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Maternal HIV Infection and Antibody Responses Against Vaccine-Preventable Diseases in Uninfected Infants

JAMA. 2011 Feb 9;305(6):576-84.

Jones et al

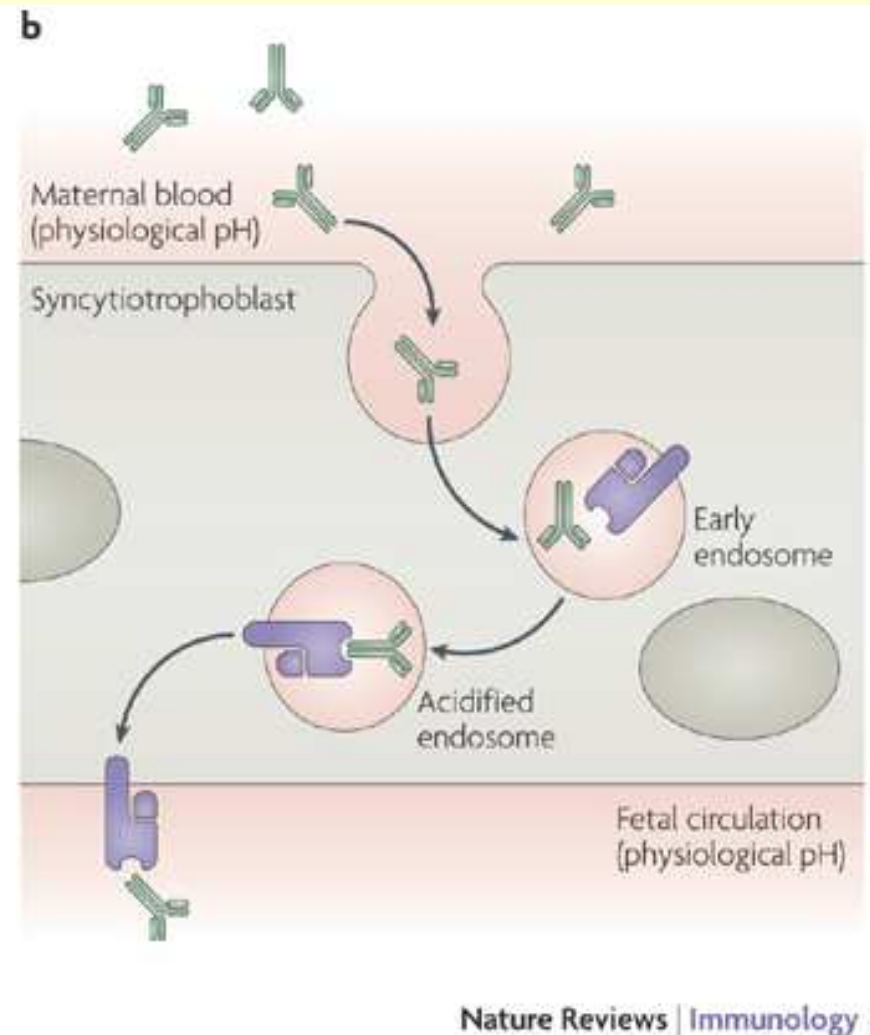
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Background

- Infectious diseases account for nearly 6 million deaths world-wide annually in children younger than 5 years
- Immunizations against vaccine-preventable infections remain essential to achieving Millennium Development Goal 4
 - reduce childhood mortality by two thirds

Background

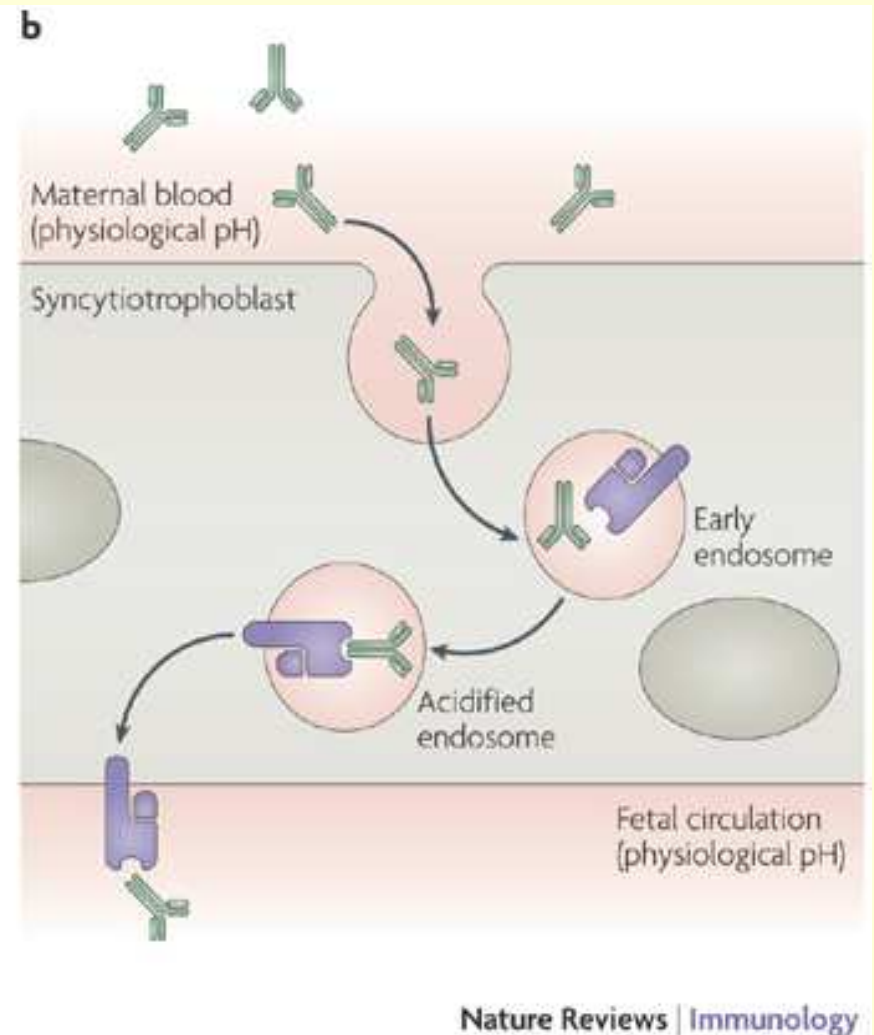
- Before acquisition of immunity, infants are protected by maternal IgG transferred across the placenta



