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Placental IgG Transfer Against Polysaccharide versus Protein Antigens in HIV-Exposed and Unexposed Infants

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ABSTRACT

Background: Little is known about differential placental transfer of IgG1 (protein) versus IgG2 (polysaccharide) antibodies in HIV–infected and HIV-uninfected mother-infant pairs. The purpose of this study was to review and reanalyze results from data obtained from several past studies of the author to see whether maternal HIV infection has an impact on the differential placental transfer of polysaccharide versus protein antigens.

Methods: All data (published and unpublished) related to antibody levels against polysaccharide (*Hemophilus influenzae* type b, *Streptococcus pneumoniae*), and protein (tetanus toxoid, measles) antigens were reviewed and reanalyzed. The study population comprised of a group of HIV-infected and uninfected pregnant women and their newborn infants. Protective antibody levels were defined for the respective antigens. Antibody assays for *Hemophilus influenzae* type b, *Streptococcus pneumoniae,* tetanus, and measles were performed using an enzyme-linked immunosorbent assay.

Results: The ratio of cord blood to maternal blood antibody (reflecting placental transfer) was significantly higher for protein antigens when compared to polysaccharide antigens. Within the HIV-exposed group, maternal CD4 counts lower than 500/mm^3 were associated with a considerably (p=0.06) lower placental transfer of protein antigen (tetanus toxoid) compared against those with CD4 counts >500/mm^3.

Conclusions: There is significantly lower antibody transfer against polysaccharide compared with protein antigens, not only in HIV-exposed infants, but also in those not exposed to HIV. Larger prospective studies are recommended to replicate these findings. Maternal immunizations during pregnancy may be the strategy to boost passive antibodies against polysaccharide antigens to improve protection of the vulnerable neonates.

Keywords: Placental transfer, IgG, Polysaccharide, Protein, HIV

BACKGROUND

Placental transfer of maternal IgG antibodies to the fetus is an important mechanism that provides protection to the infant while his/her humoral response is inefficient. IgG is the only antibody class that significantly crosses the human placenta. Factors determining placental antibody transfer from mothers to their infants may include maternal total and specific IgG levels, maternal infectious diseases, placental integrity, IgG subclass, half-life of the passive antibodies, nature of the antigen and timing of vaccination (or infection) [1-3]. Maternally acquired passive immunity generally starts to wane soon after birth, reaches a nadir at an estimated 6 months of life, and is replaced by antibodies made by the infant in response to active immunization or natural infection. Antibody response to T-cell dependent (protein) antigen is more intense compared to T-cell independent (polysaccharide) antigen during the neonatal period- a shift from Th1 (i.e., oriented towards cell-mediated immunity) towards Th2 (i.e., oriented towards humoral immunity) occurs during third trimester of pregnancy [4,5] and continues during infancy.

Neonatal IgG levels usually correlate with maternal levels. It has been suggested that once maternal total IgG levels reach a threshold (>15 g/L), neonatal Fc receptor (FcRn, or

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Brambell receptor) on placenta can become saturated [1,6] and IgG then competes for a finite number of FcRn receptors. Unbound IgG molecules are subsequently destroyed through the lysosomal degradation process within the cells. This finding had also been supported by studies demonstrating reduced IgG transfer ratios were associated with higher maternal total IgG levels [7-9]. Levels of IgG in human immunodeficiency virus (HIV) infected mothers depend on the immunological and clinical status of their disease condition. It is well established in literature that maternal chronic infections (malaria, HIV), due to hypergammaglobulinemia from the infection may reduce placental transfer of specific IgG to vaccine induced immunity [1,8-10]. Thus, HIV- infected women, who have hypergammaglobulinemia due to polyclonal activation of their B cells [10,11], may have non-specific antibodies block the receptors (FcRn) on syncytiotrophoblast cells and reduce placental transfer of specific antibodies. The reduced transfer of antibody is thought to be influenced by concomitant infection and inflammation of the placenta, a reduction in FcRn-antibody binding avidity, or *via* induction of hyper-gammaglobulinemia (IgG > 15 g/L) [12]. This phenomenon can also be applied to pregnant women in low- and middle-income countries (LMIC), where there is a high burden of infectious diseases, superimposed on malnutrition (an immune-compromising condition). Therefore, concern should remain whether there is inadequate placental transfer of specific IgG in HIV-infected women and pregnant women in LMIC. This concern remains valid regardless of whether the infant becomes infected with HIV or not. The author has already demonstrated an overall decreased antibody levels to routine vaccine preventable infections in HIV-exposed infants compared to their unexposed counterparts [13-15].

