Lessons from adopting and delivering hepatitis B prevention in Africa

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• Epidemiology of HBV in sub-Saharan Africa

• Why is the PMTCT of HBV is important?

• Current situations and challenges in implementing PMTCT in sub-Saharan Africa
EPIDEMIOLOGY OF HBV INFECTION
From the **Big Three** to the **Big Four**

Number of deaths/year

Chen DS et al., Lancet Infect Dis, 2015
Prevalence of HBsAg, 1990-2013

Schweitzer A et al., Lancet, 2015
Incidence of hepatocellular carcinoma, 2008

Serological Markers

- **HBsAg(-)**
  - Not infected with HBV
- **HBsAg(+), HBeAg(-)**
  - Infected with HBV, and relatively low replication
- **HBsAg(+), HBeAg(+)**
  - Infected with HBV, and high viral replication

- Chronic hepatitis B infection
  - Persistence of HBsAg for > 6 months
Modes of Transmission

- Mother-to-infant (perinatal)
- Child-to-child (early postnatal)
- Sexual contact
- Contaminated needles/syringe/blood products
<table>
<thead>
<tr>
<th>Prevalence of HBV</th>
<th>Area</th>
<th>MTCT (Perinatal)</th>
<th>Childhood</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Asia</td>
<td>40%</td>
<td>60%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>High</td>
<td>Sub-Saharan Africa</td>
<td>10%</td>
<td>90%</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Low</td>
<td>USA, Western Europe</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Edmunds WJ et al., Epidemiol Infect, 1996
Sero-prevalence in children

MTCT

Horizontal transmission

Whittle H et al., J Infect Dis, 1990
### TABLE I  Prevalence of HBsAg and HBV markers in the adult population of sub-Saharan Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAg+ve (%)</th>
<th>HBV marker+ve* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>11.0</td>
<td>79.0</td>
</tr>
<tr>
<td>Kenya</td>
<td>11.4</td>
<td>56.2</td>
</tr>
<tr>
<td>Mozambique</td>
<td>14.6</td>
<td>75.2</td>
</tr>
<tr>
<td>Nigeria</td>
<td>10.0</td>
<td>72.5</td>
</tr>
<tr>
<td>South Africa</td>
<td>9.6</td>
<td>76.0</td>
</tr>
<tr>
<td>Namibia</td>
<td>14.0</td>
<td>87.5</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>10.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Senegal</td>
<td>11.8</td>
<td>91.0</td>
</tr>
<tr>
<td>Gambia</td>
<td>10.0</td>
<td>90.0</td>
</tr>
<tr>
<td>Zaire</td>
<td>20.6</td>
<td>78.9</td>
</tr>
<tr>
<td>Burundi</td>
<td>11.0</td>
<td>76.0</td>
</tr>
<tr>
<td>Mali</td>
<td>11.3</td>
<td>97.7</td>
</tr>
</tbody>
</table>

*HBV marker includes HBsAg, anti-HBc, anti-HBs.

Kiire CF, Gut, 1996
## Determinants of frequency of MTCT

<table>
<thead>
<tr>
<th></th>
<th>East Asia</th>
<th>Sub-Saharan Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>% pregnant women with positive HBsAg</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>% pregnant women with positive HBeAg</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>Risk of MTCT from HBsAg+/HBeAg+ women</td>
<td>70-90%</td>
<td>40%</td>
</tr>
<tr>
<td>Risk of MTCT from HBsAg+/HBeAg- women</td>
<td>5-30%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Keane E, Funk AL, Shimakawa Y. Aliment Pharmacol Ther, 2016
Compared to Asia, the frequency of MTCT in sub-Saharan Africa was low.

However, its prevention is still important in Africa for two reasons.
1. Risk factor for chronic infection

2. Risk factor for Liver Disease

• Longitudinal population-based study in The Gambia
• People with chronic HBV infection
  – 88 born to HBV-infected mothers
  – 165 born to non-infected mothers
• After 28 years of follow-up
### Incidence of liver cancer

<table>
<thead>
<tr>
<th>Maternal HBV status</th>
<th>Person-years at risk</th>
<th>No. of events</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>4,720</td>
<td>0</td>
<td>0 / 100,000</td>
<td>N/A</td>
</tr>
<tr>
<td>Positive</td>
<td>2,240</td>
<td>2</td>
<td>89 / 100,000</td>
<td>22-356</td>
</tr>
</tbody>
</table>

### Prevalence of significant liver fibrosis

<table>
<thead>
<tr>
<th>Maternal HBV status</th>
<th>Proportion</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>4%</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15%</td>
<td>5.0</td>
<td>1.6-15.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Shimakawa Y et al., Gut, 2015
Chronic HBV infection

16%

MTCT

100

Horizontal transmission

Chronic HBV requiring treatment

Shimakawa Y et al., Gut, 2015
Shimakawa Y et al., Lancet Infect Dis, 2016
Lemoine M et al., Lancet Glob Health, 2016
To reduce the incidence of liver disease, it is critical to prevent HBV MTCT.
HBV MTCT IS A NEGLECTED PROBLEM IN AFRICA
**TABLE II**  Options for adding hepatitis B vaccination to the Expanded Programme on Immunisation schedule recommended by the World Health Organisation

