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Immunogenicity and safety of a measles and rubella-containing vaccine at age 6 and 9 months in Bangladesh: an open-label, randomised trial

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UMS led the protocol writing, conducted training of the field staff, and conducted several monitoring site visits. AA, JPA, PAR, KK, and KZ participated in conceptualisation of the study design. KZ, ABA, MY, WH, MAFK, and SR implemented the clinical trial with financial support from the US CDC. ZM, MMC, SNC, and PAR were involved in laboratory analyses. TSS, QA, and JKK conducted the statistical analysis and verified the underlying data reported in the manuscript. UMS, ZM, SNC, KK, AA conducted literature searches. TSS wrote the first draft of the manuscript with input from QA, KK, SNC, and ZM. All authors contributed to interpretation of results and reviewing the manuscript. All authors had access to the study data and agreed to submit for publication. TSS had final responsibility for the decision to submit for publication.

For the French translation of the abstract see Online for French Abstract

For the Spanish translation of the abstract see Online for Spanish Abstract

See Online for appendix

Declaration of interests

We declare no competing interests.

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Summary

Background: The first dose of measles–rubella (MR) vaccine is routinely administered to infants aged 9 months as part of a standard two-dose schedule. However, during large measles outbreaks and in other settings of increased circulation or increased risk, WHO recommends administering a supplementary dose at age 6 months to protect young infants. We aimed to assess the immunogenicity and safety of a first dose of MR vaccine administered to infants aged 6 months and its effect on the immune response to the routine MR vaccine at age 9 months.

Methods: This open-label, randomised trial enrolled healthy infants aged 6 months in Matlab, Bangladesh, who had never received an MR vaccine dose and had no history of measles or rubella. Using a computer-generated block randomisation scheme, infants were randomly assigned (1:1) to receive either two doses of the MR vaccine, one at age 6 months and the second at age 9 months (two-dose group), or one dose at age 9 months (one-dose group). Baseline characteristics were recorded for all enrolled participants at age 6 months. Blood samples were drawn for antibody assays before each vaccination and at final follow up when infants were aged 11 months. The primary outcome was immunogenicity of a first MR vaccine in infants aged 6 months or 9 months and the immunogenicity of a second MR vaccine in infants aged 9 months who received their first MR vaccine at 6 months. Immunogenicity was measured as the proportion of infants who seroconverted in the 12 weeks after vaccination at age 6 months or the 8 weeks after vaccination at age 9 months. Seroconversion was defined as a 4-times increase in IgG concentrations relative to the pre-vaccination concentrations or achieving seroprotective antibody concentrations between study timepoints. The modified intention-to-treat analysis included all infants who received MR vaccines per group assignment and had antibody results at baseline, 9 months, and 11 months. All enrolled infants were included in the safety analysis of the immediate reactions (observed by study staff at the fixed-site clinic in the first 30 min after vaccination), adverse events within 48 h of vaccination among infants in the two-dose group receiving their first MR vaccine at age 6 months, and adverse events observed by study staff or parents at any time during the study. The trial is registered on [ClinicalTrials.gov](https://clinicaltrials.gov), [NCT03071575](https://clinicaltrials.gov/ct2/show/study/NCT03071575), and is closed to enrolment.

Findings: Between March 9, 2017, and March 18, 2018, 620 infants were enrolled and randomly assigned to the two study groups (312 in the two-dose group and 308 in the one-dose group). Of the 301 infants vaccinated at 6 months, 282 seroconverted for measles (94%, 95% CI 90–96), and 283 seroconverted for rubella (94%, 91–96). By 11 months, after receiving a second dose at age 9 months, 297 (cumulative 99%, 95% CI 97–100) infants seroconverted for measles and 297 infants seroconverted for rubella (cumulative 99%, 96–100). Of the 292 infants vaccinated at 9 months only, 291 seroconverted for both antigens by age 11 months (100%, 95% CI 98–100). 123 adverse events were observed; 72 in the two-dose group and 51 in the one-dose group, with no differences in severity ($p=0.78$) or outcomes ($p=0.71$) by study group. 12 (17%) events in the two-dose group and seven (14%) in the one-dose group were severe; most events were mild, resolved without sequelae, and were unrelated to the MR vaccine. One death occurred in the one-dose group before the infant received the 9-month dose of the vaccine, and therefore was deemed to be unrelated to the MR vaccine.

Interpretation: The data presented support use of MR vaccine at 6 months to protect young infants during measles outbreaks and in settings with increased risk or high transmission. We recommend additional studies to evaluate longer-term immunity based on age at vaccination.

Funding: US Centers for Disease Control and Prevention.

Introduction

Measles is one of the leading causes of vaccine-preventable childhood morbidity and death, causing an estimated 107 500 deaths in 2023.¹ Measles-related incidence and mortality are particularly high among infants,^{2,3} many of whom are below the age of vaccination recommended by national immunisation programmes for measles-containing vaccine (MCV).^{2,3} About 12% of reported measles cases between 2013 and 2017 fell into this group of infants,² and cases among young infants have been documented in several outbreaks.^{4–6} WHO recommends two doses of MCV for all children. The first dose of MCV (MCV1) is typically recommended at 9 months of age in countries with endemic measles transmission and at 12 months of age in countries with low measles incidence. The second dose (MCV2) is administered at a later age, typically in the second year of life.³ During large measles outbreaks and in other settings of increased circulation or increased risk, WHO recommends using a MCV starting at 6 months of age to protect young infants from measles infection. This dose of MCV is considered a zero dose (MCV0); therefore, the infants still require both regularly scheduled doses and parents are advised that infants who receive an early dose of MCV should continue to receive two doses of MCV according to the national schedule.³