IgG is the only immunoglobulin class that can cross human placenta in significant amounts. There is preferential transfer of IgG subclasses across placenta; level of IgG1, but not IgG2 in cord blood has been demonstrated to exceed maternal levels of the antibodies [2,16]. Thus, placental transport of IgG2, is shown to be considerably less efficient than that of IgG1, IgG3 or IgG4 [17,18].

The primary objective of this manuscript is to review, and reanalyze data obtained from several studies of the author, from a different perspective to see if there is preferentially decreased transfer of IgG to polysaccharide antigens compared to the protein antigens, in addition to assess if maternal HIV infection has any impact on the neonate. The secondary objective is to discuss justification for immunizing mothers during pregnancy against vaccine preventable infections, particularly against polysaccharide antigens.

METHODS

Data from relevant studies of the author were reviewed and reanalyzed. All study protocols were approved by the Institutional Review Board at Meharry Medical College (MMC). All studies were performed at Meharry Medical College and adjacent General Hospital in Nashville, Tennessee (TN). All women were enrolled during their first, second, or third trimesters of pregnancy and informed written consents were obtained. All relevant information was obtained from the subjects' medical records. Pregnant women were followed prospectively up to their deliveries when cord blood samples were obtained.

Study Population

Fifteen HIV-infected and 34 HIV-uninfected pregnant women were enrolled into the study. The mean (range) ages of pregnant women at the time blood specimens were obtained were 27 (18-40) and 25 (15-41) years for HIV-infected and HIV- uninfected women, respectively. Of the fifteen HIV-infected women, sixty-two percent were on antiretroviral therapy. Their mean (range) CD4 cell count was 484 (210- 1053) cells/mm3 and their mean (range) viral load was 47,320 (400- 278,167) copies/ml.

Pregnant women

There is no record of previous exposure to pneumococcal or *Hemophilus influenzae* type b vaccines in the clinical histories of the women enrolled in this study.

Infants

All preterm infants born at less than 38 weeks were excluded from the study. Not all cord blood samples were mother-infant pairs.

Sample size and power calculation

The sample size calculation was based on a convenient sample of HIV-infected women who were available to enroll over a period of fourteen months (June' 2000- August' 2001). The control group included HIV-uninfected women at a ratio of approximately 2:1 with HIV-infected women. Due to reasons such as insufficient quantity, accidental spillage, and missed opportunity for sample collection, the final number of samples for analyses varied slightly for each category of polysaccharide and protein antigens.

Determination of antibody levels

IgG levels against twenty-three serotypes (1-5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F) as a total of pneumococcal capsular Polysaccharide (PCP) of *Streptococcus pneumoniae* (SPN), polyribosyl-phosphate (PRP) of *Hemophilus influenzae* type b (Hib) and tetanus toxoid (TT) were performed in the authors' laboratories by enzyme linked immunosorbent assay (ELISA) utilizing the kits BINDAZYMETM (Anti-Hemophilus B IgG "Kit MK 016" for H. influenzae type b and Anti-PCP IgG "Kit MK 012" for *S. pneumoniae* [ww.bindingsite.co.uk]). Correlates of immunity were defined as antibody levels >0.35 µg/ml for PCP of *Streptococcus pneumoniae* [19,20], >1.0 µg/ml for PRP of

Hemophilus influenzae type b [21], and >0.01 IU/ml for tetanus toxoid [22]. IgG against measles (MS) was performed by ELISA at specialty laboratories, Santa Monica, California. Correlates of protective immunity for measles was defined as a level >1.09 optical density ratio (ODR) [23].

Immunologic and virologic studies

T cell analyses were performed by flow cytometry in the authors' laboratories at MMC for HIV-seronegative group and at Vanderbilt University Medical Center (VUMC) core laboratories; Nashville, TN for HIV infected mothers and HIV-exposed infants. HIV viral loads in HIV- infected pregnant women and HIV deoxyribonucleic acid (DNA) testing in their infants were performed by polymerase chain reaction (PCR) at VUMC.