FcRn: the neonatal Fc receptor comes of age Derry C. Roopenian & Shreeram Akilesh Nature Reviews Immunology 7, 715-725 (September 2007)

Background

- Maternal antibody levels, immunization, infection, and infant gestational age can influence the efficiency of this process
- Although maternal antibody is essential to protect the infant in the first months of life, maternal-specific antibody can also interfere with the infant's own response to vaccine



FcRn: the neonatal Fc receptor comes of age Derry C. Roopenian & Shreeram Akilesh Nature Reviews Immunology 7, 715-725 (September 2007)

Background

- There are increasing numbers of HIV-exposed infants who are not HIV-infected themselves
 - High prevalence of maternal HIV infection in resource-poor parts of the world + Successful programs to reduce mother-to-child transmission of HIV

Background

- These babies represent a vulnerable group with increased rates of:
 - Lower respiratory tract infection
 - Meningitis
 - 4-fold higher mortality in the first year of life
- Although this is likely due to a number of factors (socioeconomic, etc), immunological phenomena might also be important

Objective

- To study the association of maternal HIV infection with maternal- and infant-specific antibody levels to:
 - *Haemophilus influenzae type b (Hib)*
 - *Pneumococcus*
 - *Bordetella pertussis antigens*
 - *Tetanus toxiod*
 - *Hepatitis B surface antigen*

Methods



- Community-based cohort study
- Khayelitsha, Western Cape Province, South Africa
 - Rapidly expanding urban informal settlement
- March 3, 2009 and April 28, 2010



Study Setting

- In this setting, all women are offered voluntary counseling and testing for HIV at antenatal care registration and participation is close to 100%
- In 2009, HIV prevalence among women attending the antenatal clinics was 32% with reported vertical transmission of 3.3%

Study Setting

- During the study period, the Prevention of Mother to Child Transmission program consisted of dual therapy for mothers and infants
 - Zidovudine (AZT) at 28 wks or more gestation
 - Zidovudine for 1 month to the infant
 - Single dose of nevirapine (NVP) to both mother and infant

Study Setting

- Mothers were eligible for HAART if:
 - CD4 count <200 cells/uL
- Exclusive formula feeding options were encouraged and mothers were provided with free formula for 6 months if they chose exclusive formula feeding

Study Setting

- The study was nested in a cohort study investigating the influence of maternal HIV and mycobacterial infection on infant immune responses to BCG vaccination
 - BCG vaccination was delayed until 6 weeks of age to allow for determination of infant HIV infection and to avoid BCG vaccination of HIV-infected infant and vaccine adverse events

Study Setting

- Infants received all other routine vaccines according to the South African Expanded Program on Immunization schedule

Study Setting-Vaccinations

- From March 3, 2009 to June 2009
 - Oral polio vaccine (Sanofi Pasteur, Lyon, France) at birth
 - At 6, 10, and 14 weeks
 - Combination diphtheria, tetanus toxoid, and pertussis vaccine and *Haemophilus influenzae* type b vaccine (DTP-Hib; Sanofi Pasteur);
 - Hepatitis B (Heber Biotec, Havana, Cuba); oral polio vaccine
 - Oral polio vaccine

Study Setting-Vaccinations

- From July 2009 to April 28, 2010
- 6 weeks
 - pneumococcal 7-valent conjugate (Wyeth, Andover, Massachusetts)
 - rotavirus vaccinations (GlaxoSmithKline, Rixensart, Belgium)
 - diphtheria, tetanus toxoid, and acellular pertussis vaccine combined with inactivated polio vaccine and Hib (DTaP-IPV/Hib; Sanofi Pasteur)
 - Hepatitis B
- 10 weeks
 - DTaP-IPV/Hib
 - Hepatitis B
- 14 weeks
 - Pneumococcal 7-valent conjugate
 - Rotavirus
 - DTaP-IPV/Hib
 - Hepatitis B

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2011

For those who fall behind or start late, see the catch-up schedule

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B ¹		HepB	HepB			HepB						
Rotavirus ²				RV	RV	RV ²						
Diphtheria, Tetanus, Pertussis ³				DTaP	DTaP	DTaP	<i>see footnote³</i>	DTaP				DTaP
<i>Haemophilus influenzae</i> type b ⁴				Hib	Hib	Hib ⁴	Hib					
Pneumococcal ⁵				PCV	PCV	PCV	PCV				PPSV	
Inactivated Poliovirus ⁶				IPV	IPV	IPV						IPV
Influenza ⁷						Influenza (Yearly)						
Measles, Mumps, Rubella ⁸							MMR		<i>see footnote⁸</i>			MMR
Varicella ⁹							Varicella		<i>see footnote⁹</i>			Varicella
Hepatitis A ¹⁰							HepA (2 doses)					HepA Series
Meningococcal ¹¹												MCV4



Range of recommended ages for all children



Range of recommended ages for certain high-risk groups

Study Setting

- No vaccines were administered to participating mothers
- Tetanus immunization is not routinely administered to pregnant women in this setting

Eligibility

- Inclusion criteria
 - Women who delivered a healthy infant at the Site B Maternal Obstetric Unit within the previous 24 hours
 - Known HIV status at antenatal care registration
 - Willing and able to provide written informed consent

Eligibility

- Excluded Mothers
 - Younger than 18 yrs (2)
 - Did not intend to return to the routine Site B baby clinic for ongoing care (15)
 - Were unwell (2)
 - Evidence of active TB or on TB treatment (1) or had current household or other close TB contact (1)

Eligibility

- Excluded Infants
 - Less than 2.5 kg or estimated at less than 36 wks gestation (8)
 - Acute illness (1)
 - Part of twin birth (2)

Eligibility

- Consecutive eligible women were enrolled irrespective of their HIV status
 - Once a sufficient number of HIV-uninfected women were reached (approximately 50% of sample), HIV-infected women were consecutively enrolled

