

# Immunising HIV Positive Babies

**Jeffrey Mphahlele**

*The HIV and Hepatitis Research Laboratory*

**Department of Virology**

**University of Limpopo, Medunsa Campus**

**PRETORIA, South Africa**

**LIMPOPO 2006 EPI SYMPOSIUM**

**Strengthening Immunisation Services in South Africa**

**Aventura Warmbaths**

**10 - 11 May 2006**

# PRESENTATION LAYOUT

## ❖ BACKGROUND INFORMATION

- Why HIV positive babies?
  - Burden of infection
  - HIV and the Immune System (IS)
- Vaccines are different
  - Replicating vaccines
  - Non-replicating vaccines
- Concerns regarding immunising HIV positive persons
  - Safety of vaccines
  - Efficacy of vaccines

## ❖ WHO/UNICEF AND ACIP (USA) GUIDELINES ON IMMUNISING HIV POSITIVE BABIES

## ❖ FIELD STUDIES ON THE IMPACT OF HIV ON CHILDHOOD VACCINES

- Classical EPI vaccines
  - BCG, DTP, OPV & Measles
- Newly introduced vaccines
  - Hib vaccine
  - Hepatitis B vaccine

# Why HIV infected babies?

- HIV has greater impact on childhood vaccines in SSA
  - Endemicity of HIV infection in the region
  - High rate of MTCT of HIV
- In sub-Saharan Africa, >90% of paediatric HIV infections acquired through MTCT
  - South Africa ~70 000 - 80 000 babies born each year are infected with HIV
  - Children experience more rapid progression of HIV infection than adults
- Immuno-compromised individuals do not respond optimally to vaccines
  - e.g. HIV positives, haemophiliacs, renal transplant patients, etc

# PAEDIATRIC HIV INFECTIONS – A CHALLENGE

- At the end of 2001:
  - 14 million surviving children lost one or both parents to HIV/AIDS
- In 2003:
  - 700,000 children became infected with HIV
  - >90% of babies acquired HIV from mothers
- Since 1981:
  - 5 million infants became infected with HIV
  - 90% of these infections occurred in Africa
  - Approx 9% (as high as 20-40% in some regions) of ANC women are HIV-infected
- MTCT of HIV (risk 15-30% in non-breastfed; 10-15% additional risk in breastfed babies):
  - In utero (during pregnancy)
  - Perinatal (around birth)
  - Breastfeeding
- Many other babies in developing world are infected through:
  - Contaminated blood or blood products
  - Unsafe injection practices
  - Sexual abuse or exploitation

**And yet many others remain undiagnosed until the onset of clinical manifestation**

# HIV infected persons need protection from VPDs

- Non-immunised HIV infected babies will suffer severe forms of VPDs
- OI's and illness often last longer in HIV infected children:
  - Advanced HIV stage is characterised by variety OI's
  - Without immunisation, HIV-pos children will have additional burden of VPD's
  - But.....some children show adult pattern of the disease (i.e. live longer)
- HIV is now a manageable chronic disease in many developing countries:
  - Without ARVs, children experience more rapid progression of HIV infection than adults
  - In industrialised countries, where children have access to ARVs, 80% are still alive by the age of 6 yrs
  - Access to ARVs is increasing in the developing world :
    - WHO/UNAIDS "3 by 5" programme: 3 million on ARVs by the end of 2005  
*"Aims to put 3 million people on antiretroviral treatment by the end of 2005"*
    - PMTCT and PMTC-plus programmes:  
*Being implemented at different rates in many countries, especially in sub-Saharan Africa*

# Vaccines are Different:- Examples of Licensed Vaccines

## ■ REPLICATING (Live attenuated) VACCINES

- OPV
- BCG - Bacillus Calmette-Guerin
- Measles
- (Yellow Fever, mumps, rubella)
- vaccinia, varicella, influenza, oral typhoid (rotavirus), etc

## ■ NON-REPLICATING VACCINES

### Killed or inactivated vaccines

- IPV
- Whole cell pertussis
- (hepatitis A)
- Influenza, rabies, cholera, etc

### Subunit and fractional vaccines

- Hepatitis B - plasma or recombinant
- Diphtheria, tetanus
- Haemophilus influenza type b
- Acellular pertussis
- (pneumococcal, meningococcal)
- typhoid Vi, Influenza, etc

