Epidemiology of Pertussis in Africa

Maternal immunization as a possible strategy for prevention

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Overview

- Vulnerability to B. pertussis in young infants
- In-utero exposure to maternal HIV infection and immunity to pertussis
- Studies from Soweto:
  - Mother-child cohort study
  - Surveillance for hospital admissions in <12 months

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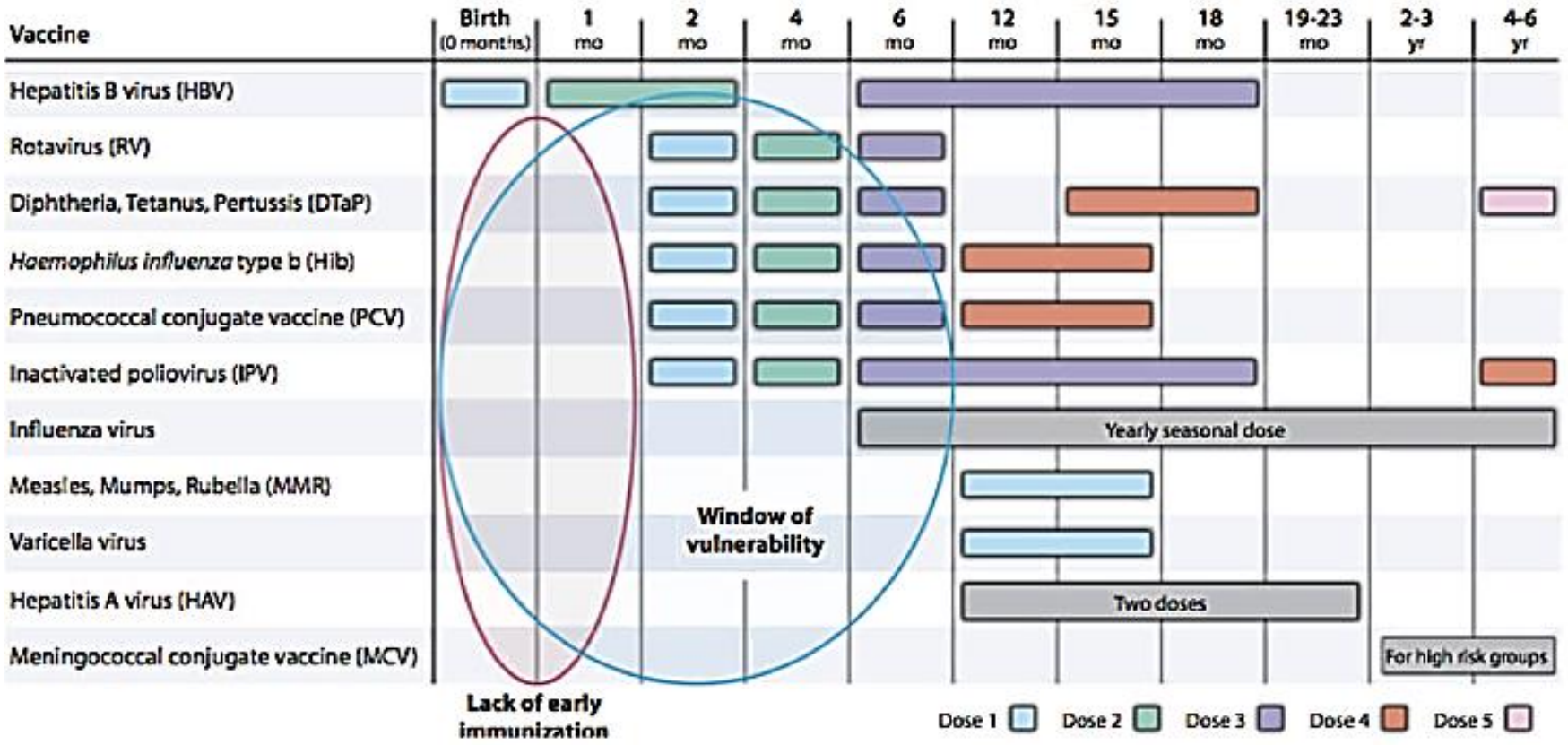
Period of vulnerability for infant infectious diseases



Jones C, *et al. Hum Vaccin Immunother* 2014;10: 2118–2122.

