Maternal antibodies shape infant immune response development in an epitope-specific manner

Helle Sadam,[a,j] Regina Maruste,[a,j] Annika Rähni,[a,b] Maarja Toots,[a] Maria Piirsalu,[a] Loviisa Pihlas,[a] Helen Ausman,[a] Alex Sirp,[a] Arno Pihlak,[a] Tõnis Laasfeld,[a] Kristiina Rull,[c] Andres Salumets,[c,d,e] Anne Antson,[f] Vallo Tillmann,[f,g] Aira Aleksejeva,[h] Tiiu Rööp,[i] Jelena Štšepetova,[i] Epp Sepp,[i] Reet Mändar,[i] and Kaia Palm[a,*]

[a]Protobios Llc, Tallinn, Estonia
[b]Department of Chemistry and Biotechnology, Tallinn University of Technology, Tallinn, Estonia
[c]Department of Obstetrics and Gynaecology, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
[d]Celvia CC AS, Tartu, Estonia
[e]Division of Obstetrics and Gynecology, Department of Clinical Science, Intervention and Technology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden
[f]Children's Clinic of Tartu University Hospital, Tartu, Estonia
[g]Department of Pediatrics, Institute of Clinical Medicine, University of Tartu, Tartu, Estonia
[h]Women's Clinic of Tartu University Hospital, Tartu, Estonia
[i]Department of Microbiology, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia

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Summary

Background The antibody repertoire in the blood encodes a comprehensive record of an individual's immunological encounters. Knowing the individuality of the repertoire would benefit in vaccinations, and also in personalising treatments. Formation of the immunoglobulin G (IgG) antibody repertoire starts before birth.

Methods Here, we used a mimotope variation analysis (MVA) method to gain deeper insight into the repertoire of maternal antibodies actively transferred to newborns during pregnancy with the follow-up at 6 months.

Findings Our study of 25 mothers and their neonates highlighted the strong correlation between maternal and neonatal antibody levels with comparable antigen-specificity shortly after birth. However, a noticeable blunting or interference in the antibody response was observed at the epitope level, revealing distinct patterns of recognition of antigenic determinants between mothers and their infants at 6 months, particularly concerning common latent viral infections like cytomegalovirus (CMV).

Interpretation Comprehensive understanding of the characteristics of placental IgG antibody transmission is essential for effectively leveraging and manipulating these mechanisms to benefit newborn health.

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Introduction

Immunological adaptative changes occurring during pregnancy allow maternal tolerance towards the foetus and placenta, which practically constitute semi-allografts as 50% of their antigens have a paternal provenience.[1] During normal pregnancy, there is a physiological transfer of immunoglobulins G (IgGs) from the mother to the foetus providing essential protection during the first few months of life when the infants' humoural response is inefficient. The functional importance of placentally transferred maternal antibodies is well established,[2] with IgG being dominant and IgG1 the most efficiently transferred subclass, followed by IgG3 and then IgG2 and IgG4.[3] Current evidence argues that passive transfer rates of IgG3, IgG4, and IgG2 can be impacted by the mother's antibody repertoire, the length of a full-term pregnancy, and recent maternal vaccination and other factors[3,4]

*Corresponding author.
E-mail address: kaia@protobios.com (K. Palm).
[j]These authors contributed equally.

Research in context

Evidence before this study

Maternal antibodies, primarily immunoglobulin G (IgG), are transported across the placenta to provide the foetus with passive immunity. This transfer begins in the second trimester and peaks in the third trimester, mediated by the neonatal Fc receptor (FcRn). The prevailing consensus is that maternal antibody transfer is an active, selective process in which not all IgG antibodies are transported with equal efficiency. An inverse relationship between the efficiency of placental transfer and corresponding maternal antibody levels has been demonstrated for antibodies against various pathogens.

Added value of this study

We used mimotope variation analysis (MVA) technology for antibody immune response profiling to quantify the plasma-derived IgG responses against herpes simplex virus 1 (HSV1), Epstein–Barr virus (EBV), cytomegalovirus (CMV) and *Helicobacter pylori* (*H. pylori*). These pathogens are typically encountered during early childhood, and maternally derived antibodies transferred across the placenta are believed to shape the neonatal immune environment during this critical period of immune development. Our analysis revealed a notable blunting or interference in the antibody response at the epitope level, highlighting distinct patterns of antigenic determinant recognition between mothers and their infants at six months of age—particularly for common pathogens as CMV.

Implications of all the available evidence

Although the underlying mechanisms remain unclear, our findings suggest that maternal antibodies can shape—and, in some cases, blunt–infant antibody responses at the epitope level, underscoring critical challenges for infant immunisation strategies and the potential risk of autoimmune conditions arising from the recognition of self-antigen epitopes.

After birth, the baby also receives antibodies through the mother's breast milk.[5]

Generally, when the mother has a high content of total IgG or of a specific antibody, the neonatal value remains below the maternal one. This inverse relationship between the efficiency of placental transfer to the respective maternal level has been demonstrated for antibodies against herpes simplex virus (HSV), tetanus toxoid, streptolysin O, and *Streptococcus pneumoniae*.[6] Interestingly, the binding affinity of the IgG receptor, the neonatal fragment crystallisable (Fc) receptor (FcRn) is influenced by the nature of its complementarity determining regions (CDR) and also by the antigen-binding fragments (Fab).[7–9] Studies of Jensen et al.[10] demonstrated that there are interaction sites in the Fab region of IgG for FcRn, in support of the Fab arm directly contacting FcRn. These phenomena indicate the involvement of antigenic specificity of the antibody in placental transfer.

The general consensus on the maternal antibody transfer is that it involves an active process where not all IgG antibodies are transported to the same extent. Maternal antibodies can impact the ability of neonates to mount an immune response, referred to as maternal antibody interference.[11] A recent study addressed blunting, e.g., the effects of the pre-existing maternal antibodies in the antibody response following infant immunisation.[12] These data concluded that although maternal immunisation may protect the infant in the first few months of life, it might increase the risk of disease in older age because of blunting of antibody response to both related (specific) and unrelated (heterologous) vaccines. This observation has sparked the notion that maternal antibodies can affect infant antibody production years later.[13] Therefore, it is essential to assess the long-term effects of maternal immunisation on the immune system of the offspring.[14]

Antibody response is especially relevant to vertically transmitted infections like the TORCH infections (*Toxoplasma*, syphilis, hepatitis B, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV)) and Zika virus which are known to cause neurological sequelae in foetuses and neonates.[15,16] Herpesviruses are commonly contracted during infancy, and they are prevalent worldwide, contributing to the human virome or virobiota.[17,18] After primary infection, herpesviruses can establish latency and persist for life with chronic or intermittent shedding for the lifetime. Based on clinical observations, it has been hypothesised that maternal antibodies protect the neonate from herpes viral neurotropic infections,[19,20] an associated neurological and sensorineural impairments.[21] On the other hand, the interplay between viruses and commensal microbiota, especially in early life, has only recently begun to be appreciated.[18] In addition, an active interplay between antibodies and microbiota occurs where both sides influence each other.[22,23]