<table>
<thead>
<tr>
<th>Age</th>
<th>Contact number</th>
<th>Option</th>
<th>ASIA</th>
<th>III</th>
<th>AFRICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>1</td>
<td>BCG</td>
<td>HBV 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>2</td>
<td>OPV 1, DTP</td>
<td>HBV 2</td>
<td>HBV 1</td>
<td>HBV 1</td>
</tr>
<tr>
<td>10 weeks</td>
<td>3</td>
<td>OPV 2, DTP 2</td>
<td>HBV 2</td>
<td>HBV 2</td>
<td>HBV 2</td>
</tr>
<tr>
<td>14 weeks</td>
<td>4</td>
<td>OPV 3, DTP 3</td>
<td></td>
<td></td>
<td>HBV 3</td>
</tr>
<tr>
<td>24–48 weeks</td>
<td>5</td>
<td>Measles</td>
<td>HBV 3</td>
<td></td>
<td>HBV 3</td>
</tr>
</tbody>
</table>

OPV: oral polio vaccine; DTP: diphtheria, tetanus, and pertussis.

Kiire CF, Gut, 1996
Hepatitis B vaccine

• Integrated in the national program in all the African countries

• Coverage in Africa: 76%  
  WHO, Wkly Epidemiol Rec, 2016

• As a combined vaccine: 6-10-14 wks
  – Pentavalent (DTaP-Hib-HepB)
  – Hexavalent (DTaP-Hib-IPV-HepB)

• Vaccine failure: 1%
  – Majority (60-90%) are due to MTCT before the vaccine was given

Ekra D et al., Vaccine, 2008
Mendy M et al., Plos One, 2013
Shimakawa Y et al., Gut, 2015
WHO recommendation since 2009

- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, to prevent MTCT and horizontal transmission during early childhood

- Monovalent vaccine (non-combined vaccine)

WHO, Wkly Epidemiol Rec, 2009
Only 10 countries in sub-Saharan Africa adopted birth dose vaccine
Why?

• GAVI does not support monovalent hep B vaccine
• Importance of HBV PMTCT has been poorly recognized
• Logistical challenges where the majority of women deliver their children at home

Shimakawa Y et al., Gut, 2015
MTCT in sub-Saharan Africa
HBV > HIV

• Estimated number of infants infected in sub-Saharan Africa each year

Keane E, Funk AL, Shimakawa Y, Aliment Pharmacol Ther, 2016
BARRIERS TO TIMELY ADMINISTRATION OF BIRTH DOSE
Practices to improve birth dose vaccine coverage (2012)

- Facility birth >> Home birth
- Home-born neonates
  - home visits >> requiring family to bring babies
- Birth notification/Pregnancy tracking
- Task shifting
- Vaccine storage out of cold chain
- Use of Uniject
- No African study identified
Vaccine coverage in The Gambia (WHO/UNICEF)
Barriers to timely administration of birth dose vaccines in The Gambia, West Africa

Reiko Miyahara\textsuperscript{a, b, c}, Momodou Jasseh\textsuperscript{a}, Pierre Gomez\textsuperscript{a}, Yusuke Shimakawa\textsuperscript{d},

- % neonates vaccinated within 24 h
  - Home birth: 1.3%
  - Facility birth: 0.6%

Days after birth
- 181-365 days
- 29-180 days
- 8-28 days
- 2-7 days
- Birth
Low coverage even in facility-birth

• Hospital
  – No hep B vaccine (as there is no EPI team)

• Health Centers
  – There are vaccines, but no communication between maternity staff & EPI staff (two vertical programs)

• Reluctance of EPI staff to open multi-dose vial (10 doses/vial)
  – Although opened vial can be used for 28 days under the cold chain

Miyahara R, et al., Vaccine, 2016
WHO, 2014
NéoVac

*Neonatal Vaccination Against Hepatitis B in Africa*

- To develop and evaluate a **community-based intervention** to improve the coverage of:
  - A timely birth dose of Hep B vaccine
  - Neonatal care practices that can improve child survival

- Funded by Total Foundation (2016-2019)
<table>
<thead>
<tr>
<th></th>
<th>Senegal</th>
<th>Burkina Faso</th>
<th>Madagascar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence of HBsAg in mothers</strong></td>
<td>11.6%</td>
<td>11.5%</td>
<td>6.9%</td>
</tr>
<tr>
<td><strong>Year started Hep B vaccine</strong></td>
<td>2005</td>
<td>2006</td>
<td>2002</td>
</tr>
<tr>
<td><strong>Year started birth dose vaccine</strong></td>
<td>2016</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>National guidelines for HBV PMTCT</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Birth attended by medical person</strong></td>
<td>65.1%</td>
<td>67.1%</td>
<td>43.9%</td>
</tr>
<tr>
<td><strong>Neonatal mortality rate (/1,000 live births)</strong></td>
<td>23.0</td>
<td>26.9</td>
<td>21.4</td>
</tr>
</tbody>
</table>
Phase 1: Formative study

