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Sero-epidemiology of measles immunoglobulin G antibodies among newborns from South-East Asia and sub-Saharan Africa: an observational, multicenter study



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ABSTRACT

Article history: Received 11 December 2024 Revised 25 February 2025 Accepted 10 March 2025 *Objectives:* To investigate the transplacental acquisition of measles immunoglobulin (Ig)G in newborns at delivery in Bangladesh, Bhutan, India, Ethiopia, Mozambique, Kenya, Nigeria, Mali, and South Africa. *Methods:* Archived cord serum, from a multicenter study on Group B *Streptococcus*, were tested for measles IgG using a commercial enzyme link immunosorbent assay (ELISA). We tested 323 randomly selected samples from each of the sites. Models using various measles antibody decay rates in infancy were explored.

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Keywords: Sero-prevalence Measles Passive immunity Antibody decay *Results*: Overall, 2,907 cord serum samples were analyzed. At birth, 49.9% of newborns were measles IgG seronegative. Measles seronegativity ranged from 21.7% in Nigeria to 73.4% in Bhutan. The adjusted odds of seronegativity in infants of mothers born after measles vaccination implementation was 1.78 times that for infants born to unvaccinated mothers (adjusted odds ratio 1.78; 95% confidence interval 1.43-2.21; P < 0.001). Modeling measles-IgG kinetics predicted that 70.8%, 88.3%, and 100% of infants would be seronegative by 2, 4, and 6 months, respectively, without further exposure.

Conclusions: Our findings suggest low transplacental acquisition of measles IgG in newborns, which is likely to yield susceptibility to measles infection at a very young age. The currently recommended measles vaccine schedules in low- and middle-income countries (LMICs), with the first dose recommended from 9 months of age and onward, warrant reconsideration, including the need for earlier dosing schedules.

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Introduction

Despite the availability of a safe and effective measles vaccine (MV), globally in 2022, measles caused approximately 5,138,698 cases, including 85,417 deaths in children under 5 years of age [1,2]. The World Health Organization (WHO) recommends that the first dose of MV (MV1) be given at 9 months of age, in part to mitigate attenuation of the immune response to MV due to circulating maternal-derived anti-measles immunoglobulin (Ig)G. The WHO does recommend an earlier dose of MV at 6 months of age be considered for certain groups, such as children born to women living with HIV, in addition to the subsequent two doses to be administered within the first 2 years of life [3].

Maternally-derived anti-measles IgG in the newborn declines over time, culminating in increased susceptibility to measles up until MV1 immunization occurs. Anti-measles IgG induced by vaccination alone results in lower titers and wanes faster compared with infection-induced immunity [4,5]. The widespread coverage of MV and lowering of infection-induced immunity results in seroepidemiologic changes that could impact the transplacental antimeasles IgG acquisition in the newborn [6,7]. Currently, women of childbearing age are more likely to have derived measles immunity from vaccination rather than infection [5]. During an outbreak of measles in South Africa in 2009-2010, it was reported that overall, 24% of measles cases occurred in children who would not have been eligible to receive MV1 at 9 months of age. An agespecific incidence rate of 302 cases per 100,000 population was reported for children under 6 months old [8]. In addition, infants younger than 6 months accounted for 37% and 32% of all reported measles cases in the African and Western Pacific region in 2017, respectively [9].

Investigation of the sero-epidemiology of anti-measles IgG in newborns could quantify susceptibility to measles from birth to when MV1 is scheduled. There is a paucity of South Asia and Africa studies investigating measles antibody levels in newborns at birth. Moreover, existing studies often suffer from small sample sizes, outdated epidemiologic conditions, or are conducted in a single site [10–12].

The objective of our study was to determine cord blood antimeasles IgG at birth in six African and three South Asian countries and model the susceptibility to measles by 2, 4, and 6 months of age.

Material and methods

Study design, sites, and population

This multicenter study included three South Asian (Bangladesh, Bhutan, and India) and six African countries (Ethiopia, Kenya, Mali, Mozambique, Nigeria and South Africa). The screening and enrolment of pregnant women occurred during the early stages of labor. For this study, we used archived cord serum, from all the countries included in the Group B *Streptococcus* (GBS) multicenter study aimed at evaluating GBS colonization and sero-epidemiology [13]. Cord blood was collected from newborns within the parent study conducted from January 10, 2016 to December 11, 2018. The criteria in the parent study were pregnant women aged 18 to 45 years, enrolled at \geq 37 weeks of gestation, and tested negative for HIV-1. The exclusion criteria were women presenting with underlying medical conditions, exposure to intrapartum antibiotics, and blood transfusion in the 30 days before delivery. Participants were included in the current study if the mothers consented to storing and using cord blood samples. Demographic data on mothers and infant-related factors such as gender and birth weight were also collected.

Cord blood samples collected immediately after delivery were centrifuged at the site to extract serum. The aliquots from the site were shipped on dry ice to the University of the Witwa-tersrand Vaccine and Infectious Disease Analytics Research Unit (Wits-VIDA) in Johannesburg, South Africa, where the serum was archived at -70° C. Although this study primarily analyzed stored cord blood specimens, maternal hemoglobin levels and other maternal-related variables were obtained from the GBS main study, where maternal blood samples were collected and analyzed. Not all stored cord blood samples were tested and analyzed; only the required sample size for the study was selected for testing and analysis.

