

Maternal iron status and total immunoglobulin-G influence transplacental antibody transfer across eight diverse geographical settings

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ABSTRACT

Transfer of antibodies across the placenta provides critical early life protection for neonates against infection. Understanding factors influencing efficient transfer is vital for enhancing neonatal immunity and improving maternal vaccination strategies.

Stored maternal and cord serum samples from studies in The Gambia, Guatemala, Mali, The Netherlands, Pakistan, Thailand, UK and Vietnam were processed for measles plaque reduction neutralisation titres (PRNT), and measles, mumps and rubella immunoglobulin G (IgG) (multiplex immunoassay) at a central laboratory ($N = 557$ pairs). Nutritional indicators (ferritin, soluble transferrin receptor, retinol binding protein) and total IgG, were measured in subsets of maternal serum. Transplacental transfer ratios (TPTRs) were calculated and factors associated with maternal IgG, cord IgG and TPTRs explored in multivariable regression.

At delivery, most mothers (range 78 % Guatemala to 100 % Pakistan, Netherlands) and infants (range 86 % Guatemala to 100 % Netherlands, UK) had PRNT above the threshold of clinical protection (0.12 IU/mL).

Maternal and cord antibody concentrations across diverse geographical settings were highly correlated. TPTRs were highest in high-income countries; geometric mean range 0.7 (Pakistan) to 2.2 (Netherlands), and were correlated across antigens. However, TPTRs varied widely within low/middle-income countries.

In models adjusting for country, higher maternal total IgG was consistently associated with lower TPTR. In multivariable regression, lower iron status, indicated by increasing soluble transferrin receptor concentration, was significantly associated with lower TPTR for measles neutralising antibody.

There is marked geographical variation in TPTRs, and following adjustment for this, measurable factors in maternal blood can inform estimates of transplacental transfer efficiency.

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1. Introduction

In the first months of life, infants can be protected from serious infections such as measles by antibodies they received from their mother during pregnancy. Transplacental transfer of antibody, predominantly immunoglobulin G (IgG), begins at around 13 weeks gestation, but the rate of transfer significantly increases in the third trimester, particularly from 36 weeks gestational age [1]. IgG is actively transported across the placenta via binding to the neonatal fragment crystallizable (Fc) receptor (FcRn) in the placental syncytiotrophoblast [1,2], and potentially other FcRs found in the placenta. The placental syncytiotrophoblast is a specialised layer of epithelial cells covering the surface of the placental villi, which are in contact with maternal blood. Following uptake by fluid-phase endocytosis, IgG binds to the FcRn within acidified endosomes which move across and fuse with the fetal side of the syncytiotrophoblast leading to an increase in pH, and release of IgG which then traverses the placental endothelium and enters the fetal blood [1,2].

The mother's antigen-specific antibody concentration determines the amount of antibody available for transfer across the placenta and maternal and neonatal antigen-specific antibody concentrations at birth are highly correlated [2]. The efficiency of antibody transfer across the placenta, measured as the trans-placental transfer ratio (TPTR) is influenced by several factors, which include gestational age, birth-weight, parity, ethnicity, placental abnormalities, maternal infections such as HIV and malaria, as well as total IgG concentration, IgG glycosylation and IgG subclass distribution in maternal blood [1–6]. However, there is uncertainty regarding some of these associations and/or their mechanisms.

The TPTR is particularly important for women with low antigen-specific antibody levels during pregnancy where the efficiency of their transplacental transfer determines whether or not their infant is born with protective levels of antibody. Several vaccines have been licenced for administration during pregnancy (e.g. influenza, pertussis, COVID-19, tetanus, respiratory syncytial virus (RSV)) or are in development (e.g. Group B Streptococcus, cytomegalovirus) [7,8] and the extent to which they will offer protection to infants will be influenced by the TPTR, which can differ between populations [9,10]. Here we used a central laboratory to quantify measles, mumps and rubella antibody concentrations in paired maternal and infant (cord) blood samples from eight countries. By removing potential confounding due to assay variation between different laboratories, we have been able to investigate the extent to which determinants of transplacental transfer can explain differences in cord blood antibody concentrations across diverse geographical locations. Understanding these factors is important for informing policy decisions on administration of vaccines in the pre-conception period and during pregnancy and for the timing of administration of first vaccine doses in infants.

2. Material and methods

2.1. Samples selection/criteria

Serum samples from mother and infant (cord) pairs were collected within seven days of delivery in The Gambia [11], Guatemala [12], Mali [13], The Netherlands [14], Pakistan [15], Thailand [16,17], United Kingdom (UK) [18] and Vietnam [19], as part of vaccination studies. The infant samples from these countries were also analysed within a larger sero-epidemiology study to assess maternal antibody waning during the first months of life [20]. The samples were collected between 2011 and 2018 (Supplementary table 1). HIV-positive women were not included in these studies. The individual vaccination status of the mother for measles/mumps/rubella was not available as these studies had been set up for other purposes (mostly to monitor immune responses to other vaccines).

All samples were collected with informed consent. Stored residual-sera from study sites were shipped to a central accredited public

health laboratory (RIVM, The Netherlands) for processing.

2.2. Country-level data

National data were extracted from online databases and publications for each participant relating to measles, mumps and rubella vaccine coverage applicable to the mother's birth cohort (Supplementary fig. 1, Supplementary methods) [21], country income classification [22], and malaria incidence (five-year average spanning study years and preceding years) [23].

2.3. Laboratory methods

2.3.1. Antibody quantification

Measles virus (hereafter referred to as 'measles')-specific antibody concentrations were assessed by two different assays:

- Measles-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 [24,25]. The WHO 3rd International Standard for measles virus antibody (3 International Units (IU)/mL; NIBSC code (97/648)) was included.
- Measles-specific IgG was assessed by fluorescent bead-based multiplex immunoassay (MIA) as previously described [26]. Measles-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 measles threshold of clinical protection is defined as PRNT ≥ 0.12 IU/mL²⁷. The 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. Mumps and rubella specific IgG concentrations were also assessed by MIA and expressed as arbitrary units/mL (RU/mL), where a value above 45 RU/mL is regarded mumps seropositive, and IU/mL respectively [26,28,29].

To minimise intra-laboratory variability, mother-cord pairs were stored and tested together, and processed within the same assay. For the MIA assay mother-cord pairs were tested on the same plate and for PRNT this applied to the majority of mother-cord pairs. In addition, all serum titrations were standardised against multiple titrations of the WHO reference serum within each assay, allowing consistency checks across plates and positions and harmonising results between assays. PRNT assays were only accepted if control plaque counts and WHO standard performance met strict criteria, with deviations leading to test rejection.