Objective
To develop a locally adapted and sustainable community-based intervention

To develop insight into birth and early infancy concepts and practices (what, why, where)

To evaluate local health system activities and capacities (formal, voluntary, informal workers)

To characterize relations between local populations and these health systems

To obtain baseline information about study communities using the Demographic Surveillance System (DSS)

Current standard of care

Formative study
- Anthropology
- Epidemiology
- Economy

To study economic feasibility of different options to deliver birth dose vaccine
Phase 2: Cluster-randomized controlled trial

To assess the impact of community-based intervention in improving birth dose vaccine coverage and neonatal survival

4-8 communities

Intervention
- Community-based intervention determined at the end of the Phase 1

4-8 communities

Control
Phase 2: Cluster-randomized controlled trial

Endpoints
- % infants vaccinated within 24 hrs
- Neonatal mortality rate

Endpoints
- % infants immune to HBV
- % infants infected with HBV

Cost-effectiveness

Intervention

Control

DSS
- Sero-survey

4-8 communities

- DSS
- Sero-survey

4-8 communities
OTHER PREVENTIVE MEASURES
Risk from HBsAg+ HBeAg+ mothers:
- No prophylaxis: 70-90%
- Timely birth dose vaccine alone: 20%
- Timely birth dose vaccine + HBIG: 5-10%
- Timely birth dose vaccine + HBIG + antiviral Tx during pregnancy: <2%

Risk from HBsAg+ HBeAg- mothers:
- No prophylaxis: 5-30%
- Timely birth dose vaccine alone: <0.5%

Sources:
- Lee C et al., Cochrane Database Syst Rev, 2006
- Machaira M et al., J Antimicrob Chemother, 2015
<table>
<thead>
<tr>
<th>Prophylaxis Method</th>
<th>Risk from HBsAg+ HBeAg+ mothers Asia</th>
<th>Risk from HBsAg+ HBeAg+ mothers Africa</th>
<th>Risk from HBsAg+ HBeAg- mothers Asia</th>
<th>Risk from HBsAg+ HBeAg- mothers Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis</td>
<td>70-90%</td>
<td>40%</td>
<td>5-30%</td>
<td>5%</td>
</tr>
<tr>
<td>Timely birth dose vaccine alone</td>
<td>20%</td>
<td>30%</td>
<td>&lt;0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Timely birth dose vaccine + HBIG</td>
<td>5-10%</td>
<td>No data</td>
<td>&lt;0.5%</td>
<td>0%</td>
</tr>
<tr>
<td>Timely birth dose vaccine + HBIG + anti-viral Tx during pregnancy</td>
<td>&lt;2%</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

Keane E, Funk AL, Shimakawa Y. Aliment Pharmacol Ther, 2016
Hepatitis B immunoglobulin (HBIG)

• WHO recognizes the efficacy of HBIG in conjunction with hep B vaccine
• However, this is not fully recommended because of:
  – Feasibility
    • Limited supply
    • High cost
  – Safety
• Rarely implemented in sub-Saharan Africa

WHO, HBV Guidelines, 2015
Antiviral treatment during pregnancy

• WHO (2015)
  – No recommendation

• American Guidelines (AASLD, 2015)
  – HBsAg+ & HBV DNA >2 x 5 log10 UI/mL

• European Guidelines (EASL, 2012)
  – HBsAg+ & HBV DNA >6-7 log10 UI/mL

In addition to birth dose vaccine & HBIG
However, the standard of care in Africa is:
  - Vaccine at 6 weeks or
  - Birth dose vaccine
Treatment during pregnancy is attractive

• Intervention starting at the point of ANC may result in higher uptake than the intervention at child delivery?
  – % pregnant women attending at least one ANC visit: 78%
  – % pregnant women delivering their baby at health facilities: 50%

UNICEF, 2016
Future questions

• Effectiveness in real-life Africa:
  – Antiviral therapy during pregnancy alone (without birth dose vaccine and HBIG) *versus* universal birth dose vaccine

• Integration into the HIV PMTCT program
Conclusions

• Lessons from HBV to HIV
  – HBV model (vaccine & HBIG at birth) in for wealthy countries; not well performed in Africa
  – Obstacles to implement birth dose vaccine
    • Lack of support from GAVI
    • Half of children born at home
    • There are tools (Uniject, out of cold chain storage), but national regulation does not allow lay health workers to immunize

• Lessons from HIV to HBV
  – HIV model (maternal screening and antiviral therapy) needs to be tested for HBV PMTCT in Africa
Thank you

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  - Dr. Maud Lemoine
  - Dr. Shevanthi Nayagam
  - Prof. Mark Thursz
- LSHTM
  - Dr. Christian Bottomley
  - Prof. Hilton Whittle
  - Sir Andrew Hall
- IARC/GHIS
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  - Dr. Dolores Pourette
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