Laboratory detection of anti-measles immunoglobulin G

Anti-measles IgG was evaluated using an indirect enzymelinked immunosorbent assay (ELISA; EuroimmunTM, Lübeck, Germany; catalog numbers: EI 2610-9601 G), as per manufacturer instructions. Each sample underwent testing in true duplicate. Seropositivity was defined as IgG titers \geq 275 mIU/ml, equivocal if titers were \geq 200 to <275 mIU/ml, and seronegative if titers were <200 mIU/ml, as per the manufacturer's criteria [14].

Among available ELISA assays, Euroimmun emerged as an alternative for evaluating human measles IgG in serum or plasma. Widely recognized for its precision and sensitivity, Euroimmun ELISA demonstrated efficacy in measles-IgG detection and quantification. Its reliability and reproducibility have earned it widespread adoption within the scientific and medical communities. The assay has also been reported to be accurate and is widely used for the detection of human measles-IgG [15]. It has been regarded as a standard assay for resolving result discrepancies between chemiluminescent immunoassay and Enzygnost [15]. Noteworthy for its accuracy, Euroimmun is cost-effective, requires less time on deck, and is user-friendly. It offers both semiquantitative and quantitative analysis options, boasting 100% sensitivity and specificity. The determination of human measles-IgG antibody activity with Euroimmun is measured in Milli international units per milliliter (mIU/ml) based on the third International Standard (IS) for Anti-measles (NIBSC code: 97/648) of the WHO.

Statistical analysis

Based on measles IgG seronegativity of 88.2% by 4.2 months of age from an earlier study in South Africa [16], we aimed for a sample size of 323 newborns per site. Samples were randomly selected from each of the sites. Models using various measles antibody decay rates in infancy were explored to estimate the proportion of measles IgG seronegativity among newborns, with 0.05 precision, assuming the true estimate is 0.30. Samples with titers <275 mIU/ml (i.e. inclusive of equivocal results) were categorized as seronegative for the analysis [17–19]. Continuous variables were described using means and standard deviation (SD), and categoric variables were described using counts and proportions. Multivariable logistic regression analysis was performed to explore the association of measles IgG immunity seronegativity with maternal demographic and clinical features. Variables/factors considered in the logistic regression analysis included study site, hemoglobin levels, middle upper arm circumference (MUAC), body mass index (BMI), maternal education, maternal occupation, parity, birth weight, gender, and whether the women were born before or after routine measles vaccination had been implemented at the study site. To investigate the association between maternal age and vaccine implementation, the year when the routine measles vaccination program was introduced in each site was used as per the WHO: Bangladesh (1980), Bhutan (1979), India (1978), Ethiopia (1980), Kenya (1980), Mali (1986), Mozambique (1981), Nigeria (1978), and South Africa (1983) [20,21]. All laboratory specimens and database variables were identified by a numerical identifier. Predictions of anti-measles IgG decay were derived using an IgG half-life estimate of 28 days based on maternal antibody half-life, as well as 40 and 64 days as proposed by Oguti et al and Cáceres et al., respectively [22,23]. Calculations for anti-measles IgG decay employed a standard quadratic equation, expressed as follows: $IgG(t) = IgG_0(\frac{1}{2})^{\frac{t}{t_{1/2}}}$. The model estimates the decline of maternally derived measles IgG levels using an exponential decay function, where antibody concentration at time t was calculated with IgGo representing the measured cord blood IgG concentration at birth, $t_{1/2}$ denoting the assumed half-life of measles IgG (set at 28, 40, or 64 days to account for biologic variability), and IgG(t) indicating the infant's age in days. The proportion of measles seronegativity is calculated from the predicted IgG at monthly intervals up to 6 months of age. Statistical analyses were performed using R v4.3 (Vienna, Austria), STATA version 18 (Texas, USA), and Graph-Pad Prism version 8.0 (San Diego, California). A P-value of ≤0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand in Johannesburg, South Africa (HREC M210850). The parent study and the present study were approved by all the site-specific ethics committees, including the archiving and further testing of serum. Written informed consent was obtained from the mothers, including on behalf of their babies, prior to any study procedure including the archiving and further testing of serum.

Results

Overall, 2,907 cord blood samples were analyzed, including 969 and 1,938 from South Asian and African countries, respectively. The

mean age of mothers was 26.2 (SD 5.5) years, ranging from 23.6 to 30.4 years with the minimum in Bangladesh and a maximum in Nigeria. Overall, 28.5% (774/2,907) had a hemoglobin level of <10.5 g/dl (i.e. anemia), with the prevalence of anemia ranging from 4.2% in Ethiopia (13/308) to 78.8% (254/322) in Bangladesh. Maternal nutritional status differed by country. The overall prevalence of undernutrition (BMI <18.5) was 6.8% (189/2,763), ranging from <2% in most countries except for India (8.7%; 28/231), Mali (17.9%; 55/306), and Mozambique (30.9%; 100/323) (Table 1). Overall, 16.5% (457/2,763) of women had a BMI \geq 30 (obese), with the highest prevalence of obesity being in South Africa (41.6%; 99/238) and Nigeria (43.3%; 140/323). A higher percentage of newborns in Bangladesh weighed <2,500 g (18.3% vs 2.5% to 11.1% elsewhere) (Table 1).

