

Prevention of mother-to-child transmission of hepatitis B virus: Guidelines on antiviral prophylaxis in pregnancy

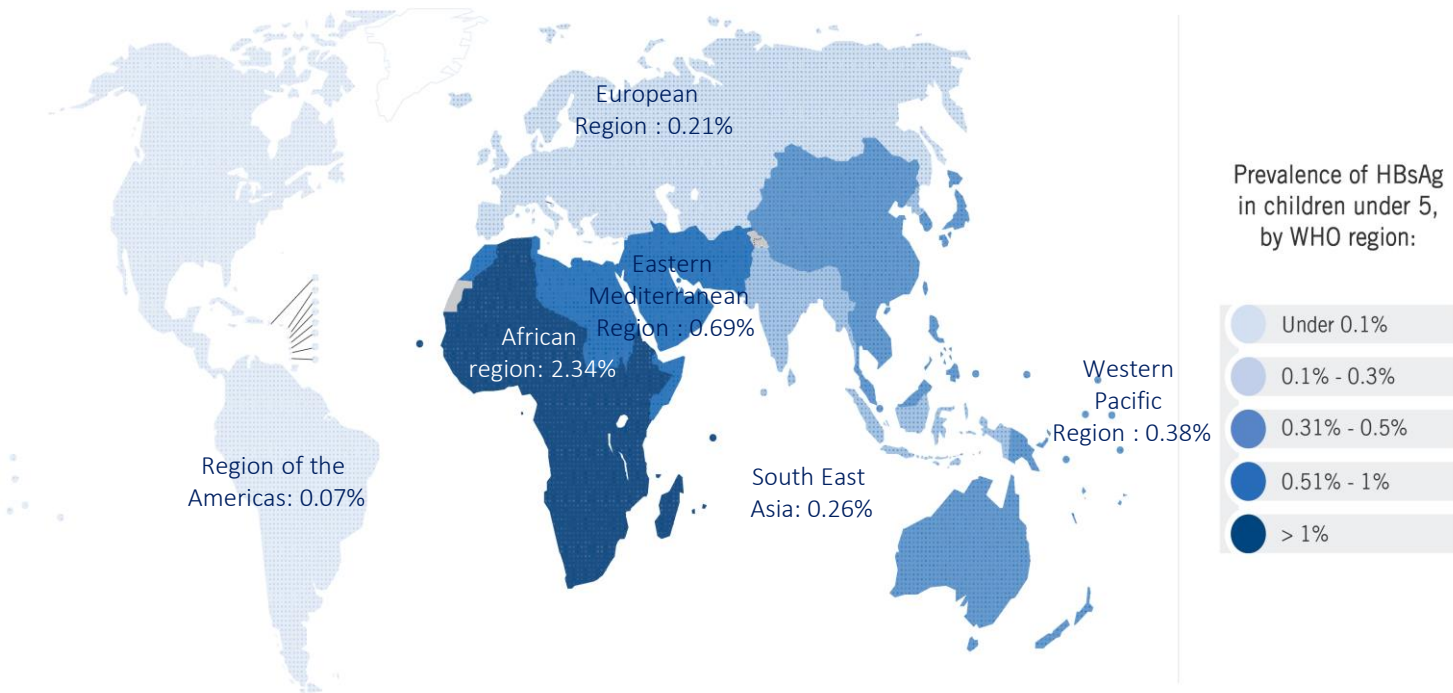
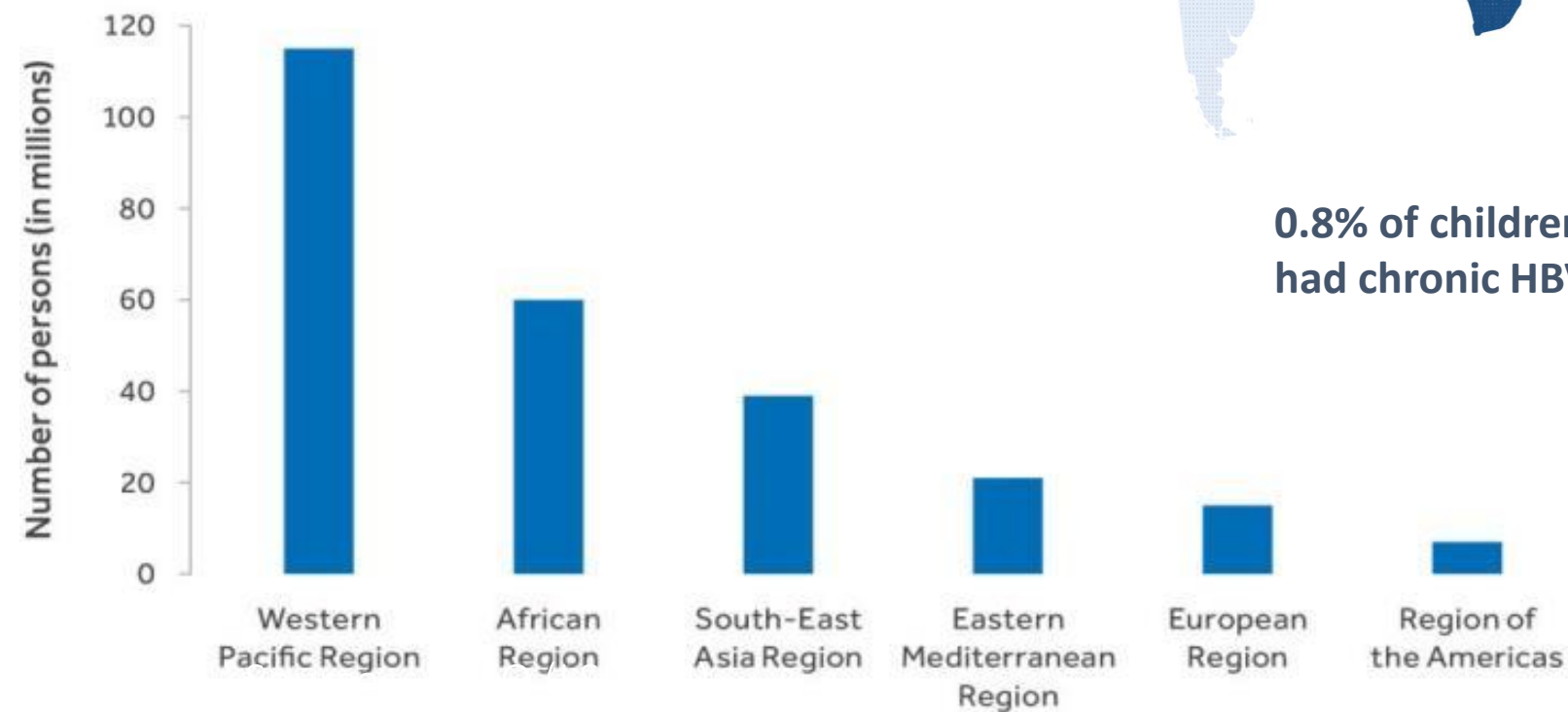
VHPB Technical Meeting: Viral Hepatitis Treatment as Prevention, 22 October 2020