Most previous studies of MCV immunogenicity in infants younger than 9 months used a monovalent measles vaccine in settings with lower vaccination rates and higher rates of circulating measles virus.^{7–10} However, almost all countries now use a combined measles–rubella (MR) vaccine, which is sometimes also combined with mumps (MMR) or mumps and varicella (MMRV). Data on the immunogenicity of MR vaccine administered at age younger than 9 months and its effect on immunogenicity of subsequent MR vaccination routinely administered at 9 months are scarce. Furthermore, a higher proportion of infants are now born to mothers whose measles immunity derives from vaccination rather than measles infection. The decline of maternal antibodies below protective levels occurs earlier in infants of vaccinated mothers than in infants of mothers with immunity from measles infection.^{11–13} As more countries replace monovalent measles vaccine with MR vaccine in their routine immunisation programmes and infants become increasingly susceptible to measles, the need for additional data on immunogenicity of MR vaccine in younger infants becomes greater.

We aimed to assess the immunogenicity and safety of a first dose of MR vaccine administered at age 6 months and its subsequent effect on the immunogenicity of a second dose of MR vaccine administered at age 9 months.

Methods

Study design and participants

This open-label, randomised trial was conducted in Matlab, a rural community in Bangladesh. We screened healthy infants aged 6 months who had never received an MR vaccine dose and had no history of measles or rubella. Infants were excluded if they were unable to participate for the full length of the study, had a diagnosis or suspicion of an immunodeficiency or bleeding disorder, had an acute infection or illness at the time of enrolment that would require admission to a hospital, had received an MCV or a rubella-containing vaccine before enrolment, or had laboratory-confirmed measles or rubella infection. Infants were also excluded if their mother had a diagnosis of rubella infection during pregnancy, the infant was diagnosed with congenital rubella syndrome, or if they were born prematurely (<37 weeks of gestation). Infants were identified as female or male through self-report by their mothers. Mothers were enrolled to assess maternal immunity and to monitor maternal factors that could affect infants' response to vaccination. Enrolled mothers had to be aged 18 years or older, provide written consent to participate along with their infants for the full length of the study, and had to be able to understand and comply with planned study procedures. Mothers were excluded if they could not give blood samples at the time of enrolment or had diagnosis or suspicion of an immunodeficiency or bleeding disorder that would contraindicate collection of blood by venipuncture. At least one parent or guardian gave written consent for their infant to participate in the study. Parents or guardians could withdraw consent to participate for any reason and at any time. Participation could also be discontinued due to loss to follow-up; an allergic reaction to the vaccine; identification of an immunodeficiency, a bleeding disorder, or another medical condition for which continued participation was contraindicated; or receipt of immunosuppressive medications. Laboratory-confirmed measles or rubella infection after enrolment was not a reason for disenrolment.

The study was approved by the Ethical Review Committee and Research Review Committee at the International Centre for Diarrheal Diseases Research, Bangladesh (icddr,b; Dhaka) protocol number PR-16077, and the US Centers for Disease Control and Prevention (CDC; Atlanta, GA) Institutional Review Board (IRB) protocol number 1U01GH001207-01. The study was monitored by a Data Safety Monitoring Board (DSMB) constituted by icddr,b and with representation outside icddr,b with input by the Ethical Review Committee. Immunogenicity data were not available for DSMB meetings because blood specimens were analysed after the completion of study field activities. The protocol is in appendix. The trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03071575), [NCT03071575](https://clinicaltrials.gov/ct2/show/study/NCT03071575).

Randomisation and masking

Using a computer-generated block randomisation scheme, infants were randomly assigned (1:1) to receive either two doses of the MR vaccine, one at age 6 months and the second at age 9 months (henceforth referred to as the two dose group), or one dose only at age 9 months (one-dose group). Sealed envelopes containing assignment numbers and instructions were delivered to the recruitment sites and opened at the time of enrolment. Each enrolled participant was assigned the next identification number on the list, and the study staff

enrolling participants did not have a priori knowledge of the randomisation scheme. Group assignment was revealed to study staff and parents after randomisation.

Procedures

Commercially available live-attenuated MR vaccine (Serum Institute of India, Hadapsar, Pune, India) was provided on site. A multidose vial with lyophilised active component was reconstituted with diluent before use. Sterile, disposable, and auto-disable syringes were provided separately. Infants in the two-dose group were administered their first dose of MR vaccine at age 6 months. MR vaccine was administered to infants aged 9 months (MCV1) in both the two-dose and one-dose groups. Participants exited the study at age 11 months, after the final follow-up visit, at which time parents were reminded to bring their child to the vaccination clinic or another Expanded Programme on Immunization (EPI) facility to receive their next routine dose of measles vaccine (MCV2) at age 15 months. Baseline characteristics were recorded for all enrolled participants at age 6 months.

1 mL blood samples were collected from all infants at ages 6 months, 9 months, and 11 months. Blood samples given at age 6 months were used as a pre-vaccination samples in immunogenicity analyses. In the two-dose group, blood samples given at 9 months (before the second MR vaccination) were used to analyse immunogenicity after the first MR dose given at age 6 months. Blood samples given at age 11 months were used to compare 8-week immunogenicity after two doses (at 6 months and 9 months) and one dose (at 9 months). All mothers gave blood samples at time of enrolment. Blood samples were processed at the Matlab laboratory, stored and shipped at -20°C to the US CDC, and tested for measles and rubella IgG in a multiplex bead assay, as previously described.^{14,15} Briefly, serum specimens were diluted 1:400 and tested in duplicate. IgG concentrations were quantitated using the international rubella standard RUBI1-94 (1600 IU/mL: National Institute for Biological Standards and Controls, Potters Bar, UK), which was previously calibrated to the 2nd International Standard for measles. Following completion of study testing, a 10% repeat of samples was performed as part of routine quality control with an overall percentage agreement of positives and negatives of 99%.

