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The waning of maternal measles antibodies: A multi-country maternal-infant seroprevalence study

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SUMMARY

Objectives: To assess geographical variation in maternal measles antibody levels from birth to nine months of age, to inform recommendations for the timing of the first measles vaccine dose.

Methods: Stored infant serum samples from 11 countries taken at delivery and/or follow-up time points prior to measles vaccination (N=2845) were tested for measles plaque reduction neutralisation (PRNT) and measles, mumps, and rubella immunoglobulin G at a central laboratory.

Antibody decay in infants was modelled using linear mixed effects models with participant-level random intercepts and random slopes. Proportions of infants with antibody concentrations above the clinical protection threshold (0.12 IU/mL) were estimated at each age.

Results: At birth, most (94%, 519/552) infants had PRNT ≥0.12 IU/mL, but geometric mean concentrations ranged from 0.32 IU/mL (Guatemala) to 1.60 IU/mL (Pakistan).

There was no geographical variation in the decay rate of PRNT nor immunoglobulin G.

Geometric mean PRNT fell below 0.12 IU/mL between ages 2.5 months (Guatemala) and 6.2 months (Pakistan).

At age 6 months, < 50% of infants had PRNT ≥0.12 IU/mL in all countries except Pakistan.

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Conclusions: Reliance on maternal antibodies for protection until age 9 months or later leaves most infants with insufficient direct protection against measles infection between ages 6–9 months.

Introduction

Measles is a highly contagious viral disease spread by airborne or droplet transmission. Symptoms include fever, maculopapular rash, cough, coryza, and conjunctivitis.[1] Complications can affect many organs and often include otitis media, laryngotracheobronchitis, pneumonia (the most common cause of death from measles in young children), stomatitis, diarrhoea and febrile seizures. Rarer complications include encephalitis and sub-acute sclerosing panencephalitis (SSPE). Complications are more common and more severe in poorly nourished and/or chronically ill children, including those who are immunosuppressed. Patient management involves mainly supportive therapy; there is no specific antiviral therapy for the treatment of measles and disease control largely depends on prevention.[1]

In contrast, mumps is normally a mild, self-limiting disease, frequently reported in children aged 5–9 years, and mostly disappears without sequelae. Rubella is typically mild in children but dangerous in pregnant women, as infection can result in miscarriage, fetal death, stillbirth, or congenital malformations, known as congenital rubella syndrome (CRS). Rubella is combined with measles in the widely used measles-rubella (MR) vaccine, and mumps is part of the measles-mumps-rubella (MMR) vaccine that is also scheduled by many countries, so although the precise timing of vaccination in early life is not critical for these infections, they are considered here alongside measles.

Only one stable serotype of the measles virus has been described, and a safe, effective live-attenuated vaccine is available. Vaccine effectiveness in preventing measles disease is estimated to be 95% after one dose and 96% after two doses.[2] Measles was among the first diseases targeted by the World Health Organization (WHO) Expanded Programme on Immunization in 1974. Global efforts towards measles elimination have increased vaccine coverage over the last six decades, and today more than 70% of the world's children under five years of age are protected by at least two vaccine doses.[3–5] However, major setbacks on the road to global measles elimination have occurred, with outbreaks occurring in areas with low vaccination coverage.[4] In addition, interruptions to immunisation programmes during the COVID-19 pandemic have had further detrimental effects.[4–6] Sustained two-dose vaccination coverage of ≥95% is required to provide sufficient herd immunity to prevent persistent measles endemicity.[7]

Increasingly, pregnant women today will have acquired their measles immunity from vaccination. Measles vaccine induces lower immunoglobulin G (IgG) antibody concentrations than natural infection. This, in combination with increasing maternal age at first childbirth and fewer opportunities for natural boosting, can result in lower maternal IgG concentrations during pregnancy and consequently fewer maternal antibodies being transferred to the infant across the placenta.[8–10] The lower IgG levels in infants at birth can result in an increased susceptibility to measles infection prior to first measles-containing vaccine (MCV1).[8,9,11]

Estimates of global measles deaths, prior to the COVID-19 pandemic, in 2019 ranged from 94,424 to 207,500.[12,13] The majority (85%) of deaths occurred in children < 5 years old[12,13]; case-fatality in this age group is estimated to be around 3%.[14] In studies of measles cases in healthcare facilities and outbreak settings in children < 5 years of age, the highest incidence was seen in those aged 6–9 months (Supplementary figure 1).[15–17]

In countries where incidence and mortality from measles in the first year of life are high, MCV1 is currently recommended at age nine months to limit the risk of interference from maternal antibodies, followed by measles-containing-vaccine second-dose (MCV2) at age 15–18 months.[7] In contrast, in countries with lower levels of measles circulation, the recommendation for MCV1 is 12 months of age, with the age of MCV2 to be based on programmatic considerations to achieve highest coverage.[7] Concerns about serious morbidity and mortality due to measles infection in very young infants have led to an earlier vaccination policy at 6 months of age in South Africa.[18] However, infants vaccinated at six months of age have been shown to mount a reduced immune response compared with those vaccinated at nine months of age, or may fail to respond at all, because there can be interference from residual maternal IgG, termed blunting, as well as differences in immune responses with age.[19] This reduction in the ability to mount robust long-term protection needs to be weighed against the need for protection early in life when the risk and severity of infection is highest.