Statistical analysis

The statistical analyses were performed using the software program Intercooled Stata version 8. Continuous variables were rounded to the nearest tenth and presented as mean $\pm$ SD; a $p \leq 0.05$ was considered significant.

1. Prevalence of protective immunity for a total of 23 serotypes of *SPN* ($\geq$0.35 µg/ml), *Hib* ($\geq$1.0 µg/ml), TT (>0.01 IU/ml) and MS ($\geq$1.09 ODR) between groups of pregnant women and their infants was performed by two-tailed Fisher's exact test.

2. Paired mother-infant differences in mean IgG levels between groups were determined by two-tailed t test.

3. Effect of confounding variables (socioeconomic status, age of mother, gestational age of babies, and number of pregnancies) on immune response was done using ANOVA with Bonferroni correction, yielding a significance level of 0.01.

RESULTS

Number of available samples

Total of fifteen HIV-infected and thirty-four HIV-uninfected mothers. Sample size distribution for each category of antigen in mothers and their infants are shown in **Table 1**.

Table 1. Distribution of samples for each category of antigen.

Antigens	Groups	Mother (n)	Infant (n)	Mother-Infant Pair (n)
SPN	HIV	8	13	8
	Control	24	26	18
PRP	HIV	8	13	8
	Control	26	26	20
Tetanus toxoid	HIV	9	9	9
	Control	24	24	24
Measles	HIV	11	13	11
	Control	33	27	23

Polysaccharide antigens (*Streptococcus pneumoniae [SPN],* [*SPN*]; *Hemophilus influenzae* type b [*Hib*])

***SPN* Immunity in HIV-infected and HIV-uninfected mothers:** The mean anti-PCPIgG level was 2-fold lower in the eight HIV-infected women (77.63 ug/ml [SD $\pm$ 66.04]) compared to their twenty-four HIV-uninfected (152.39.ug/ml [SD $\pm$ 190.27]) counterparts. All HIV-infected and HIV-uninfected mothers had protective level (anti-PCP >0.35 ug/ml) of IgG antibodies.

***SPN* immunity in HIV-exposed and HIV-unexposed infants:** Mean anti-PCPIgG was 2.5-fold lower in the HIV-exposed (50.83 ug/ml [SD $\pm$ 52.58]) compared to their HIV-unexposed (124.42 ug/ml [SD $\pm$ 167.69]) counterparts. [SPN]; protective level (anti-PCP >0.35ug/ml) of IgG was prevalent in all HIV-exposed and-HIV-unexposed cord bloods.

***SPN* immunity in matched mother-infant pairs:** While mean anti-PCPIgG was only slightly lower in HIV-exposed infants (61.02 ug/ml [SD $\pm$ 65.59]) compared to their HIV-infected mothers (77.63 ug/ml [SD $\pm$ 66.05]), mean anti-PCP was 2-fold lower in the eighteen HIV-unexposed infants (98.98 ug/ml [SD $\pm$ 134.82]) compared to their HIV-uninfected mothers (180.81 ug/ml [SD $\pm$ 246.59).

***Hib* immunity in HIV-infected versus HIV-uninfected mothers**: Mean anti-PRP IgG was 4-fold lower in the eight HIV-infected women (1.15 ug/ml [SD $\pm$ 1.41]) compared to their twenty-six HIV-uninfected counterparts (4.77 ug/ml

[SD ± 6.77]). Protective antibody levels (anti-PRP ≥1 ug/ml) were detected in only two of eight (25%) of HIV-infected mothers as compared with fourteen of twenty-six (54%) of the HIV-uninfected mothers.

***Hib* immunity in HIV-exposed versus HIV-unexposed infants:** Mean anti-PRP IgG was slightly lower (2.07 ug/ml [SD ± 4.23]) in the thirteen HIV-exposed compared to twenty-six HIV-unexposed (2.73 ug/ml [SD ± 3.03]) cord bloods. Protective antibody levels (anti-PRP≥ 1.0 ug /ml) were significantly (p=0.05) lower in HIV-exposed (three of thirteen [23%]) compared to fifteen of twenty-six (58%) of the HIV-unexposed cord bloods.

