HEPATITIS B:
Post-Vaccination Surveillance

Edina Amponsah-Dacosta
On behalf of

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WORLD HEPATITIS DAY 2013
Johannesburg, Gauteng
29th July, 2013
• Introduction of hepatitis B vaccine into NIPs

• Methods to evaluate impact of hepatitis B vaccination

• Short-term vs. long-term measure of impact of vaccination
  – Examples of representative nationwide sero-surveys of impact of hepatitis B vaccination

• Concluding Remarks
Hepatitis B vaccine is the first vaccine against cancer

- Available since the early 80’s
- Prevents >0.5 million deaths/year from acute and chronic hepatitis B virus (HBV) infection

Recommendation by WHO (1994)

- Hep B vaccine should be introduced into NIPs:
  - Countries with HBsAg prevalence ≥8% by 1995
  - Global introduction by 1997
- South Africa was among the first 10 countries to introduce hepatitis B vaccine on the African continent (April, 1995)
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</table>
• Huge discrepancies between immunization coverage estimates reported by NDoH/EPI unit and those published by WHO/UNICEF

• Routinely collected immunization coverage data is still not completely reliable and cannot as yet be used to accurately monitor coverage or infer vaccine impact
Hepatitis B prevention programme and monitoring vaccine impact

POST-VACCINATION SURVEILLANCE

Monitor Impact
- Evaluate programme effectiveness

Ensure sustainability

Identify resources & implement vaccine

Develop comprehensive prevention strategy

Assess and quantify disease burden

Define epidemiology of disease
Hepatitis B is grossly under-diagnosed and under-reported.

- difficult to quantify and assess burden of infection
- difficult to quantify and assess burden of disease

To assess impact of hepatitis B vaccination programme:

- measure the burden of disease or burden of infection?
## Comparison of methods to evaluate impact of hepatitis B vaccination

<table>
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<th>Coverage Survey</th>
<th>Sero-survey</th>
<th>Acute Disease Surveillance</th>
<th>Morbidity &amp; Mortality</th>
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<td>Feasibility</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Expense</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Frequency of evaluation</td>
<td>I*</td>
<td>I</td>
<td>I or C*</td>
<td>I or C</td>
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<tr>
<td>Program effectiveness</td>
<td>short-term</td>
<td>-</td>
<td>+++</td>
<td>+</td>
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<td>long-term</td>
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<td>Information collected</td>
<td>Coverage data</td>
<td>Prevalence of infection</td>
<td>Incidence new infection</td>
<td>Incidence chronic sequelea</td>
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<td>Risk factor information</td>
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* I=intermittent; C=continuous
Sero-surveys to assess impact of hepatitis B vaccination programme

- **Sero-surveys in targeted cohorts**
  - **Short-term** measure of impact of vaccination
  - Targeted cohorts: Vaccinated cohorts
  - Ideally, first survey within 2-5 years of start of programme
  - Periodic surveys thereafter (e.g., every 5 years)
Short-term measure of impact of hepatitis B vaccination

Studies in targeted populations (Vaccinated Cohorts) to assess effectiveness of the vaccine

1. Increase in protection in vaccinated cohorts
2. Reduction in hepatitis B chronic carriage
The first five years of universal hepatitis B vaccination in South Africa: evidence for elimination of HBsAg carriage in under 5-year-olds

Khomotso V. Tsebe *, Rosemary J. Burnett *, Nyiko P. Hlungwani *, Mbudzeni M. Sibara b, Philip A. Venter c, M. Jeffrey Mphahlele a, *

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b Faculty of Natural and Mathematical Sciences, University of the North, Soweto, Northern Province, South Africa
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Abstract