We investigated the natural decay of transplacentally transferred maternal antibodies for measles, mumps, and rubella in infant serum samples from 11 countries. This enabled us to explore geographical differences in the time when infants become susceptible to measles infection to inform decision-making on the timing of MCV1 administration.

Materials and methods

Samples selection/criteria

Residual cord/infant serum samples from vaccine studies carried out between 2011–2023 across eleven countries (The Gambia,[20] Ghana, Guatemala,[21] Mali,[22] Nepal,[23] Netherlands,[24] Pakistan,[25] Thailand,[26,27] Uganda,[23] UK,[28] Vietnam[29]) were sent to a central accredited public health laboratory (RIVM, Netherlands) for testing (Supplementary tables 1–3).

Each individual study had ethical approval for the conduct of their study collection of samples and all participants provided informed consent. Further details are available in their individual study publications (see reference list). Each site investigator ensured that appropriate ethnics approvals as required by local governing bodies were in place for the shipping and processing of samples. Results were anonymised for analysis. Sample time points according to study protocols were available for all countries (Supplementary Table 1). Data on the exact timing of sampling (in days) were received from all countries except for Pakistan. All samples were collected prior to receipt of the first scheduled measles vaccine. Samples from infants born to HIV-positive women were not available.

Laboratory methods

Measles virus (MeV)-specific antibody concentrations were assessed by two different assays:

- MeV-specific neutralising antibody concentrations were assessed using a modified plaque reduction neutralisation test (PRNT), as endorsed by the World Health Organization, following a previously established test protocol.[30,31] The WHO 3rd International Standard for measles virus antibody (3 IU/mL; NIBSC code (97/648)) was included. The PRNT threshold of clinical protection is defined as neutralising antibody concentrations ≥0·12 International Units (IU)/mL.[32]
- MeV-specific IgG was assessed by fluorescent bead-based multiplex immunoassay (MIA) as previously described.[33] MeV specific IgG concentrations of the sera were expressed in IU/mL based on the performance of the 2nd international standard for measles (serum 66/202, 5 IU/mL, NIBSC, Potters Bar, United Kingdom).

PRNT is generally considered to be the gold standard assay for measles antibody quantification. The multiplex immunoassay (MIA) is a more affordable and rapid, high-throughput assay that requires a smaller volume of serum and can simultaneously measure antibodies for multiple antigen targets. Although the MIA was calibrated against the neutralisation standard, no accurate threshold of clinical protection for the MIA assay has been defined. To assess correlation, we excluded values within the range of test uncertainty, which was considered to be ≤0.03 IU/mL for measles PRNT and ≤0.06 IU/mL for measles MIA, based on geometric mean concentrations of measles naïve sera (internal validation, RIVM).

Mumps and rubella specific IgG concentrations were also assessed by MIA and expressed as RIVM units/mL (RU/mL) and IU/mL, respectively.[33]

For Nepal and Uganda, results were available for measles and rubella IgG only.

Data cleaning

We excluded infant results for a particular assay if we observed a ≥4-fold rise in antibody concentration between visits, suggesting natural infection or unreported vaccination (number of infants: measles PRNT n=9, measles IgG n=16, mumps IgG n=40, rubella IgG n=21; there was some overlap e.g. if combined vaccines were received). Subsequent results for that infant for that assay, if available, were also excluded.

Statistical analysis

Decay models

The decay of maternal measles antibody in infants in the first year of life was modelled using linear mixed effects models incorporating participant-level random intercepts and random slopes to account for repeated samples on the same infants. Inclusion of a country-by-age interaction term to allow the model to account for variation in the rate of decay across countries was explored. Model fit was assessed as lowest Akaike Information Criterion (AIC) value. The models incorporated all countries and all participants, but models were fitted separately for measles PRNT and IgG data for measles, mumps and rubella.

The best fitting decay models were second-order polynomial including infant age and infant age-squared terms. A country-by-age interaction term was assessed in all models but did not improve model fit, with the exception of measles IgG (marginal improvement); we excluded this term from all decay models for consistency.

Models were fitted with and without Pakistan data to explore the impact of the imprecision of the infant age variable for Pakistan in the absence of metadata for this country.

The time taken to fall below the threshold of clinical protection

From model-fitted estimates, we estimated the time required to fall below the threshold of clinical protection and reported country-specific estimates with 95% confidence intervals.

Age-specific seroprotection

From model-estimated geometric mean antibody levels for each country, at each monthly time point of interest from birth to nine months of age, we bootstrapped the predicted proportion of children with antibody above the protective threshold and calculated country- and age-specific proportions seroprotected with 95% confidence intervals (see Supplementary methods).

Analyses were performed in R version 4.3.1.

Vaccine coverage data

Individual vaccination status for mothers was not available. National data were therefore extracted from online databases and publications to assess measles, mumps and rubella vaccine coverage applicable to the mother's birth cohort in each country (Supplementary methods, Supplementary table 4).[3]

Results

Vaccine programmes and coverage data

Mothers participating in these studies were born between 1971 and 2007 during periods of vaccine introduction and/or rapidly increasing measles vaccine coverage in the majority of countries (Supplementary figure 2).

Total samples

Overall, results for 1062 infants were included in the final analysis; 552 cord and 1528 follow-up results (total 2080) for measles PRNT, 569 cord and 2276 follow-up results (total 2845) for measles IgG (Supplementary table 2, Table 1). The majority of infants with gestational age data available (503/527, 95.4%) were born at term (≥37 weeks gestation), 499/1001 (50%) infants with sex known were male (Supplementary table 2).