The aim of this study was to characterise maternal transfer of IgG response to infants at the epitope specific level by using mimotope variation analysis (MVA) technology for antibody immune response profiling. Herein, we focused on four infections–HSV1, Epstein–Barr virus (EBV), CMV and *Helicobacter pylori* (*H. pylori*)—because these infections are primarily acquired during early childhood, and maternally derived antibodies transferred through the placenta are thought to influence the neonatal immune environment during

this critical developmental period. Additionally, both, herpesviruses[17,18] and *H. pylori*[24] are capable of persisting in the host in a latent or chronic state for extended durations, potentially modulating the host's immune system throughout life. Thus, we investigated the seroreactivity more specifically for HSV1, EBV, CMV and *H. pylori* at several time points from birth up to 6 months of age and assessed the possible influence of the maternal repertoire before birth and shaping of the early immune landscape of the infants.

Methods

Patient selection

Study participants were recruited from the Women's Clinic of Tartu University Hospital between May 2012 and August 2017, as described.[25] All the recruited women had uncomplicated pregnancies, were free of infectious diseases requiring antibiotic treatments, and reported no history of diabetes or hypertensive disorders during the second half of pregnancy. A total of 25 mothers (mean age: 33.1 ± 4.5 years) and their newborn infants participated in the study. This cohort included five pairs of twins. Serum samples were collected at specific time points: cord blood (CB), maternal samples one day after delivery (M_d1), infant samples at 48–72 h post-birth (C_d2–3), maternal samples at 6–8 weeks post-birth (M_w6–8), and samples from both mothers and infants at six months post-birth (M_w24, C_w24) (Table S1). Certain time point samples were unavailable due to missed appointments (Table S1). All available samples were included in this study; no additional inclusion or exclusion criteria were applied. No formal sample size determination, randomisation or blinding procedures were applied. Pairwise analysis was performed according to Table S1.

CMV, HSV1, *H. pylori* and EBV seropositivity

Serological analyses for Human Cytomegalovirus (CMV), Epstein–Barr Virus (EBV), Herpes Simplex Virus 1 (HSV1), and *Helicobacter pylori* (*H. pylori*) were performed using commercially available ELISA kits. Specifically, the following ELISA tests were used for serology analysis: anti-CMV IgG, EI 2570–9601G, Euroimmun, anti-EBV-CA IgG, EI 2791–9601G, Euroimmun, anti-HSV1-gG1, EI 2531-96012G and anti-*H. pylori* IgG, EI 2080–9601G, Euroimmun (Table S1). All analyses were carried out in accordance with the manufacturer's specifications. Absorbance was measured at 450 nm using Hidex Sense Microplate Reader.

Mimotope variation analysis (MVA)

Serum samples were processed by MVA, a method previously described in.[26–28] In brief, 2 µl of each serum sample was incubated with *E. coli* M13 phage 12-mer random peptide library (10^{11} phage particles per analysis). Following incubation, the IgG-phage complexes were captured using protein A/G-coated magnetic beads. The captured phage DNA was then amplified, indexed with unique sequences, and analysed via next-generation sequencing. On average, three million peptide-encoding DNA sequences per sample were obtained.

ELISA assays for quantitative measures of total IgGs

Total IgG content in human serum samples was determined by ELISA using 96-well MaxiSorp flat-bottom microtiter plates (Thermo Scientific, 442404). For total human IgG measurements, randomly selected samples were added from different study groups (n = 38, a sample set comprising 8 families). All analyses were performed in duplicates. Plates were coated overnight at 4 °C with goat anti-human IgG (0.5 µl/ml, Invitrogen, A56856, RRID AB_2930925) and blocked with 5% skimmed milk in PBS for 1 h at RT. Standard curve for IgG was prepared by serial dilutions of purified human IgG (Sigma, I4506) in 1% milk-PBS. Serum samples were diluted in 1% milk-PBS (1:100000, 1:300000 and 1:1000000) and transferred to coated plates. After 1 h incubation at RT, the plates were washed and then incubated with horseradish peroxidase (HRP)-conjugated secondary goat anti-human IgG (Invitrogen, 31410, RRID AB_228269) for 1 h at RT. Plate was developed using TMB Substrate (Thermo Fisher Scientific, 34021). Following incubation at RT for an additional 10 min, TMB Stop Solution (2 M sulphuric acid) was added to all wells. Optical density (OD) was measured for each well at 450 nm with a reference wavelength of 650 nm using a microplate reader (Hidex Sense microplate reader).

Immune analysis methods for epitope validation

Phage-ELISA protocol was set up to independently validate the MVA-delineated peptide epitope leads. Specifically, target epitopes identified by MVA analysis and the relevant control were recombinantly introduced to the vector backbone (Vector1, modified from M13KE (New England Biolabs)). Studied epitopes and oligonucleotide sequences to generate the constructs are provided in Table S3. Resulting recombinant M13 phages displaying respective peptides in p3 were amplified and concentrated using Polyethylene Glycol (PEG)/NaCl precipitation method.

For Phage-ELISA, 96-well MaxiSorp immuno plates (Cat no: 436110) were coated overnight at +4 °C with p8 antibody (0.5 µg/ml, Progen, B62-FE2; Cat. No. 61097, RRID AB_2904122). After blocking the unspecific binding with 5% non-fat dried milk solution and washing with 1 × PBS, purified phages were added to plates for overnight binding with p8 antibody. Next day, serum samples were precleared (to block unspecific binding to M13 phage) and allowed to bind to chimeric

phage with epitope of interest (0.1 μl of initial sera per well, serum dilution 1:1000). After overnight incubation, plates were washed, incubated with secondary antibody (Polyclonal anti-human-HRP (1:1000; 31410–Invitrogen Goat anti-Human IgG (H + L) Secondary Antibody, HRP, RRID AB_228269) and measured using SuperSignal™ ELISA Femto Substrate (ThermoFisher, Cat no: 37074; Hidex Sense microplate reader).