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Status of hepatitis B

In 2015

- 257 million people living with HBV, 68% in Africa /Western Pacific
- 900 000 deaths (cirrhosis and HCC)



0.8% of children under 5 in 2017 worldwide had chronic HBV infection

HBV: Earlier infections are more severe, particularly perinatal infection

- **Transmission of HBV**

- Exposure to blood and body fluids, including from mother to child at birth
- Acquisition of infection early in life in high endemicity area (HBsAg > 8%)
- Early childhood and perinatal transmission hard to disentangle
- Perinatal infections more common in Asia +++ than in Africa +

- **HBV infection**

- Risk of chronic infection higher if infection at birth +++ or before 5 years of age ++

- **Chronic hepatitis B**

- Chronic HBV infection evolves towards cirrhosis and hepatocellular carcinoma (30+ years), leading to death
- Risk of aggressive disease higher if perinatal infection

Global Health Sector Strategy on Viral Hepatitis (2016): Roadmap to Elimination







Goal = Eliminate viral hepatitis as a major public health threat by 2030



The World Health Assembly pledged to reach elimination (2016)

5 core interventions with sufficient coverage would lead to elimination (incidence - 90%, mortality -65%)

	Interventions	Indicator	2015	2020	2030
	3 dose HBV vaccine	Coverage	84%	90%	90%
	HBV PMTCT	Coverage	39%	50%	90%
	Blood / injection safety	Screened donations	97%	100%	100 %
		Safe injections	95%	100%	100%
	Harm reduction	Sets/PWID/year	27	200	300
	HBV and HCV testing and treatment	% diagnosed	9/20%	30%	90%
		% treated	8/7%	N/A	80%

Incremental approach to prevention of HBV infection at birth and in the first years of life

The interventions at the base of the pyramid benefit the largest number and are necessary for those at the top of the pyramid to be effective

Maternal
antiviral
prophylaxis
If high maternal viral load

Anti-viral treatment can make a difference for the subset of women with high viral load.