Comparison of assays (PRNT and measles MIA)

Correlation between measles PRNT and measles MIA across infant samples with values outside test uncertainty (N=1220) was high (R=0.87, $p < 0.001$) (Fig. 1). From the plotted regression line, the PRNT threshold of clinical protection of 0.12 IU/mL[32] was equivalent to 0.12 IU/mL for measles MIA.

Infant antibody concentrations

At birth, the majority of infants had concentrations ≥0.12 IU/mL (519/552, 94.0%) for measles PRNT or (533/569, 93.7%) for measles IgG (Table 1). Highest geometric mean PRNT cord blood concentrations were observed in Pakistan (1.60 IU/mL) and the UK (1.36 IU/mL), whereas the highest measles cord blood IgG concentrations were found in Pakistan (1.87 IU/mL) and Vietnam (1.11 IU/mL) (Table 1). Mumps concentrations were highest in cord blood in The Gambia (479 RU/mL) and Mali (209 RU/mL), and rubella in The Gambia (135 IU/mL) and the UK (115 IU/mL).

Lowest geometric mean PRNT concentrations in cord blood were seen for Guatemala, The Gambia and Thailand (0.32 IU/mL, 0.74 IU/mL and 0.74 IU/mL respectively), and similarly for Guatemala and The Gambia for measles IgG (0.30 IU/mL and 0.77 IU/mL respectively) (Table 1). Lowest mumps concentrations in cord blood were

Table 1
Antibody concentrations for measles, mumps and rubella, and time to loss of immunity and proportions above the clinical protection threshold for measles at 6 and 9 months of age.

