5th International HIV/Viral Hepatitis Co-Infection Meeting

Viral hepatitis elimination in Latin America and globally: How close are we?

Saturday - Sunday, 20-21 July 2019
Mexico City, Mexico
Expanding Access to HBV BIRTH DOSE Vaccine

Monique Andersson
Oxford University Hospitals NHS Foundation Trust
Stellenbosch University
Saturday 20th July 2019
Conflicts of Interest

• None to declare
Plan

• Introduction – case for expanding access

• How are we doing?

• What are the hurdles and possible solutions to HepB-BD access?

• Conclusion
Background

- UN 2030 Agenda for Sustainable Development include combatting viral hepatitis
- May 2016 Global Health Sector Strategy for Viral Hepatitis set targets for 2020 and 2030: to reduce new cases of chronic HBV infection by 30% by 2020 (equivalent to 1% amongst children aged 5 years) and 0.1% prevalence by 2030
Modelling elimination

• Scaling up:
  90% reduction in new chronic cases and 65% reduction in mortality – infant vaccine 90%, **HepB-BD 80%**, peripartum antivirals 80% eAg positive mothers, t&t 80% of eligible

• Avert 7.3 million deaths 2015 - 2030 (1.5 million cancer deaths)

Impact of HepB-BD Vaccine

Scenario: Both in and out of facility births with a traditional vial; variable transmission rate

Deaths

- Total deaths averted (2021-2035)
  - Max: ~1.2M
  - Min: ~0.3M
- Deaths averted per 100K vaccinated
  - Max: ~240
  - Min: ~52

Cases

- Total cases averted (2021-2035)
  - Max: ~1.5M
  - Min: ~1.2M
- Cases averted per 100K vaccinated
  - Max: ~287
  - Min: ~227

Source: Gavi HepB birth dose investment case
Health Impact across VIS Candidates

Total future deaths averted (K), 2021-2035

Source: Gavi HepB birth dose investment case
Plan

- Introduction – case for expanding access
- How are we doing?
  - What are the hurdles and possible solutions to HepB-BD access?
- Conclusion
Hepatitis B Birth dose (HepB-BD) vaccination strategies in the national immunization programme
Universal HepB-BDV

- 108 countries (56% of 194 member states) Universal BDV
- Further 20 (10%) administer only to at risk infants
- 66 countries (34%) do not have HepB-BD policy

WHO June 2019
Universal HepB-BDV

- 101 countries (52% of 194 member states) Universal BDV
- Further 20 (10%) administer only to at risk infants
- 73 countries (38%) do not have HepB-BD policy

Weekly Epidemiological Record No 7 16 February 2018
2016 Universal HepB-BD by Region

- 93% Western Pacific (except Japan and NZ)
- 76% Eastern Mediterranean
- 73% South-East Asia
- 49% Region of America (90% of regions births)
- 49% European (30% target high risk)
- 19% African region
What about coverage?
Increment in HepB-BD Coverage

- 2017: Of 101 countries, 84 administered timely HepB-BD to 54 million children

- 2017: 39% world’s live births
- 2010: 29%
- 2005: 23%
- 2000: 6%

*Based on WHO-Unicef Estimates of National Immunisation Coverage

1. WHO Weekly Epidem Rec 7; 16 Feb 2018
Global and Regional Coverage with HepB-BD 2000-2016

* This is based on the 84 countries that had WHO and UNICEF Estimates of National Immunization Coverage (WUENIC) available: 0% coverage was assumed for the remaining 17 countries providing universal HepB-BD but without data on timely HepB-BD vaccination, and 26 countries providing HepB-BD only to newborns of mothers chronically infected with HBV. All countries are included in the denominator. — Chiffres déterminés pour les 84 pays disposant d’estimations UNICEF de la couverture vaccinale nationale (WUENIC) en 2014: 0% pour les 17 pays restants qui n’ont pas de données sur la vaccination en temps utile par cette dose. Tous les pays sont inclus dans le dénominateur.
Concerns

- 2016 only 39% of newborns received timely HepB-BD
- 58% high endemic countries do not have HepB-BD
- Only 19% (9/47) countries in the African Region HepB-BD with coverage of 10%
  - In 2014 up to 30 million infants were still unvaccinated in 96 countries that provide universal HepB-BD
  - Is there some reduction in the rate of roll out of HepB-BD?