South Africa implemented a vaccine against hepatitis B virus (HBV) into the Expanded Programme on Immunisation (EPI) in April 1995. The HBV vaccine is given at 6, 10, and 14 weeks, in parallel with OPV, DTP and Hib vaccines. This study assessed the impact of universal childhood HBV vaccination programme in reducing HBsAg carriage, in the first five years (1995–1999) since its implementation. In parallel, we investigated the current burden of HBV infection in mothers of vaccinees and the adult general population. A total of 598 babies (mean age = 23.3 months) who received 3 doses of 1.5 μg/0.5 ml Hepacine-B (Chelii) were recruited from the Northern Province (one of the nine provinces in South Africa). HBsAg, anti-HBs, anti-HBc, HBeAg and anti-HBe were tested using the IMX or AxSYM kits (Abbott Laboratories). PCR assays were performed following established protocols. The overall seroprotection rate (i.e. anti-HBs titre ≥ 10 mIU/ml) was 86.6% (519/598) in vaccinated babies, while 13.2% had anti-HBs levels < 10 mIU/ml. Seroprotection rates and geometric mean titres (GMT) decreased significantly with increasing age, possibly reflecting waning anti-HBs titre over time. Total HBV exposure (positive for either HBsAg, anti-HBs, or anti-HBc) was 31.0% (58/187) in mothers of vaccinees and 40% (72/180) in the adult general population. HBsAg carrier rate was virtually similar in both groups (3.2% in mothers of vaccinees vs. 3.3% in the general population). Against this background, no vaccine failures resulting in HBsAg and HBV DNA positivity were seen in vaccinated babies, including 6 babies born to HBsAg positive carrier mothers (one carrier mother was positive for HBeAg and HBV DNA). However, 0.9% (5/582) babies, aged between 8–11 months, tested positive for anti-HBe, all of whom had anti-HBs titres > 10 mIU/ml and were negative for HBV DNA. Anti-HBe positivity was probably maternal in origin, or may represent sub-clinical averted HBV infections. It can be concluded that the HBV vaccine is highly effective within the framework of the South African EPI and already shows a positive impact in the elimination of HBsAg carrier rate in children <5 years. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Expanded Programme on Immunisation; Hepatitis B vaccine; Seroprotection; South Africa
Objectives were to assess the:
- immunogenicity of hepatitis B vaccine in the field
- the effectiveness of immunisation in reducing HBsAg carriage in <5 yrs

Cross-sectional, first five years of vaccination [1995-1999]

598 babies were recruited in Limpopo Province:
- age range: 8 - 72 months
- mean age: 23.3 months
- M:F ratio was approx. 1:1 (304 : 294)

Inspected Road-to-Health cards to ascertain the babies received 3 doses of 1.5 μg/0.5ml Hepaccine-B (Cheil)

HBsAg, anti-HBs, and anti-HBc, and when necessary, HBeAg, anti-HBe, and HBV DNA were tested
Universal immunization of infants with low doses of a low-cost, plasma-derived hepatitis B vaccine in South Africa

B.D. Schoub,¹ U. Matai,² B. Singh,³ N.K. Blackburn,⁴ & J.B. Levin⁵

Objective To evaluate the effectiveness of universal vaccination against viral hepatitis B in South Africa among 18-month-old rural children.

Methods Children were immunized with a course of low-dose (1.5 μg), plasma-derived hepatitis B vaccine at 6, 10 and 14 weeks of age, and blood samples from the children were tested for three hepatitis B markers: hepatitis B surface antigen (HBsAg), anti-HBs and anti-HBc.

Findings One year after vaccination, a protective anti-HBs antibody titre of at least 10 IU/l was present in 669/769 (87.0%) of blood serum samples tested. Only 3/756 children (0.4%) were HBsAg positive and a fourth child was anti-HBc positive (HBsAg negative). This is a marked decrease compared to the hepatitis B prevalences reported in previous studies. Among rural migrant mine-workers, for example, HBsAg prevalence was 9.9%, and was 10.1% among children 0–6 years of age in the Eastern Cape Province.

Conclusion The low-dose, plasma-derived hepatitis B vaccine, which is affordable to most developing countries, was very successful in controlling endemic hepatitis B infection, where the virus is predominantly spread by horizontal transmission among infants and young children.

Keywords Hepatitis B vaccines/administration and dosage/economics; Hepatitis B surface antigens/blood; Child; Endemic diseases/immunology; Immunization programs; Evaluation studies; Cross-sectional studies; South Africa (source: MeSH, NLM).

Mots clés Vaccin anti-hépatite B/administration et posologie/economie; Antigène HBS/sang; Enfant; Maladie endémique/immunologie; Programmes de vaccination; Etude évaluation; Etude section efficace; Afrique du Sud (source: MeSH, INSERM).

Palabras clave Vacunas contra la hepatitis B/administración y dosificación/economia; Antígenos de superficie de la hepatitis B/sangre; Niño; Enfermedades endémicas/inmunología;Programas de inmunización; Estudios de evaluación; Estudios transversales; Sudáfrica (fuente: DeCS, BIREME).

In 1999, NDoH and NICD, conducted National Survey of the effectiveness of hep B immunisation in South Africa

Study design
- cross-sectional

770 babies were recruited from rural areas in 9 provinces
- Sampling period: Feb - Nov 1999
- healthy 18-months-olds
- vaccinated at 6, 10 and 14 weeks of life

HBsAg, anti-HBs, and anti-HBc were tested
## Effectiveness of hepatitis B vaccine within EPI-SA: Two independent studies