Study Measures

- Venous blood sample collected from mother and infant within 24 hrs of delivery and transported to the laboratory within 4 hours
- All infants had a further venous blood sample collected at 16 weeks
- Mothers who tested negative for HIV during pregnancy had a rapid HIV test at enrollment with pretest and posttest counseling to confirm HIV status

Study Measures

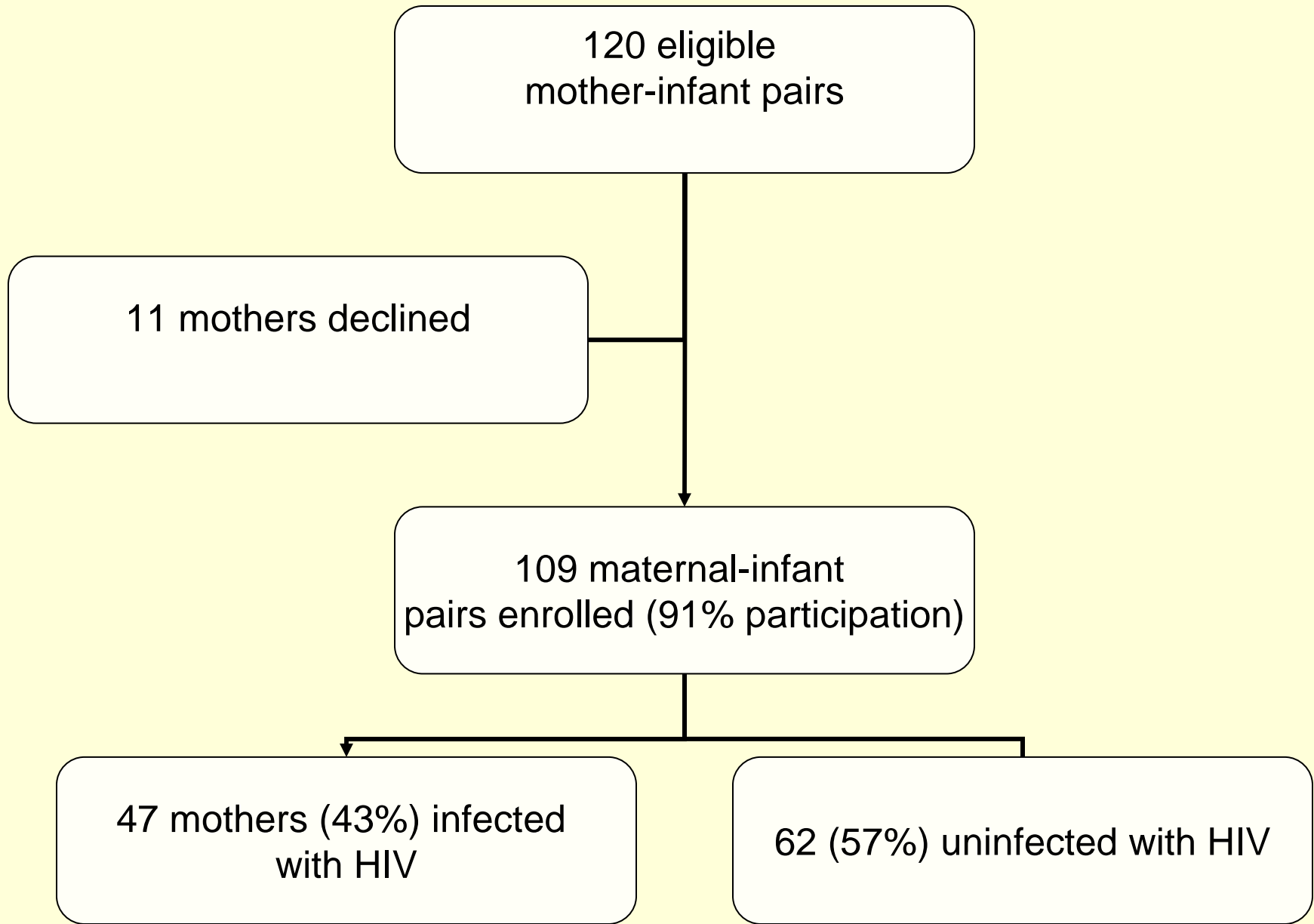
- HIV-exposed infants had an HIV PCR at ages 4 and 16 weeks
- Infant vaccination status was verified from vaccination cards
- Serum was separated and stored at -80 degrees Celcius for analysis

Laboratory Assays

- Vaccine specific IgG levels were measured using commercially available ELISA kits
- ELISAs were performed by researchers blinded to maternal HIV infection status and personal information

Laboratory Assays

- Protective titer cut-offs
 - Anti-Hib antibody titers > 1.0 mg/L
 - Pertussis antibody titers > 30 U/mL were regarded as positive
 - Tetanus antibody titers > 0.1 IU/ml
 - Hepatitis B antibody titers > 10 mIU/ml
 - “No level of protective immunity has been established for a collective response to multiple pneumococcal serotypes”



Participant Characteristics

- All women testing negative for HIV at their antenatal care registration had a further repeat negative HIV test at delivery
- Samples were collected from 105 mothers at delivery
 - 96% of maternal sample
 - 47 infected; 58 uninfected
- Samples were collected from 101 infants at delivery
 - 93% of infant sample
 - 47 were exposed to HIV; 54 were unexposed

Participant Characteristics

- Sample volumes were insufficient for 4 women and 8 infants
- One infant (1%) was determined to be infected with HIV at 4 wks and was referred for rapid initiation of ART
 - This pair was subsequently excluded from the analysis

Participant Characteristics

- Follow-up samples were available for 94 infants (87%; 38 were exposed and 55 were unexposed) at a mean postnatal age of 16.4 weeks
 - One late follow-up sample (28 weeks) was excluded from the analysis
- Final analysis was based on samples from 104 women and 100 infants collected at birth and samples from 93 infants collected at 16 weeks

Table 1. Characteristics of HIV-Infected and HIV-Uninfected Women and Their Uninfected Infants