Assay and country	Cord			Follow-up	Total	Model estimates - polynomial models without interaction				
	No. of valid results	Geometric mean concentration (95% confidence interval)[a]	Number (%) above threshold of clinical protection	No. of valid results	Number of results in model analysis	Mean time taken to cross threshold of clinical protection in months (95% confidence intervals)	Estimated geometric mean antibody concentration IU/mL at 6 months (95% confidence intervals)	Estimated proportion protected at 6 months (95% confidence intervals)	Estimated geometric mean antibody concentration IU/mL at 9 months (95% confidence intervals)	Estimated proportion protected at 9 months (95% confidence intervals)
Measles PRNT										
The Gambia	97	0.74 (0.58, 0.95)	90 (92.8%)	256	353	2.8 (1.7, 4.2)	0.04 (0.02, 0.07)	11.9 (5.0, 18.8)	0.03 (0.02, 0.05)	6.7 (1.6, 11.7)
Ghana				299	299	2.7 (1.6, 4.1)	0.04 (0.02, 0.07)	5.3 (0.6, 10.0)	0.03 (0.02, 0.05)	2.1 (0.0, 5.0)
Guatemala	93	0.32 (0.26, 0.39)	80 (86.0%)	206	299	2.5 (1.4, 3.7)	0.03 (0.02, 0.06)	5.7 (0.9, 10.5)	0.03 (0.01, 0.04)	2.5 (0.0, 5.7)
Mali	99	1.23 (0.91, 1.65)	93 (93.9%)	189	288	3.8 (2.5, 5.6)	0.06 (0.04, 0.11)	30.0 (20.3, 39.7)	0.05 (0.03, 0.08)	22.4 (13.7, 31.2)
Netherlands	66	1.31 (1.05, 1.65)	66 (100.0%)	152	218	3.4 (2.2, 5.0)	0.05 (0.03, 0.09)	15.2 (7.2, 23.2)	0.04 (0.02, 0.07)	8.3 (2.6, 14.0)
Pakistan	59	1.60 (1.20, 2.13)	58 (98.3%)	111	170	6.2 (4.2, > 9.0)	0.12 (0.07, 0.22)	51.1 (39.9, 62.4)	0.09 (0.05, 0.17)	40.0 (29.1, 50.9)
Thailand	53	0.74 (0.52, 1.03)	50 (94.3%)	101	154	3.5 (2.3, 5.1)	0.06 (0.03, 0.10)	22.6 (13.5, 31.6)	0.04 (0.02, 0.07)	14.9 (7.3, 22.5)
UK	36	1.36 (1.01, 1.83)	36 (100.0%)	58	94	5.6 (3.8, > 9.0)	0.11 (0.06, 0.19)	45.6 (33.8, 57.5)	0.08 (0.05, 0.15)	33.0 (21.9, 44.0)
Vietnam	49	1.12 (0.77, 1.64)	46 (93.9%)	156	205	4.4 (3.0, 6.7)	0.08 (0.04, 0.14)	33.6 (23.3, 43.9)	0.06 (0.03, 0.10)	24.2 (15.2, 33.3)
Overall	552	0.88 (0.79, 0.98)	519 (94.0%)	1528	2080					
Measles IgG										
The Gambia	98	0.77 (0.59, 1.00)	92 (93.9%)	255	353	2.8 (1.9, 3.9)	0.03 (0.02, 0.05)	10.2 (3.9, 16.4)	0.02 (0.01, 0.03)	3.4 (0.0, 7.0)
Ghana				299	299	2.1 (1.3, 3.1)	0.02 (0.01, 0.03)	0.5 (0.0, 2.0)	0.01 (0.01, 0.02)	0.0 (0.0, 0.4)
Guatemala	94	0.30 (0.23, 0.38)	78 (83.0%)	206	300	1.9 (1.1, 2.8)	0.02 (0.01, 0.03)	3.1 (0.0, 6.6)	0.01 (0.01, 0.02)	0.7 (0.0, 2.4)
Mali	100	1.00 (0.75, 1.35)	94 (94.0%)	194	294	2.4 (1.5, 3.4)	0.02 (0.01, 0.04)	10.8 (4.5, 17.1)	0.01 (0.01, 0.02)	4.6 (0.4, 8.7)
Nepal				350	350	2.2 (1.3, 3.1)	0.02 (0.01, 0.03)	5.2 (0.8, 9.6)	0.01 (0.01, 0.02)	1.5 (0.0, 3.9)
Netherlands	67	0.94 (0.73, 1.21)	66 (98.5%)	159	226	2.0 (1.1, 2.9)	0.02 (0.01, 0.03)	3.0 (0.0, 6.3)	0.01 (0.01, 0.02)	0.6 (0.0, 2.2)
Pakistan	59	1.87 (1.44, 2.43)	59 (100.0%)	117	176	5.3 (4.0, 7.2)	0.10 (0.05, 0.17)	41.3 (30.3, 52.2)	0.05 (0.03, 0.09)	20.9 (12.0, 29.8)
Thailand	53	0.83 (0.60, 1.15)	50 (94.3%)	103	156	2.4 (1.5, 3.3)	0.02 (0.01, 0.04)	7.7 (2.4, 13.1)	0.01 (0.01, 0.02)	2.6 (0.0, 5.8)
Uganda				350	350	3.4 (2.4, 4.5)	0.04 (0.02, 0.07)	16.8 (9.0, 24.7)	0.02 (0.01, 0.04)	6.7 (1.7, 11.7)
UK	36	0.86 (0.60, 1.24)	35 (97.2%)	69	105	3.0 (2.0, 4.1)	0.03 (0.02, 0.06)	10.8 (4.4, 17.3)	0.02 (0.01, 0.03)	3.6 (0.0, 7.4)
Vietnam	62	1.11 (0.77, 1.59)	59 (95.2%)	174	236	3.7 (2.6, 4.9)	0.05 (0.03, 0.08)	24.1 (15.5, 32.8)	0.03 (0.01, 0.04)	12.5 (5.8, 19.2)
Overall	569	0.82 (0.73, 0.92)	533 (93.7%)	2276	2845					
Mumps IgG										
The Gambia	98	478.6 (383.7, 597.1)		246	344		16.2 (8.4, 31.7)		11.2 (5.6, 21.5)	
Ghana				286	286		3.9 (2.0, 7.7)		2.7 (1.4[b], 5.2)	
Guatemala	94	104.7 (78.9, 138.9)		205	299		5.6 (2.9, 10.8)		3.8 (2.0, 7.5)	
Mali	100	208.9 (166.8, 261.7)		190	290		6.6 (3.4, 12.7)		4.5 (2.3, 8.8)	
Netherlands	67	186.2 (136.5, 254.0)		158	225		6.5 (3.3, 12.8)		4.5 (2.3, 8.8)	
Pakistan	59	208.9 (152.6, 286.1)		115	174		14.2 (7.2, 28.1)		9.8 (5.0, 19.7)	
Thailand	53	85.1 (52.7, 137.4)		100	153		3.9 (2.0, 7.7)		2.7 (1.4[b], 5.3)	
UK	36	117.5 (67.5, 204.5)		67	103		7.3 (3.7, 14.3)		5.1 (2.5, 10.1)	
Vietnam	62	125.9 (87.7, 180.6)		177	239		5.1 (2.6, 9.8)		3.5 (1.8, 6.7)	
Overall	569	177.8 (157.8, 200.3)		1544	2113					
Rubella IgG										
The Gambia	98	134.9 (107.7, 168.9)		253	351		3.2 (1.9, 5.2)		0.9 (0.6, 1.5)	
Ghana				296	296		0.9 (0.5, 1.4)		0.3 (0.2, 0.4)	
Guatemala	94	44.7 (35.2, 56.7)		206	300		1.5 (0.9, 2.4)		0.4 (0.3, 0.7)	
Mali	100	79.4 (61.5, 102.6)		195	295		1.9 (1.2, 3.1)		0.5 (0.3, 0.9)	
Nepal				349	349		1.4 (0.8, 2.3)		0.4 (0.2, 0.6)	
Netherlands	67	70.8 (57.3, 87.5)		159	226		2.0 (1.2, 3.3)		0.6 (0.3, 1.0)	
Pakistan	59	55.0 (38.6, 78.3)		115	174		2.9 (1.7, 4.9)		0.8 (0.5, 1.4)	

(*continued on next page*)

Table 1 (*continued*)