<table>
<thead>
<tr>
<th></th>
<th>Tsebe et al, 2001</th>
<th>Schoub et al, 2002</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean age (months)</strong></td>
<td>23.3 (8 months - 5 yrs)</td>
<td>18</td>
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<tr>
<td><strong>Anti-HBs positivity</strong></td>
<td>86.8% (N = 519)</td>
<td>87.0% (N = 769)</td>
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<tr>
<td>(&gt;10 mIU/ml)</td>
<td>[95.6% for 8-12 mo (n = 153)]</td>
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<tr>
<td><strong>HBsAg positivity</strong></td>
<td>0.0% (N = 578)</td>
<td>0.4% (N = 756)</td>
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<tr>
<td><strong>Anti-HBc positivity</strong></td>
<td>0.9% (N = 582)</td>
<td>0.5% (N = 770)</td>
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- Tsebe et al, Vaccine 2001; 19: 3919 - 3926
Reduced detection and levels of protective antibodies to hepatitis B vaccine in under 2-year-old HIV positive South African children at a paediatric outpatient clinic

Omphile E. Simani a, Geert Leroux-Roels b, Guido François c, Rosemary J. Burnett d, André Meheus c, M. Jeffrey Mphahlele a,e,*

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b Centre for Vaccinology, Department of Clinical Biology, Microbiology and Immunology, Ghent University, Belgium
c Department of Epidemiology and Social Medicine, University of Antwerpen, Belgium
d Department of Epidemiology, National School of Public Health, University of Limpopo, Medunsa Campus, Pretoria, South Africa
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ABSTRACT
The study evaluated and compared the prevalence of anti-HBs and exposure to hepatitis B virus (HBV) in vaccinated South African babies aged between 5 and 24 months from the Expanded Programme on Immunisation clinic [EPI group] and paediatric outpatient clinic [OPD group], and results were stratified by HIV status. A total of 303 (243 EPI group and 60 OPD group) babies were studied. All sera were tested for anti-HBs, HBsAg and anti-HBc, while IgM anti-HBc and HBV DNA were only tested in samples positive for HBsAg and/or anti-HBc. Overall, there was a gross difference in the prevalence of anti-HBs marker between the EPI and OPD groups. The EPI group demonstrated higher levels of seroconversion (89.3% vs. 81.7%; p = 0.105) and seroconversion rates (86.0% vs. 75.0%; p = 0.038), compared to the OPD babies. When the overall results were stratified by HIV status, seroconversion was 85.7% for the HIV-negatives and 78.1% for the HIV-positives, although this was not statistically significant (p = 0.125). The seroconversion rates were almost comparable between the HIV-positives (84.3%; n = 51) and the HIV-negatives (86.5%; n = 192) (p = 0.695) in the EPI group. In contrast, reduced seroconversion rates were observed between the HIV-positives (63.6%; n = 22) and HIV-negatives (81.6%; n = 38) in the OPD group, although this was not statistically significant (p = 0.123). Interestingly, no HBsAg or anti-HBc marker was detected in the OPD group, compared to total exposure rate of 4.9% (HBsAg carriage was 1.2%) in the EPI group.

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**Protective Efficacy of Hepatitis B vaccine within EPI (SA): Comparison of three (3) field studies**

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<td>18 (5 - 24 mo)</td>
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<td>11.9 (5 - 24 mo)</td>
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<td>Anti-HBs positivity</td>
<td>86.8% (N = 598)</td>
<td>87.0% (N = 769)</td>
<td>85.7% (N = 230)</td>
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<tr>
<td>(&gt;10 mIU/ml)</td>
<td>95.6% for 8-12 mo (n = 153)</td>
<td>78.1% (N = 73)</td>
<td>83.8% (N = 303)</td>
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<td>HBV chronic carriage</td>
<td>0.0% (N = 578)</td>
<td>0.4% (N = 756)</td>
<td>0.4% (N = 230)</td>
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<td>(HBsAg positivity)</td>
<td>0.4% (N = 230)</td>
<td>2.7% (N = 73)</td>
<td>0.9% (N = 303)</td>
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<td>3.0% (N = 73)</td>
<td>2.9% (N = 303)</td>
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<td>Anti-HBc positivity</td>
<td>0.9% (N = 582)</td>
<td>0.5% (N = 770)</td>
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Tsebe et al, *Vaccine* 2001; 19: 3919 – 3926  
Simani et al, *Vaccine* 2009; 27: 140-151
### Effect of Routine Infant Immunization on the Prevalence of Chronic HBV Infection

<table>
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<th>Study</th>
<th>Year</th>
<th>No. Tested</th>
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<th>Chronic HBV Infection After Program</th>
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<td>1-10</td>
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<td>1994</td>
<td>424</td>
<td>7-10</td>
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<td>1.1%</td>
</tr>
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<td>Samoa</td>
<td>1996</td>
<td>435</td>
<td>7-8</td>
<td>87%</td>
<td>7%</td>
<td>0.5%</td>
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<td>Lombok</td>
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<td>&gt;90%</td>
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<td>1.9%</td>
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<tr>
<td>Ponape</td>
<td>1994</td>
<td>364</td>
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<td>82%</td>
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<td>Micronesia</td>
<td>1992</td>
<td>544</td>
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<td>40%</td>
<td>12%</td>
<td>3.0%</td>
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<td>South Africa(^1)</td>
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<td>578</td>
<td>1-5</td>
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<td>0.0%</td>
</tr>
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<td>South Africa(^2)</td>
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<td>756</td>
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Long-term measure of the impact of hepatitis B vaccination