The concentration of total IgG, i.e. the overall immunoglobulin G concentration as opposed to individual antigen-specific IgG concentrations, was measured in a subset of maternal samples from five countries (The Gambia, Guatemala, Mali, Netherlands, Pakistan). Twelve mothers with the highest and lowest transfer ratios within each country across all three MIA assays (within the top and bottom third across all or at least one of measles, mumps and rubella) were selected for testing ($N = 120$).

Total serum IgG levels were assessed by a modification of the measles IgG assay:

Briefly mouse anti-human IgG Fc (9040–01, SouthernBiotech, Birmingham USA) was coupled to beads as previously described [26]. The beads were incubated for 45 min with prediluted serum samples followed by a 30 min incubation with a 1:400 dilution of R-phycoerythrin conjugated mouse anti kappa and lambda lightchain antibodies (9230–09 and 9180–09, SouthernBiotech, Birmingham AL, USA). Beads were finally resuspended in 100 μ L PBS and plates were read with the Flexmap3D (Luminex Corp. Austin, Texas, USA). IgG levels were expressed in mg/mL using a calibrated IgG standard (Sigma, I2511) and

human serum standard NIBSC67–099 as an additional control for inter-assay variation.

2.4. Nutritional indicators

Following observation of a possible correlation between country-level anaemia prevalence in pregnant women [30] and country-level TPTRs in our dataset (Supplementary table 3), and a suggested association in the literature [31], maternal samples with sufficient residual sera from six countries (The Gambia, Guatemala, Mali, Thailand, UK, Vietnam) ($N = 377$) were tested for the following nutritional indicators, along with C-reactive protein (CRP), an acute phase inflammatory indicator, using a Sandwich ELISA technique [32]:

- Ferritin (iron deficiency: $<15 \mu\text{g/L}$ or $< 70 \mu\text{g/L}$ in the presence of inflammation as indicated by $\text{CRP} > 5 \text{ mg/L}$ [33])
- Soluble transferrin receptor (sTfR) (iron deficiency: $\text{sTfR} > 8.3 \text{ mg/L}$ [32])
- Retinol binding protein (RBP) (Vitamin A deficiency: $\text{RBP} < 0.7 \mu\text{mol/L}$ [32])

Maternal CRP levels rise following delivery as part of the inflammatory response and peak at 24 h postpartum [34,35]. As well as being an indicator of iron deficiency, ferritin is an inflammatory marker, so levels of ferritin also rise following delivery. High CRP levels can signal that ferritin results are unreliable for the measurement of iron deficiency, because of the confounding role of inflammation [36]. Within our dataset, high CRP concentrations were frequently observed in maternal samples known to have been taken ≥ 1 day after delivery (Supplementary fig. 2), therefore maternal samples known to have been taken ≥ 1 day after delivery (approaching/at peak CRP) were excluded ($n = 68$, Supplementary table 4) leaving 309 in the final analysis (Supplementary fig. 3 and Supplementary table 5).

2.5. Statistical analysis

TPTRs were calculated for each assay by dividing each individual cord antibody concentration by its corresponding maternal antibody concentration.

Correlations were explored using scatter plots and Pearson's correlation coefficients.

PRNT and IgG concentrations, as well as TPTRs were $\log_{10}$ -transformed in plots and regression analyses.

Factors associated with maternal PRNT and IgG concentrations, TPTRs and cord PRNT and IgG concentrations were explored using linear regression in univariate and multivariable models and presented as geometric mean ratios. Geometric mean ratios indicate the fold (multiplicative) change in antibody concentration for each unit increase in predictor variable. Considering the large number of comparisons across sometimes related variables, only p -values < 0.01 were considered significant.

Possible factors associated with maternal PRNT and IgG concentrations included country, country income status, maternal age and vaccination coverage. For measles, percent coverage of the first dose of measles-containing vaccine (MCV1) was included for the mother's birth cohort in each country. For rubella and mumps, as coverage data were not widely available, vaccination coverage was included as "offered" or "not offered" (coded 1 or 0) at a national level for the mother's birth cohort. Measles-containing vaccine first dose coverage was included in models for mumps and rubella as a possible indicator of general health service delivery/availability. Additional possible factors associated with TPTR and/or cord PRNT and IgG were maternal antigen-specific antibody concentrations, gestational age, birthweight, sex of infant, and malaria incidence. Parity, nutritional indicators and maternal total IgG were explored as possible factors associated with cord and/or TPTR in sub-analyses.

Measles-containing vaccine first dose coverage decreased with increasing maternal age in all sites (range $R = -0.81$ (The Gambia) to -0.98 (UK), all $p < 0.001$) (Supplementary fig. 4). To avoid the effect of these variables cancelling each other out within the regression models, only measles-containing vaccine first dose coverage was included in multivariable models. Country, country income status, and malaria incidence could not be included in the same models as these factors were co-linear so of these, country was selected for inclusion.

Heatmaps for TPTRs across measles, mumps and rubella IgG were produced using the ComplexHeatmap function in R. Deviation from the mean was calculated as z-scores whereby after log-transformation of TPTRs, the overall mean TPTR across all countries for a particular assay was subtracted from each participant's TPTR for that assay and then divided by the standard deviation for that assay so that zero represented the overall mean across all countries on the log-scale, positive z-scores represented higher TPTRs than the overall mean for each specific assay, and negative z-scores represented lower TPTRs than the overall mean for each specific assay. This was then translated into a colour scale (Supplementary fig. 5). Only mother-infant pairs with measles, mumps and rubella TPTRs available were included; each row in the heatmap represents one mother-infant pair. Rows were clustered within each country such that mother-infant pairs with higher ratios are visible at the top of each country and those with lower ratios are visible at the bottom. In addition, to illustrate the relationship between mother's total IgG concentration and TPTR a second heatmap was produced using the subset of mothers with total IgG concentrations available ($N = 120$) and using the same z-scores as the main heatmap. This subset of mother-infant pairs was ordered by mother's total IgG concentration.

Analyses were performed in R version 4.3.1.

3. Results

In total, measles, mumps and rubella IgG concentrations were measured in 599 maternal and 569 cord blood samples (557 mother-infant pairs), of which 579 and 552 respectively (533 pairs) also had a PRNT result (Supplementary table 5). The mean age of mothers ranged from 24.0 years (Guatemala) to 33.6 years (UK), with mean gestational age ranging from 34.6 weeks (Pakistan) to 40.6 weeks (UK) (Supplementary table 1).

3.1. Maternal antibody concentrations

Overall, 92.1 % of mothers (533/579) had measles PRNT $\geq 0.12 \text{ IU/mL}$ threshold of clinical protection [27] at delivery, ranging from 78.0 % (78/100) in Guatemala to 100 % in Pakistan (54/54) and the UK (37/37) (Fig. 1, Supplementary table 5). Geometric mean maternal PRNT concentrations ranged from 0.23 IU/mL in Guatemala to 2.19 IU/mL in Pakistan (Supplementary table 5).