Measles IgG seronegativity

Overall, 49.9% (95% confidence interval [CI] 48.1-51.7%; n = 1,451/2,907) of the newborns were seronegative for measles IgG, with seronegativity being the highest in newborns from Bhutan (73.4%, 95% CI 68.3-77.9%; n = 237/323). Measles IgG seronegativity was also high among newborns from Kenya (65.0%, 95% CI 59.6-70%; n = 210/323), Mali (63.8%, 95% CI 58.4-68.8; n = 206/323), and South Africa (63.2%, 95% CI 57.7-68.3%; n = 204/323) (Figure 1) (Supplementary Table S1).

We further analyzed the risk factors associated with measles IgG seronegativity in newborns at birth. Newborns of mothers born after the widespread implementation of measles vaccination exhibited a significantly higher likelihood of seronegativity compared with those born prior to the MV1 widespread distribution (adjusted odds ratio [aOR] 1.78; 95% CI 1.43-2.21; P < 0.001) (Table 2). Compared with South Africa as a reference group, pregnant women residing in Bhutan and Mali were more likely to give birth to newborns who were seronegative for measles IgG (aOR 1.71; 95% CI 1.14-2.58 and aOR 4.8; 95% CI 1.18-32.5, respectively) (Table 2).

In site-stratified analysis, no association was observed between measles IgG seronegativity and the investigated variables on risk factors of the mothers and infants in Bangladesh, India, and Nigeria (Supplementary Tables S2, S5, S9).

In Bhutan, however, newborns of mothers born postwidespread MV implementation exhibited a 3.41-fold increased likelihood of measles IgG seronegativity compared with their counterparts born from mothers with measles infection-induced immunization (aOR 3.41; 95% CI 1.68-6.9; P = 0.001) (Supplementary Table S3). The findings also indicate a diminished correlation between maternal hemoglobin levels and measles IgG seronegativity in neonates. Newborns, born from mothers with mild anemia show a decreased likelihood of measles IgG seronegativity when contrasted with neonates born to mothers with normal levels of hemoglobin (aOR 0.42; 95% CI 0.21-0.84; P = 0.01 and aOR 0.30; 95% CI 0.10-0.90; P = 0.03, respectively) (Supplementary Table S3).

In Ethiopia, a similar increased trend of measles seronegativity was observed in newborns of mothers born post-widespread of MV1 immunization compared with newborns of mothers with pre-widespread MV1 immunization (aOR 1.93; 95% CI 1.09-3.43; P = 0.02) (Supplementary Table S4). Furthermore, the birth weight of the newborn also emerged as a significant factor. The odds of being measles IgG seronegative for underweight newborns (<2.5 g) were 6.64 times than the odds of those with normal-weight (\geq 2.5-4.5 kg) (aOR 6.64; 95% CI 1.15-38.17; P = 0.034) (Supplementary Table S4).

Findings in Kenya observed a positive correlation between newborns of mothers with vaccine-induced immunity and the proportion of seronegative children, as opposed to newborns of mothers naturally immunized against measles (aOR 1.89; 95% CI 1.01-3.54; P = 0.04) (Supplementary Table S6). Furthermore, based C. Bokop, N. Dhar, A. Izu et al.