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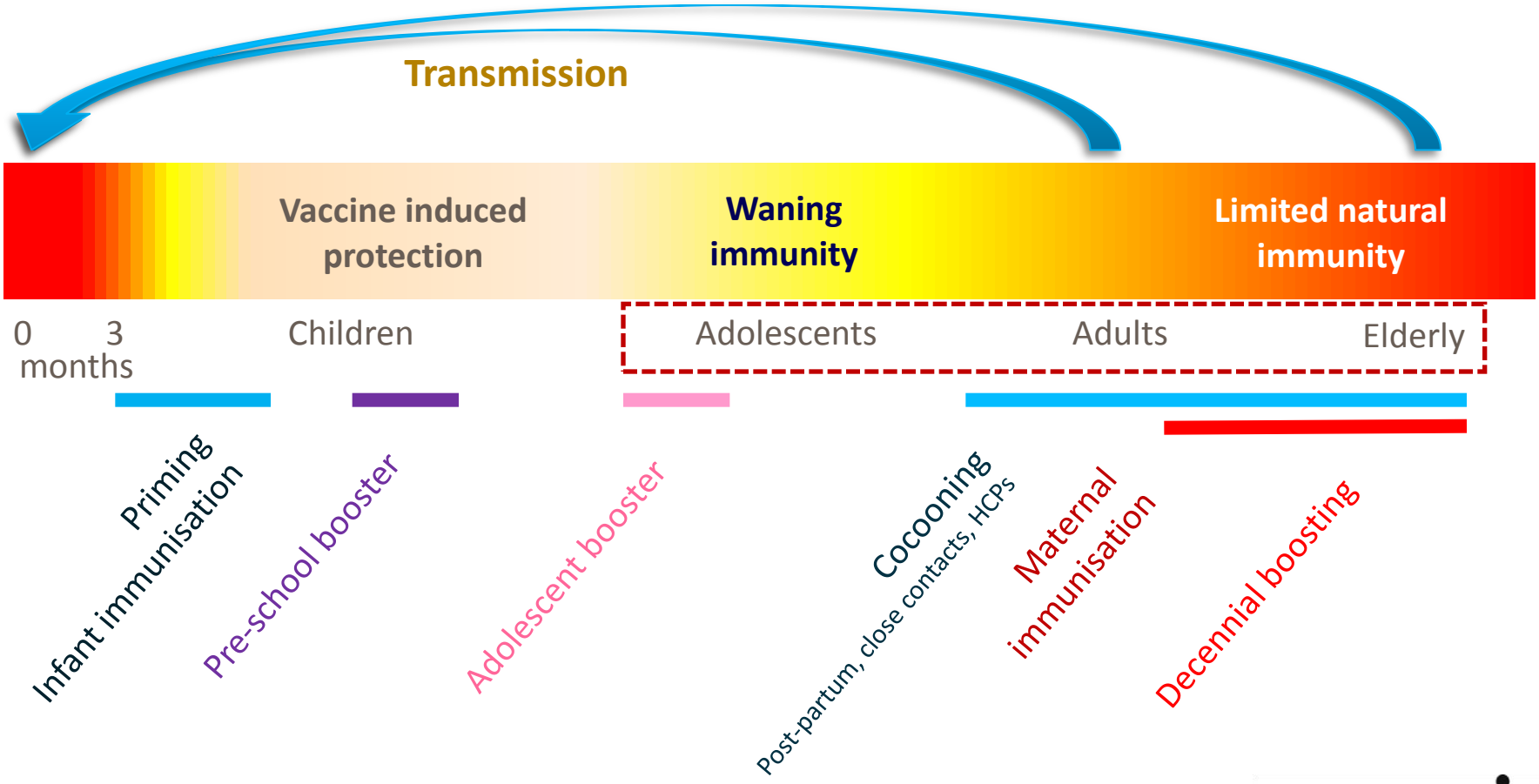
Pertussis prevention strategies throughout life



Adapted from Wendelboe, *et al. Pediatr Infect Dis J* 2005; 24: S58–S61.