In models that adjusted only for country, lower measles-containing vaccine first dose coverage and older maternal age were each significantly associated with higher maternal measles PRNT and higher maternal measles IgG (Supplementary table 6).

In the subset of maternal blood samples tested, median maternal total IgG concentration was highest in The Gambia and lowest in The Netherlands (Supplementary fig. 6). After adjusting for country, higher maternal total IgG was significantly associated with higher maternal mumps IgG ($p < 0.003$) but this relationship was not significant for other antigen-specific IgG concentrations (Supplementary table 6).

3.2. Infants (cord blood) antibody concentrations

For infants, 94.0 % (519/552) had measles PRNT $\geq 0.12 \text{ IU/mL}$ in cord blood, ranging from 86 % (80/93) in Guatemala to 100 % in The Netherlands (66/66) and the UK (36/36) (Fig. 1, Supplementary table 5). Geometric mean cord PRNT concentrations ranged from 0.32 IU/mL in Guatemala to 1.60 IU/mL in Pakistan (Supplementary table 5).

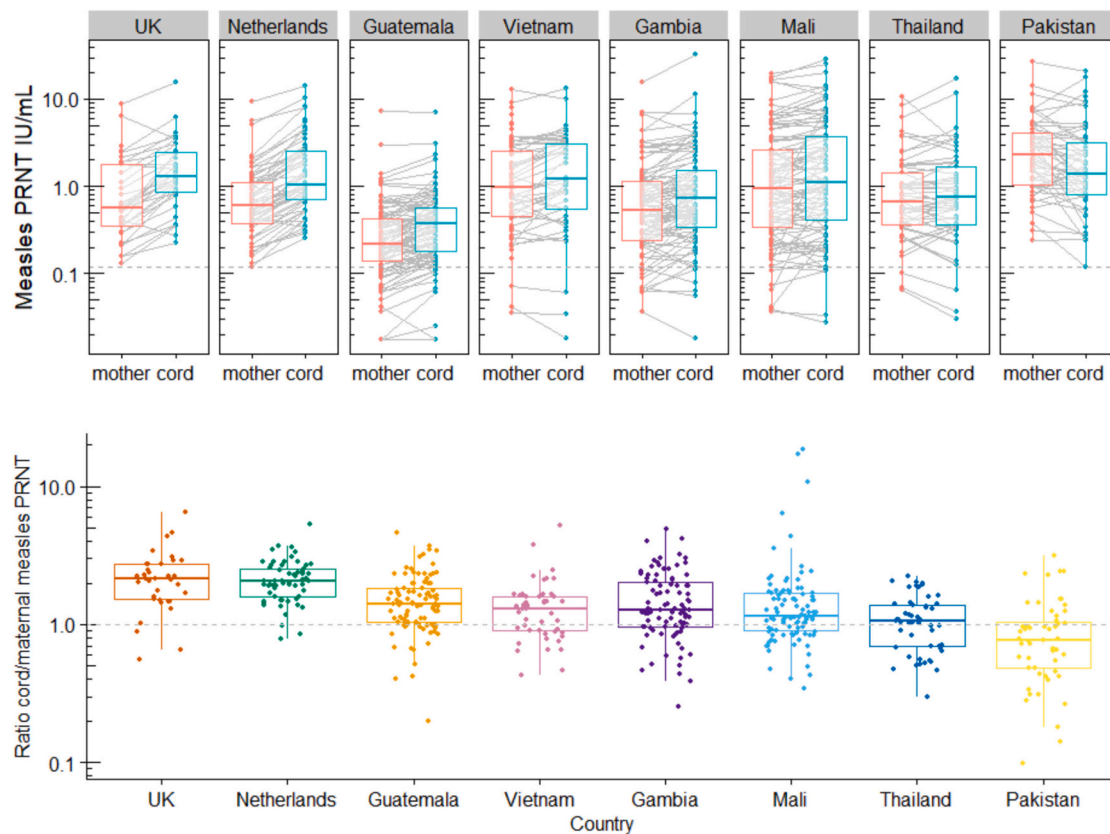


Fig. 1. Mother and cord PRNT (top panel) and cord/maternal ratio (bottom panel) by country. Countries in order of descending median cord/maternal ratio. Dashed line indicates threshold of clinical protection (0.12 IU/mL) (top panel), and cord/maternal ratio of 1 (bottom panel).

Table 1

Factors associated with cord blood concentrations of measles neutralising antibody (measles plaque reduction neutralisation test (PRNT)) and measles, mumps and rubella immunoglobulin G.