Table 1

Baseline characteristics of mothers and newborns at delivery in nine l	low- and middle-income African and South Asian countries.
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Characteristics	Bangladesh	Bhutan	Ethiopia	India	Kenya	Mali	Mozambique	Nigeria	South Africa	Overall
Total participants Maternal age, mean (SD), year Hemoglobin (g/dl)	323 23.6 (4.6)	323 26.3 (4.9)	323 25.1 (4.4)	323 26.4 (4.2)	323 25.8 (5.1)	323 26.1 (6.2)	323 25.3 (6.4)	323 30.4 (4.6)	323 26.7 (5.9)	2907 26.2 (5.5)
Median (interquartile range)	10 (9-10)	12.7 (11.8-13.2)	12.7 (12-13.5)	11.9 (11.1-12.6)	11 (9-12)	11.35 (10.7-12)	10.8 (9.9-11.8)	11.3 (10.6-12)	12.1 (11.1-12.9)	11.6 (10.2-12.6)
12-16 (Normal) 10.6-11.9 (mild	27 (8.4) 41 (12.7)	226 (73.4) 64 (20.8)	239 (77.6) 56 (18.2)	151 (46.7) 138 (42.7)	89 (29.2) 66 (21.6)	64 (38.1) 65 (38.7)	74 (22.9) 106 (32.8)	93 (31.7) 127 (43.3)	178 (55.4) 93 (28.9)	1.141 (40.7) 756 (28.3)
anemia) ≤10.5) (anemia) Maternal mid-upper arm	254 (78.8)	18 (5.8)	13 (4.2)	34 (10.5)	150 (49.2)	39 (23.2)	143 (44.3)	73 (24.9)	50 (15.6)	774 (28.9)
circumference (cm) Under-weight (<23)) 24 (7.4)	17 (5.5)	72 (22.9)	21 (8.1)	30 (9.3)	(0)	6 (1.9)	4 (1.2)	13 (4.4)	187 (7.5)
Normal weight $(\geq 23 \text{ to } < 33)$	299 (92.6)	284 (92.2)	243 (77.1)	198 (75.9)	280 (86.7)	31 (93.9)	302 (93.5)	265 (82.1)	213 (72.2)	2,115 (84.5)
Overweight (≥33) Maternal body mass index	(0)	7 (2.3)	(0)	42 (16.1)	13 (4.1)	2 (6.1)	15 (4.5)	54 (16.7)	69 (23.4)	202 (8.1)
Underweight (<18.5)	0 (0)	0 (0)	2 (0.7)	28 (8.7)	0 (0.0)	55 (17.9)	100 (30.9)	(0)	4 (1.7)	189 (6.8)
Normal weight (18.6-24.9)	144 (44.6)	70 (22.1)	156 (53.2)	130 (40.5)	154 (48.1)	225 (73.5)	159 (49.2)	58 (17.9)	73 (30.7)	1.169 (49.1)
Overweight (25-29.9)	179 (55.4)	161 (50.9)	116 (39.6)	102 (31.8)	113 (35.3)	26 (8.5)	64 (19.8)	125 (38.7)	62 (26.1)	948 (34.3)
Obese (≥ 30) Highest level of education	(0)	85 (26.9)	19 (6.5)	61 (19.0)	53 (16.6)	0 (0)	(0)	140 (43.3)	99 (41.6)	457 (16.5)
No schooling Primary school High school Tertiary	21 (6.5) 45 (13.9) 182 (56.3) 75 (23.2)	60 (18.6) 46 (14.2) 150 (46.4) 67 (20.7)	45 (13.9) 166 (51.4) 51 (15.8) 61 (18.9)	3 (0.9) 17 (5.3) 67 (20.7) 236 (73.1)	39 (12.1) 187 (57.9) 69 (21.4) 28 (8.7)	189 (58.5) 86 (26.6) 42 (13.0) 6 (1.9)	30 (9.3) 120 (37.1) 165 (51.1) 8 (2.5)	1 (0.3) 44 (13.6) 138 (42.7) 140 (43.3)	16 (4.9) 260 (80.5) 47 (14.6)	388 (13.4) 727 (25.1) 1,124 (38.7) 668 (23.0)
Parity Primigravida 1-2	151 (46.7) 144 (44.6)	197 (60.9) 109 (33.7)	187 (57.9) 112 (34.7)	172 (53.2) 131 (40.6)	106 (32.8) 132 (40.9)	54 (16.7) 130 (40.2)	80 (24.8) 146 (45.2)	69 (21.4) 151 (46.8)	121 (37.5) 170 (52.6)	1,137 (39.1) 1,225 (42.1)
≥3 Newborn characteristics Weight (kgs)	28 (8.7)	17 (5.3)	24 (7.4)	20 (6.2)	85 (26.3)	139 (43.0)	97 (30.0)	103 (31.9)	32 (9.9)	545 (18.8)
<2.5 ≥2.5-4.5 ≥4.5	59 (18.3) 264 (81.7) 0 (0.0)	14 (4.3) 306 (94.8) 3 (0.9)	9 (2.8) 312 (96.6) 2 (0.6)	36 (11.1) 286 (88.5) 1 (0.3)	28 (8.7) 295 (91.3) 0 (0.0)	34 (10.5) 286 (88.5) 3 (0.9)	13 (4.0) 308 (95.4) 2 (0.6)	8 (2.5) 312 (96.6) 3 (0.9)	10 (3.1) 310 (95.9) 3 (0.9)	211 (7.3) 2,679 (92.2) 17 (0.6)
Gender Male Female	166 (51.4) 157 (48.6)	179 (55.4) 144 (44.6)	176 (54.5) 147 (45.5)	169 (52.3) 154 (47.7)	160 (49.5) 163 (50.5)	190 (58.8) 133 (41.2)	185 (57.3) 138 (42.7)	163 (50.5) 160 (49.5)	168 (52.1) 155 (47.9)	1,556 (53.5) 1,351 (46.5)

on BMI, newborns from women classified as obese in Kenya, exhibited a positive association with an increase measles IgG seronegativity in newborns (aOR 2.85; 95% CI 1.16-6.98; P = 0.02) (Supplementary Table S6).

In Mali, relative to newborns of naturally immunized mothers, there was a high odds of being measles IgG seronegative in newborns of mothers born post-widespread MV distribution (aOR 1.92; 95% CI 1.00-3.7; P = 0.049) (Supplementary Table S7). In multivariate logistic regression analysis, there was no difference in odds of newborns from mothers being measles IgG seronegative based on parity, hemoglobin level strata, maternal mid-upper arm circumference or BMI, maternal occupation, and education.

The findings from Mozambique reveal two positive associations of measles IgG seronegativity: one between newborns from mothers possessing vaccine-induced immunity (aOR 1.89; 95% CI 1.01-3.5; P = 0.04), and between newborns from mothers classified as overweight based on BMI (aOR 2.86; 95% CI 1.16-6.98; P = 0.02) (Supplementary Table S8).

In the final site examined, South Africa, newborns of mothers born post-widespread MV distribution exhibited a 2.12-fold increased likelihood of seronegativity compared with their counterparts born prior to newborns from mothers born before the vaccine's dissemination (aOR 2.12; 95% CI 1.03-4.34; P = 0.04) (Supplementary Table S10).