ELISA assay for quantitative measures of subtype-specific IgGs

Epitope-specific IgG subclasses were determined using chemiluminescence-based ELISA assay in white 96-well flat-bottom Nunc-MaxiSorp plates (Thermo Scientific, 436110). Plates were coated overnight with anti-M13-p8 antibody (0.5 μg/ml, Progen, 61097, RRID AB_2904122). Plates were washed and blocked with 5% skim milk in PBS for 1 h at RT. 5×10^{10} selected M13 phage particles (Table S3) were added to each well and incubated overnight at 4 °C. Subsequently, sera were diluted in 1% milk-PBS and incubated overnight to allow antibody binding to the displayed epitopes. After washing to remove unbound components, HRP-conjugated secondary antibodies specific to IgG1 (Invitrogen, A55739, RRID AB_2925764), IgG2 (Invitrogen, MH1722, RRID AB_10376169), IgG3 (Invitrogen, MH1732, RRID AB_2539713) or IgG4 (Invitrogen, MH1742, RRID AB_2539714), each diluted 1:1000 in 1% milk-PBS, were added to the wells and incubated for 1 h at RT. After the final washing step, chemiluminescence substrate (Thermo Scientific, 37075) was added and the signal was measured (Hidex Sense microplate reader). Raw data was analysed using four parameters logistic (5 PL) fit function in GraphPad Prism 10.4.0 software (GraphPad).

Statistics

Identification of epitope sequences

The most immunodominant epitopes in captured peptides were determined by clustering analysis (defining epitopes ranging from 5 to 11 amino acids in length, each containing a consistent sequence of 5 fixed amino acids) and identifying shared sequence patterns by fixing 5 amino acids within sequences from 5 to 11 amino acids in length using SPEXS2 Software.[26]

Cohort-specific antibody epitope validation

Pathogen-specific epitopes were previously identified by comparing immunoprofile data from seropositive and seronegative samples.[26] For pathogen-associated epitope (n = 56, Table S2) validation, immune response of seronegative and seropositive groups (CMV, n = 42/105; EBV, n = 17/129; HSV1, n = 44/99; *H. pylori*, n = 71/64 (seronegative/seropositive)) were compared using ROC, hypergeometric test and Wilcoxon rank sum test analysis. For statistical evaluation, permutation and multi-test (Bonferroni-Holm) corrections were applied. Epitope-specific seropositivity was defined by using threshold formula: threshold = $\mu_{negatives} + k \times \sigma_{negatives}$, where μ = mean of seronegatives (measured by EUROIMMUN ELISA kit), σ = standard deviation, k = 3. The results from seropositive individuals were then expressed as deviations from the seronegative threshold.

Sample comparisons

Categorical values (number of ELISA seropositive and seronegative samples in different groups) were compared using the chi-squared test with Yates's continuity correction. Sample comparisons were performed by Wilcoxon rank sum test, Student t-test and Pearson's correlation analysis. For statistical evaluation, permutation and multi-test (Bonferroni-Holm) corrections were applied. For immunoprofile similarity analysis, the cosine similarity index (CSI) was used to compare read counts of 5000 most abundantly detected peptides, as well as 56 pathogen-specific epitopes (Table S2), between the mother-child pairs and unrelated individuals (Table S1). No thresholds were used, CSI scores ranged from 0 to 1 with higher values indicating higher similarity. Enrichment of IgG bound peptides in samples was assessed by calculating fold-change relative to the phage library input.

Epitope alignment analysis using data of UNIPROT data

To precisely describe the specific antigens, the selected 56 epitopes were aligned against the known antigens of different strains of CMV, EBV, HSV1 and *H. pylori* from reviewed UNIPROT database (2898 proteins, date accessed: 08.11.2024) (Table S2). Sample-specific alignment score represents the abundance of aligned epitope sequences (≥5 aa match), calculated by multiplying the number of matched epitopes by the detected abundance of each individual epitope. To evaluate the non-specific alignments, alignment scores obtained from randomised epitope sequences were plotted as a reference.

All statistical analyses were performed using R version 4.4.2. R packages used in the data analysis were "datatable", "tidyverse", "cutpointr", "pROC", "coin", "lsa", "rstatix". R packages used in the visualisation were "ggplot2", "ggpubr", "pheatmap", "viridis", "RColorBrewer".

Ethics

This study was approved by the Research Ethics Committee of the University of Tartu (381/T-8: 21.08.2023) and written informed consent was obtained from each participant prior to the study. All methods were performed in accordance with the relevant guidelines and regulations.

Role of funders

Funders had no role in study design, data collection, data analyses, interpretation, or writing. While several authors are affiliated with Protobios, it is important to

note that the company provided funding for this study only through grants, which are acknowledged in the manuscript.

Results

Overview of the study group

A total of 25 mothers with median age of 33 years (range 21–43 y) with their infants were enrolled (Fig. 1A, Table S1). Two-thirds of women (n = 16) delivered via Caesarean section, receiving prophylactic cefuroxime treatment prior to the incision. All infants were term with median gestational age of 40 weeks (range 37–42 w) and had normal birth weights (median weight: 3276 g; range 2708–4848 g). Six women were not multiparous. Five pairs included twins. Regarding infant feeding practices, four infants received exclusively breastfeeding for six months, and six infants for four months, while the remaining infants were breastfed for less than one month. Unfortunately, breastfeeding data was unavailable for three infants. A total of 148 biological samples were collected from these mother-infant dyads for subsequent analyses (Fig. 1A, Table S1).

Newborn IgG repertoire reflecting maternal immunodominant antibody response

To investigate the early-life antibody immune response evolution, we took advantage of the MVA immunoprofiling analysis method (Fig. 1B) that enables antibody immune response characterisation in an epitope-specific manner. MVA was performed on a total of 148 samples collected longitudinally from mother-infant pairs (n = 24) at birth (mother—M_d1, cord blood–CB), at 48–72 h after birth (child—C_d2–3), at 6–8 weeks (mother—M_w6–8) and six months after birth (mother—M_w24, child—w_24) (n = 148, Fig. 1A and B, Table S1). At the peptide level, our analysis revealed distinct clustering patterns. Peptides targeted by the IgG seroreactivity at birth in newborns and their mothers clustered together (average CSI was 0.809) if compared to the IgG response detected in infants and mothers from separate families (average CSI was 0.041) (Fig. 1C). However, by six months of age, infants