All participants were observed by study staff at the fixed-site clinic for 30 min after vaccination to monitor for immediate reactions. In the two-dose group, infants receiving their first MR vaccine at age 6 months had a household safety monitoring visit 48 h later to record potential adverse events. At the end of the study visit, study staff provided parents with a phone number for a study nurse if they had any questions or if their child experienced reactions to the vaccine. Skilled medical personnel were available free of charge to participants experiencing adverse reactions. Since MR vaccination at 9 months is routine in Bangladesh, no follow-up household safety monitoring visits were made to infants receiving their MR vaccine dose (first or second) at age 9 months. At follow up visits, and before a second vaccination was administered, parents were asked about possible adverse events since their previous study visit.

Outcomes

The primary outcome was immunogenicity of a first MR vaccine in infants aged 6 months or 9 months and the immunogenicity of a second MR vaccine in infants aged 9 months who received their first MR vaccine at 6 months. Immunogenicity was measured as the proportion of infants who seroconverted in the 12 weeks after vaccination at age 6 months or the 8 weeks after vaccination at age 9 months. Seroconversion was defined as a 4-times increase in IgG concentrations relative to the pre-vaccination concentrations or achieving seroprotective antibody concentrations between study timepoints. Seroprotective antibody concentrations were defined as at least 153 mIU/mL for measles IgG and at least 9·36 IU/mL for rubella IgG.¹⁴

The study had seven secondary outcomes, six of which are reported here: the safety profile of adverse reactions following administration of MR vaccine at age 6 months; the immunogenicity of the MR vaccine first dose administered at age 6 months versus age 9 months; the proportion of mothers with undetectable, detectable, and protective measles and rubella IgG concentrations; the extent of variation in measles antibodies in a convenience sample of women of childbearing age in a population with a long-standing measles vaccination programme; the extent of variation in rubella IgG concentration in a convenience sample of women of childbearing age in a population in which rubella vaccine have been recently introduced; and an assessment if variation in IgG concentrations in infants aged 6 months is predominately explained by variation in starting IgG concentrations in the mother in this population. A seventh planned secondary outcome, the half-life of decay of measles and rubella antibodies in infants, could not be reported because of data paucity.

Adverse events were subcategorised as vaccination-related or not by the principal investigator and periodically discussed by the team of investigators. All serious adverse events were reported by the principal investigator to the regulatory agencies, ethical review committees, and DSMB within 24 h. The investigational team reported clusters of adverse events (at least three within 1 week) to the DSMB periodically for further evaluation.

Statistical analysis

Sample size calculations were based on equality comparisons with 10% attrition. Assuming 50% MR seroconversion to a dose at age 6 months, a sample size of 271 per group would provide a precision of $\pm 5\%$ with a 0·90 probability of obtaining an estimate within the desired range. Adjusting for 10% attrition, the enrolment target was 302. Assuming a seroconversion for measles of 75% following a single dose given at age 9 months, a seroconversion of 65% for a 9-month dose preceded by a 6-month dose, and power of 80%, a sample size of at least 279 per group was required. Adjusting for 10% attrition, this sample size was increased to 310 infants per group and 620 infants in total.

Descriptive statistics (frequencies and percentages) were calculated for baseline characteristics and adverse events. The proportion of infants who seroconverted across study groups was compared using χ^2 tests, and median antibody concentrations of measles and rubella antibodies by study group using the Kruskal–Wallis test. Proportions of adverse

events by study group were compared using χ^2 tests. We used box plots, box-and-whisker plots, and reverse cumulative distribution function (RCDF) curves to visualise differences in IgG concentrations. We compared the RCDF curves between study groups using the log-rank test. To investigate associations between maternal and infant antibodies and potential impact of maternal antibody on baseline antibody concentrations and seroconversion, we computed linear correlation between maternal and infant antibody concentrations at each timepoint. We also computed the slope of change in IgG concentrations between baseline and age 9 months using a linear mixed model and assessed its associated p value.

Immunogenicity was analysed in the modified intention-to-treat population, which included infants who received MR vaccines per group assignment and had antibody results at baseline, 9 months, and 11 months. All infants were included in the safety analysis. All analyses were conducted in R (version 4.2.2).

Role of the funding source

Funding was provided by the US CDC through a cooperative agreement with icddr. CDC staff participated as investigators in the study. The funder had no role in data collection but participated in study design, data analysis, data interpretation, and writing of and the decision to submit the manuscript.

Results

637 infants and their mothers were screened between March 9, 2017, and March 18, 2018. 17 (3%) participants were found ineligible, and 620 infants were randomly assigned to the two-dose group (n=312) and the one-dose group (n=308; figure 1). Following all exclusions, 301 infants were included in two-dose group and 292 infants were included in the one-dose group for the primary and secondary immunogenicity analyses.

Baseline characteristics measured at age 6 months were similar for infants in the study groups (table 1). The distributions of measles and rubella IgG concentrations in infants at baseline and throughout the study are shown in figure 2 and appendix (pp 1–2). The proportions of mothers with undetectable, detectable, and protective concentrations of measles and rubella IgG were similar between groups at baseline (figure 2; table 1; appendix pp 1–2). We found a strong correlation in infant and maternal IgG concentrations for both measles and rubella (appendix p 3). However, there was limited variation in infant IgG concentrations at age 6 months for both measles and rubella (table 1); and the decay of antibodies in infants from 6 months to 9 months was seen only in rubella antibodies in infants in the one-dose group (vaccination at 9 months) whose mothers were antibody positive at baseline (appendix pp 4–5).