Antibody decay

Based on a predictive model assuming an IgG half-life of 28 days, an estimated 65.0% (1,891/2,907), 78.5% (2,283/2,907), and 90.2% (2,622/2,907) of infants would be measles IgG seronegative at 1, 2, and 3 months, respectively, in the absence of additional exposure. Newborns in Bhutan had a high seronegativity rate at birth (73.4%, n = 237/323), and by 3 months, except for three infants, every infant was predicted to be measles IgG seronegative (99.1%, n = 320/323). Although newborns from Nigeria had the lowest seronegativity rate at birth (21.7%, n = 70/323) compared with other study sites, according to our predictions, it would take 4 months for all newborns to be measles IgG seronegative (Supplementary Table S11). Furthermore, this model predicted that all newborns from each geographical site would attain seronegativity by the age of 4 months. However, by the age of 3 months, infants from certain sites demonstrated a more rapid attainment of

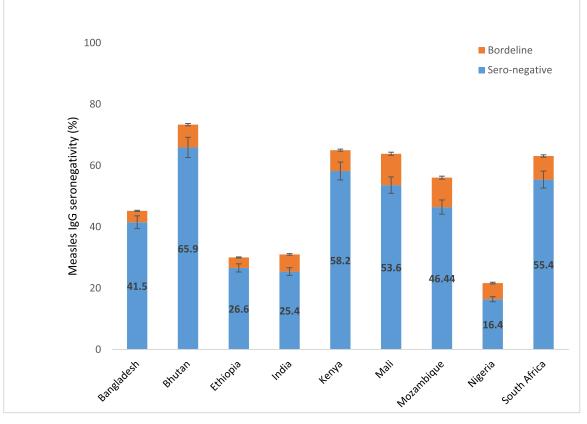


Figure 1. Measles immunoglobulin G seronegative status of newborns at birth in nine low- and middle-income countries.

seronegativity, with percentages exceeding 90%. Notably, this phenomenon was observed in infants in Mali (95.7%, n = 309/323), South Africa (95.0%, n = 307/323), Kenya (93.8%, n = 303/323), and Mozambique (93.8%, n = 303/323) (Supplementary Table S11) (Figure 2a).

Based on a predictive model assuming an IgG half-life of 40 days, 70.8% (2,055/2,907), 88.3% (2,568/2,907), and 100% (323/323) of all infants included in the study were predicted to be measles IgG seronegative at 2, 4, and 6 months, respectively (Supplementary Table S12). By the end of the 4th month, infants born in Mozambique, Kenya, South Africa, Mali, and Bhutan were predicted to reach measles IgG seronegativity levels surpassing 90%, with percentages standing at 92.3% (298/323), 92.6% (299/323), 94.1% (304/323), 94.1% (304/323), and 98.1% (317/323), respectively (Supplementary Table S12). In our predictive model, it was discerned that by the 5th month, measles IgG seronegativity levels in infants were predicted to increase within the range of 90.7-100%. Notably, within this framework, infants from Bhutan emerged as the earliest cohort to achieve full measles IgG susceptibility by the age of 5 months (Supplementary Table S12) (Figure 2b).

In our final predictive model featuring a half-life of 64 days, 63.3% (1,839/2,907), 75.2% (2,185/2,907), and 86% (2,500/2,907) of infants under investigation were predicted to be measles IgG seronegative at 2, 4, and 6 months, respectively (Supplementary Table S13). Although this model depicts a slow decay of measles IgG in comparison to the preceding two models, except for newborns in India, it was predicted that in all other sites, measles IgG seronegativity would exceed 50% at 3 months of age, ranging from 50.8-89.9%. Universal susceptibility was not observed by the 6th month, however, infants in Mozambique, Kenya, South Africa, Mali, and Bhutan were predicted to exhibit measles IgG seronegativity levels above 90%, with rates at 90.4%

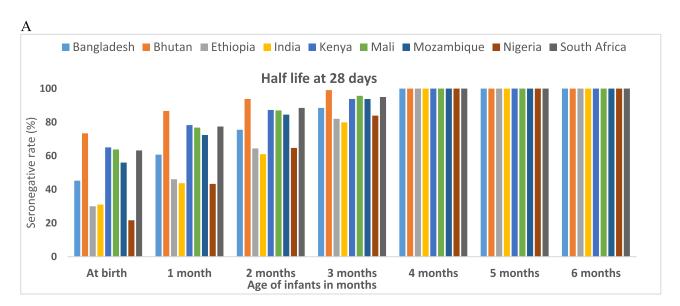
(292/323), 91.3 (295/323), 92.6 (299/323), 93.2 (301/323), and 96.3 (311/323), respectively (Supplementary Table 13) (Figure 2c).