HBsAg testing, linkage-to-care, follow-up of infants. When available, HBIG for infants born to HBsAg+ and HBeAg+ mothers

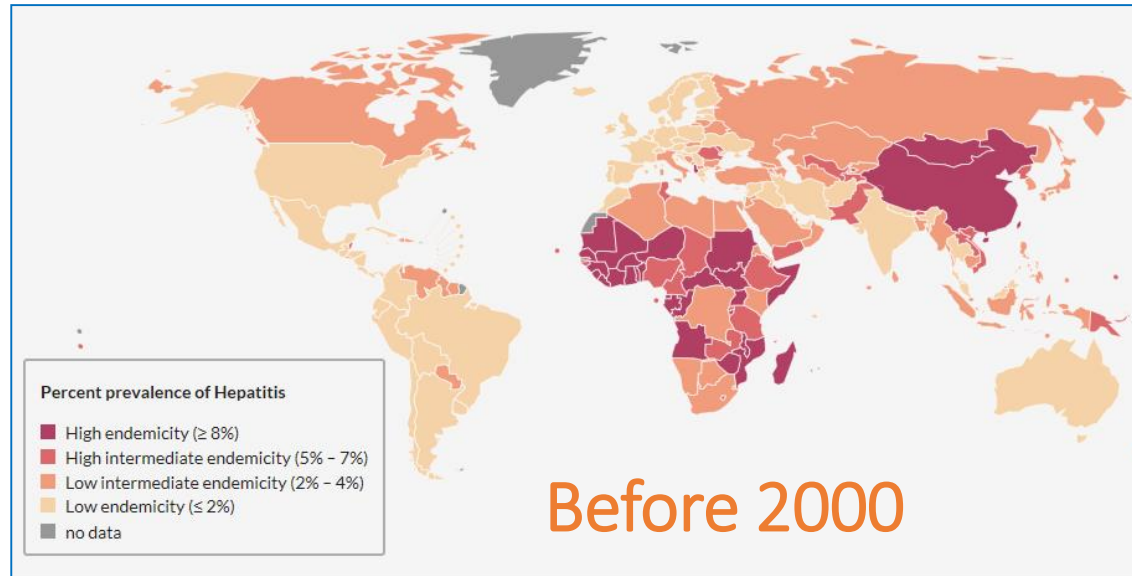
HBIG is used many high income countries, but there are supply issues (quantity, quality) in middle and low income countries.

A strong **system to test and link to care** is the foundation of more interventions and allows impact monitoring.

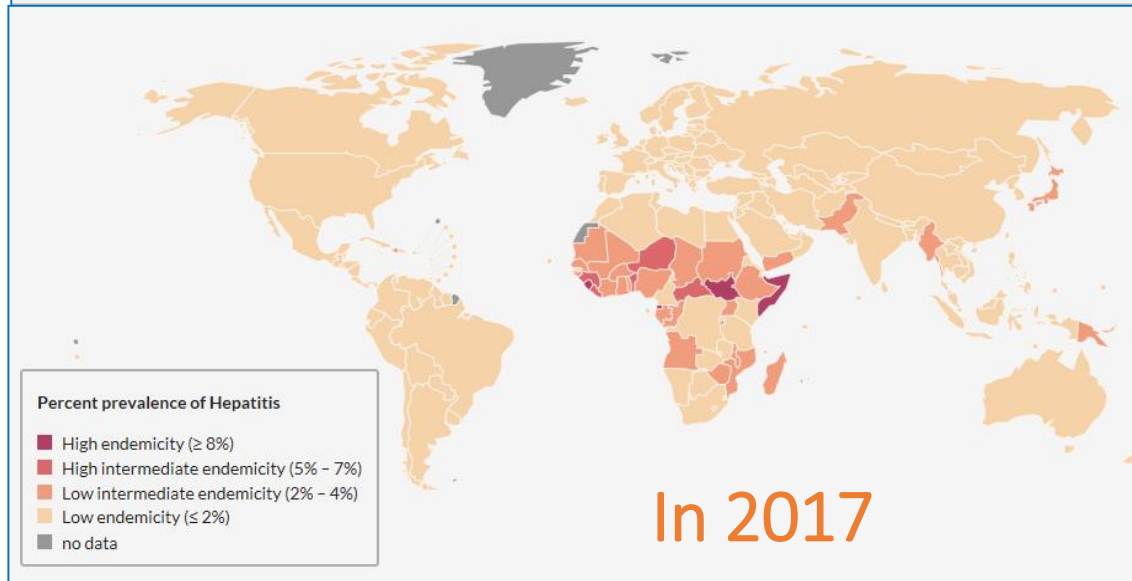
At least 3 doses of hepatitis B vaccine including a timely birth dose within 24 hours