Characteristics	No. (%) of Participants		P Value
	HIV-Infected Women and Exposed Infants (n = 46 at Birth)	HIV-Uninfected Women and Unexposed Infants (n = 54 at Birth)	
Maternal age, median (IQR), y	27.0 (24.0-31.3)	24.0 (20.0-27.5)	.002 ^a
Maternal primigravidity	10 (21)	28 (45)	.01 ^b
Female infant sex	25 (57)	33 (57)	.68 ^b
Infant delivered by normal vaginal delivery	46 (100)	54 (100)	>.99
Birth weight, mean (SD), kg	3.16 (0.35)	3.23 (0.44)	.38 ^c
Weight at 16 wks, mean (SD), kg ^d	6.81 (0.93)	6.60 (0.93)	.29 ^c
Exclusive breast feeding at birth ^e	0	54 (100)	<.001
Exclusive breast feeding at 16 wks ^e	0	23 (42)	<.001
Household lives in informal structure ^f	36 (78)	34 (54)	.02 ^b

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.

^aMann-Whitney U test.

^bFisher exact test.

^ct Test.

^dWeight at 16 weeks available for all infants followed up to 16 weeks (38 HIV-exposed infants and 55 HIV-unexposed infants).

^eNo breast feeding was reported at any study visit for HIV-exposed infants.

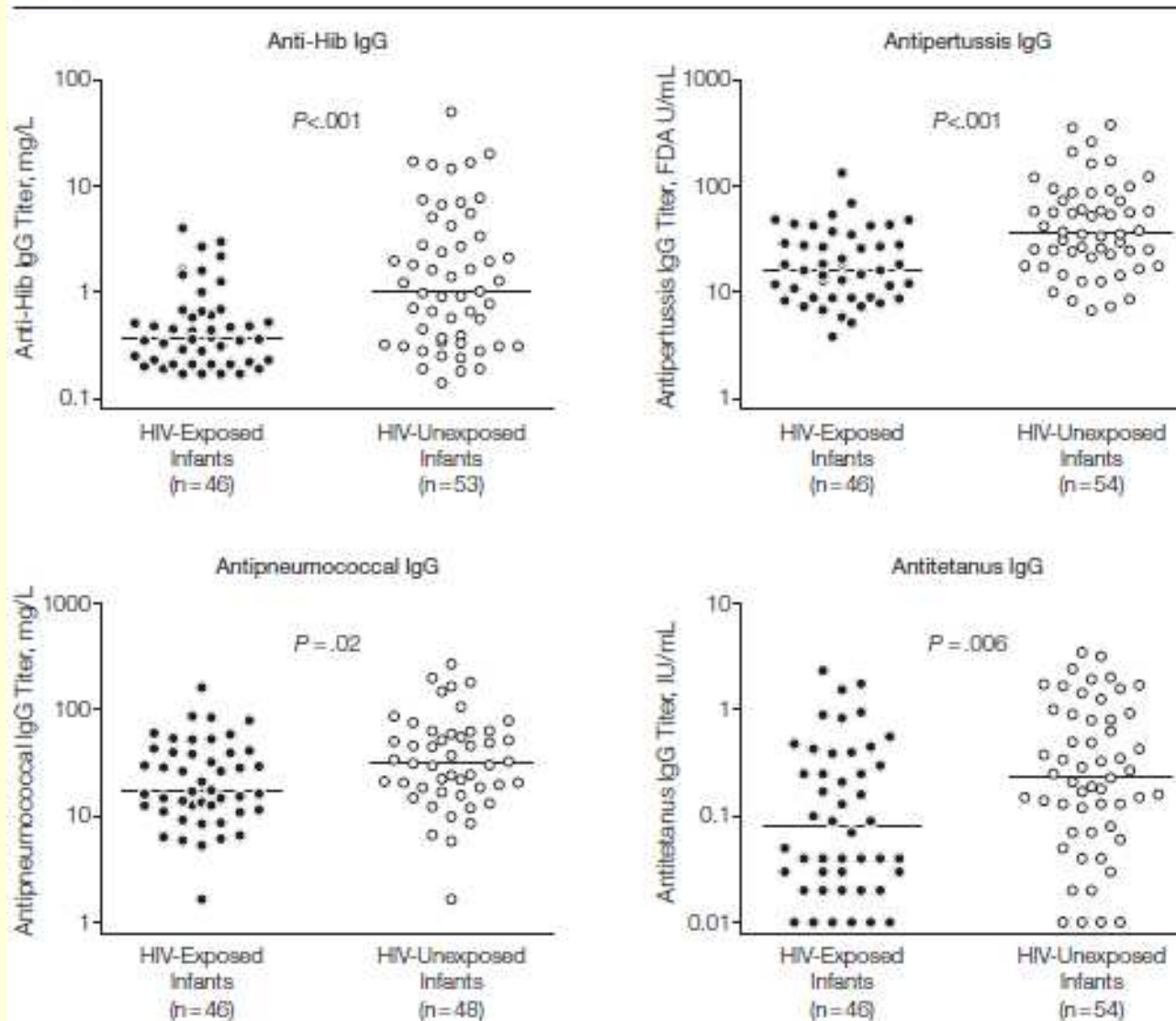
^fAn informal structure is a shack constructed of materials such as wood and corrugated iron.