***Hib* immunity in matched mother-infant pairs:** While mean anti-PRPIgG was comparable between the eight HIV-exposed (1.39 ug/ml [SD ± 2.18]) and their HIV-infected mothers (1.16 ug/ml [SD ± 1.41]), mean anti-PRP was 2-fold lower (p=0.09) in twenty HIV-unexposed infants (2.93 ug/ml [SD ± 3.0]) compared to their HIV-uninfected mothers (5.98 ug/ml [SD ± 7.27]).

Protein Antigens (Tetanus Toxoid [TT] and Measles [MS])

Tetanus toxoid immunity in HIV-infected versus HIV-uninfected mothers: The mean anti-TT IgG was 1.5- fold lower in the nine HIV-infected (1.37 IU/ml [SD ± 1.37]) women compared to their twenty-four HIV-uninfected (2.09 IU/ml [SD ± 2.39]) counterparts. Protective antibody level (anti-TT > 0.01 IU/ml) was prevalent in seven of nine (78%) HIV-infected compared to thirteen of twenty-four (54%) of the HIV-uninfected mothers.

Tetanus toxoid immunity in HIV-exposed versus HIV-unexposed infants: Mean anti-TT IgG was 2-fold lower in the nine HIV-exposed infants (1.59 IU/ml [SD ± 1.70]) compared to their twenty-four HIV-unexposed (2.85 [SD ± 4.21]) counterparts. Protective antibody level (anti-TT > 0.01IU/ml) was prevalent in seven of nine (78%) HIV-exposed compared to thirteen of twenty-four (54%) of the HIV-unexposed cord bloods.

TT immunity in matched mother-infant pairs: Mean anti-TT IgG was slightly higher in both nine HIV- exposed (1.59 IU/ml [SD ± 1.70]) and twenty-four HIV- unexposed cord bloods (2.85 IU/ml [SD ± 4.21]) compared to their HIV-infected (1.37 IU/ml [SD ± 1.37]) and HIV-uninfected mothers (2.09 IU/ml [SD ± 2.39]), respectively.

Measles immunity in HIV-infected versus HIV-uninfected mothers: Mean anti- MS IgG was significantly (p=0.03) lower in the eleven HIV-infected (1.39 ODR [SD ± 0.77]) women compared to their thirty-three HIV-uninfected (2.09 ODR [SD ± 0.97]) counterparts. Protective antibody levels (anti-MS ≥1.09 ODR) were prevalent in six of eleven (54%) HIV-infected mothers compared to twenty-eight of thirty-three (85%) of HIV-uninfected mothers.

Measles immunity in HIV-exposed versus HIV-unexposed infants: Mean anti-MS IgG was considerably lower (p=0.06) in thirteen HIV-exposed cord bloods (1.50 ODR [SD ± 1.10]) compared to their twenty-seven HIV-unexposed (2.41 [SD ± 1.52)]) counterparts. Protective antibody (anti-MS ≥1.09 ODR) was prevalent in nine of thirteen (59%) HIV-exposed compared to twenty-one of twenty-seven (78%) of the HIV-unexposed cord bloods.

MS immunity in matched mother-infant pairs: Mean anti-MS IgG was slightly higher in both eleven HIV-exposed (1.65 ODR [SD ± 1.11]) and twenty-three HIV-unexposed cord bloods (2.53 ODR [SD ± 1.56]) compared to their HIV-infected (1.39 ODR [SD ± 0.77]) and their HIV-uninfected mothers (2.06 ODR [SD ± 1.05]), respectively.

DISCUSSION

This manuscript describes a review and analyses from a different perspective, of data collected from past passive immunity studies of the author. The primary objective of this data analysis was to assess if differences existed in the placental transfer of antibodies specific for polysaccharide versus protein antigens and between HIV- exposed and unexposed neonates. The secondary objective was to assess if results from this analysis would support maternal immunization during pregnancy of not only HIV-infected women but also HIV-uninfected women in resource limited settings, with ultimate goals to boost passive immunities in their neonates against vaccine preventable diseases.

As shown in **Table 2**, it is interesting to note that the placental transfer of antibodies (ratio of cord blood/maternal blood) was significantly lower for the polysaccharide antigens (PCP and PRP) compared to the protein antigens (tetanus toxoid and measles) within the HIV- uninfected mother-infant pairs **(Figure 1)**.