Three doses of vaccine reduce incidence, ensure effectiveness of interventions at birth. Universal timely birth dose is the first line of defence against perinatal infection for all infants.

Impact of hepatitis B vaccine on prevalence of HBsAg in under 5

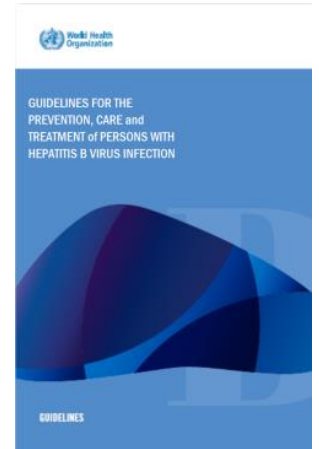


- The prevalence of HBV infection was reduced from 4.7 % in the pre-vaccine era to 0.8 % in 2017



Current HBV testing and treatment recommendations by WHO

- Existing recommendation on immunization from SAGE
 - All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. The birth dose should be followed by 2 or 3 doses to complete the primary series
- 2015 HBV guidelines recommendations on who to treat:
 - Compensated or decompensated cirrhosis regardless of ALT levels, HBeAg or HBV DNA (*strong recommendation, moderate-quality evidence*)
 - No cirrhosis but persistent abnormal ALT levels +/- ongoing HBV replication (HBV DNA >20,000 IU/mL or HBeAg +ve (*strong recommendation, moderate-quality evidence*))
 - In HBV-monoinfected pregnant women, indications for treatment are the same as for other adults, and tenofovir is recommended. **No recommendation was made on the routine use of antiviral treatment to prevent mother-to-child transmission.**
- Existing recommendation on testing of pregnant women; for HIV and syphilis from the 2019 consolidated guidelines on HIV testing services, and for hepatitis B from the 2017 WHO guidelines on hepatitis B and C testing:
 - All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)* at least once and as early as possible (*HIV standing recommendation since 2007; syphilis: strong recommendation, moderate-quality evidence; HBsAg*: strong recommendation, low-quality evidence*).



* Particularly in settings with a $\geq 2\%$ seroprevalence in the general population

New context since the 2015 WHO HBV guidelines

Three main reasons to reconsider a PMTCT recommendation

- New evidence available
- Requests from regions and countries in the context of “triple elimination”
- Concerns that timely birth dose alone may not be sufficient to reach the elimination goal (0.1% prevalence of HBsAg in children under 5 by 2030)

WHO HBV PMTCT guidelines process

- Public health perspective
- Guideline Review Committee handbook
 - PICO questions
 - Evidence
 - Harms and benefits
 - Acceptability, value, preferences
 - Equity, ethics and human rights
 - Resource use and financial implications
 - Feasibility and constraints

Evidence: two systematic reviews and meta-analyses

1. Efficacy and safety of antiviral therapy during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus
2. Performance of hepatitis B e antigen (HBeAg) test, as an alternative to HBV DNA, to assess eligibility for initiating antiviral prophylaxis during pregnancy to prevent mother-to-child transmission
 - To evaluate the DNA viral load threshold for mother-to-child transmission
 - To evaluate the sensitivity and specificity of maternal HBeAg to identify pregnant women with DNA levels above this threshold