The proportions of infants who seroconverted for measles and rubella are shown in table 2. Seroconversions for measles and rubella after the first dose of MR vaccine at age 6 months (two-dose group) were lower than in infants receiving their first MR vaccine dose at 9 months (one-dose group). However, by final follow up at age 11 months, almost all infants seroconverted for measles and rubella regardless of whether they had received two or one MR vaccine doses.

Median measles IgG and rubella IgG concentrations among infants who seroconverted after receiving each vaccine dose are shown in figure 3. The median measles IgG concentration among infants who seroconverted at 11 months was lower in the one-dose group than in the two-dose group (1311 mIU/mL [IQR 881–1976] *vs* 1453 mIU/mL [1057–2094]; $p=0.029$). In the two-dose group, the median rubella IgG antibody concentration among seroconverting infants was higher after the first dose at age 6 months than after two doses (102 IU/mL [IQR 59–166] *vs* 94 IU/mL [60–137]), although this was not compared statistically.

123 adverse events were observed or reported over the duration of the study; 72 in the two-dose group and 51 in the one-dose group (table 3). There were no statistically significant differences between study groups in severity or outcome of adverse events or their relation to the MR vaccine. 12 (17%) events in the two-dose group and seven (14%) in the one-dose group were severe; most events were mild, resolved without sequelae, and were unrelated to the MR vaccine. The ongoing events were classified as mild, and the death in the one-dose group was deemed unrelated to the MR vaccine. 11 (4%) infants receiving the MR dose at age 6 months experienced adverse symptoms within 48 h, the most prevalent symptom being fever. There were three reports of redness at the site of injection reported within 30 min of vaccination; these were all in infants in the two-dose group receiving their first vaccine at age 6 months. No adverse events were reported within 30 min of vaccination among infants receiving MR vaccine at 9 months.

Discussion

This study showed the immunogenicity and safety of the MR vaccine administered at age 6 months. For the population enrolled in this trial, less than 5% of infants were seropositive for either measles or rubella antibodies at age 6 months, and 94% of infants vaccinated with MR at age 6 months seroconverted after a single dose, with minimal adverse events. Although seroconversion after a first dose at age 6 months (94%) was lower than when a first dose was given at age 9 months (100%), seroconversion at 11 months was equivalent (99% in the two-dose group *vs* 100% in the one-dose group). Nearly all infants had seroconverted by age 11 months, whether they received one or two doses. We detected a significant difference in rubella antibody concentrations at 11 months between the two-dose and one-dose groups; however, the clinical significance is uncertain because the median antibody concentrations exceeded clinical protection thresholds in both groups. The MR vaccine was safe, both when administered early at 6 months, before routine vaccination, and at the age of the routine first dose (9 months).

The immunogenicity of measles vaccine depends on several factors, including the presence and potential interference of maternally derived antibodies and the maturity of the immune system of the vaccine recipient. A systematic review of previous studies reported a higher immunogenicity of measles vaccine when administered at a later age, with 76% seroconversion at age 6 months.¹⁰ Although some studies have directly demonstrated a negative association between maternal antibody concentrations and vaccine immunogenicity,^{7,16} declining maternal antibody concentrations in the vaccine era might limit such concerns.

A history of vaccination or measles or rubella infection among the mothers enrolled in this trial were not solicited due to challenges with verification. More than 80% of mothers in both study groups had seroprotective concentrations of measles and rubella antibodies at baseline. It is likely that for most of the mothers, measles seroprotection derived from vaccination rather than previous infection. Bangladesh introduced MCV1 into the EPI schedule in 1989, with periodic supplementary immunisation activities since that time.¹⁷ MCV2 was introduced in 2012. Bangladesh's estimated coverage was 97% for MCV1 and 93% for MCV2 in 2018 according to WHO and UNICEF estimates of national immunisation coverage (WUENIC).¹⁸ Measles has been well controlled in Bangladesh over the 30 years before the enrolment period for this study. Maternal rubella seroprotection could have derived from vaccination or infection; a nationwide MR catch-up campaign was conducted in 2014 with a target age of 9 months–15 years.¹⁹ The epidemiological context seen in Bangladesh is representative of many countries where measles and rubella are eliminated or well controlled.

Although most mothers were seropositive for both measles and rubella antibodies in this study population, infants at age 6 months had low concentrations of maternally derived antibody concentrations. Low levels of seroprotection at age 6 months have been documented previously.^{20–23} Results of one study in Matlab, reported in 1998, showed that 95% of infants were seronegative by age 8 months.²⁴ This observation is consistent with the more rapid decline of maternal antibodies in infants born to mothers with vaccine-induced immunity.^{11,12} As the number of infants born to mothers with vaccine-induced immunity continues to increase, pockets of susceptibility to measles and rubella will continue to accumulate among the vulnerable age group of infants too young to be vaccinated and therefore ineligible for the MR vaccine, posing a challenge for global immunisation programmes, particularly those still endemic for measles with ongoing transmission.

Measles and rubella seroconversion rates after a first dose of MR vaccine at age 6 months were unexpectedly high among the infants enrolled in the two-dose group. This seropositivity appears to be sustained after receiving a second dose at age 9 months, giving no indication of immunological blunting. Although few studies have investigated immunological blunting, most have shown high seropositivity and vaccine effectiveness when MCV doses are administered early.²⁵ However, some studies have suggested longer-term effects on the durability of the immune response, which need to be further investigated. For example, studies from the Netherlands have showed that early receipt of MCV at age 6–12 months results in lower measles antibody concentrations after subsequent doses.^{13,26} One such study showed that 11% of children receiving MCV before age 9 months ultimately lost protective immunity to measles later in life.²⁶ Our study does not assess immunogenicity across a longer observation period because no long-term follow-up was planned.