Variable	Measles PRNT						Measles IgG						Mumps IgG						Rubella IgG					
	Univariate ^a			Multivariable (N=455)			Univariate ^a			Multivariable (N=473)			Univariate ^a			Multivariable (N=473)			Univariate ^a			Multivariable (N=473)		
	No.	GMR ^b	p-value	GMR	p-value	GMR	No.	GMR	p-value	GMR	p-value	GMR	No.	GMR	p-value	GMR	p-value	GMR	No.	GMR	p-value	GMR	p-value	GMR
Country	552		<0.001	0.94	<0.001	0.93	569		<0.001	0.96	<0.001	0.96	569		<0.001	1.02	<0.001	0.96	569		<0.001	0.98	<0.001	1.56
The Gambia		0.61	0.004	0.94	0.451	1.26	0.256		0.76	0.138	0.96	0.587		2.27	<0.001	1.02	0.860	1.40	0.113		1.70	0.009	0.98	0.036
Guatemala		0.26	<0.001	0.96	0.629	0.79	0.234		0.30	<0.001	0.99	0.907		0.50	<0.001	1.04	0.705	0.86	0.462		0.56	0.004	1.03	0.919
Mali			Baseline		Baseline		Baseline			Baseline		Baseline			Baseline		Baseline		Baseline			Baseline		Baseline
Netherlands		1.07	0.736	1.42	<0.001	0.86	0.443		0.94	0.758	1.67	<0.001		0.88	0.555	1.63	<0.001	0.91	0.648		0.89	0.600	1.67	<0.001
Pakistan ^c		1.30	0.188			0.78	0.226		1.87	0.003				1.00	0.998			0.77	0.201		0.70	0.120		0.72
Thailand		0.60	0.013	0.72	0.001				0.83	0.389	0.96	0.673		0.41	<0.001	0.95	0.645				0.30	<0.001	0.91	0.314
UK		1.11	0.670	1.37	0.005				0.86	0.541	1.46	0.001		0.56	0.029	1.41	0.007				1.44	0.181	1.60	<0.001
Vietnam		0.91	0.671	0.91	0.316				1.10	0.634	0.95	0.522		0.60	0.019	0.87	0.142				0.35	<0.001	0.82	0.023
Gestational age (weeks)	468	1.02	0.687	1.00	0.825			485	1.05	0.265	1.01	0.455		485	1.04	0.409	1.01	0.787		485	1.11	0.027	0.99	0.645
Birthweight (change per 100 grams)	487	1.02	0.183	1.01	0.215			504	1.02	0.089	1.00	0.421		504	1.49	0.781	1.50	0.537		504	1.04	0.017	1.00	0.803
Sex of infant (female baseline)	491	1.15	0.204	0.98	0.729			508	1.22	0.088	1.07	0.145		508	1.46	0.002	1.10	0.071		508	1.11	0.414	1.12	0.022
Maternal age (years)	491	1.04	<0.001					508	1.04	0.001				508	1.03	0.027	1.00	0.544		508	1.01	0.316	0.99	0.195
Measles vaccine (MCV1) coverage (10% change)	491	0.92	<0.001					508	0.92	0.002				508	0.94	0.016				508	0.96	0.172		
Mumps vaccine offered (0/1)														508	0.86	0.675								
Rubella vaccine offered (0/1)																			508	0.50	0.019			
log ₁₀ (mother antigen-specific IgG titre) ^d	533	8.54	<0.001	8.55	<0.001	7.56	<0.001	557	8.76	<0.001	8.62	<0.001	9.25	<0.001	557	9.36	<0.001	9.47	<0.001	8.04	<0.001	557	8.69	<0.001
log ₁₀ (mother total IgG) ^e	120	0.39	0.037			0.19	<0.001	120	0.81	0.675			0.24	<0.001	120	1.06	0.891		0.23	<0.001	120	0.87	0.764	0.25
Country income status	552		<0.001					569		0.279			569		<0.001				569		<0.001			
Low (Gambia, Mali)		1.37	0.012						1.18	0.190				2.57	<0.001					2.79	<0.001			
Middle (Guatemala, Pakistan, Thailand, Vietnam)			Baseline						Baseline					Baseline						Baseline				
High (NL, UK)		1.89	<0.001						1.23	0.190				1.29	0.112					2.27	<0.001			
Malaria (incidence per 1,000 population)	552	1.00	0.016					569	1.00	0.114			569	1.00	<0.001				569	1.00	<0.001			

^aIn univariate analysis, all variables (with the exception of country income status and malaria incidence which are both country-level variables) are adjusted for country to account for country-level differences. p-values <0.01 are in bold.

^bgeometric mean ratio.

^cmeta data not available.

^dmother's PRNT (IU/mL), measles IgG (IU/mL), mumps IgG (RU/mL), rubella IgG (IU/mL) as relevant.

Measles vaccine coverage is included in univariate analysis for mumps and rubella as this may give an indication of general health service delivery/availability.

^eTwelve mothers with the highest and lowest placental transfer ratios within each country across all three MIA assays (within the top and bottom third across all or at least one of measles, mumps and rubella) were selected for testing (total = 120).

In models that only adjusted for country, lower measles-containing vaccine first dose coverage and older maternal age were significantly associated with higher cord blood measles PRNT and measles IgG concentrations (Table 1).

Higher maternal antigen-specific antibody concentrations, were significantly associated with higher cord blood antigen-specific antibody concentrations ($p < 0.001$) across all assays both in univariate and multivariable analyses (Table 1).

In the subset of samples tested, in models that only adjusted for country, maternal total IgG concentration was not significantly associated with cord blood PRNT or antigen-specific IgG concentrations (p -value range 0.037–0.891) but in models that adjusted for country and mother's antigen-specific IgG concentration, higher maternal total IgG concentration was significantly associated with lower cord blood PRNT or antigen-specific IgG concentrations across all assays ($p < 0.001$) (Table 1).

3.3. Transfer from mother to infant (TPTR)

Maternal and cord PRNTs were highly correlated within each country (range $R = 0.78$ (Pakistan) to $R = 0.93$ (Netherlands, Thailand, Vietnam), all $p < 0.001$) (Supplementary fig. 7a). No plateau in cord blood measles PRNT or antigen-specific IgG concentrations was observed at higher maternal PRNT nor antigen-specific IgG concentrations, suggesting a constant transfer ratio across the range of maternal

PRNT or antigen-specific IgG concentrations regardless of antigen or country (Supplementary figs. 7a–d).

The highest geometric mean of TPTRs, for PRNT and measles, mumps and rubella IgG, were recorded in The Netherlands and the UK (1.9 to 2.2 depending on antigen/assay) (Fig. 1, Supplementary table 5). Pakistan had the lowest geometric mean cord/maternal ratios across all assays (0.7 to 0.9 depending on antigen/assay). Despite the low TPTRs in Pakistan, cord blood antigen-specific antibody concentrations in infants were in line with other countries because the maternal blood antigen-specific antibody concentrations in Pakistan were high (Supplementary table 5).

Women with higher TPTR for measles IgG, also generally had higher TPTR for rubella and mumps IgG (Fig. 2 and Supplementary fig. 8).

Across all assays, high-income countries (Netherlands, UK) had significantly higher TPTRs than low/middle-income countries (Table 2) ($p < 0.001$). No other factors (gestational age, birthweight, sex, maternal age, measles vaccine coverage, mumps/rubella vaccine offered) were significantly associated with TPTR across any assay (Table 2).

Higher parity was not significant in multivariable regression across any assay (Supplementary table 7).

3.4. Nutritional indicators and total IgG

Maternal blood ferritin concentrations and retinol binding protein concentrations were not significantly associated with TPTR for any assay