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Immunization against Pertussis in South Africa

DTwP-Hib at 6, 10, and 14 weeks + 18 months

From July 2009
DTaP-IPV/Hib at 6, 10, and 14 weeks + 18 months

diphtheria (D), tetanus (T), acellular-pertussis (aP) components [pertussis toxoid (PT) and filamentous hemagglutinin (FHA)] inactivated polioviruses (IPV) types 1 – 3, Haemophilus influenzae type b (Hib)

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Maternal HIV infection and antibody levels against Pertussis

2009 to 2010 in a community health center in Khayelitsha, Western Cape Province, South Africa

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

Characteristics	No. (%) of Participants: HIV-Infected Women and Exposed Infants (n = 46 at Birth)	No. (%) of Participants: HIV-Uninfected Women and Unexposed Infants (n = 54 at Birth)	*P* Value
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.
[a] Mann-Whitney U test.
[b] Fisher exact test.
[c] *t* Test.
[d] Weight at 16 weeks available for all infants followed up to 16 weeks (38 HIV-exposed infants and 55 HIV-unexposed infants).
[e] No breast feeding was reported at any study visit for HIV-exposed infants.
[f] An informal structure is a shack constructed of materials such as wood and corrugated iron.

CD4 count, mean (SD)	252 cells/µL
HIV viral load, median (IQR)	800 (357-6000) copies/mL.
CD4 counts <200 cells/µL	7 women

Jones C.E., et al., JAMA, 2011. 305(6): p. 576-84.

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Maternal antibody levels against Pertussis and transplacental antibody transfer

HIV+ vs. HIV- anti-pertussis titers (22.07 FDA U/mL vs. 23.64 FDA U/mL; p=0.26) and proportion with protective antibody titers (24% vs. 38%; p=0.14) were similar.

CD4+ cell count was positively correlated with the level of antibody to pertussis.

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		
Haemophilus influenzae type b	0.57 (0.45-0.79)	0.74 (0.61-1.00)	23	.002
Bordetella pertussis	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

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.
[a] Placental transfer of antibody from mother to infant is expressed as a ratio of infant/maternal specific IgG concentration at birth.
[b] Percentage reduction in placental transfer between HIV-infected and HIV-uninfected women; calculated as the ratio of the placental transfer from HIV-infected women:placental transfer from HIV-uninfected women, subtracted from 100.
[c] Mann-Whitney U test.

Jones C.E., et al., JAMA, 2011. 305(6): p. 576-84.