WHO. Weekly Epidemiol Rec 2015;46(90):617-32
Cumulative incidence of chronic HBV in children <5yrs

Source WHO 2015

Prevalence of HBsAg (%)

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Map key</th>
<th>Best</th>
<th>Lower</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Region</td>
<td></td>
<td>3.0</td>
<td>2.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Region of the Americas</td>
<td></td>
<td>0.2</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Eastern Mediterranean Region</td>
<td></td>
<td>1.6</td>
<td>1.2</td>
<td>2.1</td>
</tr>
<tr>
<td>European Region</td>
<td></td>
<td>0.4</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>South-East Asia Region</td>
<td></td>
<td>0.7</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Western Pacific Region</td>
<td></td>
<td>0.9</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1.3</td>
<td>0.9</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Source WHO 2015
Concerns

- 2016 only 39% of newborns received timely HepB-BD
- 58% high endemic countries do not have HepB-BD
- Only 19% (9/47) countries in the African Region HepB-BD with coverage of 10%
- In 2014 up to 30 million infants were still unvaccinated in 96 countries that provide universal HepB-BD
- *Is there some reduction in the rate of roll out of HepB-BD?*

WHO. Weekly Epidemiol Rec 2015;46(90):617-32
Global and Regional Coverage with timely HepB-BD 2000-2016

* This is based on the 84 countries that had WHO and UNICEF Estimates of National Immunization Coverage (NV/UNIC) available: 6% coverage was assumed for the remaining 17 countries providing universal HepB-BD but without data on timely HepB-BD vaccination, and 20 countries providing HepB-BD only to newborns of mothers chronically infected with HBV. All countries are included in the denominator. – Chiffres déterminés pour les 84 pays disposant d’estimations ONUS/UNICEF de la couverture vaccinale nationale (NV/UNIC), on a supposé une couverture de 6% pour les 17 pays restants qui délivraient une DN de HepB universelle, mais sans disposer de données sur la vaccination en temps utile par cette dose. Tous les pays sont inclus dans le dénominateur.
Plan

• Introduction – case for expanding access

• How far have we come?

• What are the hurdles and possible solutions to HepB-BD access?

• Conclusion
Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
Increasing universal HepB-BD Access

- Strategic alliances to increase political pressure
- Encourage dialogue around misconceptions about HepB-BD
- Call for funding for programmatic expansion eg. Gavi, Clinton, Gates, other
- Ensure strong links with associated frameworks eg. triple elimination, NCD strategies
- Engagement of civil society
Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
Impact of home delivery

• 25% of infants worldwide and 54% infants in least developed countries are born at home\(^1\)

Improving IDR

- Increasing IDR can improve HepB-BD whilst also improving other maternal and neonatal health outcomes.
- Provision of financial incentives and encouraging patients increases timely HepB-BD in Cambodia\(^1\)
- Encourage early attendance at facility post delivery
- IDR increase alone is not enough, ensure HCW education, access to vaccine, clear lines of responsibility

Empowering the community

• Skilled birth attendants trained to administer HepB-BD in the community\(^1\)

• Community health volunteers who monitor and report recent deliveries\(^2\)

2. Li et al. Vaccine 2017 35;4396-4401
Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
Importance of education

- MeKongDelta Vietnam
- Cross sectional survey conducted 2015-2016 mothers of 526 children aged 6-11 months in urban, rural, remote areas interviewed and vaccine documents checked. Three stage sampling method using WHO 30-cluster sampling.
- Overall HepB-BD 46.6%
- Main reason for not receiving – not offered by health care worker (53.0%) and illness of infant (27.2%)

Thi Pham et al. Vaccine 2018 36;5760-5765
Education

- Parents need educating on importance of timely HBV vaccine\(^1\)
- Mothers can be educated during ANC visits or community care workers
- Educating CCW to improve liaison between the community and health care facility can increase coverage \(^2,3\)