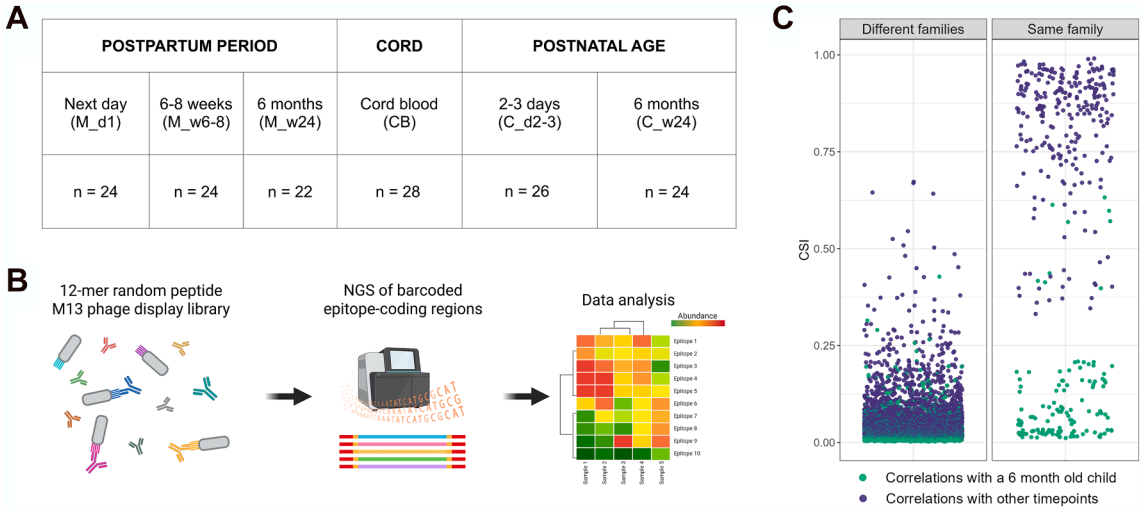


Fig. 1: **Top features in antibody epitope profiles are shared by mothers and their newborns at birth whereas the child's IgG response changes over time. A)** Clinical study design. Samples were collected from each mother-infant pair (n = 25) at birth or 2–3 days after birth, at 6–8 weeks and 6 months after birth (n = 148). **B)** A scheme of the antibody epitope profiling by using the MVA method. MVA workflow comprised of different sequential steps: i) immunocapture of IgG-phage complexes from a sample using the phage library (random 12-mer peptide M13 phage library), ii) high-throughput next generation DNA sequencing of bar-coded phage DNA; iii) bioinformatical analysis resulting in antibody epitope identification. The obtained sequenced DNA reads were quality checked, translated to peptide sequences, and sample- and cohort-specific epitopes from peptide sets were developed by SPEXS2 pattern search algorithm. Created in BioRender. Palm, K. (2025) https://BioRender.com/y63do32 (agreement number QB292AAYN0). **C)** Highly individual immunoreactive epitope profiles shared similar features in paired sera (n = 25 families) samples as observed from MVA analysis. The 5000 most IgG-bound abundant peptide values (read counts) from each sample were taken into immunoprofile similarity analysis. For all sample pairs, the normalised scalar products of peptide count vectors were calculated for the cosine similarity index (CSI, R package "lsa") and are depicted on panel **c**. The correlation between samples from different families is low (left panel) compared in those from the same family (right panel) (purple—correlations between M_d1, M_w6–8, M_w24, CB, C_d2–3). Similarly, correlation between samples of 6-month-old children (C_w24) with samples from any other timepoint of their mothers is also low (green—correlations between C_w24 and all the other groups individually). y-axis: CSI; x-axis: group category. M_d1, serum of mother after delivery; M_w6–8, serum of mother 6–8 weeks after delivery; M_w24, serum of mother 6 months after delivery; CB, serum from the cord blood; C_d2–3, sera of infants 2–3 days after birth; C_w24, serum of child 6 months after birth; MVA, mimotope variation analysis; NGS, next generation sequencing; CSI, cosine similarity index.

exhibited a significantly more discriminative antibody repertoire (Fig. 1C, right panel). These findings indicate that the immunodominant IgG-response that was passively transferred from mothers to their infants at birth, underwent a substantial shift by six months of age, suggesting the development of an independent and evolving immune profile in infants.

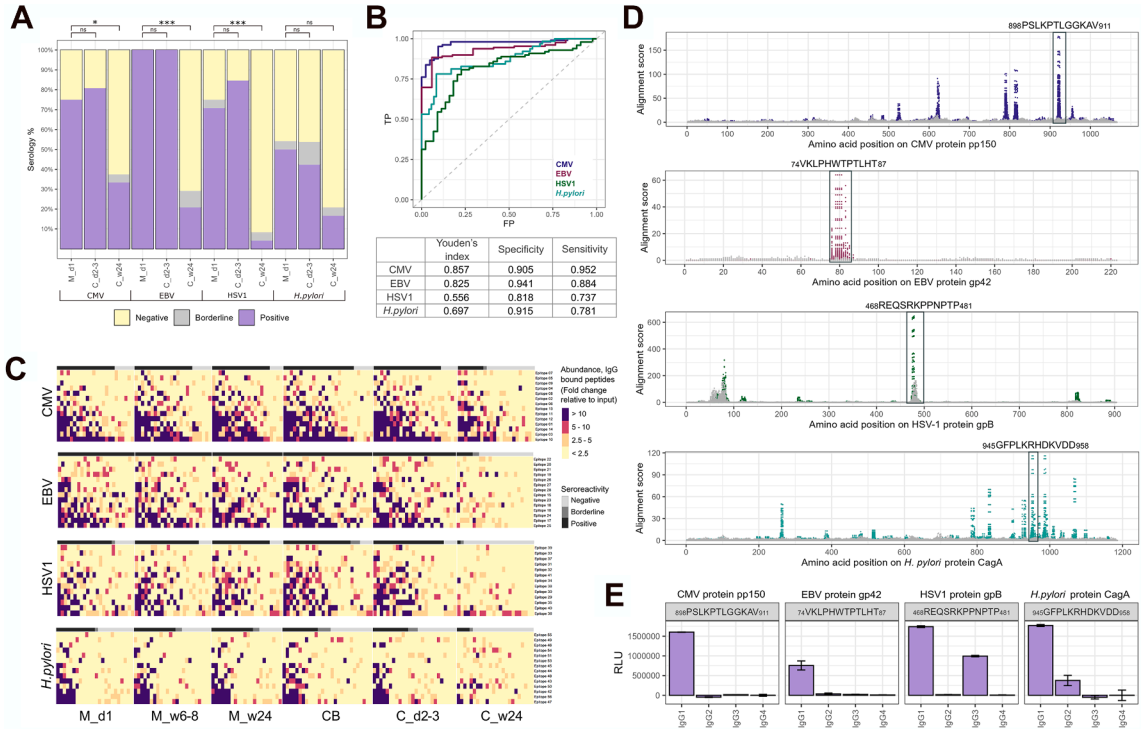
Newborn antibody repertoire against CMV, EBV, HSV1 and *H. pylori* antigens vs. maternal IgG profiles

To gain deeper insight into the pathogen-specific targets within the repertoire of maternal antibodies actively transferred to newborns, we investigated the association of captured immune features with common viral (CMV, EBV, HSV1) and bacterial (*H. pylori*) infections as epidemiologically frequent in populations. First, we measured the serologic background for these pathogens by using conventional clinical ELISA testing (Fig. 2A). Infection-associated antibodies were measured in 24 mothers (M_d1 samples), 26 neonate (C_d2–3 samples), and 24 newborn (C_w24) samples (Table S1, Figure S1). Consistent with widespread exposure, all the mothers exhibited anti-EBV antibodies throughout the study period (Fig. 2A). Approximately 70–80% of mothers had also antibodies against CMV and HSV1, while about half of the mothers were seropositive for *H. pylori* (Fig. 2A). Notably, newborns of seropositive mothers were seropositive for these pathogens at or shortly after birth (C_d2–3) (Figure S1). However, by six months of age the proportion of CMV, EBV, HSV1 and *H. pylori* seropositivity was significantly lower in infants (C_w24) compared to the maternal first timepoints (M_d1) (CMV: χ^2 (1, n = 47) = 6.1445, p = 0.0132); EBV: χ^2 (1, n = 46) = 26.194, p < 0.001); HSV1: χ^2 (1, n = 46) = 20.536, p < 0.001) (Fig. 2A).