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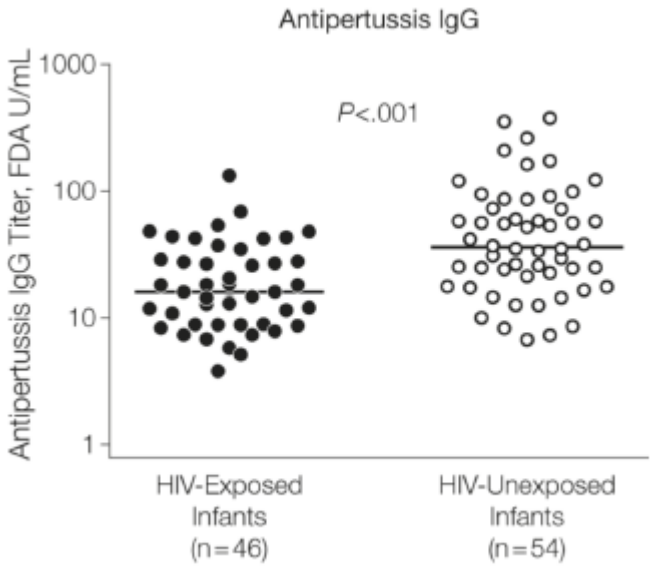
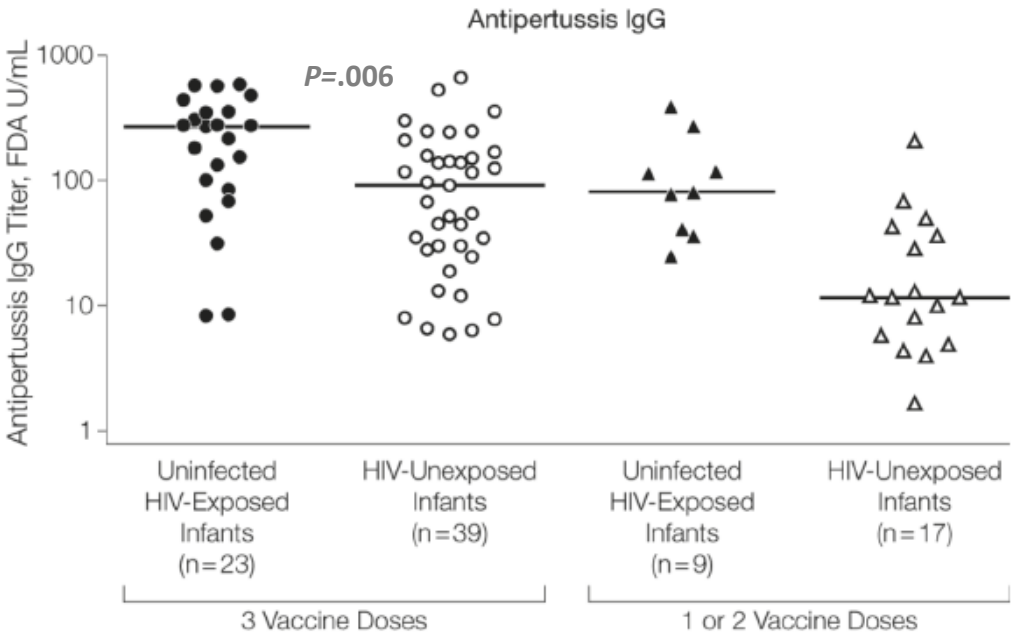
Maternal HIV infection and antibody levels against Pertussis

Serum samples collected within 24 hours of birth



Specific vaccine-induced antibody responses at 16 weeks



Fold-increase in pertussis antibody level pre- to post-vaccination was significantly higher in the HEU than in the HUU infants
(9.51-fold vs. 2.16-fold; p=0.002)

Jones C.E., et al., JAMA, 2011. 305(6): p. 576-84.

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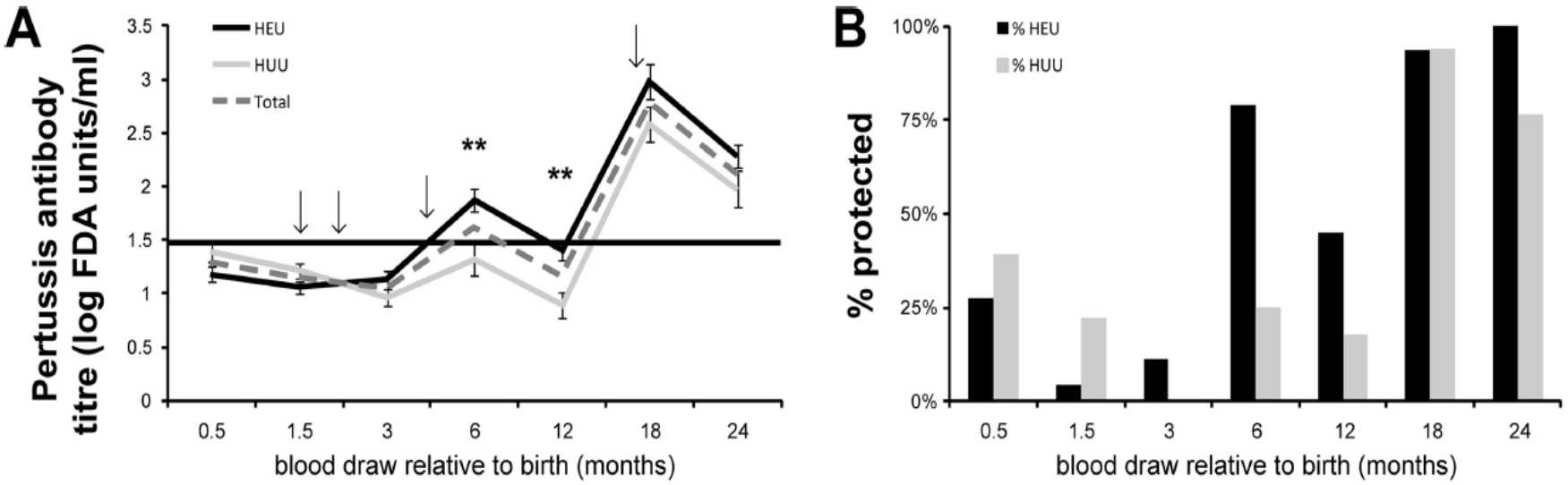
Maternal HIV infection and antibody levels against Pertussis