2. Li et al. Vaccine 2017 35;4396-4401
HepB-BD coverage, institutional delivery, ANC visits in 5 African countries

<table>
<thead>
<tr>
<th>Country</th>
<th>% HBsAg prevalence (min %, max %)</th>
<th>Year HepB-BD introduced</th>
<th>Annual Births (1000s) (^1)</th>
<th>Institutional deliveries % (^2)</th>
<th>Births attended by SBA (%^2)</th>
<th>&gt;1 ANC visit (%^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>5.3, 10.6 (35–37)</td>
<td>Pre 2000</td>
<td>55</td>
<td>100</td>
<td>95</td>
<td>94</td>
</tr>
<tr>
<td>Gambia</td>
<td>8.5, 9.1 (38–40)</td>
<td>1990</td>
<td>83</td>
<td>63</td>
<td>57</td>
<td>86</td>
</tr>
<tr>
<td>Namibia</td>
<td>7.8, 13.6 (41–43)</td>
<td>2014</td>
<td>72</td>
<td>87</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6.7, 17.2 (44–46)</td>
<td>2004</td>
<td>7,133</td>
<td>36</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>Sao Tome and Principe (^3)</td>
<td>6.1, 10 (47)</td>
<td>2002</td>
<td>6</td>
<td>91</td>
<td>93</td>
<td>98</td>
</tr>
</tbody>
</table>

\(^1\) Annual birth data is derived from the WHO Immunization Monitoring System (updated May 2016) [http://apps.who.int/immunization_monitoring/globalsummary/](http://apps.who.int/immunization_monitoring/globalsummary/).

\(^2\) Data derived from UNICEF (updated February 2016) [www.data.unicef.org](http://www.data.unicef.org)

\(^3\) Sao Tome and Principe does not offer the birth dose universally, but follow a selective policy where infants of mothers that test HBsAg are offered vaccine

Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
HBV vaccine and the Cold Chain

• WHO guidelines recommend HBV vaccines in standard cold chain (2-8°C)
• Requires a dedicated supply chain
• Often compromised by poor infrastructure/staff training
• Result: restricted access to remote villages and rural communities
  home deliveries are vaccinated late or not at all
• Result is exposure to perinatal infection and early horizontal transmission

HBV Vaccine and Cold Chain

- Robust data showing many HBV vaccines are sufficiently heat stable to be effective even if removed from cold supply chain
- Some heat stable beyond 2-8°C as long as held at ambient temperature no more than 40°C
- Field studies showing adequate antibody production after vaccination with vaccines outside of CTC

Traditional Cold Chain and CTC

- Cold chain is gold standard but it too has limitations
- Reduced vaccine efficacy due to freezing eg. Mongolia\(^1\) and Indonesia\(^2\)
- Controlled Temperature Chain outreach improves coverage

### How Does a CTC Compare to a Traditional Cold Chain?

<table>
<thead>
<tr>
<th><strong>Traditional Cold Chain</strong></th>
<th><strong>Controlled Temperature Chain (CTC)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine label indicates +2°C to +8°C for all storage and transport.</td>
<td>Vaccine label indicates +2°C to +8°C for initial storage and transport, and permits up to 40°C for at least 3 days prior to use.</td>
</tr>
<tr>
<td>Vaccine vial monitors protect potency and quality by monitoring cumulative exposure to heat.</td>
<td>Vaccine vial monitors and peak temperature threshold indicators protect potency and quality by monitoring cumulative and peak exposure to heat.</td>
</tr>
<tr>
<td>Conditioned ice packs or cool water packs are required in vaccine carriers.</td>
<td>No ice packs or cool water packs are required in vaccine carriers. Reduced risk of freezing.</td>
</tr>
<tr>
<td>No need for additional training, monitoring or supervision.</td>
<td>Health workers need additional training, monitoring and supervision.</td>
</tr>
<tr>
<td>When implemented correctly, preserves the safety and potency of the vaccine.</td>
<td>When implemented correctly, preserves the safety and potency of the vaccine.</td>
</tr>
<tr>
<td>Requires cooling equipment, transport, and human resources at all levels to maintain cold chain.</td>
<td>Half the cost. Fewer freezers, fewer journeys and less staff time are needed to manage and maintain cold chain requirements.</td>
</tr>
</tbody>
</table>
Number of ice packs needed daily to vaccinate 1,000 people: 80