Participant Characteristics

- All HIV-infected women chose exclusive formula replacement feeding
- Mean CD4 count among HIV-infected women was 474 cells/uL and median VL was 800 copies/mL
 - 7 women had CD4 counts < 200 cells/uL
 - 3 of these were on HAART and 4 were referred to start HAART

Results: Infant-Specific Antibody Responses at Birth

Figure 1. Specific Antibody Titers in Uninfected HIV-Exposed and HIV-Unexposed Infants at Birth



Results: Infant-Specific Antibody Responses at Birth

- HIV-exposed compared to HIV-unexposed infants
 - Significantly lower antibody levels at birth to
 - Hib (0.37 mg/L vs 1.02 mg/L; $P < .001$)
 - Pertussis (16.07 U/mL vs 36.11 U/mL; $P < .001$)
 - Pneumococcus (17.24 mg/L vs 31.97 mg/L; $P = .02$)
 - Tetanus (0.08 IU/mL vs 0.24 IU/mL; $P = .006$)

Results: Infant-Specific Antibody Responses at Birth

- There was a significantly lower proportion of HIV-exposed compared to HIV-unexposed infants with protective antibody levels to:
 - Hib (17% vs 52%; $P=0.001$)
 - Pertussis (24% vs 57%; $P=0.001$)
 - Tetanus (43% vs 74%; $P=0.002$)
 - Hepatitis B (21% vs 54%; $P=0.01$)

Infant-Specific Antibody Responses at Birth

- In multiple linear regression model for factors associated with magnitude of specific antibody response at birth, HIV exposure remained associated with reduced titers to
 - Hib ($P=.001$)
 - pertussis ($P=.001$)
 - pneumococcus ($P=.01$)
 - tetanus ($P=.002$) levels
- There was no association with maternal age, gravidity, housing structure, infant sex or birth weight for Hib, pneumococcus, and tetanus levels
- However, increased maternal age was associated with higher pertussis-specific antibody titers ($P=.03$)

Maternal-Specific Antibody Responses

- HIV-infected women had lower specific antibody levels than uninfected women to:
 - Hib (0.67 mg/L vs 1.34 mg/L; $P=.009$)
 - Pneumococcus (33.47 mg/L vs 50.84 mg/L; $P=.03$)
- No differences were observed for:
 - Pertussis (22.07 U/mL vs 23.64 = U/mL; $P=.26$)
 - Tetanus (0.09 IU/mL vs 0.15 IU/mL; $P = .12$)

Maternal-Specific Antibody Responses

- In multiple regression model for factors associated with level of maternal-specific antibody response, maternal HIV infection was associated with:
 - Low Hib and pneumococcal antibody levels
- There was no significant association with maternal age, gravidity, or housing structure for any of the specific antibody responses

Maternal-Specific Antibody Responses

- HIV-infected women were less likely to have anti-Hib antibody levels considered to be protective (35% vs 59%; $p=0.02$)
- BUT there was no significant difference in the proportion protected against
 - Pertussis (24% vs 38%; $P=.14$)
 - Tetanus (47% vs 64%; $P=.11$)
 - Hep B (26% vs 33%; $P=.52$)

Maternal-Specific Antibody Responses

- In HIV-infected women, CD4 count was positively correlated with the level of antibody to
 - Pertussis (P=0.04)
 - Pneumococcus (P=0.03)
 - Tetanus (P=0.01)
 - But NOT Hib (P=0.63)
- No correlation between maternal HIV VL and any specific antibody level

Maternal-Specific Antibody Responses

- In HIV-infected women and their infants, the correlation between maternal- and infant-specific antibody responses was statistically significant for:
 - Hib ($P < 0.001$)
 - Pertussis ($P < 0.001$)
 - Pneumococcus ($P < 0.001$)
 - Tetanus ($P < 0.001$)

Maternal-Specific Antibody Responses

- In HIV-negative women and their infants, the correlation between maternal- and infant-specific antibody responses was also statistically significant for:
 - Hib ($P < 0.001$)
 - Pertussis ($P < 0.001$)
 - Pneumococcus ($P < 0.001$)
 - Tetanus ($P < 0.001$)

Association of Maternal HIV with Placental Transfer of Specific Antibody

- The proportion of maternal-specific antibody transferred across the placenta to infants was significantly reduced among HIV-infected women and their infants
- Used infant:maternal antibody ratios as a proxy for placental transfer

Association of Maternal HIV with Placental Transfer of Specific Antibody

Table 2. Influence of Maternal HIV Infection on Placental Antibody Transfer

Specific Antibody	Placental Transfer, Median (IQR) ^a		Reduction, % ^b	P Value ^c
	HIV-Infected Mother-Exposed Uninfected Infant Pairs	HIV-Uninfected Mother-Unexposed Infant Pairs		
<i>Haemophilus influenzae</i> type b	0.57 (0.45-0.79)	0.74 (0.61-1.00)	23	.002
<i>Bordetella pertussis</i>	0.91 (0.61-1.20)	1.51 (1.15-2.06)	40	<.001
Pneumococcus	0.62 (0.41-0.77)	0.73 (0.53-0.94)	15	.05
Tetanus toxoid	0.95 (0.60-1.12)	1.30 (1.03-1.86)	27	<.001

- HIV-infected women had significant reductions in placental transfer of Hib, pertussis, and tetanus
- Trend toward reduction in placental transfer for pneumococcal specific antibodies
- There was no association between maternal CD4 count or VL and placental transfer among HIV-infected women

Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- In stratified analysis for infants who had received 1, 2, or 3 doses of DTP-Hib vaccine (n=6, 22 and 65) there was no difference in antibody levels between infants who had received 1 or 2 doses, so these groups were combined for further analysis
- Data also combined for infants who had received 1 or 2 doses of pneumococcal capsular polysaccharide (n=15, 34)

Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

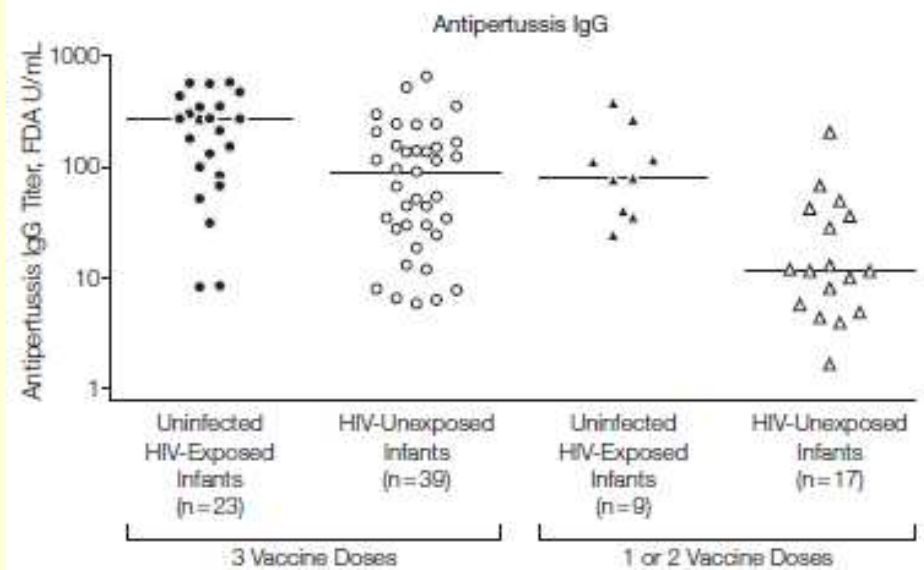
- NO statistical difference in the proportion of HIV-exposed and HIV-unexposed infants who received fewer than 3 doses of DTP-Hib vaccine (25% vs 15%; $p=0.31$) or fewer than 2 doses of pneumococcal capsular polysaccharide (20% vs 49%; $p=0.06$) before the 16-wk sampling

Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- Despite initially lower titers at birth, HIV-exposed uninfected infants mounted robust responses following vaccination.

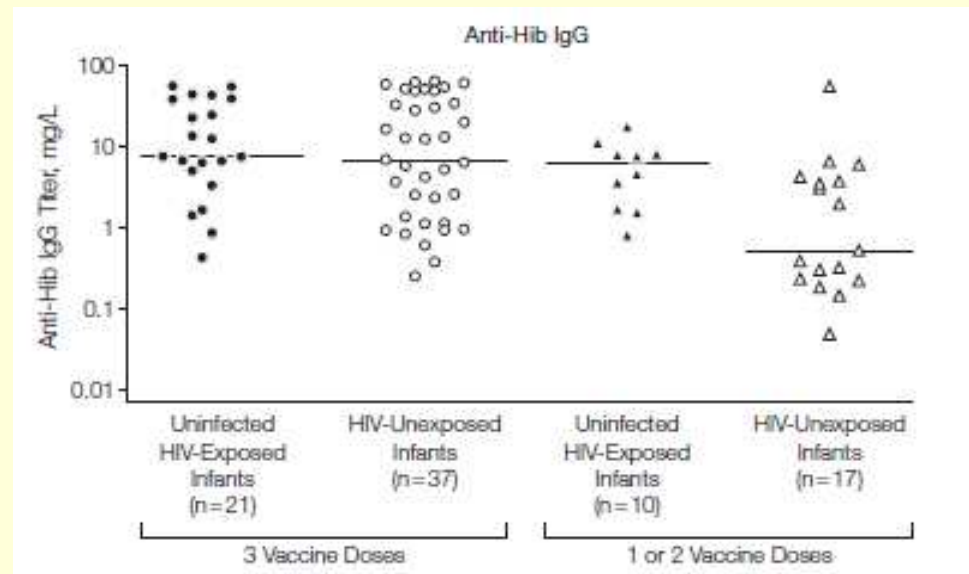
Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- Group that received all 3 scheduled doses of DTP-Hib: HIV-exposed infants had significantly higher responses to pertussis (270.1 U/ml vs 91.7 U/ml; $P=0.006$) than unexposed infants
- Group that received 1 or 2 doses of DTP-Hib: HIV-exposed infants had higher pertussis response (81.16 U/ml vs 11.6 U/ml; $P=0.001$)



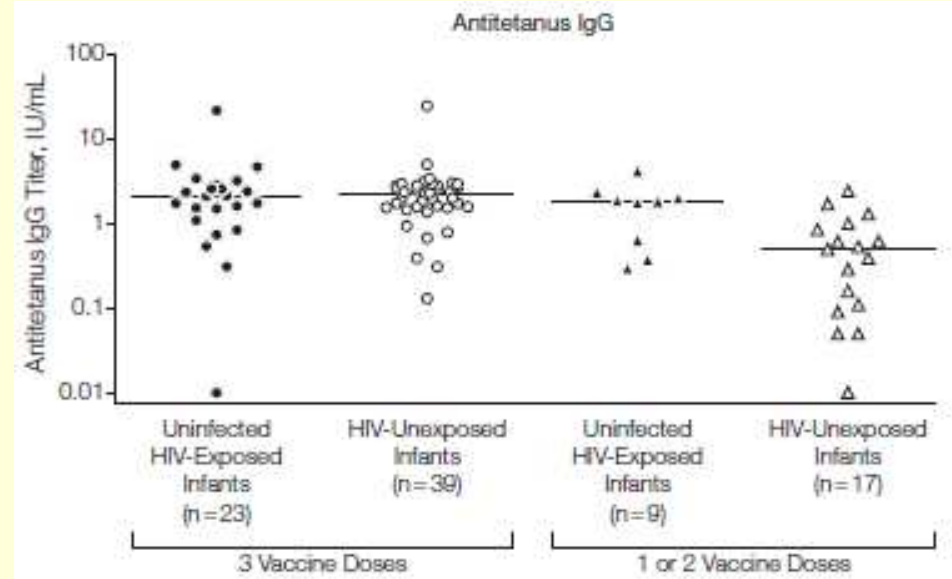
Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- Group that received all 3 scheduled doses of DTP-Hib: HIV-exposed infants had similar responses to Hib
- Group that received 1 or 2 doses of DTP-Hib: HIV-exposed infants had higher Hib response (6.46 mg/L vs 0.54 mg/L; $P=0.02$)