# PROS & CONS OF REPLICATING VACCINES

## Potential Safety Concerns

- Weakened from pathogenic strain
- Replicate in host cells
  - cautious about host immune status  
e.g. immunocompromised, HIV infected, pregnant women, etc
  - severe reactions possible
- Reversion to virulence possible
  - under-attenuation
  - back mutation
  - recombination
- Heat labile
- Contamination with adventitious agents found in culture
- Interference with circulating maternal antibodies; e.g. measles
- Advantage - Herd Immunity; e.g. OPV

# Concerns in immunising HIV-positive persons

## SAFETY ISSUES:

- Are vaccines safe (AEs) in HIV infected individuals?
- Are there vaccines which are particularly NOT safe in HIV-infected persons?
- Will vaccination overburden the Immune System?
- Will vaccination lead to activation APCs and T cells, thereby increase HIV viral load?

## EFFICACY ISSUES:

- Will the vaccine achieve reasonable immunogenicity?
- What about the strength of antibody titre and duration of protective antibodies?
- Will the vaccine protect against the disease?

Vaccine	Type	WHO / UNICEF		ACIP (Advisory Committee on Immunisation Practices)
		Asymptomatic HIV	Symptomatic HIV	HIV-infected
BCG	Live attenuated	YES	NO	NO
OPV	Live attenuated	YES	YES / IPV if available	NO
Measles	Live attenuated	YES (6 and 9 months)	YES	YES (if CD4+ >15%)
Yellow Fever	Live attenuated	YES (CD4+ >200 cells/mm <sup>3</sup> )	NO (pending further investigations)	YES
DTwP/DTaP	Inactivated	YES	YES	NO to DTwP
IPV	Inactivated	YES	YES	YES
Hepatitis B	Inactivated	YES	YES	YES
Haemophilus influenzae type b	Inactivated	No recommendation	No recommendation	YES
Pneumococcal	Inactivated	No recommendation	No recommendation	YES
Meningococcal	Inactivated	No recommendation	No recommendation	YES (not <6 months)

# **Immunising HIV Positive Babies**

**LESSONS LEARNED FROM FIELD STUDIES ON THE  
IMPACT OF HIV ON CHILDHOOD VACCINES**

**CLASSICAL EPI VACCINES**

## Adverse Events associated with BCG vaccination in HIV-infected children (Reviewed by Moss et al, Bull WHO, 2003)

Country	No. studied	Adverse Events	Reference
Uganda	54 children born to HIV infected women	No complications	Carswell (1987)
France	18	Disseminated BCG infection in 3 (17%)	Blanche (1986)
France	67	BCG lymphadenitis in 7 (10%)	Bregere (1988)
Zambia	42	BCG lymphadenitis in 1 (3%)	Hira (1989)
Congo	21	BCG lymphadenitis in 5 (24%)	Lallement (1991)
Rwanda	37	BCG lymphadenitis in 2 (5%)	MMWR (1991)
Zaire	21	No complications	Green (1991)
Zaire	48 HIV infected 640 HIV uninfected	BCG lymphadenitis in 5% and Fistulae in 5% BCG lymphadenitis in 3.5% and Fistulae in up 8%	Ruder (1993)
France	68	AE's in 9 (13%): 4 with lymphadenitis; 3 with fistula, 2 with disseminated BCG	Besnard (1993)
Haiti	13	BCG lymphadenitis, ulceration or abscess in 4 (31%); received double dose of BCG	O'Brien (1995)
Thailand	26	No complications	Thaithumyanon (2000)

# Immunogenicity and Safety of Polio Vaccines in HIV-infected children (Reviewed by Moss et al, Bull WHO, 2003)

Country	Vaccine	No. studied	Safety	% of HIV-infected persons developing protective antibody titres	Reference
France	OPV	15	No AE's	40% to type 2 33% to types 1 and 3	Blanche (1986)
USA	OPV	24	NO AE's	91%, lower titres with advanced disease	Krasinski (1987)
Italy	IPV	9	No EA's	100% to types 1 and 2; 88% to type 3	Barbi (1992)
Italy	OPV/IPV	12	No AE's	100% to type 2; 92% to types 1 and 3; decrease in titres over 4 yrs in 2 children	Barbi (1992)
Romania	OPV	1	Flaccid paralysis with vaccine polio 2	No Abs to polio 1, 2 and 3 despite having received OPV during 1 <sup>st</sup> year of life	Ion-Nedelcu (1994)
Zimbabwe	OPV	1	Paralysis of right leg 2 wks post 2 <sup>nd</sup> dose	No Abs to type 1 and 3 despite having received OPV during 1 <sup>st</sup> year of life	Chitsike (1999)