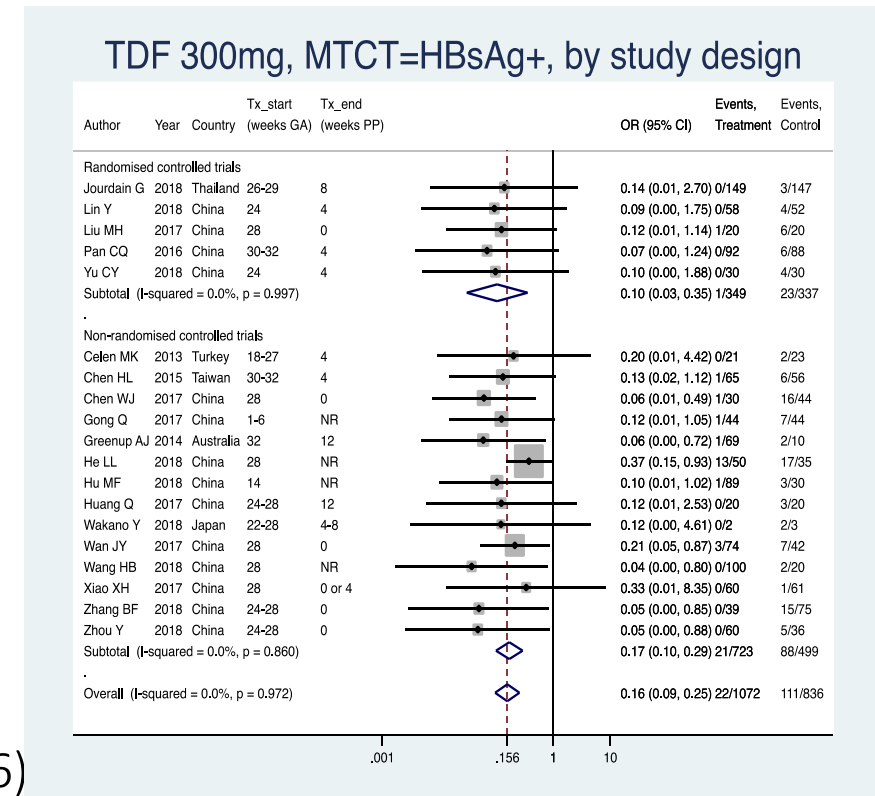
Systematic review and meta-analysis on efficacy and safety of antiviral therapy during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus

Background:

- Increased risk of chronic infection and liver disease if HBV infection is acquired early in life
 - Therefore, perinatal mother to child transmission (MTCT) is a major contributor to the incidence of HBV-related liver disease
- WHO recommends administration of timely birth dose HBV vaccine to all newborns
 - BUT: 20-30% of high viral load mothers infect their infants despite birth dose (*Lee C et al., 2006; Keane E et al, 2016*)
- In high-income countries, Hepatitis B immunoglobulin is additionally administered to children of mothers at high risk of HBV transmission
 - BUT: despite both birth dose & HBIG, infants of mothers with a very high viral load are still at risk of infection (*Chen HL et al., 2012*)
- Therefore, antiviral therapy during pregnancy is now recommended in some countries