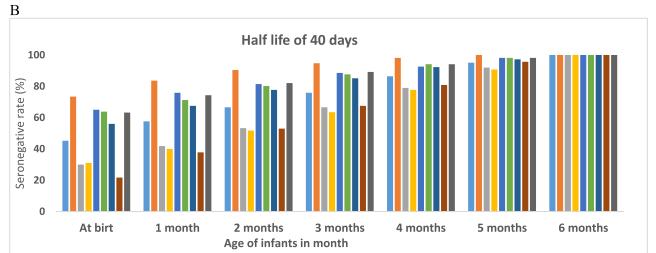
Discussion

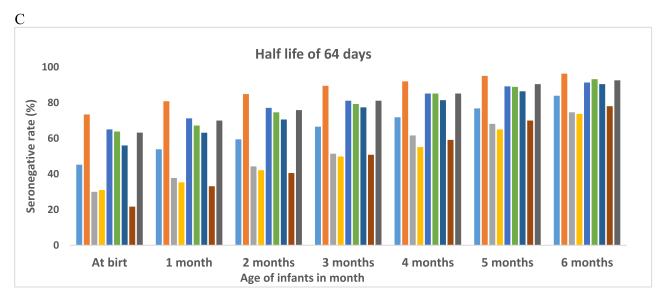
This study, from low-middle-income settings, revealed a high (49.9%) measles IgG seronegativity among newborns at birth. Our study also reported that most (73.4%) of newborns from Bhutan were measles IgG seronegative. Furthermore, newborns of mothers born after measles vaccination had higher odds (aOR 1.8) of measles seronegativity than infants born to mothers with no vaccination history. In addition, our predictive models on the measles IgG antibody decay kinetics predicted that 70.8%, 88.3%, and 100% of newborns would be measles IgG seronegative by 2, 4, and 6 months of age, respectively.

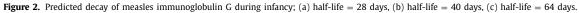
The findings from our study indicate that nearly half of the newborns are born without adequate protection against measles, placing them at immediate risk of infection. This rate is considerably higher than those reported in previous studies, where seronegativity rates ranged from 7.6% in South Africa to 30.4% in China [24–26]. The discrepancy between our findings and these earlier studies could be attributed to differences in maternal immunity, regional vaccination coverage, and environmental factors affecting transplacental antibody transfer [27,28].

Another informative observation in our study is the strong dependence of infant measles IgG levels on maternal antibody concentrations, emphasizing the importance of transplacental-acquired immunity in protecting newborns during the first months of life. This finding aligns with earlier research, suggesting that reduced transplacental transfer of maternal anti-measles IgG contributes to the increasing seronegativity observed in young infants [5,23]. Studies have shown that maternal immunity acquisition, whether through vaccination or natural infection, significantly in-









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Table 2

Overall association of maternal characteristics with measles seronegative status of newborns at birth in nine low- and middle-income African and South Asian countries.

Characteristic of mothers	Measles IgG seronegative	Measles IgG seropositive	Crude_OR	P-value	Adjusted_OR ^a	P-value
Maternal year of birth						
Before vaccine	549/1451 (37.8)	797/1456 (54.7)	Ref			
After vaccine	902/1451 (62.2)	659/1456 (45.3)	1.99 (1.71-2.3)	< 0.001	1.78 (1.43-2.21)	< 0.001
Sites						
South Africa	204/1451 (14.1)	119/1456 (8.2)	Ref			
Bangladesh	146/1451 (10.1)	177/1456 (12.2)	0.48 (0.35-0.66)	< 0.001	0.53 (0.35-0.79)	0.002
Bhutan	237/1451 (16.3)	86/1456 (5.9)	1.61 (1.15-2.25)	0.005	1.71 (1.14-2.58)	0.010
Ethiopia	97/1451 (6.7)	226/1456 (15.5)	0.25 (0.18-0.35)	< 0.001	0.28 (0.18-0.43)	< 0.001
India	100/1451 (6.9)	223/1456 (15.3)	0.26 (0.19-0.36)	< 0.001	0.3 (0.2-0.46)	< 0.001
Kenya	210/1451 (14.5)	113/1456 (7.8)	1.08 (0.79-1.5)	0.623	1.25 (0.82-1.9)	0.295
Mali	206/1451 (14.2)	117/1456 (8.0)	1.03 (0.75-1.42)	0.870	4.8 (1.18-32.55)	0.05
Mozambique	181/1451 (12.5)	142/1456 (9.7)	0.74 (0.54-1.02)	0.065	0.89 (0.59-1.35)	0.589
Nigeria	70/1451 (4.8)	253/1456 (17.4)	0.16 (0.11-0.23)	< 0.001	0.22 (0.15-0.33)	< 0.001
Hemoglobin (g/dl)						
Normal (12-16)	579/1315 (44.0)	562/1356 (41.4)	Ref			
Mild anemia (10.6-11.9)	348/1315 (26.5)	408/1356 (30.1)	0.83 (0.69-1)	0.044	0.88 (0.7-1.11)	0.290
Anemia (≤10.5)	388/1315 (29.5)	386/1356 (28.5)	0.98 (0.81-1.17)	0.791	0.86 (0.66-1.11)	0.238
Maternal MUAC			. ,		. ,	
Normal weight (≥ 23 to < 33)	86/1228 (7.0)	101/1276 (7.9)	Ref			
Under-nutrition (<22.9)	1057/1228 (86.1)	1058/1276 (82.9)	1.17 (0.87-1.59)	0.296	0.92 (0.65-1.32)	0.661
Overweight (\geq 33)	85/1228 (6.9)	117/1276 (9.2)	0.85 (0.57-1.27)	0.438	0.68 (0.4-1.15)	0.149
Maternal BMI			. ,		· · · ·	
Underweight (<18.5)	109/1370 (7.9)	80/1393 (5.7)	Ref			
Normal weight (18.6-24.9)	596/1370 (43.5)	573/1393 (41.1)	0.76 (0.56-1.04)	0.088	0.89 (0.59-1.36)	0.595
Overweight (25-29.9)	437/1370 (31.9)	511/1393 (36.7)	0.63 (0.46-0.86)	0.004	0.89 (0.57-1.39)	0.617
Obese (>30)	228/1370 (16.6)	229/1393 (16.4)	0.73 (0.52-1.03)	0.072	1.41 (0.85-2.35)	0.185
Highest level of education			. ,			
No schooling	227/1451 (15.6)	161/1456 (11.1)	Ref			
Primary school	376/1451 (25.9)	351/1456 (24.1)	0.76 (0.59-0.97)	0.030	1.11 (0.76-1.62)	0.589
High school	592/1451 (40.8)	532/1456 (36.5)	0.79 (0.62-1)	0.047	1.03 (0.71-1.5)	0.870
Tertiary	256/1451 (17.6)	412/1456 (28.3)	0.44 (0.34-0.57)	< 0.001	1.03 (0.68-1.56)	0.884
Parity		,	()		(,	
Primigravida	592/1451 (40.8)	545/1456 (37.4)	Ref			
1-2	631/1451 (43.5)	594/1456 (40.8)	0.98 (0.83-1.15)	0.787	1.11 (0.89-1.37)	0.354
>3	228/1451 (15.7)	317/1456 (21.8)	0.66 (0.54-0.81)	< 0.001	0.76 (0.55-1.06)	0.105
Newborn characteristics	220/1101 (1017)	5177188 (2118)				01100
Weight (kgs)						
2.5-4.5	1341/1451 (92.4)	1338/1456 (91.9)	Ref			
<2.5	103/1451 (7.1)	108/1456 (7.4)	0.95 (0.72-1.26)	0.729	0.98 (0.7-1.39)	0.931
>4.5	7/1451 (0.5)	10/1456 (0.7)	0.7 (0.25-1.82)	0.468	1.08 (0.32-3.57)	0.898
Gender	.,. 151 (0.5)	10,1100 (0.7)	3.7 (0.23 1.02)	0.100	1.00 (0.52 5.57)	0.000
Male	781/1451 (53.8)	775/1456 (53.2)	Ref			
Female	670/1451 (46.2)	681/1456 (46.8)	0.98 (0.84-1.13)	0.747	0.99 (0.83-1.19)	0.941
	0.01101 (10.2)		3.30 (0.01 1.13)	0.7 17	0.00 (0.00 1.10)	