Longitudinal cohort study from March 2009 in Cape Town, South Africa

Infants of mothers with known HIV infection status were recruited at birth from the labor ward and evaluated at 0.5, 1.5, 3, 6, 12, 18, and 24 months.
HUU=28
HEU=27 (26 were exclusively formula fed)



Reikie B. A., et al., Clin Vaccine Immunol. 2013. 20(1): p. 33-8.

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In utero exposure to maternal HIV infection and T-cell immune responses

- Longitudinal cohort study 2010-2012 in Khayelitsha, Western Cape Province, South Africa
- 48 HUU and 48 HEU
- Vaccine-specific T-cell proliferation (Ki67 expression) and intracellular expression of four cytokines (INF-γ, IL-2, IL-13 and IL-17) were measured after whole blood stimulation with antigens at 6 and 14 weeks of age
- HEU had elevated BCG-specific and SEB CD4+ and CD8+ T-cell proliferative responses at 14 weeks, although pertussis-specific T-cells proliferated comparably between the two study groups
- HEU had diminished cytokine expressing T-cells in response to BCG, *Bordetella pertussis* and SEB stimulation

Kidzeru, E.B., et al. AIDS, 2014. 28(10): p. 1421-30.

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Soweto – South Africa

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- Population 1.2 million[1]
- <5 population 120 000[1]
- <1 population 24 200[1]
- HIV-infection prevalence among pregnant women ≈28%[2]
- HIV-infection prevalence among neonates ≈1.5%[2]
- Only one public hospital with pediatric admissions CHBAH (300 pediatric beds). Secondary-tertiary teaching hospital affiliated to University of the Witwatersrand

1. STATSSA, Mid-year population estimates. http://www.statssa.gov.za
2. ASSA2003 Full and Provincional AIDS and Demografic Models. Actuarial Society of South Africa. http://www.assa.org.za.

Mother-Infant cohort studies (2011-2012)

- Double-blind, randomized, placebo-controlled trial in Soweto, South Africa, on the immunogenicity and efficacy of Trivalent Influenza Vaccine (IIV3) in pregnant women (2011 and 2012).
- Study participants: pregnant women with confirmed HIV status at an estimated gestational age of 20-36 weeks.
- Participants followed up until 24 weeks post-partum/of age for acute respiratory illness or hospitalization for acute cardio-pulmonary illness.
- At the time of illness episodes, NPA from infant and oro & nasal pharyngeal swabs from mothers were collected.

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Mother-Infant cohort follow-up

- Subjects attended unsolicited illness visits to the study centre
- Active surveillance among hospitalized patients at CHBAH
- Weekly home visits of study participants

  - **Investigation for illness in infants:**
    - Fever, OR
    - Mother's perception of infant hot plus at least 1 symptom of ARTI within 72hrs, OR
    - At least two signs/symptoms of ARTI within the past 72hrs.
  - **Investigation for illness in mothers (symptom onset within past 7 days):**
    - Fever, OR feeling feverish, OR chills/rigors, AND
    - Any of cough/ sore throat/ pharyngitis, OR
    - Any of muscle/joint/headache, OR
    - Any of feeling short of breath/ difficulty breathing/chest pain