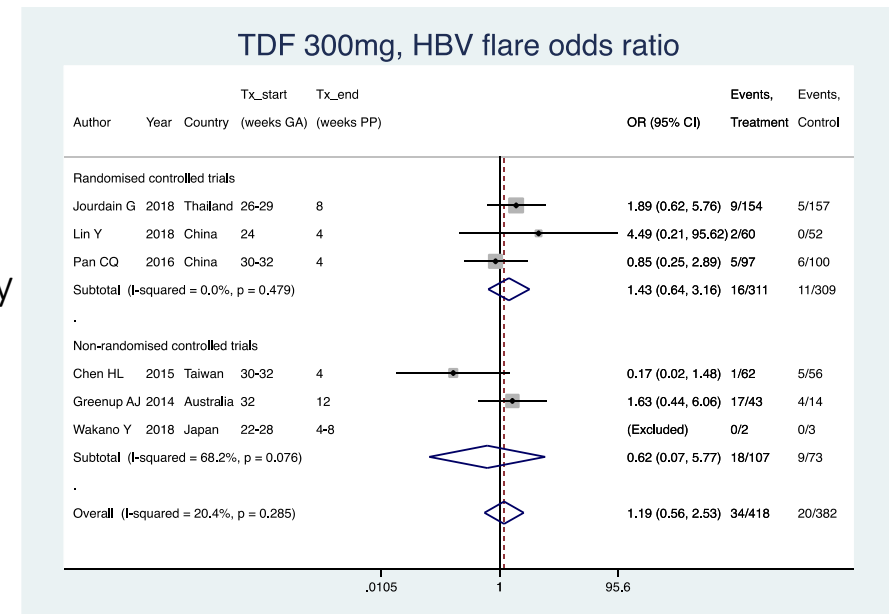
Results on efficacy of TDF

- 129 studies included (all antivirals)
- TDF 300mg: 19 studies, 25 treatment arms
 - Randomised controlled trials (n=5)
 - Prospective observational studies (n=6)
 - Retrospective observational studies (n=8)
- Recruitment: 2007 - 2018
- Countries:
 - China (Mainland, n=14 & Taiwan, n=1)
 - Japan (n=1)
 - Australia (n=1)
 - Thailand (n=1)
 - Turkey (n=1)
- Meta-analysis TDF 300mg: OR 0.16 (95% CI: 0.10-0.26)



Results on safety of TDF

- TDF 300mg infant safety
 - Examined in one study (*Jourdain G, 2018, Salvadori, 2019*)
 - Infant lumbar spine bone mineral density was measured in 62 of the infants from the treatment group, and 53 infants from the control group at 1 year of age with mean 0.324 (SD +/- 0.036), and mean 0.330 (SD +/- 0.036), respectively. There was no difference between the two groups.
- TDF 300mg maternal safety
 - Six studies included
 - 35 of 418 mothers (8%) who received TDF during pregnancy experienced a flare after discontinuation, compared with 23 of 382 mothers (6%) who did not receive the medicine at a matched timepoint.



Conclusions

- Meta-analysis indicated a protective effect regardless of the antiviral used to prevent mother-to child transmission
- TDF medicine of choice, as it has a high barrier to drug resistance and is recommended by WHO as treatment for HBV infection
- No harmful effects of TDF were seen (risk of maternal flare; bone mineral density outcomes in infants), but data quality was limited.

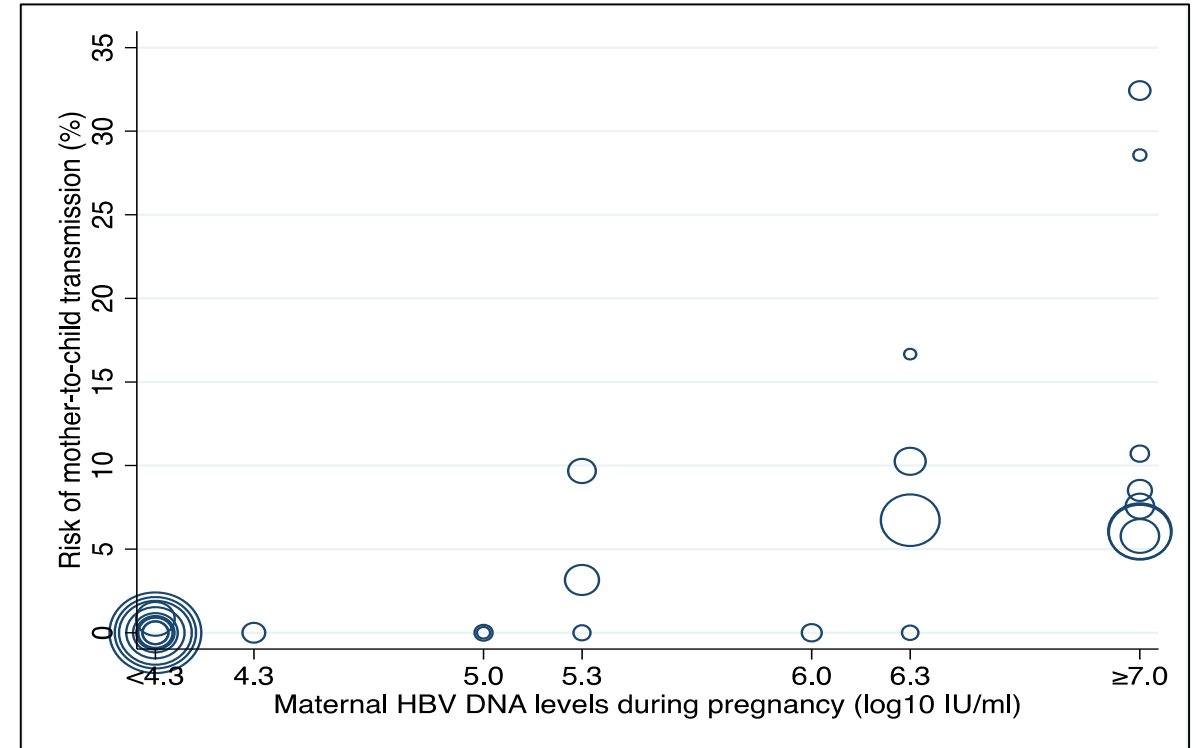
Systematic review and meta-analysis on performance of HBeAg test, as an alternative to HBV DNA, to assess eligibility for initiating antiviral prophylaxis during pregnancy to prevent mother-to-child transmission

