding antibody responses in each study group overall and by age subgroup**

	Adolescents (age 12–17 years)		Older children (age 4–11 years)		Other	
	EBL2002	EBL3001	EBL2002	EBL3001	EBL3001 (young children [age 1–3 years])	EBL2005 (infants [age 4–11 months])
Locations	Burkina Faso, Côte d'Ivoire, Kenya, Uganda	Sierra Leone	Burkina Faso, Côte d'Ivoire, Kenya, Uganda	Sierra Leone	Sierra Leone	Guinea, Sierra Leone
Number of participants*	53	134	53	124	124	74
21 days post-dose 2						
GMC (95% CI), EU/mL	13 532 (10 732–17 061)	9929 (8172–12 064)	17 388 (12 973–23 306)	10 212 (8419–12 388)	22 568 (18 426–27 642)	24 309 (19 695–30 005)
Responder rate (%), n/N†	53/53 (100%)	131/134 (98%)	51/51 (100%)	119/120 (99%)	118/121 (98%)	74/74 (100%)
12 months post-dose 1						
GMC (95% CI), EU/mL	541 (433–678)	386 (326–457)	637 (529–767)	436 (375–506)	750 (629–894)	1466 (1090–1971)
Responder rate (%), n/N†	47/52 (90%)	92/132 (70%)	51/52 (98%)	85/119 (71%)	112/117 (96%)	69/72 (96%)

Data are reported for participants who received the Ad26.ZEBOV on day 1 and MVA-BN-Filo on day 57. Data from studies EBL2002 and EBL3001 have been reported previously.[17,19] Binding antibody levels are reported as GMC (95% CI) and responder rate. EU=enzyme-linked immunosorbent assay unit. GMC=geometric mean concentration. *n is the number of participants with data at 21 days post-dose 2. †N is the number of participants with data at baseline and that timepoint.

Table 3: **Comparison of antibody results from different paediatric trials of the two-dose Ebola vaccine regimen in Africa**

was 40 EU/mL (95% CI <LLOQ–82). A small number of responders were observed in the control group, including one (5%) of 19 at day 78 and four (21%) of 19 at day 365 in the 4–8 months subgroup and one (7%) of 14 in the 9–11 months subgroup at day 365.

A post-hoc analysis showed that the binding antibody levels in the Ebola vaccine group were higher in Guinea than in Sierra Leone, especially in the younger age subgroup. Among infants in the 4–8 months subgroup, the day 78 GMC was 45 363 EU/mL (95% CI 31 819–64 670) in Guinea and 19 134 EU/mL (12 633–28 980) in Sierra Leone. This difference was maintained to the end of the study, when the day 365 GMC was 2691 EU/mL (1666–4346) in Guinea and 608 EU/mL (318–1160) in Sierra Leone.

Baseline anti-Ad26 neutralising antibodies were observed in six (10%) of 61 infants in the 4–8 months subgroup, four (10%) of 42 in the Ebola vaccine group, and two (11%) of 19 in the control group (appendix 2 p 11). Overall, the GMTs at baseline for both the Ebola vaccine and control groups were less than the LLOQ.

Discussion

This is the first clinical trial to administer and evaluate the safety and immunogenicity of Ebola vaccines in children younger than 1 year. We found that the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen was well tolerated in infants aged 4–11 months. The reactogenicity consisted of mild-to-moderate adverse events. The most common local adverse event was injection-site pain, and the most common systemic adverse events were irritability, decreased appetite, pyrexia, and decreased activity. The safety profile of Ad26.ZEBOV and MVA-BN-Filo observed in this study was comparable to that previously observed in other paediatric age groups.[17,19]

There were no serious adverse events related to the vaccines and no safety concerns related to vaccination.

The two-dose Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen induced robust antibody responses in 100% of infants 21 days after receiving dose two. The serum antibody levels declined over the follow-up period, but 93% of the younger and 100% of the older infants were still considered responders 12 months post-dose 1.

Titres of pre-existing neutralising antibodies against the Ad26 vector, which could potentially interfere with immune response, were less than the LLOQ for both age subgroups in the Ebola vaccine and control groups. Since only four infants in the Ebola vaccine group were positive for neutralising antibodies against the Ad26 vector at baseline, a meaningful correlation analysis could not be performed to determine whether this had any effect on the vaccine-induced immune response.

In general, the observed GMCs and responder rates in infants are comparable to those reported in a previous trial among children aged 1–3 years in Sierra Leone (table 3).[17] The infant GMCs reported here are numerically higher than the GMCs reported in previous trials in children aged 4–11 years and in adolescents aged 12–17 years in African countries at two timepoints (21 days post-dose 2 and 12 months post-dose 1). As age decreases from adults and adolescents to children and infants, GMCs increase, both at 21 days post-dose 2 and 12 months post-dose 1.[17,19,20] The reason behind this trend is currently unknown. However, infants and children received the same dosage of Ad26.ZEBOV and MVA-BN-Filo as adults and adolescents.[17,19] An average adult participant in the EBL3001 study weighed eight times as much as an infant in this study. It is possible that the higher dose of vaccine relative to bodyweight that infant and children participants received would elicit a stronger humoral immune response than in adults and adolescents.