However, similar discrepancy was not noted within the HIV-infected group of mother-infant pairs, except for between PCP of *SPN* and tetanus toxoid antigens. This finding reinforces findings in literature that antibodies to polysaccharide antigens (IgG2) may have significantly lower avidity for placental transfer compared to protein antigens (IgG1, IgG3 or IgG4) [4,5]. Our study results further suggest that, among the antigens analyzed in this study, antibody against tetanus toxoid may have the strongest avidity and antibody against PCP may have the weakest avidity for trans-placental transfer.

One of the objectives of our study was to examine impact of HIV infection in pregnant mothers on passive immunities in their newborns **(Figures 2 and 3)**.

Table 2. Placental IgG transfer (Cord blood/Maternal blood ratio): Polysaccharide versus protein antigens.

Antigens	HIV Group Mean (± SD) (n)	Control Group Mean (± SD) (n)	*P Value
Measles	1.22 ODR (± 0.72) (11)	1.19 ODR (± 0.38) (23)	ns
PRP	1. 08 ug/ml (± 0.46) (8)	0.76 ug/ml (± 0.46) (20)	ns
***P Value**	ns	**0.002**	
Measles	1.22 ODR (± 0.72) (11)	1.19 ODR (± 0.38) (23)	ns
PCP	0.68 ug/ml (± 0.38) (8)	0.62 ug/ml (± 0.29) (18)	ns
***P Value**	ns	**< 0.000**	
Tetanus Toxoid	1.2 IU/ml (± 0.62) (9)	2.94 IU/ml (± 4.86) (24)	ns
PRP	1. 08 ug/ml (± 0.46) (8)	0.76 ug/ml (± 0.46) (20)	ns
***P Value**	ns	**0.05**	
Tetanus Toxoid	1.2 IU/ml (± 0.62) (9)	2.94 IU/ml (± 4.86) (24)	ns
PCP	0.68 ug/ml (± 0.38) (8)	0.62 ug/ml (± 0.29) (18)	ns
***P Value**	**0.05**	**0.05**	

**Two-Tailed T-test*

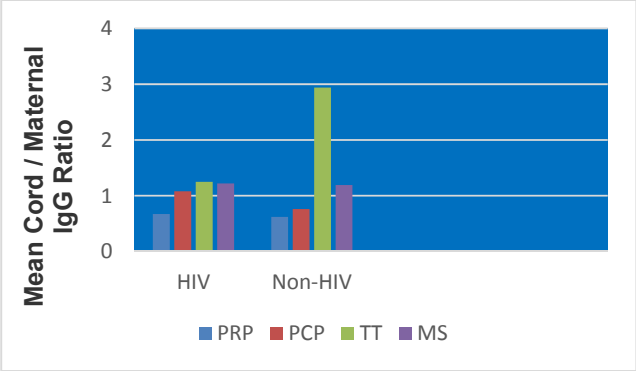

Figure 1. Cord blood/maternal blood IgG ratio: Reflecting placental transfer: HIV and control groups.

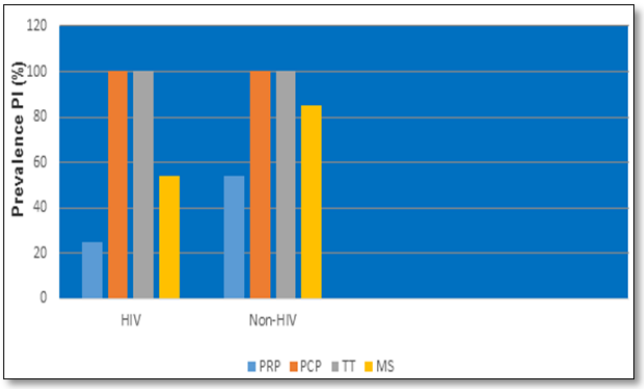

Figure 2. Prevalence of Protective Immunity (PI): HIV vs. Control Mothers.