The findings of this trial support the use of a supplementary dose of the MR vaccine for infants younger than 9 months during periods of intense transmission.³ However, the trial was conducted in a setting with high vaccination rates among infants. Results might therefore differ in settings where vaccination rates are lower or with different measles and rubella epidemiology. Infants are more likely to receive a higher concentration of passively transferred antibodies from mothers who have been infected, and these might

interact with the MR vaccine to reduce immunogenicity. Further studies in similar and different environments are needed to ensure the robustness of the findings. Future studies might also assess cell-mediated immunity markers and long-term humoral immunity. Any considerations to vaccinate infants routinely at an age younger than 9 months should balance the potential risk of primary vaccine failure and long-term effects on the immune response against the risk of measles infection and measles-related complications, including death, during periods of intense transmission.

Our study had some limitations. First, the study only followed up participants up to age 11 months, and therefore we were unable to assess the longer-term effects of MR vaccination at 6 months on the routine second dose of MCV at age 9 months and beyond. Second, data were collected in 2017–18, but delays in transfer and testing of samples and the COVID-19 pandemic significantly delayed data analysis and dissemination. Further limitations are associated with the open-label study design, such as potential bias in reporting of adverse events, which could affect interpretation of results. However, the laboratory and data analysts were not involved in implementation of the trial and did not have access to the data until the trial had ended, which might have reduced biases.

In summary, the MR vaccine was well tolerated and had high immunogenicity in infants aged 6 months. At age 11 months, after receiving their second dose of the MR vaccine at age 9 months, their immunogenicity was equivalent to those infants aged 11 months who received their first MR vaccine at age 9 months. We thus recommend additional studies to evaluate antibody concentrations over time to assess longer-term immunity based on age at vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data sharing

Requests for anonymised data can be submitted to the corresponding author and will be reviewed according to the US CDC and icddr,b obligations.

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Research in context

Evidence before this study

We searched PubMed for articles published from database inception to March 13, 2024, using the following search terms with Boolean operators: “measles”, “rubella”, “early vaccination”, “infants”, “6 months”, “vaccine efficacy”, “seroconversion”, and “maternal antibody”. Abstracts from the resulting search were screened to determine contextual relevance. Studies were excluded if exclusively focused on animal models, focused on vaccines other than measles and rubella, or otherwise did not include age-appropriate analyses on vaccine immunogenicity or prevalence of maternal antibody. We identified 30 studies that focused on immunogenicity after early receipt of measles-containing vaccine (n=19), rubella vaccine (n=1), or the prevalence of maternal antibodies in infants in this context (n=10). Notably, data on early receipt of the measles–rubella (MR) vaccine were scarce. Although immunogenicity of measles vaccine given at age 6 months is well studied, few studies have assessed immunogenicity of the combined MR vaccine administered at age 6 months and its effect on MR vaccine effectiveness given at later timepoints. Most studies have reported 60–80% seroconversion to measles-containing vaccine in infants younger than 9 months with the proportion of infants who seroconvert increasing with age. Some studies have reported a negative association between early receipt of measles-containing vaccine and antibody concentrations following subsequent MCV doses. A single study reported seroconversion to rubella vaccination at 6 months above 90%.

Added value of this study

This trial provides data on the immunogenicity of MR vaccine administered at age 6 months and the subsequent impact on immunogenicity of routine MR vaccination at 9 months. Despite high seropositivity among their mothers (>80%), most infants were seronegative at age 6 months. Almost all infants seroconverted by 11 months of age, regardless of whether they received one or two doses, and 94% (95% CI 90–96) and 94% (91–96) of those receiving two doses seroconverted for measles and rubella, respectively, after the first dose at 6 months. These data demonstrate robust immunogenicity for the MR vaccine at 6 months, with no observed interference from maternal antibodies and no observed effect on the immune response to a subsequent dose.

Implications of all the available evidence

The MR vaccine was immunogenic, safe, and well tolerated at age 6 months. These data support the administration of MR vaccine at age 6 months to close immunity gaps among vulnerable infants during measles outbreaks and in other settings of increased circulation or increased risk; however, additional research is needed to fully assess the long-term effect of early MR vaccination on the immune response.