Next, we evaluated the classifying power of seroreactivity to pathogen-specific epitopes identified by MVA (Fig. 2B and Figure S2). Altogether, 56 pathogen-specific epitopes were described (Table S2), classifying the studied pathogen seroreactivities at high specificity (CMV: specificity 0.905; EBV: specificity 0.941; HSV1: specificity 0.818; *H. pylori*: specificity 0.915, Fig. 2B; Wilcoxon adjusted p values < 0.0001, Figure S2). We found that although the antibody immune response to epitopes of CMV, EBV, HSV1 and *H. pylori* was highly individual, these immune features were greatly shared between mother-infant paired sera (n = 25 families) (Fig. 2C). Annotation of these defined epitopes using the reviewed pathogen protein from the UNIPROT database (Table S2) revealed that the most dominant epitopes were for CMV, the epitope $_{898}$PSLKPTLGGKAV$_{911}$ of the large structural phosphoprotein (pp150, P08318), for EBV, the epitope $_{74}$VKLPHWTPTLHT$_{87}$ of the glycoprotein 42 (gp42, P03205), for HSV1, the epitope $_{468}$REQSRKPPNPTP$_{481}$ of the envelope glycoprotein B (gpB, P10211) and for *H. pylori* the epitope $_{945}$GFPLKRHDKVDD$_{958}$ of the cytotoxicity-associated immunodominant antigen (CagA, P55980) (Fig. 2D and Figure S3, Table S2). Finally, we defined the IgG subtypes of the described dominant antibodies (Fig. 2E). All epitopes were recognised by anti-IgG1 subtype-specific antibodies whereas HSV1 the epitope $_{468}$REQSRKPPNPTP$_{481}$ of gpB was additionally recognised by anti-IgG3 subtype antibodies and *H. pylori* the epitope $_{945}$GFPLKRHDKVDD$_{958}$ of CagA was additionally recognised by anti-IgG2 subtype antibodies (Fig. 2E).

Distinct patterns of maternal-to-neonatal placental transfer for pathogen-associated antibodies

Next, we compared antibody levels targeting specific pathogen-associated antigens upon placental transfer from mother to child shortly after birth (Fig. 3). To address this, the total IgG content was confirmed across samples (Figure S4) revealing comparable levels of IgG levels across all studied cohorts (Wilcoxon rank sum test p > 0.05). While the overall Ig levels were similar across groups studied, the epitope-specific Ig levels showed considerable variations. Fig. 3A presents the correlations of antibody response to all studied epitopes across the study cohort. The cosine similarity matrix analysis reveals that seroreactivity values from samples within the same family cluster together, exhibiting high similarity indices (average CSI >0.75; Fig. 3A). The correlation analysis of cord blood (CB) and neonatal (C_d2–3) samples revealed a high rate of successful maternal IgG transfer (Pearson r > 0.7; Figures S5 and S6, Table S2). In contrast, a significantly lower correlation was observed for C_w24 samples collected at six months of age (Pearson r < 0.4; Figures S5 and S7, Table S2). Moreover, these correlation patterns were consistently observed across all examined seroreactivities against the studied pathogens (Figure S5). However, notable epitope-specific differences were observed (and validated by ELISA): (i) for certain epitopes, antibody levels were found to be higher in majority of newborns as compared to their mothers (e.g., the pp150 and gpB epitopes of CMV (Fig. 3B and Figure S8, Table S2); (ii) for other epitopes, a strong positive correlation was observed (Pearson r > 0.8, Figure S5, Table S2), indicating that higher maternal antibody levels corresponded to greater transfer of epitope-specific IgGs were to the newborn (Fig. 3B and Figure S8), (iii) for some epitopes, antibody levels exhibited significant differences in mothers and their infants (Table S2); and notably, (iv) no significant differences were observed in antibody transfer when comparing pathogens of viral (CMV, EBV, HSV1) or bacterial (*H. pylori*) origin (Figure S5, Table S2).



	Youden's index	Specificity	Sensitivity
CMV	0.857	0.905	0.952
EBV	0.825	0.941	0.884
HSV1	0.556	0.818	0.737
H.pylori	0.697	0.915	0.781

Fig. 2: **Repertoire of antibodies against sets of CMV, EBV, HSV1 and *H. pylori* antigens in newborns follow the antibody response patterns in mothers. A)** IgG response measured by ELISA for common microbes and/or their specific antigens. Serology was measured for 24 M_d1 samples, 26 C_d2–3 samples and 24 C_w24 samples (Table S1). CMV group—17/6/0 M_d1, 21/5/0 C_d2–3, 8/14/1 C_w24; EBV—23/0/0 M_d1, 26/0/0 C_d2–3, 5/16/2 C_w24; HSV1—16/6/1 M_d1, 22/4/0 C_d2–3, 1/21/1 C_w24; H. pylori—11/11/1 M_d1, 11/12/3 C_d2–3, 4/18/1 C_w24 (seropositive/seronegative/borderline). Differences in serology results (positive vs. negative) between M_d1 and C_d2–3, as well as between M_d1 and C_w24, were assessed using a Chi-squared test with Yates' correction. Significance levels: ns, $p > 0.05$; $p \leq 0.05$ (*); $p \leq 0.01$ (); $p \leq 0.001$ (*). y-axis: seropositivity and seronegativity (% of total samples); x-axis: group (M_d1, C_d2–3, C_w24) and serology (CMV, EBV, HSV1, H. pylori). **B)** The ROC values for CMV, EBV, HSV1, and H. pylori specific sets of epitopes in distinguishing seropositive from seronegative samples by Youden Index identifying the optimal sensitivity and specificity values (purple—CMV, AUC (95% CI) = 0.97 [0.944—0.995]; red—EBV, AUC (95% CI) = 0.932 [0.886—0.977], green—HSV1, AUC (95% CI) = 0.816 [0.743—0.888]; turquoise–H. pylori, AUC (95% CI) = 0.873 [0.813—0.934]). y-axis: true positive rate; x-axis: false positive rate. **C)** Heatmap illustrating epitope enrichment across the analysed samples in comparison to the library input (see colour scale on the right). Enrichment was calculated by dividing each epitope's detection in the sample by its detected abundance in the phage library. Epitopes were then categorised into four enrichment levels: less than 2.5-fold over library input (yellow), 2.5- to 5-fold (orange), 5- to 10-fold (pink), and >10-fold (purple). Columns (samples) were clustered independently for each pathogen panel; therefore, column positions are not consistent across panels. Columns–study samples (n = 148), rows—epitopes (n = 56). **D)** Most immunodominant antigens and epitopes–pp150 of CMV, gp42 of EBV, gpB of HSV1 and CagA of H. pylori. y-axes—number of aligned epitope sequences (≥5 aa match) (purple, red, green, turquoise—epitope alignment, grey—randomised epitope sequence alignment); x -axes—protein sequences of CMV pp150 (UNIPROT ID P08318), EBV gp42 (UNIPROT ID P03205), HSV1 gpB (UNIPROT ID P10211), and H pylori CagA (UNIPROT ID P55980). **E)** ELISA assay for quantitative detection of subtype-specific IgG antibodies. CMV, the epitope $_{898}$PSLKPTLGGKAV$_{911}$ of the large structural phosphoprotein 150 (pp150, P08318), for EBV, the epitope $_{74}$VKLPHWTPTLHT$_{87}$ of the glycoprotein 42 (gp42, P03205), for HSV1, the epitope $_{468}$REQSRKPPNPTP$_{481}$ of the envelope glycoprotein B (gpB, P10211), and for H. pylori the epitope $_{945}$GFPLKRHDKVDD$_{958}$ of the cytotoxicity-associated immunodominant antigen (CagA, P55980). y-axis: RLU; x-axis: IgG subtype (IgG1, IgG2, IgG3, IgG4). M_d1, serum of mother one day after delivery; M_w6–8, serum of mother 6–8 weeks after delivery; M_w24, serum of mother 6 months after delivery; CB, serum from cord blood of newborn; C_d2–3, serum of infant; C_w24, serum of child 6 months after birth; CMV, cytomegalovirus; HSV1, herpes simplex virus 1; EBV, Epstein–Barr virus; *H. pylori*, *Helicobacter pylori*.