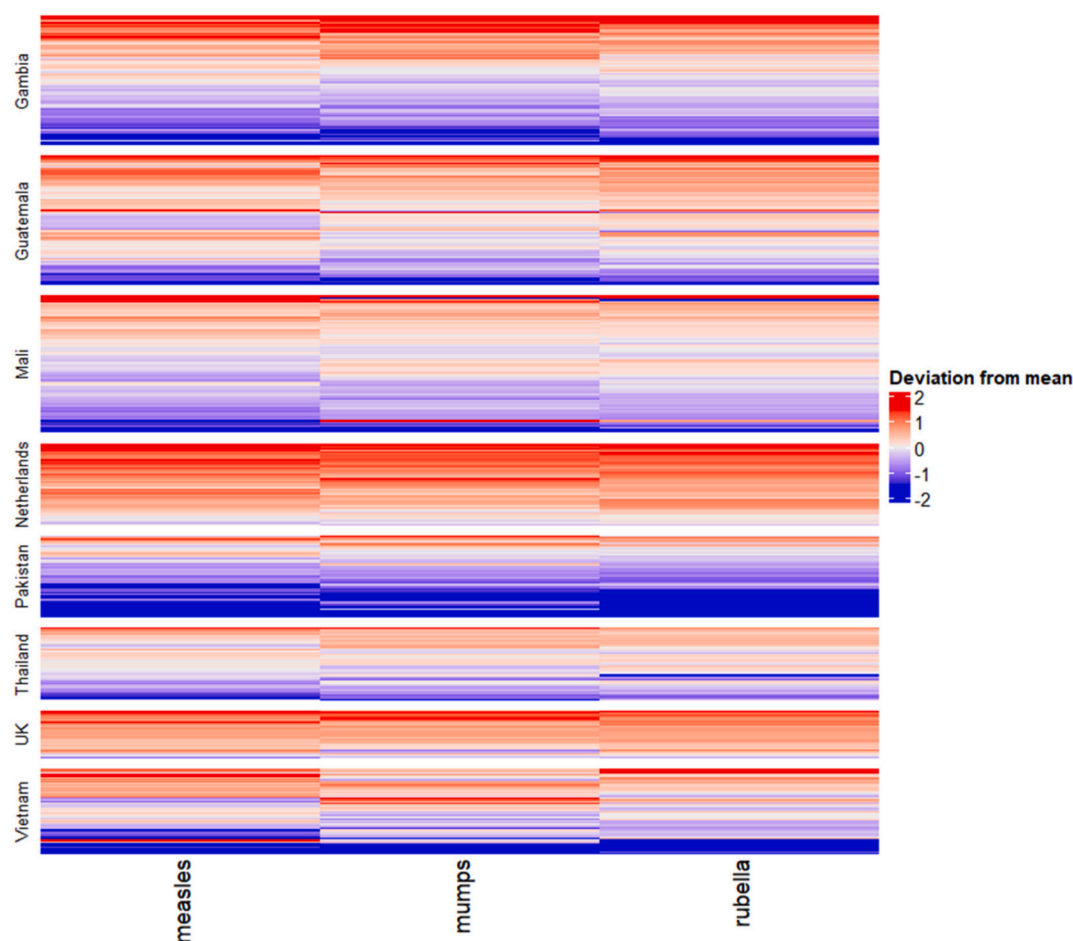


Fig. 2. Heat maps of transplacental transfer ratios for measles, mumps and rubella immunoglobulin G. Red indicates good (above all-country mean on log-scale), blue indicates poor (below all-country mean on log-scale) placental transfer. Each horizontal line represents one mother-infant pair. Upper panel: rows are clustered within each country such that mother-infant pairs with higher ratios are visible at the top of each country and those with lower ratios are visible at the bottom. Lower panel: subset of mothers from five countries with mother's TOTAL IgG results available ($N = 119$; one outlier mother-infant pair excluded), ordered by mother's TOTAL IgG concentration, ascending from top (lowest TOTAL IgG concentration) to bottom (highest TOTAL IgG concentration). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

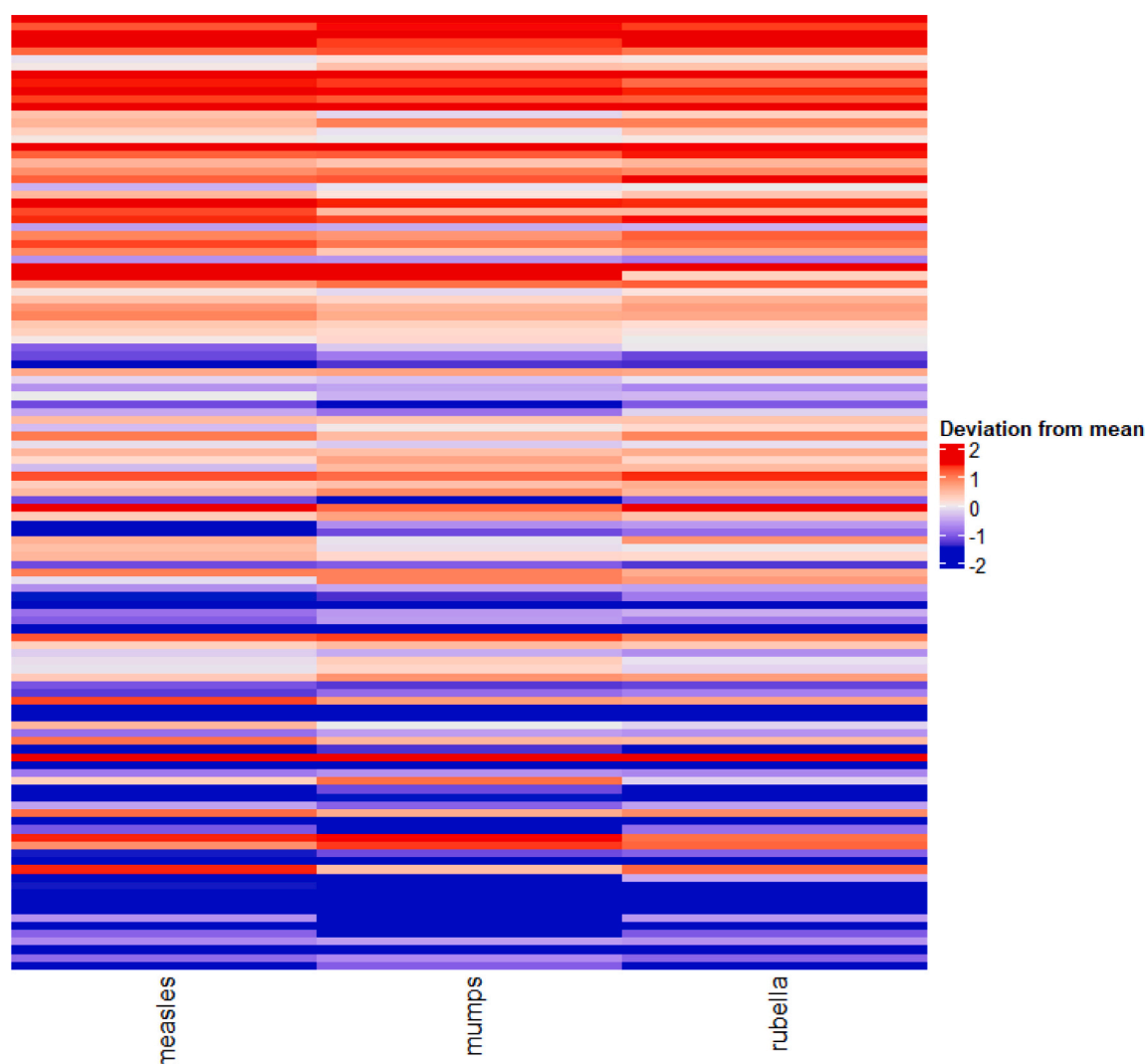


Fig. 2. (continued).