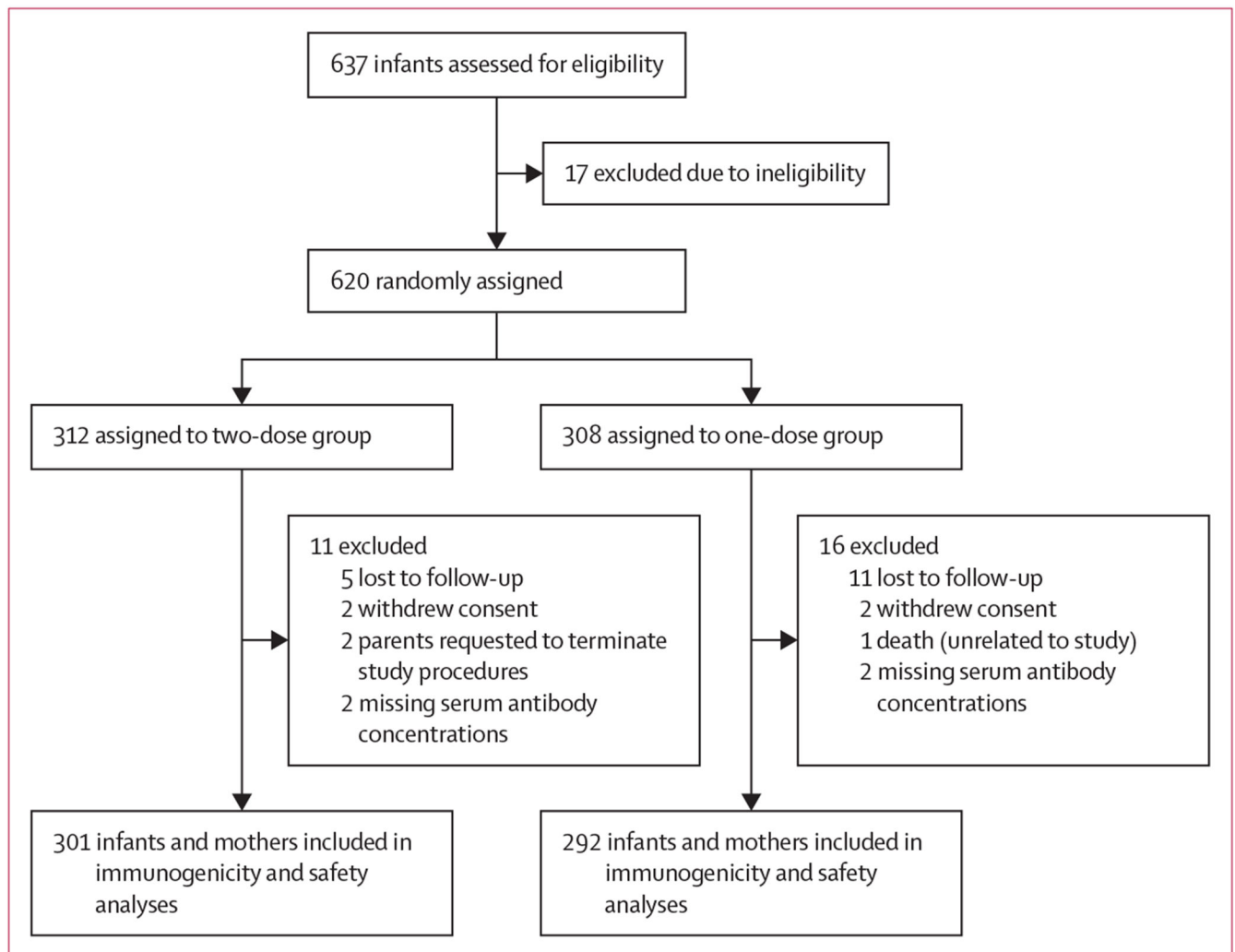


Figure 1: Trial profile

Infants in the two-dose group received the measles–rubella vaccine at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months.