Evidence of antibody interference on infant antibody repertoire development at six-months

Considering the critical role of maternal antibody lifespan in shaping infant's susceptibility to infection, we further investigated the observed divergence in infants' immune profiles from their maternal patterns by sixth month of age. Across the study set, we detected the anti-CMV response in eight, anti-EBV in five, anti-HSV1 in one, and anti-*H. pylori* in four infants (Fig. 2A). Based on these data, we focused on anti-CMV antibody transfer in seropositive 6-month-old infants. Similar to mothers, the most immunodominant CMV antigen in

infants was pp150 (Table S2). However, at the epitope level, we observed a mutually exclusive pattern of antibody response between mothers and their 6-month-old infants (paired M_d1 and C_w24 samples, Fig. 4A, Figures S5, S7 and S9). The results show that the high correlation values observed between M_d1 and C_w1 are not maintained for the C_w24 time-point. For example, the Pearson's correlation coefficient of the immunodominant epitope of antigen pp150 of HCMV $_{470}$GSQKPTSGPLNI$_{483}$, as shown in Fig. 4A, between the M_d2–3 and C_d2–3 samples is high (r > 0.9, permutation-adjusted p-value 0.0056, Figure S6, Table S2). In contrast, the correlation between the M_d1 and C_w24 samples is very weak (r = –0.12, permutation-adjusted p-value >0.05; Figure S7, Table S2). Fig. 4B shows data on the antibody response patterns to pp150 CMV across different epitopes for mother and her infant from the same family (Mother/Child #15, Table S1). For example, if a mother exhibited an active response against epitopes $_{470}$GSQKPTSGPLNI$_{483}$ and $_{794}$STPVQGRLEKQV$_{807}$, the infant did not show this corresponding response pattern. Instead, the infant developed antibody immune response against different epitopes of pp150 CMV, namely against epitopes of $_{508}$RDSAWDVRPLTE$_{521}$ and $_{898}$PSLKPTLGGKAV$_{911}$, to which there were no antibodies detected in the mother (Fig. 4B). One apparent explanation for the findings was that maternal antibodies might have inhibited the development of antibodies targeting the same epitopes of the pathogen, suggesting the occurrence of active antibody interference. Moreover, mothers maintained similar stable antibody response patterns by six months period following delivery (Table S2). Interestingly, although the CMV-seropositive twins displayed comparable patterns of interference with the maternal antibody response, the newly developed epitope-specific antibody response exhibited variability both between the co-twins and when compared to their mother (Figure S10).

Discussion

Here, we explored the effects of maternal antibody transfer to the development of the infant antibody repertoire. We used mimotope variation analysis (MVA) method to quantify the plasma derived IgG response against 87 epitopes of human pathogens in infants at birth and at six months of age. Our findings reveal that maternal antibody transfer significantly influenced the infant's IgG repertoire against human pathogens right