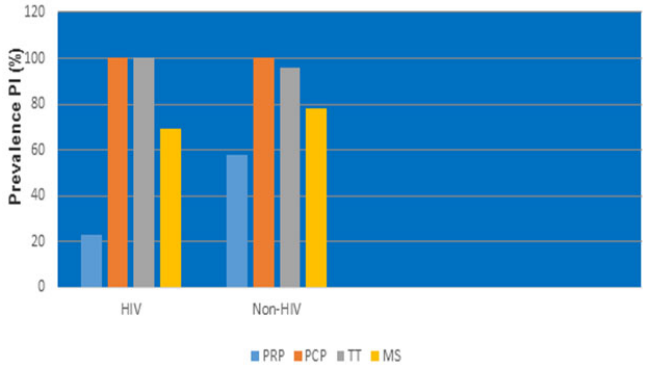

Figure 3. Prevalence of Protective Immunity (PI): HIV vs. Control Infants.

While no significant differences in mean antibody levels were noted in our study between HIV-infected and HIV-uninfected groups of mothers or infants, except those for measles, mean antibody levels were consistently lower for both polysaccharide and protein antigens in the HIV-infected group, compared to their HIV-uninfected counterparts. Although protective antibody levels prevailed for tetanus toxoid and *SPN* in all mothers and infants of both groups, suboptimal protection was noted for measles and *Hemophilus influenzae* type b in the HIV group compared to their HIV-uninfected counterparts **(Tables 3 and 4)**. Indeed, a high level of protective immunity to *SPN* and TT in this population may be attributable to subclinical infections and herd immunity to *SPN* and TT, respectively. Although, our study underlined interesting differences that support the

contention of lower passive immunities in HIV- infected mothers and their exposed infants, further efforts to increase sample size should allow for improved confidence in significant differences between groups.

Table 3. Prevalence of protective immunity in HIV and control groups: Polysaccharide (PRP & PCP) vs. Protein (MS) antigens

	Antigens	HIV Group Proportion (%)	Control Group Proportion (%)	*P Value
Mother	MS	6/11 (54)	28/33 (85)	0.09
	PRP	2/08 (25)	14/26 (54)	ns
***P Value**		ns	**0.02**	
Infant	MS	9/13 (69)	21/27 (78)	ns
	PRP	4/13 (31)	15/26 (58)	ns
***P Value**		ns	ns	
Mother	MS	6/11 (54)	28/33 (85)	0.09
	PCP	8/08 (100)	24/24 (100)	ns
***P Value**		ns	ns	
Infant	MS	9/13 (69)	21/27 (78)	ns
	PCP	13/13 (100)	26/26 (100)	ns
***P Value**		ns	ns	

**Two-Tailed Fisher's Exact-test*

Table 4. Prevalence of protective immunity in HIV and control groups: Polysaccharide (PRP & PCP) vs. protein (TT) antigens.

	Antigens	HIV Group Proportion (%)	Control Group Proportion (%)	*P value
Mother	**TT**	9/9 (100)	24/24 (100)	ns
	PRP	2/8 (25)	14/26 (54)	ns
***P Value**		**0.002**	**0.000**	
Infant	TT	9/9 (100)	23/24 (96)	ns
	PRP	4/13 (31)	15/26 (58)	ns
***P Value**		**0.002**	**0.002**	
Mother	TT	9/9 (100)	24/24 (100)	ns
	PCP	08/08 (100)	24/24 (100)	ns
***P Value**		ns	ns	
Infant	TT	9/9 (100)	23/24 (96)	ns
	PCP	13/13 (100)	26/26 (100)	ns
***P Value**		ns	ns	

**Two-Tailed Fisher's Exact-test*

We have further noted that antibody levels to the protein antigens were higher in the cord blood compared to those in their maternal blood samples in both HIV-infected and uninfected groups **(Table 5)**. This finding may be explained by that immune response during the neonatal period is T cell dependent for protein antigens only [2,16]. Thus, trans-placental transfer of antibody only against tetanus toxoid was influenced by maternal CD4 counts in our study population. The above finding re-emphasizes the recommendation to maintain optimal CD4 counts and undetectable viral loads during pregnancy in HIV-infected mothers with use of highly active antiretroviral therapy to augment placental antibody transfer, in addition to maintaining optimal levels of specific antibodies during pregnancy.

Table 5. Antibody levels against polysaccharide and protein antigens: HIV and control groups (all subjects).