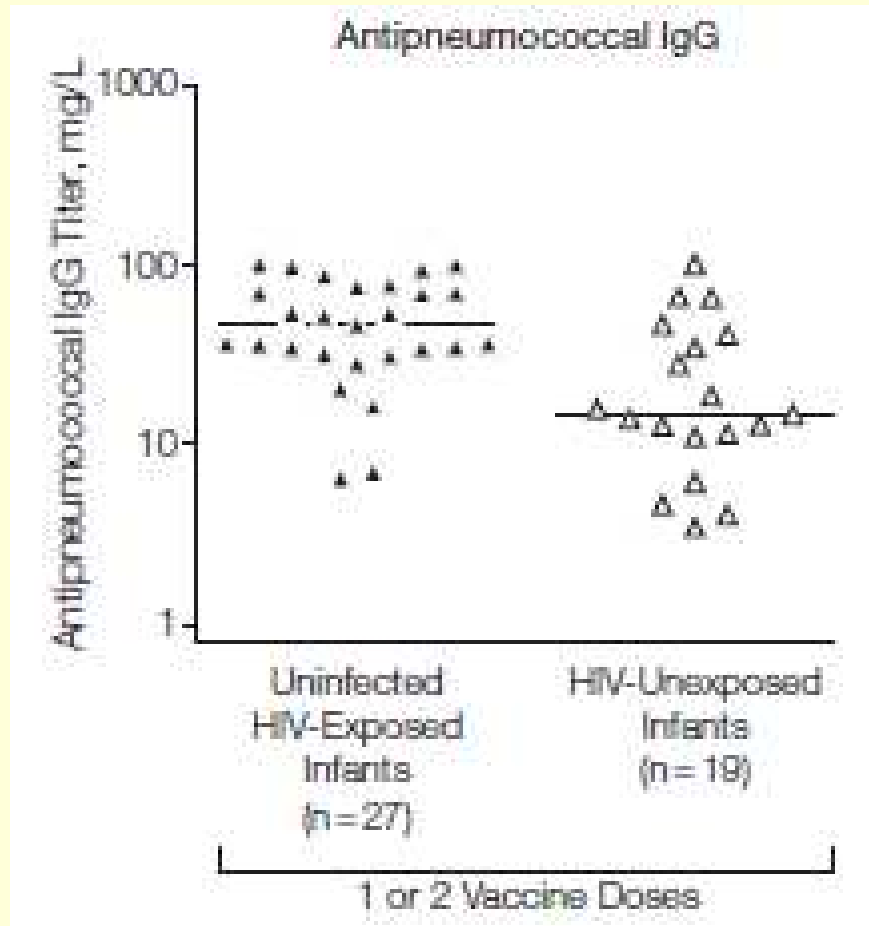
Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- Group that received all 3 scheduled doses of DTP-Hib, HIV-exposed infants had similar responses to tetanus
- Group that received 1 or 2 doses of DTP-Hib: HIV-exposed infants had higher tetanus response (1.86 IU/ml vs 0.50 IU/ml; $P=0.01$)



Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- HIV-exposed infants had significantly higher responses to pneumococcal-specific antibody (47.23 mg/L vs 14.77 mg/L; $P=0.001$) than unexposed infants

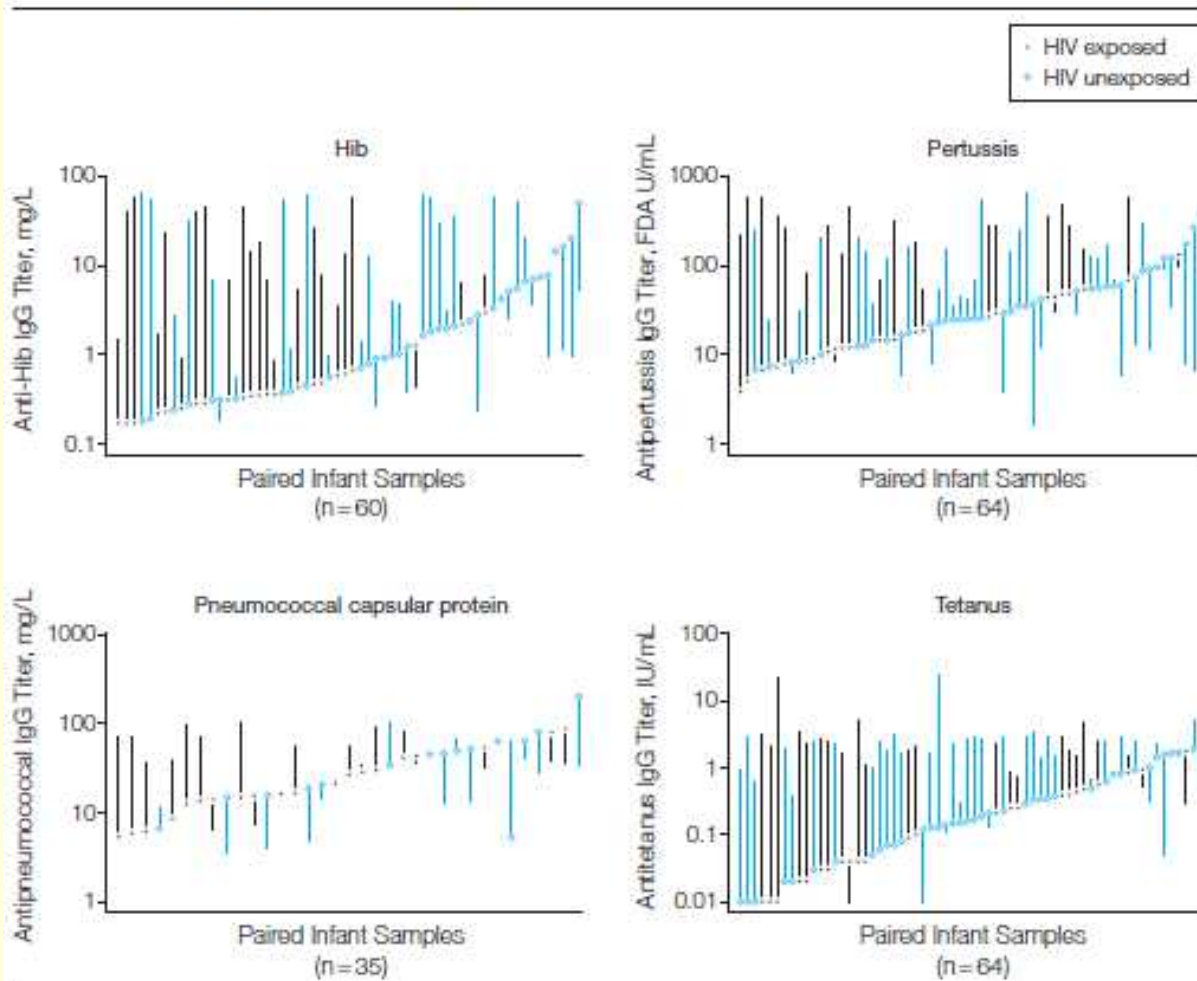


Specific Vaccine-Induced Antibody Responses in Infants at 16 Weeks

- Before and after vaccination, HIV-exposed infants had a significantly higher fold increase in antibody levels vs HIV-unexposed infants
 - Hib (21.15-fold vs 2.97-fold increase; $P=.007$)
 - Pertussis (9.51-fold vs 2.16-fold increase; $P=.002$)
 - Pneumococcus (2.06-fold vs 0.31-fold increase; $P<.001$)
- No difference for tetanus (14-fold vs 12-fold increase; $P=.45$) pre and post vaccination