## Immunogenicity of Diphtheria, Tetanus and Pertussis Vaccines in HIV-infected children (Reviewed by Moss et al, Bull WHO, 2003)

Vaccine	Country	No. studied	% of HIV-infected persons developing protective antibody titres	Reference
Tetanus toxoid	USA	5	40%; titres lower than in controls	Bernstein (1986)
	France	13	62%; lower titres in children with OI's	Blanche (1986)
	Italy	17	77%; titres lower than in controls	Barbi (1992)
DTP	USA	17	60% to tetanus; 18% to diphtheria; CMI in some children without Protective Abs	Borkowsky (1987)
	USA	37	91% to tetanus; 18% to diphtheria; younger children responded better	Borkowsky (1992)
	Zaire	48	96% to tetanus; 71% to diphtheria; titres lower than in controls	Ryder (1993)
Acellular Pertussis	Italy	12	75%; titres lower than in controls; correlated with CD4 cell counts	DeMartino (1997)

# HIV infection and measles

- Is HIV potential obstacle in eliminating measles?
  - Reduced immune response to vaccine
  - Defective transfer of maternal antibodies from HIV-infected mothers
  - More severe clinical manifestations
  - Prolonged shedding
  - Unusual clinical presentations, e.g. absence of rash
    - Result - complicate case definition
    - Difficulties in finding and reporting cases
  - Nosocomial transmissions
  - Approx 50% of measles-related deaths occur in sub-Saharan Africa
- Targeted measles vaccination in HIV-positive babies
  - Vaccination at 6 and 9 months
    - Prime IS while immunocompetent; effective T-cell response
    - Reduce poorer immune response and nosocomial infections
- Measles infection can contribute to immunosuppression
  - Infection of CD4+ cells

# Immunogenicity of Measles vaccine in HIV-infected children (Reviewed by Moss et al, Bull WHO, 2003)

Country	No studied	Age range (months)	Response to primary immunisation	Response to repeat immunisation	Reference
USA	37	9	36% of 11 symptomatic 77% of 26 asymptomatic	unknown	Oxtoby (1989)
USA	8	11 - 41	25%	unknown	Krasinski (1989)
USA	35	12 - 194	37%	0%	Palumbo (1992)
USA	2	unknown	unknown	50%	Brena (1993)
USA	4	22 - 121	unknown	0%	Frenkel (1994)
USA	11	72 - 120	unknown	36%	Brunell (1995)
USA	7	31 - 120	unknown	14%	Arpadi (1996)
Thailand	16	9	57%	unknown	Thaithumyanon (1994)

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**LESSONS LEARNED FROM FIELD STUDIES ON THE  
IMPACT OF HIV ON CHILDHOOD VACCINES**