(Supplementary table 8). Increasing maternal iron-deficiency, as indicated by increasing sTfR concentration, was correlated with a reduction in TPTR across most antigen-specific antibodies and countries (R range – 0.36 to 0.12) but none reached statistical significance (Fig. 3, Supplementary fig. 9). Increasing maternal iron deficiency, as indicated by increasing sTfR concentration, was significantly associated with lower TPTR for measles PRNT after adjusting for country and retained significance in multivariable regression ($p = 0.001$) (Supplementary table 8).

Higher maternal total IgG was significantly associated ($p < 0.001$) with lower antigen-specific antibody TPTR after adjusting for country across all four assays (Table 2, Fig. 3).

4. Discussion

This study of >500 mother-infant pairs reveals substantial differences in placental transfer of MMR-specific antibodies across different populations worldwide. Comparison of antibody concentrations in maternal and cord blood samples from different countries has previously been hampered by inter-laboratory assay variability in different studies. By combining samples from eight countries in a single laboratory for processing by the same technician, the inter-laboratory variability is removed in our study, yet large inter-country differences in antibody concentrations and placental transfer ratios remain. These are important observations for developers of vaccines used in the pre-conception period and during pregnancy, as well as public health policy-makers,

as vaccines for which protection relies on placental transfer of antibodies may have substantially different levels of effectiveness in different settings. Maternal antibody concentration is highly correlated with cord antibody concentration and therefore the key determinant of cord antibody concentration at birth [2,38]. Women from high-income settings had higher antibody transfer ratios (efficiency) compared with women in low- and middle-income countries (LMICs), as has been found in previous studies [9,10]. However, substantial variability remained even within LMICs, revealing that country income status is only part of the story.

Previously suggested causes of differences in efficiency of placental transfer across different country settings include higher incidence of maternal hypergammaglobulinemia in low-income countries, poor nutrition including iron-deficiency anaemia, and higher incidence of HIV and placental malaria, which can itself induce hypergammaglobulinemia [31,39]. We were able to explore some of these factors across our different study populations.

Hypergammaglobulinemia is the overproduction of immunoglobulins by plasma cells, resulting in a higher total IgG concentration [40]. It is usually a symptom of a health condition such as an infection, autoimmune disorder, or malignancy. However, different total IgG titres can also arise from different levels of pathogen exposure. An inverse correlation between total IgG and placental measles antibody transfer has previously been reported in individual country studies [41,42]. In our study, higher maternal total IgG was significantly associated with less

Table 2

Factors associated with transplacental transfer ratios for measles neutralising antibody (measles plaque reduction neutralisation test (PRNT)) and measles, mumps and rubella immunoglobulin G.

Variable	Measles PRNT					Measles IgG					Mumps IgG					Rubella IgG				
	Univariate ^a		Multivariable (N=455)			Univariate ^a		Multivariable (N=473)			Univariate ^a		Multivariable (N=473)			Univariate ^a		Multivariable (N=473)		
	No.	GMR [§]	p-value	GMR	p-value	No.	GMR	p-value	GMR	p-value	No.	GMR	p-value	GMR	p-value	No.	GMR	p-value	GMR	p-value
Country	533		<0.001		<0.001	557		<0.001		<0.001	557		<0.001		0.004	557		<0.001		<0.001
The Gambia		1.03	0.705	0.92	0.418		1.01	0.936	0.86	0.136		0.99	0.950	1.00	0.954		0.99	0.883	0.95	0.495
Guatemala		1.08	0.318	1.01	0.957		1.10	0.191	0.98	0.822		1.04	0.664	1.05	0.575		1.14	0.102	1.07	0.417
Mali		Baseline		Baseline			Baseline		Baseline			Baseline		Baseline			Baseline		Baseline	
Netherlands		1.58	<0.001	1.36	0.013		1.72	<0.001	1.51	<0.001		1.60	<0.001	1.70	0.005		1.67	<0.001	1.95	<0.001
Pakistan*		0.57	<0.001				0.62	<0.001				0.64	<0.001				0.54	<0.001		
Thailand		0.78	0.007	0.71	0.001		0.99	0.898	0.93	0.423		0.96	0.671	0.97	0.801		0.99	0.930	1.05	0.685
UK		1.56	<0.001	1.35	0.013		1.54	<0.001	1.40	0.003		1.43	0.002	1.45	0.004		1.57	<0.001	1.80	<0.001
Vietnam		0.96	0.702	0.88	0.213		0.96	0.620	0.89	0.193		0.87	0.132	0.88	0.169		0.88	0.154	0.87	0.104
Gestational age (weeks)	455	1.01	0.497	1.00	0.836	473	1.01	0.638	1.01	0.569	473	1.01	0.536	1.00	0.812	473	0.99	0.512	0.99	0.423
Birthweight (change per 100 grams)	473	1.01	0.316	1.01	0.228	492	1.00	0.536	1.00	0.405	492	1.00	0.594	1.00	0.515	492	1.00	0.796	1.00	0.964
Sex of infant (female baseline)	477	0.97	0.591	0.97	0.593	496	1.04	0.401	1.07	0.180	496	1.11	0.046	1.09	0.090	496	1.10	0.036	1.12	0.017
Maternal age (years)	477	0.99	0.129			496	0.99	0.114			496	1.00	0.685	1.00	0.465	496	1.00	0.315	0.99	0.165
Measles vaccine (MCV1) coverage (10% change)	477	1.01	0.268	1.01	0.381	496	1.02	0.041	1.02	0.046	496	0.99	0.476			496	1.01	0.405		
Mumps vaccine offered (0/1)											496	0.97	0.826	0.98	0.873					
Rubella vaccine offered (0/1)																496	0.91	0.385	0.90	0.373
log ₁₀ (mother total IgG) [§]	120	0.17	<0.001			120	0.23	<0.001			120	0.20	<0.001			120	0.23	<0.001		
Country income status	533		<0.001			557		<0.001			557		<0.001			557		<0.001		
Low (Gambia, Mali)		1.18	0.002				1.09	0.091				1.13	0.027				1.12	0.031		
Middle (Guatemala, Pakistan, Thailand, Vietnam)		Baseline					Baseline					Baseline					Baseline			
High (NL, UK)		1.83	<0.001				1.79	<0.001				1.75	<0.001				1.84	<0.001		
Malaria (incidence per 1,000 population)	533	1.00	0.798			557	1.00	0.211			557	1.00	0.696			557	1.00	0.475		

^aIn univariate analysis, all variables (with the exception of country income status and malaria incidence which are both country-level variables) are adjusted for country to account for country-level differences.

p-values <0.01 are in bold.

[§]geometric mean ratio.

*meta data not available.

Measles vaccine coverage included in univariate analysis for mumps and rubella as this may give an indication of general health service delivery/availability.