Pre and post vaccination antibody levels for individual infants

Figure 3. Change in Specific Antibody Titers Between Birth and 16 Weeks in Uninfected HIV-Exposed and HIV-Unexposed Infants



- HIV exposure was associated with a greater magnitude of change between birth and 16 weeks

Discussion

- HIV-exposed uninfected infants have lower specific antibody levels at birth than their non-HIV exposed peers
- This is shown to be due to
 - Lower antibody titers to Hib and pneumococcus in HIV-infected pregnant women
 - Reduced transplacental transfer of Hib, pertussis, pneumococcal and tetanus antibody

Discussion

- Findings are consistent with studies of HIV-infected women from Kenya indicating that maternal HIV is associated lower tetanus and measles-specific antibody in cord blood and also with reduced placental antibody transfer
 - Note: lower tetanus antibody levels may be due to vaccination practice during pregnancy

Discussion

- Although it is known that measles, Hib, and pneumococcal vaccine responses are reduced in children infected with HIV, there are few studies investigating the influence of infant HIV exposure (in the absence of infection) on responses to vaccines

Discussion

- Increased vaccine response in HIV-exposed vs unexposed infants to pertussis and pneumococcus following completion of the immunization schedule
 - Explained by lower maternally derived antibody levels at birth
- Higher levels of maternal antibody among HIV-unexposed infants at birth corresponded with lower responses postvaccination

Discussion

- Other studies have also reported that maternal antibodies can inhibit infant responses to measles, tetanus, whole cell pertussis, and Hib vaccines
 - Mechanisms not fully understood
 - Perhaps maternal antibody masks or hides vaccine antigenic epitopes, preventing recognition and binding by infant B cells
 - Maternal antibody-to-vaccine antigen ratio is likely a key determinant

Discussion

- In infants that missed a dose of vaccine, HIV-exposed infants had higher antibody responses than unexposed infants
 - Higher maternal antibody in HIV unexposed infants may influence the response to the first dose of vaccine but not subsequent doses
 - Shown in other studies - infants with high levels of maternal antibody to Hib had lower anti-Hib antibody after first vaccination but not after the 2nd vaccination

Study Limitations

- Single center
- Modest numbers of mother-infant pairs
- No data on maternal vaccination history
 - Limitations in recall and documentation
- Women in study group with statistically different ages
 - May not be clinically relevant (27 vs 24 years of age)
 - Could infer similar maternal vaccination history based on date of introduction of the universal Expanded Program on Immunization schedule in South Africa (1973)

Study Limitations

- Although antibody levels can be used to indicate potential susceptibility to infection, some uncertainty remains regarding the functional relevance of a single so-called protective level
- Protective levels for collective response to multiple pneumococcal serotypes are unclear
- There is minimal evidence for defining protective levels for other antibodies such as pertussis

Study Limitations

- Unable to correlate of antibody levels with long-term vaccine responses or clinical outcomes in women or infants

Discussion

- Data contributes to a potential explanation for the higher morbidity and mortality observed among African HIV-exposed infants
 - Lower pneumococcal-specific antibody among HIV-exposed infants before vaccination might be associated with increased severity of pneumonia observed in these infants

Future Study

- Larger prospective studies to determine whether the lower antibody levels in HIV-exposed infants at birth translate into increased morbidity from vaccine-preventable infections
- Evaluation of novel maternal and neonatal immunization strategies to augment specific antibody responses and potentially prevent infections in infants early life

Future Study

- Implementation of vaccination programs in pregnancy
 - May impair infant response to vaccination as a result of increased maternal antibody
- Evaluation of pneumococcal or pertussis vaccination strategies during or before pregnancy in settings with high HIV prevalence may be beneficial

Future Study

- Neonatal vaccination could also be considered
 - Neonatal pertussis vaccination is safe and results in early antibody responses

eTable 3. Association of level of specific antibody and number of doses of vaccine received prior blood sampling at 16 weeks

	Median (IQR) level of antibody according to number of doses of vaccine received			P values
	1	2	3	
Hib (mg/L)	0.54 (0.26 - 4.11)	1.77 (0.23 - 4.22)	7.75 (2.07 - 37.52)	<0.001 †‡
Pertussis (FDA U/mL)	10.55 (3.71 - 27.74)	41.89 (11.60 - 105.5)	129.1 (33.79 - 275.4)	<0.001 †‡
Pneumococcus (mg/L)	30.44 (12.01 - 42.64)	37.06 (16.05 - 76.32)	N/A	0.097 §
Tetanus (IU/mL)	0.44 (0.30 - 0.67)	0.82 (0.19 - 1.89)	2.13 (1.52 - 2.85)	<0.001 †‡

The Kruskal-Wallis test was used to compare the level of specific antibody measured for 3 groups of infants receiving 1 (n=6), 2 (n=22) or 3 (n=65) doses of vaccine containing Hib, pertussis and tetanus antigens. Dunn's post-test was used to compare the difference between each column; * denotes a statistically significant difference at the P<.05 level between infants who received 1 vs. 2 vaccine doses, † between infants who received 1 vs. 3 vaccine doses and ‡ between infants who received 2 vs. 3 vaccine doses. § The unpaired t-test was used to compare infants who had received 1 vs 2 doses of pneumococcal vaccine (PCV7). Only 2 doses of vaccine are routinely scheduled before 16 weeks and this vaccine was introduced during the study period, therefore only 49 infants received this vaccine (n=15 received 1 dose, n=34 received 2 doses).