Percentage of health facilities in surveyed countries that have no refrigerators: 22%

Number of freezers needed to freeze 80 ice packs in 24 hours: 5

Percentage of cold chain equipment in surveyed countries that is non-functional: 12%

Weight of vaccine carrier without ice packs: 1.6 kg

Weight of carrier loaded with conditioned ice packs: 4.0 kg

Percentage of vaccinators in Benin who agreed that CTC was useful or very useful in allowing them to vaccinate more persons: 98.7%
Cost effectiveness of CTC: modelling study

- CTC strategy improves coverage and timing to all GBD regions
- The strategy is cost saving in east Asia and Pacific, Latin America and Caribbean, North Africa and Middle East, sub-Saharan Africa where additional costs of vaccine delivery were offset by cost-saving from prevented disease
- Where HBsAg prevalence is above 3.8% or birth dose coverage below 67% cost saved and DALYs averted were greater

CTC licensing

• Package inserts for 2 monovalent vaccines indicate that vaccine is stable for 1 month at 37°C and 1 week at 45°C

• Additional vaccines are in the development and licensure pipeline for CTC compatibility

Hurdles to HepB-BDV

1. Cost of programmatic implementation
2. Home delivery
3. Lack of HBV knowledge
   - women, men, communities
   - health care workers
4. Relicensing monovalent vaccine CTC use
6. Hesitancy
7. Engaging private sector
Parental Refusal

- Vaccine hesitancy is problematic and may have greater impact over time on uptake
- Gilmartin et al. Cross sectional study\(^1\)
  137/1574 (8.7%) declined vaccination
  - 55.8% ‘baby too young’
  - 45% perceived low risk
  - 42% overloading immune system
- Problem in LMICs too\(^2\)

Impact of presumed AEFI

- Rapid response to vaccine scares
- Thorough investigation and resolution
- Reassure public through preparedness for a timely response to media and public enquiries
Strategies to Increase Access

• Integration with other programmes
  - Triple elimination (HIV, HBV and syphilis)
  - HepB-BD with newborn care
  - Maternal and child health card
  - NCD agenda

• Novel delivery mechanisms
CPADs

• The use of compact pre-filled auto-disposable injection devices in China, Indonesia and PNG improved timely HepB-BD and was widely accepted eg. Uniject

• CPAD require minimal training, do not require a skilled HCW and can be delivered by trained volunteers

Disposable microneedles

- 350 microns diameter at base
- 650 microns length
- Microneedles dissolve
- Patch mounted on adhesive strip which is discarded after use
- No pain, no waste, administered by parent (any time/any place)
- HBV vaccine immunogenic in mice and rhesus macaques

Disposable microneedles
Conclusion

• Improving access and coverage to HepB-BD is critical to reaching elimination goals
• Access has improved over time but more needs to be done
• Funding for implementation, education of parents, community and health care workers, CTC licensing, increasing IDR and training community health workers with access to novel delivery systems is all possible
• But do we have the will to advocate for implementation?
Acknowledgements

• Charles Wiysonge
• Cynthia Tamandjou
• Tongai Maponga
• Philippa Matthews
• Tammy Meyers
• Po-Lin Chan
• Marc Bulterys
  Shalini Desai
• Lance Rodewald
  Mark Prausnitz
HepB-BD June 2019

- HepB-BD introduced to date:
  - Afghanistan, Albania, Algeria, Andorra, Angola, Argentina, Armenia, Australia, Azerbaijan, Bangladesh, Barbados, Benin, Bolivia (Plurinational State of), Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo (the), Costa Rica, Côte d'Ivoire, Croatia, Cyprus, Democratic Republic of Congo, Eritrea, Ethiopia, Gabon, Germany, Ghana, Greece, Guinea, Guinea-Bissau, Guyana, Haiti, Hungary, Ireland, Israel, Jamaica, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Malta, Mauritius, Monaco, Montenegro, Mozambique, Nepal, Nicaragua, Niger (the), Pakistan, Rwanda, San Marino, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sri Lanka, Sudan, Suriname, Syria, Tajikistan, Thailand, Timor-Leste, Tonga, Turkey, Turkmenistan, Tuvalu, Uganda, United Arab Emirates, United Kingdom, United Republic of Tanzania, Uruguay, Yemen, Zambia, Zimbabwe.