Mother-Infant cohort studies

Maternal characteristics	HIV-infected 2011 N=194	HIV-uninfected 2011 N=1060	HIV-uninfected 2012 N=1056
Mean age (SD), years	28.2 (5.1)	26.2 (5.3)	26.2 (5.3)
Mean Gestational Age (SD), weeks	27.3 (3.8)	26.9 (4.3)	26.8 (4.4)
Median BMI (IQR)	28.0 (24.9, 32.0)	28.1 (24.6, 32.4)	27.6 (24.3, 31.9)
Mean follow-up time (SD), months	7.9 (1.5)	8.0 (1.8)	8.0 (1.7)
Median CD4+ count cells/ml (IQR)	393.5 (271, 557)	-	-
Women with CD4+ cell count ≤350 cells/ml, n (%)	75 (39.5)	-	-
Women with CD4+ cell count 351-500 cells/ml, n (%)	57 (30.0)	-	-
Women with CD4+ cell count >500 cells/ml, n (%)	58 (30.5)	-	-
Median HIV-1 viral load, copies per milliliter (IQR)	1067 (61, 13923)	-	-
On ART, n (%)	153 (78.9)	-	-

Adapted from: Madhi SA, *N Engl J Med* 2014;371:918–31.

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Mother-Infant cohort studies

Fetal and newborn outcomes	HIV-exposed 2011 N=188	HIV-unexposed 2011 N=1028	HIV-unexposed 2012 N=1021
Preterm birth <37, n (%)	26 (13.8)*	70 (6.8)*	134 (13.1)
Median birth weight (range), kg	3.0 (0.8, 4.3)	3.1 (0.5, 4.6)	3.1 (0.5, 4.8)
Low birth weight (<2500gr), n (%)	29 (15.6)	118 (11.5)	137 (13.4)
Mean follow-up time (SD), months	5.2 (1.3)	5.4 (0.9)	5.5 (0.8)

*p=0.001

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B. Pertussis in infants <6 months old

	HIV-exposed 2011 N=188	HIV-unexposed 2011 N=1028	HIV-unexposed 2012 N=1021
At least 1 illness visit, n (%)	143 (76.1)	734 (71.4)	759 (74.3)
Total specimens tested	433	1887	1976
Overall			
B. Pertussis cases	7	29	8
B. Pertussis incidence rate (1000 child/months) (95%CI)	7.4 (3.0, 15.1)	5.3 (3.5, 7.6)	1.4 (0.6, 2.8)
0-3 months of age			
B. Pertussis cases	6	18	4
B. Pertussis incidence rate (1000 child/months) (95%CI)	6.3 (2.3, 13.7)	3.3 (1.9, 5.2)	0.7 (0.2, 1.8)
>3-6 months of age			
B. Pertussis cases	1	11	4
B. Pertussis incidence rate (1000 child/months) (95%CI)	1.0 (0.03, 5.7)	2.0 (1.0, 3.5)	0.7 (0.2, 1.8)

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B. Pertussis in infants <6 months old

	HIV-exposed 2011 N=7	HIV-unexposed 2011 N=29	HIV-unexposed 2012 N=8
Age 0-3 mths of age, n (%)	6 (85.7)	18 (62.1)	4 (50.0)
>3-6 mths of age, n (%)	1 (14.3)	11 (37.9)	4 (50.0)
Mean age (SD), days	67.3 (49.3)	72.3 (50.3)	87.5 (23.9)
Median (range), days	56 (19, 169)	64 (2, 177)	90 (57, 114)
Hospitalized within 28 days of sample collection	2 (28.6)	5 (16.7)	1 (12.5)
Death*	-	1	-
Presented with, n (%): Cough	6 (85.7)	23 (79.3)	7 (87.5)
Fever/feverish	1 (14.3)	3 (10.0)	1 (12.5)
Wheezing	1 (14.3)	1 (3.5)	-
Difficulty breathing	1 (14.3)	2 (6.9)	-

*NPA collected during hospitalization, infant died 4 days later at the age of 61 days.