Assay and country	Cord			Follow-up	Total	Model estimates - polynomial models without interaction				
	No. of valid results	Geometric mean concentration (95% confidence interval)[a]	Number (%) above threshold of clinical protection	No. of valid results	Number of results in model analysis	Mean time taken to cross threshold of clinical protection in months (95% confidence intervals)	Estimated geometric mean antibody concentration IU/mL at 6 months (95% confidence intervals)	Estimated proportion protected at 6 months (95% confidence intervals)	Estimated geometric mean antibody concentration IU/mL at 9 months (95% confidence intervals)	Estimated proportion protected at 9 months (95% confidence intervals)
Thailand	53	24.0 (15.7, 36.7)		101	154		1.1 (0.7, 1.9)		0.3 (0.2, 0.5)	
Uganda				347	347		2.7 (1.7, 4.4)		0.8 (0.5, 1.3)	
UK	36	114.8 (92.2, 143.0)		69	105		4.4 (2.6, 7.5)		1.3 (0.7, 2.2)	
Vietnam	62	27.5 (14.8, 51.1)		176	238		1.4 (0.8, 2.3)		0.4 (0.2, 0.7)	
Overall	569	61.2 (54.1, 69.3)		2266	2835					

PRNT=plaque reduction neutralisation test
[a] IU/mL PRNT, measles IgG, rubella IgG, RU/mL mumps IgG
[b] below lower limit of detection (1.5).

found in Thailand (85 RU/mL) and Guatemala (105 RU/mL) and rubella in Thailand (24 IU/mL) and Vietnam (28 IU/mL).

Best-fitting models did not include a country-by-age interaction term hence the rate of decay of maternal PRNT/IgG was the same across all country settings for each assay. The key determinant for PRNT/IgG levels in later infancy was therefore the infant's starting antibody concentration at birth.

The age at which geometric mean infant measles PRNT fell below 0.12 IU/mL ranged from 2.5 months (Guatemala) to 6.2 months (Pakistan), and for measles IgG below 0.12 IU/mL ranged from 1.9 months (Guatemala) to 5.3 months (Pakistan) (Fig. 2, Table 1).

At six months of age, less than 50% of infants had measles PRNT ≥0.12 IU/mL or measles IgG ≥0.12 IU/mL in all countries, except Pakistan for PRNT where the percentage of infants with concentrations above 0.12 IU/mL was 51% (Fig. 3, Supplementary figure 3, Table 1). This percentage was below 25% in 5/9 countries for measles PRNT and 10/11 countries for measles IgG. By nine months of age, < 10% of infants had concentrations above the protective threshold in 4/9 countries for PRNT and 9/11 countries for measles IgG.

Sensitivity analyses of models excluding Pakistan gave similar estimates (Supplementary figure 4 and Supplementary table 5).

At six months of age, geometric mean mumps concentrations ranged from 4 RU/mL (Ghana and Thailand) to 16 RU/mL (The Gambia), and geometric mean rubella concentrations ranged from 0.9 IU/mL (Ghana) to 4.4 IU/mL (UK) (Table 1).

Discussion

Key findings

We have surveyed measles immunity in diverse regions in a systematic manner by bringing together samples from multiple countries and testing them in a single laboratory with one operator responsible for testing all samples.

Most infants, regardless of where they were born, had sufficient measles antibodies at birth to protect them against disease based on the threshold of 0.12 IU/mL, but by 6 months of age, this was no longer the case. Our results are supported by other individual-country studies, which have identified waning of maternal antibody-derived measles immunity below protective levels from around 2–4 months of age.[34–39] The majority of infants were susceptible to measles at an age when the consequences of infection are more severe than older-age infection, and before they are eligible for their first measles vaccine dose. This finding holds across both high- and low-income settings. These estimates may even over-estimate protection in the population as the majority of our infants were born at term due to study design. In preterm infants (approximately 1 in 10 babies globally[40]), antibody concentrations at birth are generally lower.[41]

An important finding is that no major differences in maternal antibody decay rates were seen across the different countries included in this study. The infant antibody concentration at birth is therefore critical in determining the duration of protection from maternal antibodies.

An infant's antibody concentration at birth depends on his/her mother's antibody concentration and the efficiency of transplacental transfer, both of which vary by country.[42,43] In the absence of individual vaccination status for each mother, we included national estimates of vaccination coverage for context, though acknowledge this will vary regionally. The high measles antibody concentrations in infants from Pakistan may relate to the lower national measles vaccine coverage for their mother's birth cohorts as compared with Guatemala,[3] resulting in higher levels of infection. In Guatemala ≤1 measles case annually has been reported since 1996 whereas in Pakistan measles incidence is high and outbreaks have recently been reported, giving further opportunities for natural boosting.[3,44]