Population-based studies to assess immunity and chronic carriage to HBV

1. Has vaccination influenced population immunity?

2. Has vaccination influenced the epidemiology of HBV?
   • Hepatitis B chronic carriage?
Health facility-based population study shows increased immunity to, and reduced chronic carriage of, HBV after nearly two decades of universal hepatitis B vaccination in South Africa

Edina Amponsah-Dacosta¹, Ramokone L. Lebelo¹, J. Nare Rakgole¹, Rosemary J. Burnett¹, Selokela G. Selabe¹ and M. Jeffrey Mphahlele¹#

¹ HIV and Hepatitis Research Unit, Department of Virology, University of Limpopo (Medunsa Campus) and National Health Laboratory Service, Pretoria, South Africa
<table>
<thead>
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<th>Mean age (standard deviation)</th>
<th>Sex (%)</th>
<th>Provinces (No. of samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Post-Vaccine Intro.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-16 years (n=635)</td>
<td>8.7 years (4.9)</td>
<td>276</td>
<td>350</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(49.2%)</td>
<td>(50.5%)</td>
</tr>
<tr>
<td>Pre-Vaccine Intro.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17-25 years (n=571)</td>
<td>21.9 years (2.4)</td>
<td>131</td>
<td>439</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(23.3%)</td>
<td>(76.5%)</td>
</tr>
<tr>
<td>Total (N=1206)</td>
<td>17 years (7.2)</td>
<td>407</td>
<td>789</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(33.7%)</td>
<td>(65.4%)</td>
</tr>
</tbody>
</table>

*Subjects’ gender not recorded
Has hepatitis B vaccination influenced population immunity?
Immunity (anti-HBs alone; ≥2 mIU/mL) to hepatitis B

- 1-16 yrs (post-vaccine introduction): 57.0%
- 17-25 yrs (pre-vaccine introduction): 13.0%

$p < 0.0001$
Detectable immunity (anti-HBs alone) within the post-vaccine introduction population.
Has population hepatitis B chronic carriage decreased?
Immunity (anti-HBs alone; ≥2 mIU/mL) and hepatitis B chronic carriage (HBsAg)

- **Immunity**:
  - 1-16 yrs: 57.0%
  - 17-25 yrs: 13.0%

- **Chronic carriage**:
  - 1-16 yrs: 1.4%
  - 17-25 yrs: 4.2%

Significance: $p=0.003$
Immunity (anti-HBs alone; ≥2 mIU/mL) and chronic carriage (HBsAg) in the post-vaccine introduction group

- 1-5 yrs: 76.1% Immunity, 0.5% Chronic carriage
- 6-10 yrs: 50.0% Immunity, 1.3% Chronic carriage
- 11-16 yrs: 46.3% Immunity, 2.2% Chronic carriage
1. 17 years of universal hepatitis B vaccination has been a remarkable success
   – Population immunity to HBV is high (57.0%)
   – Chronic carriage is significantly reduced in the population

2. However, the observation that chronic carriage increases as immunity wanes sparks the debate for a pre-adolescence hepB vaccine booster

3. A representative nationwide hepatitis B sero-survey is recommended to better ascertain the long-term impact of universal hepB vaccination in South Africa
Key issues for conducting nationwide sero-surveys of the impact of hepB vaccine

1. Timing of survey relative to introduction of vaccination programme
2. Age group of interest
3. Sampling procedure
4. Sample=Blood
5. Human resources
6. Laboratory vs. point-of-care tests
7. Laboratory testing algorithm
8. Ethical considerations
Inherent limitations associated with sero-surveys

• Good approach for measuring the **burden of infection** but:
  – requires representative samples
  – often conducted in convenient populations, not representative for the general population
    • children visiting health centers (e.g. EPI clinics)
    • pregnant women, armed force recruits, blood donors, etc

• Other limiting factors include:
  – need for a blood sample
  – Time-consuming, expensive
  – *Most important factor: laboratory capacity*
Concluding Remarks

- There is evidence for elimination of chronic carriage in vaccinated cohorts – Short-term impact
  - Averting future HBV related liver disease, cirrhosis, HCC and death

- Almost 17 years after vaccine introduction, there is also evidence for shifting HBV epidemiology in the population – Long-term impact
  - Increased population immunity to, and reduced chronic carriage of, HBV

- There is a need for a representative nationwide sero-survey to assess the long-term impact of universal hepatitis B vaccination in South Africa.
Thank You For Your Attention