^a ORs were adjusted for all variables in the analysis including sites, vaccine generation, hemoglobin, MUAC, BMI, education, occupation, parity, weight, gender.BMI: body mass index; Ig: immunoglobulin; MUAC: mid-upper arm circumference; OR: odds ratio; Ref, reference.

fluences the quality and quantity of antibodies transferred to the fetus [29]. In this study, maternal measles vaccination status was inferred based on the year routine measles immunization was introduced into the public immunization program in each country, rather than being directly ascertained. This approach provides an estimate of maternal immunity sources (natural infection vs vaccination) at a population level, but it does not account for individual variations, such as catch-up vaccinations or private immunization programs. Nevertheless, this method aligns with previous studies assessing population-level immunity trends. Vaccineinduced immunity, for instance, may result in antibodies with altered epitope specificity or avidity, impairing their transplacental transfer efficiency [5]. Our study supports this, as we observed higher seronegativity in newborns born to mothers with vaccineinduced immunity. Our results corroborate findings from previous studies in South Africa [16,24], Belgium [5], and other regions [30,31]. Although antibodies are a reliable indicator of measles immunity, cell-mediated immunity (CMI) plays a crucial role in longterm protection [32]. The CMI may be as necessary as antibodies in providing immunity against measles. A strong maternal CMI response typically results in higher levels of transferred measles antibodies, which can delay the rate of antibody decay in the infant [33]. Adequate activation of the CMI response may be essential for the development and long-term maintenance of measles antibodies [33]. Maternal antibodies can interfere with measles vaccination, leading to potential vaccine failure in infants. Studies have shown that even low levels of maternal antibodies can inhibit the production of measles-specific antibodies in vaccinated infants, although T-cell responses may still occur. In addition, residual maternal antibodies can neutralize the live attenuated measles virus in the vaccine, preventing adequate seroconversion and leading to primary vaccine failure [34].

Nigeria, one of our study sites, exhibited the highest seropositivity of measles IgG (78.3%) among newborns, suggesting robust natural immunity among women in this region. Our findings corroborate a previous study in Nigeria, suggesting immunity to measles in all newborns investigated at birth [10]. The frequent circulation of the measles virus in these regions might lead to women developing higher natural immunity over time, potentially resulting in a high transplacental transfer to newborns [35]. This could also be due to the frequent circulation of the measles virus in densely populated areas, leading to repeated natural boosts in immunity. Vaccination remains the preferred strategy for measles control. Although natural infection results in robust immunity, it comes at the cost of significant morbidity and mortality, particularly in infants and immunocompromised individuals.