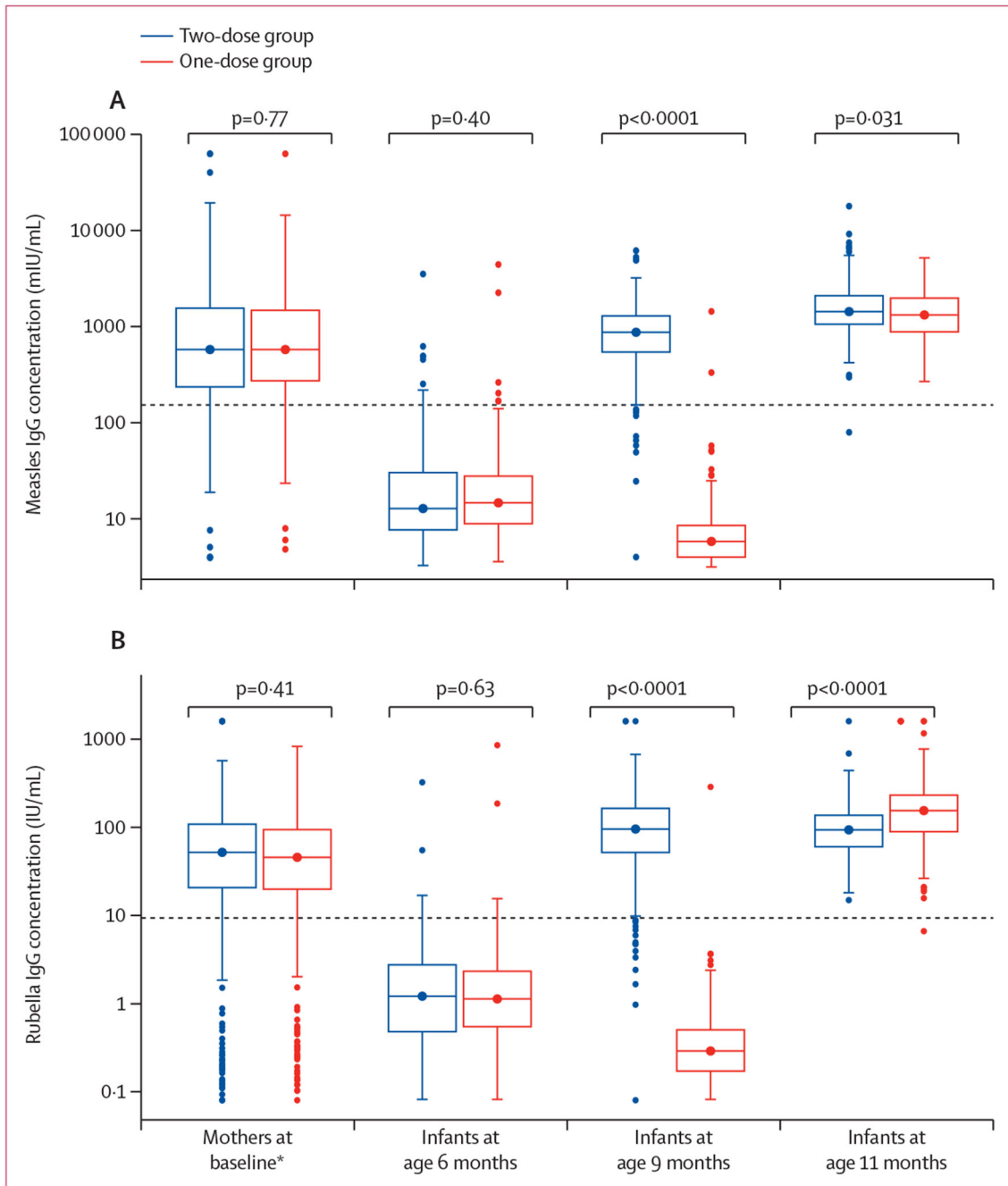


Figure 2: Measles and rubella IgG concentrations for mothers at baseline and for infants at baseline (age 6 months) and at follow-up at age 9 months and 11 months

Shown are box and whisker plots for measles (A) and rubella (B), where the centre of each box indicates the median value, the upper line indicates the upper quartile, and the lower line indicates the lower quartile for IgG concentration each timepoint. Whiskers show outlier values of IgG concentration. The horizontal dashed line indicates the seroprotective IgG concentrations, defined as at least 153 mIU/mL for measles and at least 9.36 IU/mL for rubella.¹⁴ p values compare median IgG concentrations between groups for mothers and for infants at each timepoint. Infants in the two-dose group received the measles–rubella vaccine

at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months. IgG was measured in blood sampled before vaccination. *Antibody concentrations for all mothers were assessed only at the baseline visit when their infants were aged 6 months; mothers did not receive any vaccine and are categorised according to their infants' assigned treatment group.

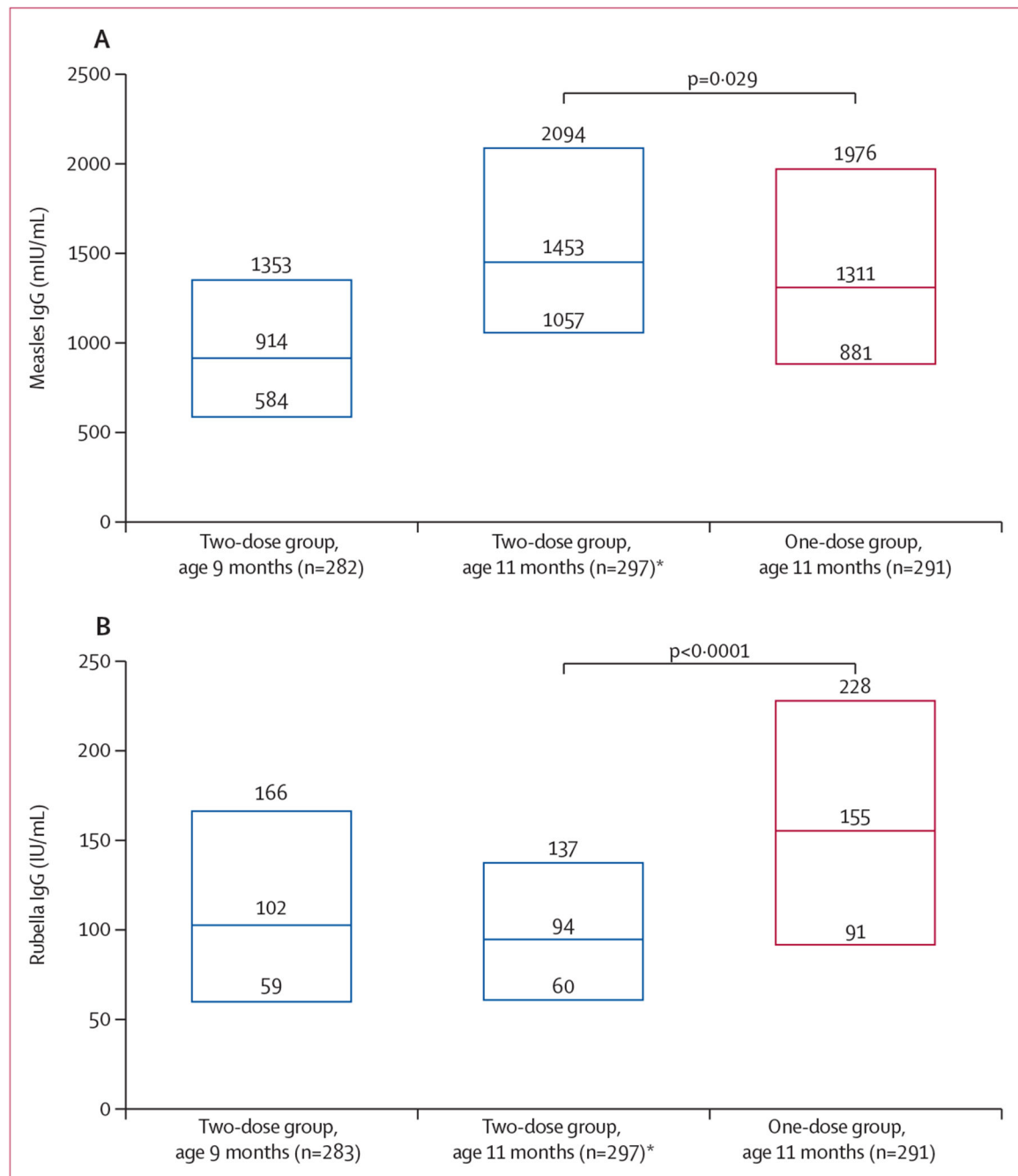


Figure 3: Median measles and rubella IgG concentrations among infants who seroconverted
 Shown are box plots for measles (A) and rubella (B), where the centre of the box indicates the median value, the upper line indicates the upper quartile, and the lower line indicates the lower quartile. Infants in the two-dose group received the measles–rubella vaccine at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months. Infants in the two-dose group who seroconverted after receiving the first vaccine dose at age 6 months had a median measles IgG concentration of 914 mIU/mL (IQR 584–1353) at age 9 months. At age 11 months, infants in the two-dose group who