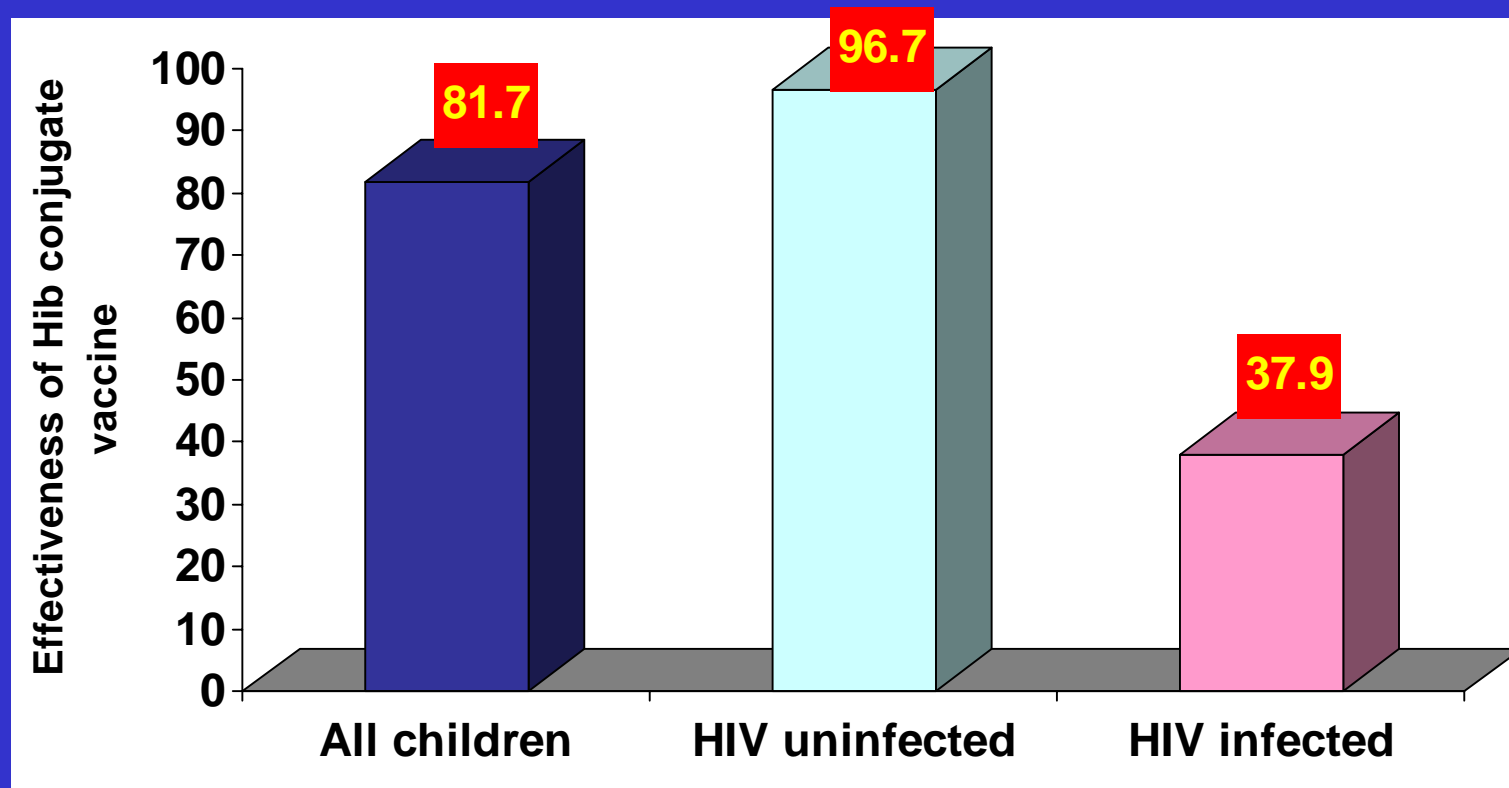
**NEWLY INTRODUCED EPI VACCINES**

# EFFICACY of Hib CV in Developed and Developing World

(Madhi SA, Vaccinology Meeting, Western Cape, Oct 2004)

Country	Hib CV type	% Efficacy	95% C.I	Reference
USA	PRP-CRM <sub>197</sub>	100	47 - 100	Black S, PIDJ 1991
USA	PRP-OMP	93	53 - 98	Santosham M, NEJM 1991
UK	PRP-T	95	74 - 100	Booy R, Lancet 1994
Finland	PRP-CRM <sub>197</sub>	95	76 - 99	Peltola H, Pediatrisc Adolesc Med 1994
Finland	PRP-T	100	93 - 100	Eskola J, J Hosp Infect 1995
Chile	PRP-T	92	65 - 100	Lagos , PIDJ 1996
The Gambia	PRP-T	95	67 - 100	Mulholland KM, Lancet 1997

# EFFECTIVENESS OF Hib-CRM<sub>197</sub> CONJUGATE VACCINE IN 20 000 SOUTH AFRICAN CHILDREN



CI<sub>95%</sub> 59.4; 91.8

CI<sub>95%</sub> 76.2; 99.6

CI<sub>95%</sub> -78.3; 78.4

**QUANTITATIVE antibody response to Hib CV among  
HIV-infected and HIV-uninfected children**  
(Madhi SA, Vaccinology Meeting, Western Cape, Oct 2004)