Because newborns were not followed up after birth, the precise value of the decay could not be reported. The prediction of antibody decay was evaluated using three models. Our predictive models indicate a rapid decline in measles IgG levels, with most newborns likely to become susceptible to measles before reaching 4 months of age. This accelerated loss of immunity highlights a critical vulnerability period for infants, which is earlier than the current WHO recommended age for MV1 at 9 months. Previous studies have shown similar trends of early antibody decay, with seronegativity rates rising dramatically by 6 months of age in various countries, including Nigeria [10], India [36], Canada [37], and South Africa [38]. Furthermore, due to the lack of a natural immunologic booster by measles virus not circulating endemically, a concerning trend was observed among infants of naturally immune mothers who tend to become more susceptible to measles at an average of 3-6 months of age, a period potentially shorter in newborns of vaccinated mothers [39]. Supporting this observation, research by Leuridan et al. found the median duration of maternal anti-measles antibodies in infants born from naturally immune mothers was approximately 3.78 months, whereas in infants born to vaccinated mothers, it was notably shorter at 0.97 months [5]. If newborns have antibody concentrations below the protective threshold at birth, their susceptibility to severe measles illness increases [40]. This early loss of immunity calls into question the adequacy of the current vaccination schedule in protecting young infants in regions with high measles exposure. Although our modelbased approach relied on established half-life estimates to predict the timing of seronegativity, we recognize that antibody decay can be influenced by individual variability and environmental factors. To account for this, we used varying half-life values conducted in sensitivity analyses, all of which produced similar findings. The lack of serial serologic measurements in this study means that the exact rate of antibody decay and the timing at which individual infants become susceptible remain uncertain. Future research incorporating prospective follow-up of infants, with repeated serologic assessments and documentation of measles exposure or infection, would be critical to validate these findings. Moreover, such studies could inform whether alternative immunization strategies, such as earlier measles vaccination or maternal immunization during pregnancy, could effectively reduce early-life vulnerability.

The WHO recommended age for measles immunization in children was based on the assumption that maternal immunity would protect infants for at least 9 months after birth. However, infants younger than 6 months of age accounted for more than 32% of all reported measles cases in the African and Western Pacific region [9]. Moreover, findings from our study observed a substantial number of newborns at risk of measles infection from birth. Findings from this study support the emerging concern of measles susceptibility during early infancy and before the age (9 months) which WHO recommends for MV1. Strategies aimed at mitigating measles susceptibility prior to the age at which the first vaccine is given warrant urgent consideration within public health frameworks. A booster dose of MV in non-pregnant women of reproductive age could also assist in boosting immunity and enhancing transplacental anti-measles IgG in a future pregnancy. However, whether measles vaccination of non-pregnant women enhances transplacental measles IgG transfer in a future pregnancy has not been evaluated and such a strategy may be challenging to implement. Another strategy could be early vaccination of infants at 4-6 months of age. Evidence from studies evaluating early measles vaccination suggests that immunization as early as 4.5 months and at 6 months has been explored, including in South Africa, with varying outcomes in terms of immunogenicity and protection [16,41]. Although early vaccination may provide critical protection in settings with high measles transmission and waning maternal antibodies, concerns remain regarding potential vaccine failure due to interference from residual maternal antibodies. More data would be required to determine whether maternal-acquired measles IgG may interfere with infant immune responses and to refine the optimal timing of early immunization to maximize both its safety and effectiveness.

In conclusion, current WHO recommendations for MV1 at 9 months may leave a significant window of susceptibility for infants, particularly in regions with high measles seronegativity rates. Consideration should be given to lowering the age of the first vaccine dose to 4-6 months to better protect infants during their most vulnerable early months, possibly coupled with two additional doses before 2 years of age.

The study's main limitation is the lack of longitudinal follow-up data, which prevents direct assessment of how measles-IgG antibodies decay over time in newborns. Instead, the study relies on predictive models, which may not fully capture the actual dynamics of antibody decline. Nevertheless, the seronegativity at birth already showed a high proportion of neonates would be susceptible to measles. In addition, enrolling pregnant women only from 37 weeks of gestation onward may lead to an underestimation of the association between maternal antibody levels and measles seronegativity with adverse outcomes, such as preterm birth or stillbirth. Another limitation of this study is the lack of data on certain confounding factors that may influence transplacental antibody transfer. Although our study did not include HIV-positive participants, we enrolled otherwise healthy mother-newborn pairs, thereby minimizing the influence of major maternal comorbidities on transplacental antibody transfer. Consequently, although our findings may not be fully generalizable to the broader population, they likely represent a conservative estimate of neonatal measles susceptibility. Other unmeasured factors, such as maternal co-infections and broader indicators of nutritional status beyond anemia and obesity may further accentuate the observed trends. These considerations should be taken into account when interpreting our results.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

CB, ND, SAM, and GK conceptualized the study. CB did the sample analysis. CB, ND, AI, SAM, and GK did the statistical analysis. GA, MMA, JAB, MMB, TEC, CLC, PD, MI, AMK, NM, SaM, StM, SO, RDS, SKS, SS, RS, BS, EAFS, SOS, MDT, BV, GK, and SAM are site principal investigators and enrolled participants, collected data. CB and GK accessed and verified the data. CB prepared the first draft. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

De-identified individual-level participant data and data dictionary will be available for sharing after approval of a proposal by the University of the Witwatersrand Human Ethics Research Committee and following a signed data access agreement. Requests for data sharing can be directed to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107882.

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