- HepB-BD only for infants born to HBsAG-positive mothers:
  - Belgium, Chile, Czech Republic (the), Denmark, France, Italy, Japan, Latvia, Luxembourg, Netherlands (the), New Zealand, Norway, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

- HepB in schedule but no HepB-BD:
  - Antigua and Barbuda, Austria, Bahamas (the), Bangladesh, Barbados, Benin, Bolivia (Plurinational State of), Burkina Faso, Burundi, Cameroon, Canada, Central African Republic, Chad, Comoros, Congo (the), Costa Rica, Côte d'Ivoire, Croatia, Cyprus, Democratic Republic of the Congo, Eritrea, Ethiopia, Gabon, Germany, Ghana, Greece, Guinea, Guinea-Bissau, Guyana, Haiti, Hungary, Ireland, Jamaica, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Malta, Mauritius, Monaco, Montenegro, Mozambique, Nepal, Nicaragua, Niger (the), Pakistan, Rwanda, San Marino, Seychelles, Sierra Leone, Somalia, South Africa, South Sudan, Sri Lanka, Sudan, Suriname, Syria, Tajikistan, Thailand, Timor-Leste, Tonga, Turkey, Turkmenistan, Tuvalu, Ukraine, United Arab Emirates (the), United Kingdom, Uzbekistan, Vanuatu, Venezuela (Bolivarian Republic of), Viet Nam.

- HepB given only for risk groups or adolescents:
  - Finland, Iceland.

- Finland, Iceland.
Vietnam

- 2010 21.4%; 2012 75%; 2013 56%
- Blamed on AEFI in 2007 and 2013 emergence of anti-vaccine movement

- 19% drop in coverage: increase burden by 130,675 new chronic HBV infections
  25,197 HBV-associated deaths those born in 2013¹

¹ Li et al. Vaccine 2016;34(6);869-73
Vaccines

- Recombinant vaccines 1986
  Contain SHB (small HBV protein). Yeast derived are most widely used. Lack preS domain and lack glycosylation
- Glycosylated preS1/preS2/S containing vaccine produced in mammalian cell lines used in Israel
- All formulations require formulation w adjuvants
  (renal pts- Yeast based with 500ug Al and 50ugASO4C)
- Monovalent or quad/pent or with HAV
Vaccine escape mutants: what role do they play?

• JID ramsay may 2018 218:726
Hepb-3 coverage
To study the effects of delayed second dose of HepB vaccine, a study in Thailand assessed the risk of developing chronic HBV infection in infants born to chronically HBV-infected mothers. The risk of an infant becoming chronically infected, despite receipt of HepB-BD, was 3.74 times higher if the interval between the first and the second dose exceeded 10 weeks. While more studies are needed, these findings suggest that immunization programmes should ensure timely second-dose vaccination to infants born to mothers with chronic HBV infection.

• Failure to complete series associated with risk of liver disease later in life

• Chien et al 20 year cohort study Hepatology 2014
Why is HepB-BD so important?

• Risk of infection for infants born HBsAg pos mothers increased significantly when first dose was received 7 days after birth compared with those vaccinated at 1-3 days (OR 8.6)\(^1\)

• Meta-analysis of RCTs found infants who had first dose at birth compared to those who had placebo or no intervention RR 0.28; 95%CI 0.20-0.40)\(^2\)

2. Lee et al. Cochrane Database of Systematic Reviews 2006;(2):CD004790
• 257 million people living with chronic HBV infection
• 887,000 deaths from longstanding complications like cirrhosis and HCC
• Majority of infections are acquired perinatally
• WHO recommends at least three doses with the first dose to be administered within 24 hours of birth
• HBIG may be given as an adjunct, especially for those who are HBeAg positive
• HBIG is limited by high cost and cold chain storage
• WHO currently exploring evidence to make a recommendation on antiviral use