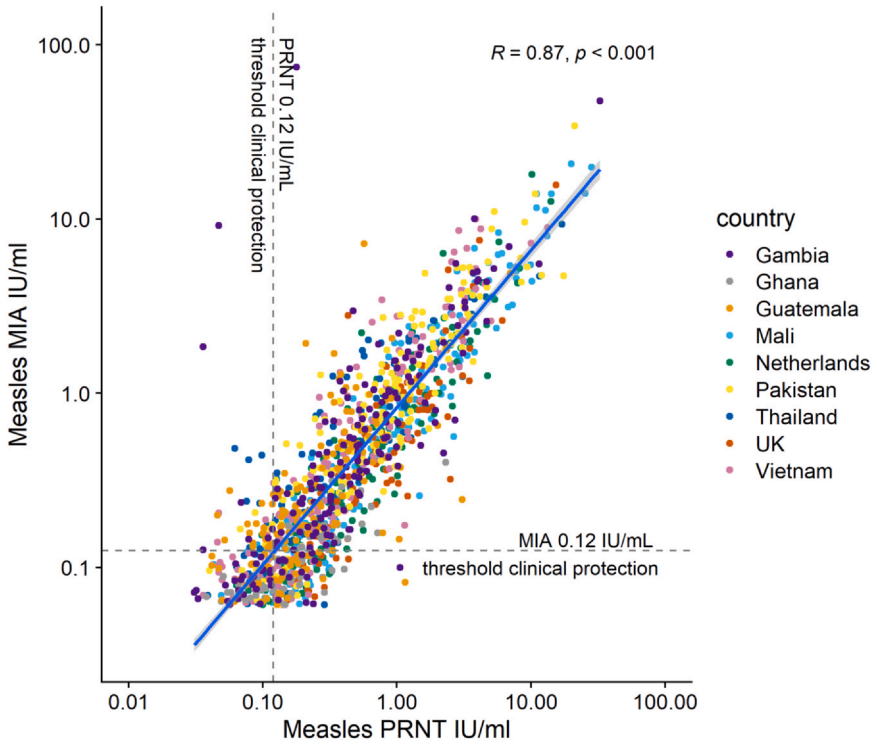

Fig. 1. Correlation between measles PRNT and measles MIA assays for infant samples from nine countries (N=1220)*$. *To assess correlation, we excluded values within the range of test uncertainty, which was considered to be ≤0.03 IU/mL for measles PRNT and ≤0.06 IU/mL for measles MIA, based on geometric mean concentrations of measles naïve sera (internal validation, RIVM). R indicates the Pearson correlation coefficient. $PRNT results were not available for Nepal or Uganda.

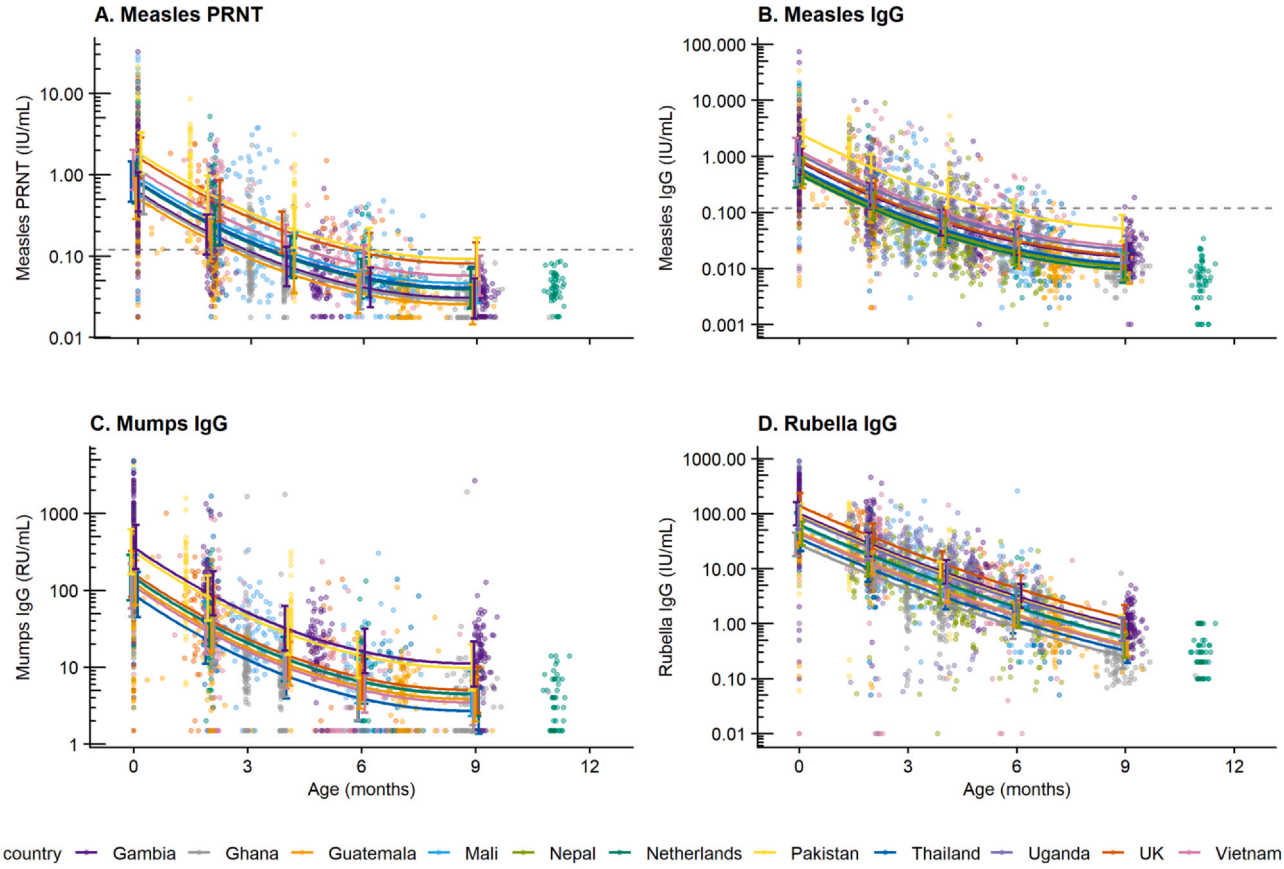

Fig. 2. Maternal measles, mumps and rubella antibody decay in infants prior to receipt of first measles-containing vaccine. Dashed lines indicate threshold of clinical protection 0.12 IU/mL measles PRNT, 0.12 IU/mL measles IgG. NB Only measles IgG and rubella IgG results are available for Nepal and Uganda.