B. Pertussis in pregnant women and women in the first 6 months post-partum

	HIV-infected 2011 N=194	HIV-uninfected 2011 N=1060	HIV-uninfected 2012 N=1056
At least 1 illness visit, n (%)	145 (74.7)*	610 (57.5)*	690 (65.3)
Total specimens tested	437	1349	1847
B. Pertussis cases	11	18	5
B. Pertussis incidence rate (1000 woman/months) (95%CI)	7.5* (3.8, 13.4)	2.2* (1.3, 3.4)	0.6 (0.2, 1.4)
B. Pertussis cases including indeterminate	15	53	6
B. Pertussis incidence rate including indeterminate (1000 woman/months)	10.3 (5.8, 17.0)	6.5 (4.8, 8.5)	0.7 (0.3, 1.5)

* $p<0.01$

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B. Pertussis in pregnant women and women in the first 6 months post-partum

	HIV-infected 2011 N=15	HIV-uninfected 2011 N=53	HIV-uninfected 2012 N=6
During pregnancy	6	28	2
From -1 month of delivery to +1 month post-delivery	5	19	0
From -1 month of delivery to +3 month post-delivery	8	29	2

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Mother-infant *B. Pertussis* infections

	HIV-exposed 2011	HIV-unexposed 2011	HIV-unexposed 2012
Mother-infant infections	3	7	2
Mother-infant infections same day	1	1	2
Mother at least 3 weeks before the infant	3	4	2
Mother more than 3 weeks before the infant	0	3	0

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Babies of Soweto study - BoSS

- Surveillance at CHBAH for daily hospital admissions including sleep-over wards.
- <12 months old infants.

SARI (<3 months old)	Any child with diagnosis of suspected sepsis OR Physician diagnosed LRTI irrespective of signs and symptoms OR Apnoea
Physician diagnosed LRTI (≥3 months to <12 months old)	Any child with physician-diagnosed LRTI including bronchiolitis, pneumonia, bronchitis and pleural effusion.
SARI (≥3months to <12 months old)	Any child with cough or difficult breathing, AND Any general danger sign, OR Chest indrawing or stridor in a calm child, OR Tachypnoea Patient presenting within 7 days of the onset of illness.

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B. pertussis PCR in BoSS

Age category	Pertussis +	% Pertussis +	Pertussis -	Total
0-91 days	**32**	**4.2**	723	760
92-181 days	**4**	**1.2**	357	364
182-365 days	**3**	**0.2**	408	414
Total infants tested	**39**	**2.5**	1488	1538

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B. pertussis in hospitalized infants <12 months old

	PCR *B. Pertussis* Overall N=39	PCR *B. Pertussis* 0-3 months N=32	PCR *B. Pertussis* >3-12 months N=7
Age, mean days (SD)	75.6 (68.4)	50.7 (19.4)	189.7 (96.0)
Age, median days (range)	53 (15, 344)	51 (15, 88)	169 (100, 344)
HIV-exposed, n (%)	11/34 (32.4)	11/27 (40.7)	0
Presented with, n (%)			
Cough	34/35 (97.1)	27/28 (96.4)	7/7 (100)
Apnea	4/30 (13.3)	4/23 (17.4)	0
Difficulty breathing	16/32 (50.0)	11/25 (44.0)	5/7 (71.4)
Wheezing	17/35 (48.6)	12/28 (42.9)	5/7 (71.4)
Death*	1	1	
Incidence per 100,000 infants, overall (95%CI)	161.2 (114.6, 220.2)	132.2 (90.5, 186.6)	28.9 (11.6, 59.6)
Incidence per 100,000 infants, HIV-exposed	-	162 to 192	-
Incidence per 100,000 infants, HIV-unexposed	-	103 to 109	-

*64 day old infant, HIV-infected

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Immunization status of hospitalized infants infected with *B. pertussis*

Age	PCR *B. Pertussis*	Vax history available	Pentaxim d1 (6 weeks)	Pentaxim d2 (10 weeks)	Pentaxim d3 (14 weeks)
0-6 weeks	14	13	2	0	0
7-10 weeks	15	10	7	0	0
11-24 weeks	10	7	7	5*	3**
Total	39	30	16	5	3

* 1) 8 days post-vax, 4) 23-129 days post-vax
** 1) 5 days post-vax, 2) 21-24 days post-vax

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Discussion

- HIV-infected mothers have high rates of *B. Pertussis* infection.
- Mothers are a possible source of infection to the young infants.
- *B. Pertussis* associated hospitalization in your setting in young infants was 161 per 100,000 infants.
- Immunization of pregnant women would probably decrease the burden of *B. Pertussis* in your setting.
- What vaccine to use??

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Acknowledgments

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