Subjects	Antigens	HIV Group Mean (± SD) (n)	Control Group Mean (± SD) (n)	*P value	Difference
Mother	**PRP**	1.16 ug/ml (± 1.41) (8)	4.77 ug/ml (± 6.77) 26)	ns	**4- fold**
Infant		2.07 ug/ml (± 4.23) (13)	2.73 ug/ml (± 3.03) (26)	ns	**1.3- fold**
Mother	**PCP**	77.63 ug/ml (± 66.05) (8)	152. 39 ug/ml (± 190.27) (24)	ns	**2-fold**
Infant		50.83 ug/ml (± 52.58) (13)	124.42 ug/ml (± 124.42) (26)	ns	**2.4-fold**
Mother	**MS**	1.39 ODR (± 0.77) (11)	2.09 ODR (± 0.97) (33)	**0.03**	**1.5-fold**
Infant		1.50 ODR (± 1.10) (13)	2.41 ODR (± 1.52) (27)	**0.06**	**1.6- fold**
Mother	**TT**	1.37 IU/ml (± 1.37) (9)	2.09 IU/ml (± 2.39) (24)	ns	**1.5-fold**
Infant		1.59 IU/ml (± 1.70) (9)	2.85 IU/ml (± 4.21) (24)	ns	**1.8-fold**

**Two-Tailed T- test*

It is well documented that pregnant women and newborns are more vulnerable to infectious diseases than the overall population; nevertheless, vaccination rates are often low in pregnant women, particularly in LMIC. This may suggest why approximately 2.6 million children had died during the neonatal period (0-27 days of age) and five and a half million children died before 5 years of age worldwide in 2015 [24]. Among the serious infections during neonatal period, influenza and pertussis are associated with significant morbidities and mortalities [25]. Thus, maternal immunization during pregnancy against these infectious diseases, have been implemented in resource limited settings [26]. Fortunately, the immune response against these infections, are T-cell dependent with favorable avidity of these antibodies for trans-placental transfer. However, secondary bacterial infections following infection with influenza are not uncommon, accounting for a considerable number of morbidities and mortalities in neonates and younger children. Most common bacteria known to cause supra-infections are *Streptococcus pneumoniae* and *Hemophilus influenzae* type b [27], which are not isolated in most cases [28]. Therefore, it may be reasonable to conclude that the incidence of supra-infection (bacterial pneumonia) caused by these bacteria may be underestimated. The immune response to these bacteria is T-cell independent, with poor avidity of these antibodies for trans-placental transfer indeed. Therefore, concern for supra-infection (bacterial pneumonia) with these encapsulated bacteria in patients following an influenza infection should remain a priority.

It is well known that neonates are unable to mount a fully protective immune response to many pathogens, notably the intracellular pathogens and bacterial polysaccharides [4,5]. As mentioned earlier, this is a T-cell independent phenomenon in neonates [4,5]. This Th2-skewed response suppresses cytotoxic T-lymphocytes and stimulates B lymphocytes to increase the production of antibodies [25]. During this period, infants rely on these passively transferred maternal antibodies for their protection. It has been suggested that the levels of antibodies present in infants at birth correlate to the levels of maternal antibodies. However, maternal specific antibody levels are often suboptimal and therefore may not be sufficient to confer full protective immunity to the infants or may protect them for only a short period of time (approximately 6 months). Hypothetically, maternal immunization during pregnancy can increase specific antibody concentrations to augment passive transfer to their fetuses. This will reduce the window of vulnerability for the infants until the appropriate time for infant vaccinations or the period of greatest susceptibility has passed.

CONCLUSIONS

This study has demonstrated significantly lower placental antibody transfer against *SPN* and *Hib* antigens in not only HIV-exposed, but also HIV-unexposed-infants. Therefore, we strongly support maternal immunization during pregnancy against vaccine preventable infections in vulnerable populations, including HIV-infected women and pregnant women in LMIC, particularly against the encapsulated bacteria. Additionally, we recommend pneumococcal polysaccharide vaccine (PPV23) to mitigate invasive pneumococcal disease in infants against a wider spectrum of serotypes, for immunizing mothers during pregnancy. We further recommend that larger prospective studies should examine specific serotypes of *SPN* not only quantitatively, but also qualitatively by assessing functional abilities of the opsonic antibodies through killing assays, and also examine duration of their immune protection.

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