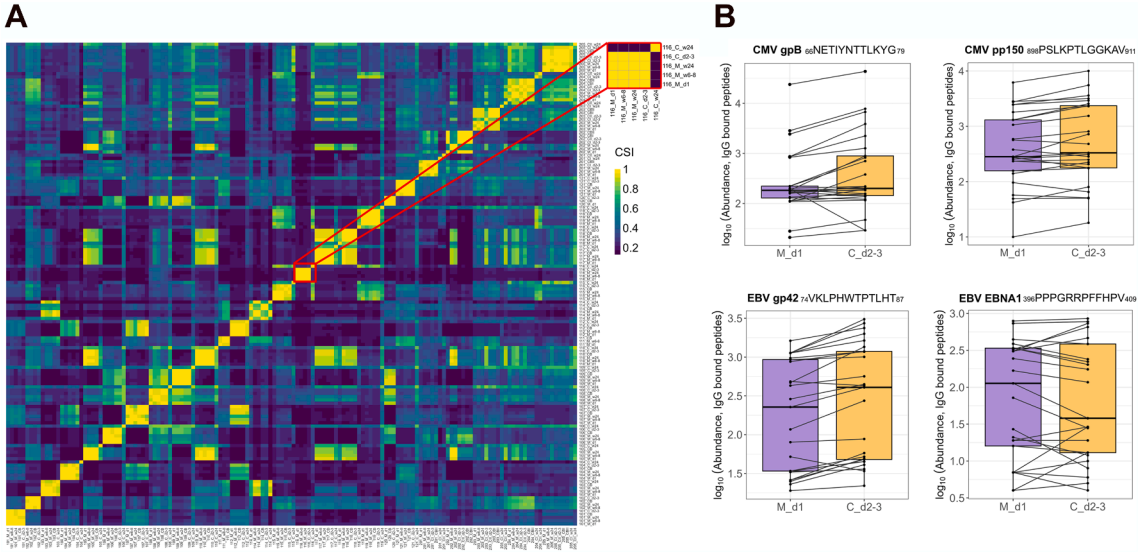


***Fig. 3:* Pathogen-associated antibody transfer from mother to child is differential. A)** Individual and shared immunoreactive infection (CMV, EBV, HSV1 and *H. pylori*) associated epitope profiles shared similar features in paired sera samples (n = 148) as observed from MVA data. The infection associated IgG-bound (abundant) peptide values (read counts) from each sample were taken into immunoprofile similarity analysis. y- and x-axis: sample pairs. For all sample pairs, the cosine similarity indexes were calculated (colour code on the right). **B)** MVA immunoprofiles of epitopes $_{898}$PSLKPTLGGKAV$_{911}$ of CMV pp150 and $_{66}$NETIYNTTLKYG$_{79}$ of CMV gB, $_{396}$PPPGRRPFFHPV$_{409}$ of EBV EBNA1 and $_{74}$VKLPHWTPTLHT$_{87}$ of EBV gp42 in M_d1 and C_d2–3 study groups. y-axes: log10 of abundance of peptides containing the epitope; x-axes: individual data points from groups M_d1 and C_d2–3 (n = 25). M_d1, serum of mother after delivery; M_w6–8, serum of mother 6–8 weeks after delivery; M_w24, serum of mother 6 months after delivery; CB, serum from cord blood of newborn; C_d2–3, serum of infant; C_w24, serum of child 6 months after birth; CMV, cytomegalovirus; HSV1, herpes simplex virus 1; EBV, Epstein–Barr virus; *H. pylori*, *Helicobacter pylori*; pp150, phosphoprotein 150; gpB, glycoprotein B; EBNA1, Epstein–Barr nuclear antigen 1; gp42, glycoprotein 42; CSI, cosine similarity index.

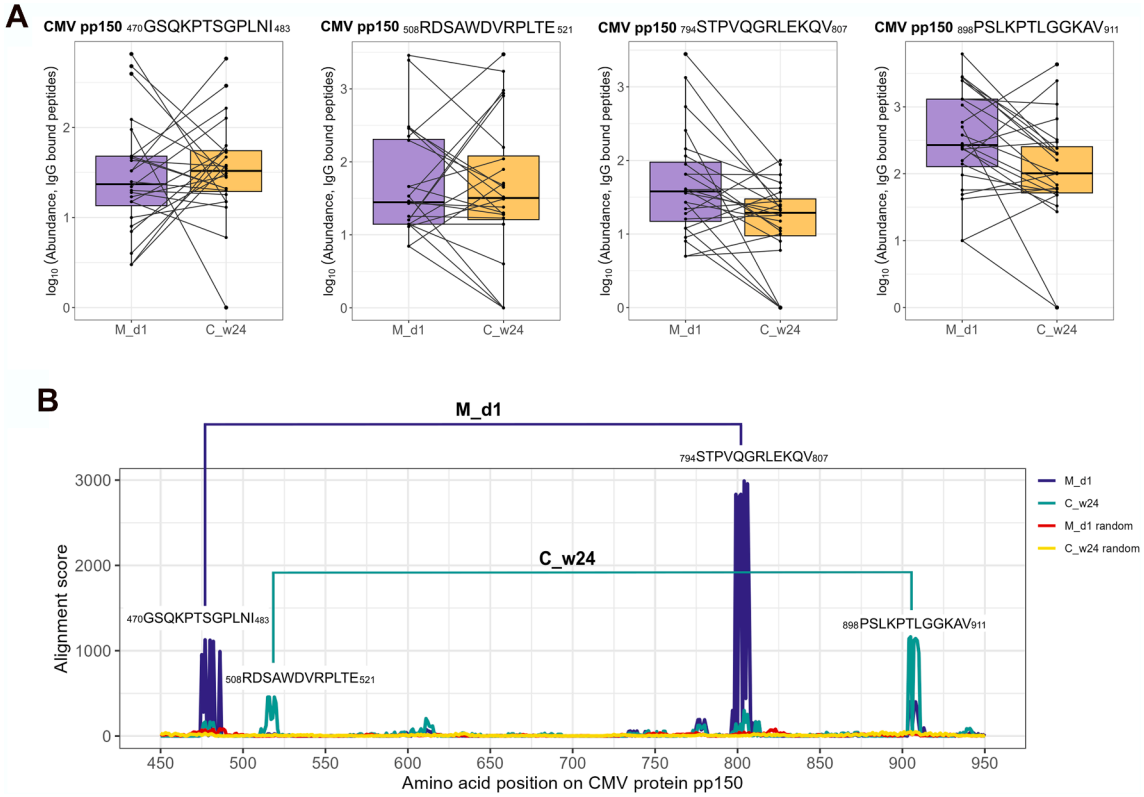


Fig. 4: **Children show differences in their antibody response against specific epitopes at 6 months than their mothers for the same antigens. A)** Mutual exclusivity in seroreactivity patterns to the immunodominant epitopes of antigen pp150 of HCMV–$_{470}$GSQKPTSGPLNI$_{483}$; $_{508}$RDSAWDVRPLTE$_{521}$; $_{794}$STPVQGRLEKQV$_{807}$ and $_{898}$PSLKPTLGGKAV$_{911}$ are shown in paired CMV-seropositive mother-child samples (M_d1, C_w24). y-axes: log10 of abundance of IgG bound peptides containing the epitope; x-axes: individual data points from groups M_d1 (n = 20) and C_w24 (n = 24). **B)** Epitopes located in the C-terminal region of pp150 encompassing amino acids $_{470}$GSQKPTSGPLNI$_{483}$; $_{508}$RDSAWDVRPLTE$_{521}$; $_{794}$STPVQGRLEKQV$_{807}$ and $_{898}$PSLKPTLGGKAV$_{911}$ in a mother one day after delivery (M_d1, purple) and in her child 2–3 days after birth (C_d2–3, teal). y-axis: alignment score representing the abundance of aligned epitope sequences (≥5 aa match) that was calculated by multiplying the number of matched epitopes by the abundance of each individual epitope. To correct for non-specific alignment, alignment scores derived from randomised epitope sequences of both the mother (M_d1 random, red) and the child (C_d2–3 random, yellow) were plotted for reference. x-axis: protein sequence of CMV pp150 (UNIPROT ID P08318). M_d1, serum of mother after delivery; M_w6–8, serum of mother 6–8 weeks after delivery; M_w24, serum of mother 6 months after delivery; CB, serum from cord blood of newborn; C_d2–3, serum of infants; C_w24, serum of child six months after birth; CMV, cytomegalovirus; pp150, phosphoprotein 150.

from birth. This resulted in differences in both, the breadth of the repertoire reflecting the number of epitope targets for which antibodies were generated–and the magnitude, or antibody levels measured, already within the first 72 h of life, when compared to the maternal antibody levels during pregnancy and one day postpartum. The neonatal antibody epitope repertoire was predominantly characterised by antibodies against latent chronic pathogens (herpesviruses, *H. pylori*). However, by six months of age, a significant shift in the targeted epitopes against these pathogens was observed likely due to the waning of maternally-derived antibodies or the exposures to the new antigens in infants. The interference with epitope-specific anti-pathogen IgG repertoire development observed in infants by six months of age could potentially contribute to immune dysfunctions later in life.