seroconverted had a median measles IgG concentration of 1453 mIU/mL (IQR 1057–2094), whereas infants in the one-dose group who seroconverted after their first vaccine dose at age 9 months had a median measles IgG concentration of 1311 mIU/mL (IQR 881–1976). The median rubella IgG antibody concentration among seroconverting infants in the two-dose group was 102 IU/mL (IQR 59–166) after the first dose at age 6 months. At age 11 months, infants in the two-dose group who seroconverted had a median rubella IgG concentration of 94 IU/mL (IQR 60–137), whereas infants in the one-dose group who seroconverted after their first vaccine dose at 9 months had a median IgG concentration of 155 IU/mL (91–228). *IgG concentrations in the two-dose group at 11 months are for cumulative seroconverters after the second dose at age 9 months.

Table 1:

Baseline characteristics

	Two-dose group (n=301)	One-dose group (n=292)*
Infant's sex		
Male	145 (48%)	146 (50%)
Female	156 (52%)	146 (50%)
Mother's education		
No formal school	13 (4%)	12 (4%)
Primary school	56 (19%)	54 (18%)
Middle school	143 (48%)	131 (45%)
High school	81 (27%)	84 (29%)
College or university	8 (3%)	11 (4%)
Father's education		
No formal school	19 (6%)	15 (5%)
Primary school	85 (28%)	79 (27%)
Middle school	110 (37%)	110 (38%)
High school	65 (22%)	71 (24%)
College or university	22 (7%)	17 (6%)
Mother's age, years	26.5 (5.4)	26.4 (5.6)
Infant's age, days	179.8 (3.3)	179.5 (3.3)
Stunting present	29 (10%)	35 (12%)
Wasting present	15 (5%)	12 (4%)
Measles		
Seropositive infants	10 (3%)	6 (2%)
Seropositive mothers	255 (85%)	255 (87%)
Infants' median (IQR) antibody concentration, mIU/mL	12.8 (7.7–30.3)	14.7 (8.9–27.8)
Mothers' geometric mean (95% CI) antibody concentration, mIU/mL	602 (508–712)	607 (522–706)
Rubella		
Seropositive infants	8 (3%)	9 (3%)
Seropositive mothers	249 (83%)	239 (82%)
Infants' median (IQR) antibody concentration, IU/mL	1.2 (0.5–2.8)	1.1 (0.5–2.3)
Mothers' geometric mean (95% CI) antibody concentration, IU/mL	31 (25–39)	29 (23–36)

Data are n (%) or mean (SD), unless otherwise stated. Percentages might not equal 100% because of rounding. Infants in the two-dose group received the measles–rubella vaccine at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months.

* Baseline characteristics in the one-dose group were recorded 3 months before infants received their first vaccine dose at age 9 months.

Table 2:
Measles–rubella vaccine immunogenicity, by antigen and vaccine dose group

	Two-dose group (n=301)		One-dose group (n=292)	
	Number of seroconverters/total	% (95% CI)	Number of seroconverters/total	% (95% CI)
Measles				
Seroconverted 6–9 months	282/301	94% (90–96)	..	..
Seroconverted 9–11 months	15/19	79% (54–93)	291/292	100% (98–100)
Seroconverted after all doses	297/301	99% (97–100)	291/292	100% (98–100)
Rubella				
Seroconverted 6–9 months	283/301	94% (91–96)	..	..
Seroconverted 9–11 months	14/18	78% (52–93)	291/292	100% (98–100)
Seroconverted after all doses	297/301	99% (96–100)	291/292	100% (98–100)

Infants in the two-dose group received the measles–rubella vaccine at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months.

Table 3:

Safety analysis

	Two-dose group (n=301)	One-dose group (n=292)	p value
Any adverse events during study period			
Severity	..	..	0.78
Mild	51/72 (71%)	39/51 (76%)	..
Moderate	9/72 (12%)	5/51 (10%)	..
Severe	12/72 (17%)	7/51 (14%)	..
Outcome	..	..	0.71
Ongoing	1/72 (1%)	1/51 (2%)	..
Resolved without sequelae	71/72 (99%)	49/51 (96%)	..
Resolved with sequelae	0	0	..
Death	0	1/51 (2%)	..
Relation to vaccine	..	..	0.42
Yes	0	1/51 (2%)	..
No	69/72 (96%)	49/51 (96%)	..
Missing	3/72 (4%)	1/51 (2%)	..
Solicited adverse events within 48 h of vaccination at 6 months			
Type of adverse event			
Fever	7/16 (44%)	..	..
Redness at injection site	3/16 (19%)	..	..
Cough, runny nose, sneezing, or cold	5/16 (31%)	..	..
Rash	1/16 (6%)	..	..
Solicited immediate events within 30 min of vaccination *			
Type of immediate event			
Redness at injection site	3/3 (100%)	0	..

Data are number of events/total events (%). Infants in the two-dose group received the measles–rubella vaccine at ages 6 months and 9 months, and infants in the one-dose group received the measles–rubella vaccine at age 9 months. Comparisons between study groups used χ^2 tests.

* No adverse events were reported within 30 min of vaccination at the 9-month visit.