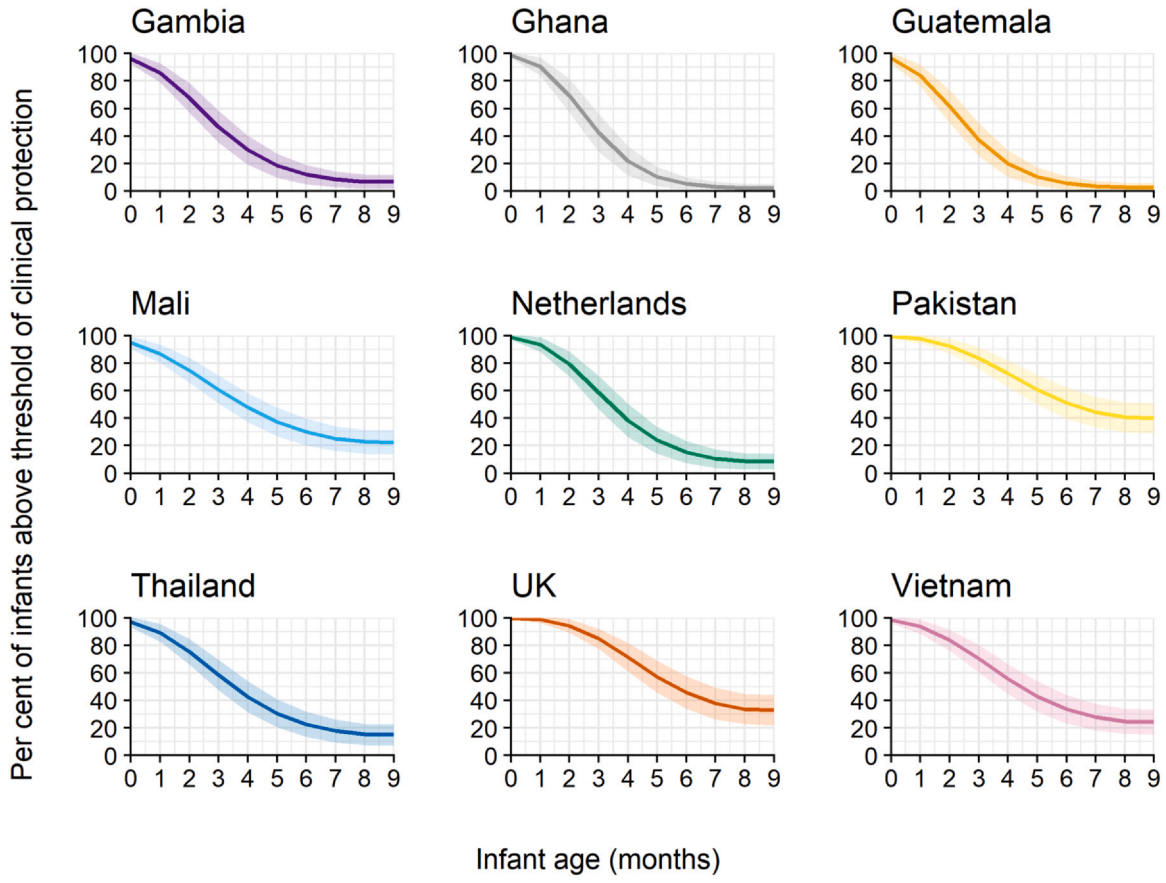

Fig. 3. Proportion of infants above threshold of clinical protection (≥0.12 IU/mL) for measles PRNT at ages 0–9 months, based on model predictions and individual country sample standard deviations.

Early vaccination

High (≥95%) vaccination coverage is paramount to achieving measles control. However, in settings where this has not been achieved, the timing of the first dose of vaccine is particularly important. Given the susceptibility identified in early life, bringing forward the age of first measles vaccine could provide critical protection for young infants. The protection provided by MCV1 is a key consideration for children who only receive a one dose schedule or in those who have a delayed or missed second dose.

A systematic review of early measles vaccination found that when MCV1 was administered to infants younger than 9 months, a large proportion of infants seroconverted, and the vaccine was safe.[45] However, the efficacy of the first dose of vaccine was 51% in infants who received MCV1 at less than 9 months of age compared with 83% in those who were older.[45] Other systematic reviews have also found improved protection, and higher antibody concentrations, at older ages of MCV1 administration when comparing responses at least one-year post vaccination[46] and at unrestricted follow-up times.[47]

This reduced response to early vaccination can arise because of interference with maternal antibodies as well as changes in way the infant immune system responds at different ages.[48] Geometric mean measles PRNT in all our participating countries was ≤0.12 IU/mL by 6 months of age, but lower concentrations than this may still cause interference or blunting of the infant response. We observed only a small decline in antibody concentrations between six and nine months of age (a reduction in average measles PRNT of 0.01–0.03 IU/mL depending on country). This suggests we would not expect much variation in responses to vaccines given at 6 compared with 9 months of age in terms of blunting from residual maternal antibody, but there may still be differences in the response to vaccines at each age as the immune system develops.[49]