Geographical variations in post-vaccination antibody levels can be seen in previous paediatric trial participants receiving the same Ebola vaccine regimen.[17,19] For example, the 21 days post-dose 2 GMC was numerically higher in children aged 4–11 years and adolescents aged 12–17 years who were enrolled in the EBL2002 study in Burkina Faso, Côte d'Ivoire, Kenya, and Uganda than in those enrolled in the EBL3001 study in Sierra Leone (table 3). Consistent with this, the infant GMCs in this study, especially in the age 4–8 months subgroup, were higher in Guinea than in Sierra Leone at both post-vaccination timepoints. We do not yet know what factors might have contributed to these differences, but they might be related to variability in pathogen burdens, micronutrient deficiencies, or activation states of the immune system found in different regions.[21,22] Trial participants from Sierra Leone lived in a rural area around a small town called Kambia, whereas participants from Guinea lived in the capital city of Conakry. Populations residing in rural settings in sub-Saharan Africa frequently have poorer health status and access to health care, as well as higher rates of malnutrition, stunting, and mortality in children younger than 5 years, compared with those in urban settings,[23–26] which might have affected the immune responses in infants from a rural community in Sierra Leone. Further research is needed to determine whether any of these factors influenced the immunogenicity of the Ebola vaccine regimen within the study population.

One of the study limitations is that it is unknown whether Ad26.ZEBOV and MVA-BN-Filo can protect infants against EVD because there are no clinical vaccine efficacy data, and a correlate of protection has not been established.[27] However, this vaccine regimen can protect non-human primates from a lethal challenge, and survival is correlated with the level of EBOV glycoprotein-specific binding antibodies.[28] The likelihood of vaccine protective effect was inferred by immunobridging from non-human primates to humans and is the basis for licensure of the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen.[27,28] The level of binding antibodies also strongly correlated with the level of neutralising antibodies in non-human primate challenge studies and previous clinical trials.[17,20,28,29]

In conclusion, the safety and immunogenicity results of this study add novel data and complement the existing data on paediatric Ebola vaccination by showing that the Ad26.ZEBOV and MVA-BN-Filo vaccine regimen is immunogenic, safe, and well tolerated in infants younger than 1 year, which is a population particularly vulnerable to EVD-associated morbidity and mortality. There were no safety concerns related to vaccination. In addition to its EMA-approved use in individuals aged 1 year or older,[16] the current study results could support the use of Ad26.ZEBOV and MVA-BN-Filo in infants aged 4–11 months, as recommended for off-label use by SAGE in 2021.[18]

Contributors

EM-LC and BLa wrote the first draft of the manuscript. BLa, MOA, BMA, FB, JF, DM, DI, CR, BG, and DW-J contributed to the design of the study, review and analysis of the data, and writing of the manuscript. MD contributed to the design of the study. In Sierra Leone, EM-LC and JF were responsible for trial coordination and organisation of the independent data monitoring committee; MOA and FB were responsible for trial management; YN and DK were responsible for data management; BLo, BJL, and GTO were responsible for laboratory sample safety analysis, sample management, and laboratory results interpretation; IBS was a lead study physician and assistant trial coordinator, and was responsible for randomisation of participants, participants' pre-vaccination eligibility assessment, post-vaccination safety assessment, and the management and reporting of serious adverse events; ABK and MMK were study physicians responsible for participants' pre-vaccination eligibility assessment, post-vaccination safety assessment, and the management and reporting of serious adverse events; and BLe was the clinical trial principal investigator. In Guinea, BLa was the lead paediatrician and contributed to study coordination; CB and CS were responsible for trial management and coordination; BH was the pharmacy coordinator and was responsible for vaccine management; E'DO contributed to trial coordination and to the design of the study; CMK was a co-principal investigator and included the participants; RV coordinated the laboratory support to generate the data for safety assessment and immunogenicity testing; MAD was the lead anthropologist and was responsible for the recruitment and follow-up community strategy; and AHB was a clinical trial principal investigator. BK was the study responsible physician and was involved in the study concept and design, study conduct, results interpretation, and

manuscript revision. WvD, AG, ML, and KL contributed to the design of the study and review and analysis of the data. MS contributed to the design and conduct of the study, data collection, and manuscript revision. DA contributed to the statistical analysis of the data. GFD was involved in the interpretation of the data. CM was involved in review and analysis of the data. RT contributed to the design of the study and review of the data. EM-LC, AG, and CM verified the underlying data. All authors had full access to the data, reviewed the manuscript, and approved the final draft for publication.

Declaration of interests

Janssen Vaccines & Prevention was the vaccine manufacturer and donated the vaccine for this study. BK, WvD, AG, DA, CM, ML, KL, CR, and MD were full-time employees of Janssen Pharmaceuticals at the time of the study and hold stock or stock options in Janssen Pharmaceuticals. All other authors declare funding from the Innovative Medicines Initiative 2 Joint Undertaking.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu.

Equitable partnership declaration

See **Online** for appendix 3

The authors of this paper have submitted an equitable partnership declaration (appendix 3). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet* journals' broader goal to decolonise global health.

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