Maternal IgG transfer to the foetus is an active and selective process, where not all IgG antibodies are transported equally (Figs. 1 and 2). The level of the maternal antibody is the most predictive factor of transplacental antibody transfer.[29] Higher gestational age, recent maternal vaccinations, maternal nutritional status and male sex of the newborn have all positive impact on maternal antibody concentrations in the infant.[30–32] By the end of pregnancy, foetal IgG antibody levels against protein antigens have been observed to be elevated.[33] Our MVA data, along with independent validation through epitope-specific ELISA assays, revealed remarkably similar patterns of antigenic

epitope recognition for CMV (pp150, gpB), EBV (EBNA1), and HSV1 viral antigens between paired mother and term umbilical cord sera (Figs. 2 and 3). This confirms a significant transfer of maternal antibody repertoire to the newborn, specifically relating to targeted protein antigens. The reasons behind the varying transfer impairments of antibody specificities in different studies remain unclear.[34] Likely explanations include variations in the IgG subclass-specific response to different antigens and the unique affinities that these subclasses exhibit for the IgG-transporting FcRn receptors on cells.[35,36] In neonates, studies have shown a delayed onset, lower titres and affinities, reduced heterogeneity, and a shorter duration of antigen-specific antibody response compared to mothers. Furthermore, research indicates differences in IgG isotype distribution, with neonates displaying lower levels of the IgG2 subclass-specific response. For example, neonates demonstrate an inadequate IgG response to bacterial polysaccharides.[37] In the case of *H. pylori*, it has been reported that the transfer of antibodies against specific antigens is inefficient. The IgGs acquired transplacentally do not provide adequate protection for neonates against *H. pylori* colonisation.[38–40] Our study did not observe any changes in the antibody repertoire against *H. pylori* major (protein) antigens in newborns at 72 h compared to cord blood levels (Figs. 2 and 3). This suggests that potential *H. pylori* colonisation may influence the development of gut microbial composition and physiological functioning.[41] Overall, our data support previous findings that maternal IgG concentration and IgG subtype are the primary determinants of the IgG repertoire in newborns (Fig. 3). Nevertheless, the observed variability in epitope-specific maternal-to-neonate IgG transfer underscores the need for further investigation into additional contributing factors that modulate this process.

We found regulatory differences in the recognition of immunodominant epitopes of viral antigens between samples from infants at 6 months and their mothers (Figs. 3 and 4). For example, 14 different epitopes of CMV antigens were differentially targeted in seropositive infants at six months compared to those in cord blood. Additionally, if a mother had a strong response to a particular CMV epitope, her infant often demonstrated an immunodominant response to adjacent epitopes of the same antigen (Fig. 4B). Several studies have explored the relationship between maternal and infant antibody composition and titres, highlighting a phenomenon known as 'blunting'. This occurs when pre-existing maternal antibodies influence the antibody response evolvement in neonates to immunising antigens.[13] The precise mechanism by which maternal antibodies inhibit antibody epitope-specific response in infants is not yet fully understood, but some plausible explanations have been proposed. One such explanation is that maternal antibodies may mask antigenic epitopes thereby shaping the infant's antigen-specific antibody repertoire.[42] While newborns exhibit a universal IgM immune profile, their IgG repertories vary depending on individual immune "experience".[43] Latent pathogens, like CMV, EBV, HSV1 cannot be eliminated from the body, resulting in repeated challenges to the immune system.[44] Consequently, maternal IgGs against these latent pathogens reflect the mother's acquired immune response. As a result, a neonate's ability to combat these infectious diseases relies heavily on the immunological imprinting outcome provided by maternal antibodies.[45] However, while the developed IgG response to external viral antigens is generally protective, it can, under certain pathological conditions, become self-aggressive. Studies have demonstrated significant correlations between the development of multiple sclerosis and infections with EBV and CMV, as indicated by seroprevalence data. While a positive association has been established with EBV, a negative correlation has been noted for CMV.[46] Additionally, *H. pylori*, which often persists in the body as a latent pathogen,[47] along with metabolic syndrome (MetS), both of which may contribute to increased inflammation, have been considered for their combined effects on the pathophysiological processes of neurodegeneration.[48] Our findings indicate that the maternal anti-CMV-specific IgG repertoire significantly influences the composition of epitope repertoire in infants by six months of age. While the underlying mechanism remains unclear, the antibodies developed during this period may provide insights into the disruption of immune homoeostasis and the potential for autoimmune diseases associated with the recognition of self-antigen epitopes.

Our study has a few limitations that are important to consider. The relatively small sample size limited our ability to make robust comparisons between maternal and infant stage-specific antibody repertoires, particularly when assessing group-specific differences. Nonetheless, validation of key findings using independent methods supports the reliability of our results. The absence of an external validation cohort may constrain the generalisability of the model to other populations, and future studies are needed to confirm the findings on independent datasets. Second, we choose to study a set of pathogens. These are known significantly influence and regulate a large portion of the immune response and thus, our study is highlighting the associations these pathogens might have with the development of major chronic diseases during the process of immunological ageing. Third, MVA allows high-depth measurement of antibody epitope profiles using small sample volumes. Therefore, the method is inherently limited to detecting antibodies with relatively high abundance. Nevertheless, this limitation strengthens our data regarding the potential cross-reactivity of

defined epitopes to epitopes of self-antigens, which may serve as a measure for assessing the risk of autoimmune diseases.

In conclusion, our findings demonstrate that maternal immunological experiences with latent infections significantly influence the composition and evolution of the passively transferred pathogen-specific IgG repertoires in infants. While the underlying mechanisms remain unclear, this initial shaping of the immune system in early life likely plays a role in the emergence of health disparities in childhood.

Contributors

HS, RMä and KP contributed to the conception and design of the study. KR, ASa, AAn, VT, AAl, TR, JŠ, ES and RMä contributed to the clinical data collection. KR, AAn and AAl conducted the clinical examination of the study participants. HS, RMa, AR, MT, MP, LP, HA and ASi immunoproliferation and validation experiments. HS, RMa, AR, MP, LP, AS, AP and TL contributed to the data analysis and making of the figures and tables. HS, RMa, ES, RMä and KP contributed to drafting and writing of the manuscript. HS, RM and KP had access and verified the underlying data. All authors were involved in the data interpretation, review, and approval of the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

Data supporting the main figures have been included as supplementary files. Further data that support the findings of this study are available from the corresponding author (kaia@protobios.com) upon reasonable request. Due to patient confidentiality and ethical restrictions, access to the data may require institutional review and approval.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.106056.

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