In general, first exposure to a pathogen primes the immune system to respond to future exposures; the quality of this initial response is crucial and continues to affect antibody responses to booster vaccines.[48] Therefore, a change to the schedule that results in a reduced response to the first dose may lead children to respond less well to subsequent doses or may result in the need for further booster doses. In a systematic review of the effect of measles vaccination in infants younger than 9 months on the immune response to subsequent doses of measles vaccine, there was evidence of lower antibody concentrations after one or two subsequent doses of MCV compared with children who received their first measles vaccination at 9 months of age or older.[50] However, seropositivity and vaccine effectiveness were high after a two-dose MCV schedule starting before 9 months of age, with no evidence of lesser protection than after a two-dose MCV schedule starting at 9 months of age or later.[50] These assessments were only available for the short term (2 weeks – 12 months) following second dose. In a recent study in the Netherlands, children vaccinated with MMR at 6–8 months of age and then 14 months had a reduced antibody response three years after the 14-month dose compared with children who had received one dose at 14 months only.[19] Further follow-up of these children found that those vaccinated before 8.5 months of age exhibited a markedly faster antibody decay and lost their protective (≥0.12 IU/mL) neutralising antibody levels over 6 years, in contrast with children who did not receive the additional early vaccination, and those who received the additional vaccination between 8.5 and 12 months of age.[51] It is not clear what this means in terms of a child's ability to respond to measles virus. There is some evidence that two-dose protection may be reduced with early (<9 month) MCV1

administration, but data are limited.[47] If vaccination coverage is high, or the reduced concentrations are still sufficient for protection, children vaccinated earlier may still be protected. In addition, the T-cell response to measles vaccine, which may be critical to prevent severe disease, appears to be unaffected by maternal antibodies.[50,52] Schedules that result in poor immune responses may benefit from the addition of booster doses later in life, but there are limited data on the need for or impact of additional boosters.

An example of early measles vaccine administration comes from South Africa where the Expanded Program on Immunizations (EPI) has scheduled measles vaccination at 6 months and a second vaccine at 12 months since August 2016 (previously these vaccines were scheduled at 9 and 18 months of age). However, the impact of this change is difficult to assess because the vaccine was changed at the same time (Schwarz to MeasBio).[18]

The implications for longer-term protection based on different ages of MCV1 and MCV2 administration are still unclear. It will be important to consider what adjustments to the immunisation schedule may be necessary for booster doses if the age of first dose is brought forward, so that the response to the booster dose and seroconversion rates can be maximised. A six-month vaccine appointment is not currently scheduled in many countries but could align with vitamin A supplementation and future scheduling of malaria vaccine in LMICs. Removing measles from the 9 month appointment would also remove interference and improve the response to yellow fever vaccine which is currently scheduled at 9 months in affected countries.[53] In addition, moving the MCV1 age from nine to six months needs to be considered in terms of vaccination coverage. Higher vaccine coverage is generally achieved with an earlier age of vaccine administration, but whether this would outweigh the risk from a lower antibody response is unclear.

Laboratory assays/thresholds

Throughout our measles antibody analyses we have applied the PRNT threshold of clinical protection of PRNT of 0.12 IU/mL (or equivalent MIA threshold) which is widely-used, and referenced in the measles module of the WHO Immunological Basis for Immunization Series.[32,54] However, this threshold has limitations as it was based on a small cohort of adults in the United States and was not performed with World Health Organization International Serum Standards for measles.[55] Ideally, we would apply a threshold applicable to infant populations, but no such threshold is currently available. We observed a strong correlation between the measles PRNT and MIA assays, suggesting the MIA assay may offer an acceptable and more affordable alternative to PRNT. The calculated measles MIA 0.12 IU/mL threshold for clinical protection (with acknowledged limitations) can be applied to this assay going forward in situations where there are not sufficient sera available for PRNT or where PRNT is not affordable. Should a threshold for clinical protection that is specifically relevant to infant populations become available in the future, it should be straightforward to apply it to the antibody decay curves in this analysis.

Limitations

It is possible that differences in sample collection, processing and storage across the different country sites could have resulted in variations in sample degradation that we were unable to account for in our analyses.

The infants participating in the studies within each country were from the specific geographical areas of the study site(s) and as such may differ in their representativeness from infants in the country as a whole. However, regardless of this, the data for each country represents a different global geographical population, as such the similarities in antibody decay rates, and widespread susceptibility by six months of age is striking.

Our interpretation of the rubella and mumps data is limited in the absence of an accepted threshold of clinical protection, but the mean concentrations have been provided and can be used to interpret protection should a threshold become available in the future.

Conclusions/implications

Achieving uniformly high vaccination coverage in all regions is paramount to achieving measles control. Given the high proportion of infants with maternal antibody concentrations below the threshold of clinical protection and the high risk of measles infection at 6–9 months of age in high-incidence settings, early vaccination could potentially provide protection at this vulnerable age. However, this needs to be weighed against the risk of inducing lower measles antibody levels in young infants, and an understanding of whether these antibody levels would be sufficient to prevent severe disease. Without a robust estimate of the threshold of clinical protection, this is difficult to determine.

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Author contributions

MV designed the study. KST performed the data analysis. KST and MV interpreted the data and drafted the manuscript. HtH-vO performed the laboratory analysis. HtH-vO, RvB, FvdK advised on laboratory methodology and interpretation. All other authors provided residual study samples. All authors reviewed and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106531.

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