*Twelve mothers with the highest and lowest placental transfer ratios within each country across all three MIA assays (within the top and bottom third across all or at least one of measles, mumps and rubella) were selected for testing (total = 120).

Mother's total IgG is not included in multivariable regression because numbers in this subset with available information for all variables are limited.

efficient placental transfer of measles, mumps and rubella IgG. This could explain why transplacental transfer ratios for measles, mumps and rubella IgG were highly correlated, with mothers generally having consistently above or below average antibody transfer. This finding is supported by a study in German women that found transplacental transfer ratios were correlated across seven different antigens [43].

At higher total IgG concentrations there may be more competition between antibodies to cross the placenta. It has been suggested that antibody transfer is a saturable process; once all neonatal Fc-receptors are bound to antibody, defined as at a total IgG threshold of 15 mg/mL, no further antibody can be transported across the placenta [1,44]. The threshold of 15 mg/mL is based on a 1966 study of concentrations of total IgG in mothers and newborns in Switzerland (17 pairs) and central Africa (Republic of the Congo) (38 pairs) [37]. The majority of mothers with total IgG >15 mg/mL (all from Congo) had a transplacental transfer ratio less than 1 and mothers with total IgG <15 mg/mL (all from Switzerland) had a ratio above 1; however, this study did not adjust for any other factors, e.g. gestational age [37]. A similar study of 32 German and 32 Nigerian mother-infant pairs found that the majority of German mothers had total IgG concentrations below 14 mg/mL and immunoglobulins could be concentrated via the placenta, in contrast to the Nigerian mothers who mostly had total IgG concentrations below 14 mg/mL and a transfer ratio below 1 [41]. Whilst we observed a negative correlation between total IgG and placental transfer ratios, our study of 120 mother-infant pairs, showed no evidence that a saturation point exists. Other factors that differentially influence transfer ratios in different settings may have caused the findings seen in previous studies.

Vaccination during pregnancy induces production of vaccine-specific antibodies, which then contribute to the total IgG pool. However, this has not been shown to be sufficient to change the total IgG concentration overall or influence transfer ratios [6,45].

Variation in placental transfer across countries could also partly be explained by differences in the balance of IgG subclasses (IgG1–4) [6] that make up total IgG in women across different countries, genetic variations in IgG [46], as well as other factors that influence IgG variability such as glycosylation [47]. Unfortunately, data on these factors were not available to us for further exploration.

Anaemia and vitamin A deficiency disproportionately affect pregnant women in low-income settings [48,49]. Measurement of these factors could provide a means of assessing the general health of mothers. This in turn could relate to general placental health, and/or may signify a more direct mechanism in placental transfer e.g. vitamin A has been suggested as a possible influence on FcRn expression [50]. We did not find a significant relationship between vitamin A, measured as retinol binding protein, and placental transfer in our study, but interpretation of retinol binding protein data at delivery is complicated as this protein is a negative acute phase inflammatory marker [51], and in addition can be influenced by hormonal changes during pregnancy [52].

Maternal anaemia, assessed as haemoglobin level, was previously reported to associate with reduced placental transfer of IgG antibody to tetanus toxoid, diphtheria toxoid and varicella-zoster virus in a Sri Lankan study [31] and pertussis antibody in Mozambique [51]. We therefore considered whether iron biomarkers predicted TPTR in our study. Ferritin is the most widely used marker of iron status, but did not