Category	No. studied	GMC anti-HibPS	95% C.I	% anti-HibPS $\geq$ 1.0 mcg/ml
HIV-uninfected	127	10.8	8.5 - 13.7	95.3
HIV-infected	66	2.0	1.2 - 3.1	51.5
CDC category N/A	34	3.8	1.9 - 7.4	61.8
CDC category B	8	1.8	0.3 - 10.6	50.0
CDC category C	24	0.8	0.4 - 1.5	37.5

## Effectiveness of hepatitis B vaccine within EPI (SA): Comparison with previous field studies

	Tsebe et al, 2001	Schoub et al, 2002	Unpublished study		
			HIV-ve	HIV+ve	TOTAL
Mean age (months)	23.3  (8 mo - 5 yrs)	18	11.9  (5 - 24 mo)	10.9  (5 - 24 mo)	11.4  (5 - 24 mo)
Anti-HBs positivity (>10 mIU/ml)	86.8% (N = 519)  95.6% for 8-12 mo (n = 153)	87.0% (N = 769)	87.0% (91.0%)* (N = 209)	78.0% (81.0%)* (N = 94)	84.0% (87.8%)* (N = 303)
HBV chronic carriage (HBsAg positivity)	0.0% (N = 578)	0.4% (N = 756)	0.0% (N = 94)	3.3% (N = 94)	0.9% (N = 303)
Anti-HBc positivity	0.9% (N = 582)	0.5% (N = 770)	3.3% (N = 209)	1.1% (N = 94)	3.0% (N = 303)

Schoub et al, Bull of WHO 2002; 80 (4): 277 - 281

Tsebe et al, Vaccine 2001; 19: 3919 – 3926

\*seroconversion rate = any baby with detectable “anti-HBs alone” serological profile

# Anti-HBs response after 3 or 6 Genhevac B 20 µg according to CD4 cell count

Rey D et al. *Vaccine* 2000; 18: 1161

CD4	3 injections		6 injections		Total
	N	anti-HBs >10	N	anti-HBs >10	
>500/µl	8	7 (87.5%)	1	0 (0.0%)	7/8 (87.5%)
<500/µl	12	4 (33.3%)	8	7 (87.5%)	11/12 (91.7%)
<b>Total</b>	<b>20</b>	<b>11 (55.0%)</b>	<b>9</b>	<b>7 (77.8%)</b>	<b>18/20 (90.0%)</b>

# SUMMARY-1: Interaction of HIV with Childhood Vaccines

- Most HIV-infected children have the capacity to mount both cellular and humoral immune responses during the first two years of life, or when relatively healthy
- Studies of the immunogenicity of EPI-recommended vaccines have shown satisfactory seroconversion rates in the early stages of HIV infection
- Antibody levels or seroprotection rates induced by the EPI vaccines tend to be lower in HIV-infected individuals and to fall more rapidly over time than in non-infected persons.
- Proportion of responders decreases with progression from HIV infection to AIDS (decline in cellular and humoral immune responses)
- Certain EPI vaccines are contraindicated in symptomatic HIV individuals:
  - BCG
  - Yellow Fever
- Ideally, other EPI vaccines (live attenuated vaccines) should be used with caution in symptomatic HIV persons.
  - Measles, OPV and DTwP
  - Challenges :
    - identifying HIV-infected babies before 2 yrs of age
    - establishing the degree of immunodeficiency in infected babies

## SUMMARY-2: Interaction of HIV with Childhood Vaccines

- The increasing HIV infection in babies could reverse the gains made by infant immunisation programmes in HIV endemic regions (e.g. sub-Saharan Africa), if no intervention of MTCT of HIV is made
- Although HIV infection is generally NOT regarded as a contra-indication, high infection rates may result in high rates of vaccine failures after immunisation, leading to lower vaccine effectiveness and low level of population immunity
- This is added challenge for new EPI antigens, as it may take several decades before HIV endemic regions could realise the benefit of vaccination
- Limited data on immunogenicity and effectiveness of childhood vaccines in HIV endemic regions

**THANK YOU FOR YOUR  
ATTENTION**