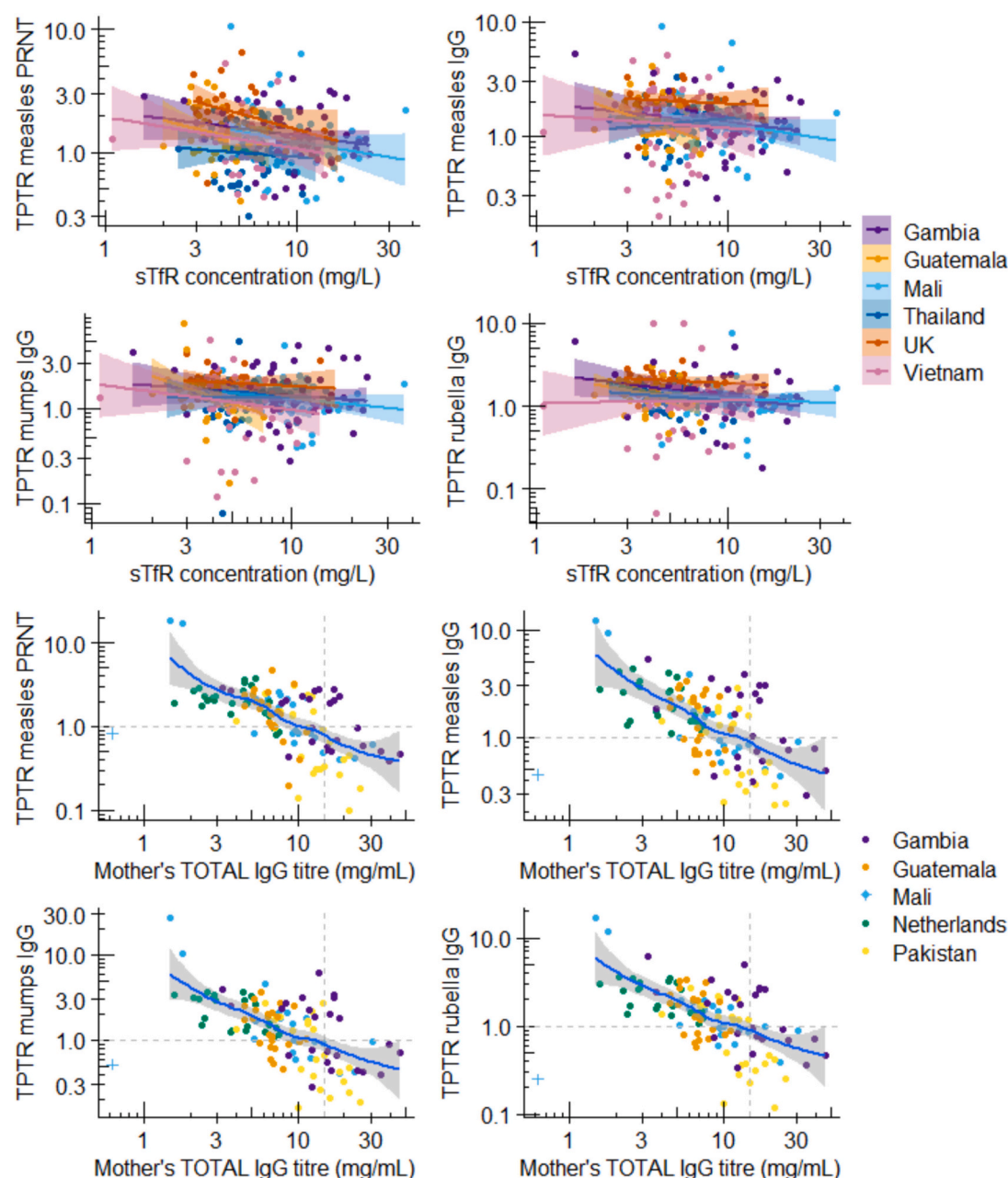


Fig. 3. Correlation between antigen-specific transplacental transfer ratios (TPTRs) for each assay and [top four panels] soluble transferrin receptor (sTfR) concentration whereby increasing concentration indicates increasing iron-deficiency and [bottom four panels] mother's TOTAL IgG concentration i.e. the mother's overall (as opposed to antigen-specific) IgG concentration. Trend lines are indicated with shaded 95% confidence intervals. On total IgG figures, the horizontal dashed line indicates ratio of 1, the vertical dashed line indicates commonly quoted 15 g/L saturation point for total IgG [37]. One outlying point from Mali (indicated by blue cross) has been excluded when fitting the lines.

associate with TPTR in univariate or multivariable models; however, ferritin is highly susceptible to confounding in the presence of inflammation, which is apparent around labour. We therefore also investigated soluble transferrin receptor (sTfR) as another biomarker of iron status that is typically less influenced by inflammation. It is elevated during periods of iron demand, particularly erythropoietic need, and therefore also reflects iron status. Our results indicated associations between high levels of sTfR (indicating iron deficiency) and reduced placental transfer for measles PRNT in both univariate and multivariable models, though not for other antibodies. Further studies are warranted to confirm this relationship, ideally designed to reduce the confounding effect of inflammation on interpretation of iron biomarkers.

Most study locations, with the exception of Mali and The Gambia

were low risk for malaria [23]. We did not have information on individual infection so could not adequately explore this variable and questions remain as to its influence on placental transfer [5,42]. Similarly, individual-level measles/mumps/rubella vaccination status data were not available. Whilst efforts were made to obtain as complete information as possible regarding national coverage, coverage will vary regionally within each country and at best it is only a probability of vaccination for each mother, and does not take second dose coverage and additional vaccination campaigns into account.

The majority of our infants were born at term which may explain why gestational age was not significantly associated with placental transfer in our dataset. Although individual meta data were not available for Pakistan, the reported average gestational age was lower than in

other countries which could partly explain the lower placental transfer ratios in Pakistan [15]. Expression of FcRn has been shown to increase during pregnancy, and is highest in the third trimester, consistent with increased placental transfer [52]. It is notable that the high maternal antibody concentrations in Pakistan compensated for the low placental transfer efficiency so that the vast majority of cord blood measles antibody concentrations were still above the protective threshold.

Results from a recent study in Belgium suggested efficiency of transplacental transport of Tdap-specific IgG antibodies is reduced in successive Tdap-vaccinated pregnancies [53]. In contrast we did not find a significant influence of parity within our dataset, similar to the findings of other studies [42,54]. The effect of parity on placental transfer within the Belgium cohort appeared to be linked to the time between successive vaccines received during pregnancy, which may explain why this effect was not seen in ours or others' data, which did not assess antibody induced by vaccination during pregnancy.

The majority of infants in our study had measles PRNT ≥ 0.12 IU/mL at birth, however, the percentage of infants born with PRNT below this threshold was as high as 14 % in Guatemala. This threshold is a guide rather than an absolute cut-off; although widely used, it was based on a small cohort of adults in the United States and not performed with World Health Organization International Serum Standards for measles [27,55]. The low maternal concentrations observed for measles IgG in Guatemala relative to other countries could be related to acquisition of antibodies from vaccination rather than natural infection in this low-incidence country (≤ 1 annual case reported since 1996 [21]), and lack of natural boosting from circulating measles virus. In contrast, measles incidence is high in Pakistan and outbreaks have recently been reported [21,56].

It is possible that differences in sample 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, beyond adjustment for country.

5. Conclusions

Whilst maternal antibody is the most important determinant of antibody concentration in the infant at birth, understanding factors that influence placental transfer is particularly important for mothers with low antibody concentrations who may not transfer sufficient antibody to achieve clinical protection in their infant if their transfer efficiency is low. This study highlights the wide variation in placental transfer efficiency that exists both across different country settings and within LMICs. Given the correlation of transplacental transfer ratios across measles, mumps and rubella it seems plausible that our results would be generalisable to the transfer of antibody against other viral antigens. With the development of more maternal vaccines, factors influencing placental transfer are increasingly important to understand. Total IgG, iron deficiency indicators and/or other variables in maternal blood could be measured during pregnancy alongside antigen-specific IgG to inform estimates of protection for the infant.

Author contribution

MV and KST designed the study, interpreted the data and drafted the manuscript. KST performed the data analysis. HtH-vO performed the laboratory analysis. HtH-vO, RvB, FvdK advised on laboratory methodology and interpretation. AEA provided advice on the nutritional indicators analysis and interpretation. BH suggested testing of maternal total IgG and provided UK residual study samples. All other authors provided residual study samples. All authors reviewed and approved the manuscript.

CRedit authorship contribution statement

Karen S. Tiley: Writing – review & editing, Writing – original draft,

Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hinke ten Hulscher-van Overbeek:** Writing – review & editing, Investigation. **Andrew E. Armitage:** Writing – review & editing, Methodology. **Rob van Binnendijk:** Writing – review & editing, Supervision, Methodology. **Beth Holder:** Writing – review & editing, Methodology, Investigation, Data curation. **Ed Clarke:** Writing – review & editing, Investigation, Data curation. **Stephen Cose:** Writing – review & editing, Investigation, Data curation. **Duc Anh Dang:** Writing – review & editing, Investigation, Data curation. **Ha Thi Thu Hoang:** Writing – review & editing, Investigation, Data curation. **Beate Kampmann:** Writing – review & editing, Investigation, Data curation. **Fiona van der Klis:** Writing – review & editing, Supervision, Methodology. **Abdul Momin Kazi:** Writing – review & editing, Investigation, Data curation. **Elke Leuridan:** Writing – review & editing, Investigation, Data curation. **Kirsten Maertens:** Writing – review & editing, Investigation, Data curation. **Herberth Maldonado:** Writing – review & editing, Investigation, Data curation. **Saad Omer:** Writing – review & editing, Investigation, Data curation. **Marcela F. Pasetti:** Writing – review & editing, Investigation, Data curation. **Nynke Rots:** Writing – review & editing, Investigation, Data curation. **Milagritos Tapia:** Writing – review & editing, Investigation, Data curation. **Nasamon Wanlapakorn:** Writing – review & editing, Investigation, Data curation. **Merryn Voysey:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2025.128132>.

Data availability

Data are provided as supplementary

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