Background:

- In low- and middle-income countries:
 - Access to the current standard assay to measure viral load (PCR) is limited because:
 - Expensive
 - Need a sophisticated laboratory
 - Need highly skilled laboratory staff
- Potential alternative solution: treat HBeAg-positive women:
 - HBeAg test may be more accessible for people in resource limited settings
 - Detection of HBeAg by
 - Laboratory-based immunoassay
 - Rapid diagnostic test (RDT)
 - The risk of MTCT from HBeAg-negative mother is limited
 - In infants who received timely birth dose without HBIG: <1.0% (Machaira M, 2015)
 - However, HBeAg-negative women can have high viral load

Results on evaluation of DNA viral load threshold for MTCT

- When timely birth dose and HBIG was used, there was no breakthrough infection reported when maternal HBV DNA viral load was below 5.3 log IU/ml (200 000 IU/ml)



Results on evaluation of the performance of maternal HBeAg to identify pregnant women with high DNA levels and to predict the risk of MTCT

- To estimate the performance (sensitivity and specificity) of HBeAg tests in pregnant women with HBV infection to identify women with high HBV DNA levels ($\geq 5.3 \log_{10}$ IU/mL).
 - The overall sensitivity and specificity of HBeAg for diagnosis of HBV viremia based on a DNA threshold $\geq 5.3 \log_{10}$ IU/mL was 88.2% (95% CI:83.9-91.5) and 92.6% (95% CI:90-94.5), respectively
- To estimate the performance (sensitivity and specificity) of HBeAg tests to predict the risk of mother to child transmission
 - The overall sensitivity and specificity of HBeAg to predict the risk of mother to child transmission was 99.1% (95% CI:61.8-100) and 55.7% (95% CI:34.0-75.5), respectively.

Conclusions

- When timely birth dose and HBIG was used, there was no breakthrough infection reported when maternal HBV DNA viral load was below 5.3 log IU/ml (200 000 IU/ml)
- HBeAg has a high sensitivity but lower specificity compared to HBV DNA for predicting the risk of mother-to-child transmission

New WHO recommendations on prevention of mother-to child transmission of HBV: Guidelines on antiviral prophylaxis in pregnancy

- WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA 200,000 IU/mL ($\geq 5.3 \log_{10}$ IU/ml)(1) receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother to child transmission of HBV. This is in addition to three doses of HBV vaccination, including timely birth dose (*conditional recommendation, moderate quality of evidence*).
- WHO recommends that in settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis, to prevent mother to child transmission of HBV (*conditional recommendation, moderate quality of evidence*).

• 1. HBV DNA $\geq 5.3 \log_{10}$ IU/ml is equivalent to $\geq 200\,000$ IU/ml

Implementation considerations in different WHO regions

- Parameters to plan approach to PMTCT of HBV
 - Epidemiology (prevalence of HBV infection, prevalence of HBeAg in persons with HBV infection)
 - Service coverage of immunization, including birth dose
 - Availability of commodities for diagnostics and treatment
 - Experience with testing and antiviral prophylaxis
- WHO regions with different scenarios with respect to parameters
 - **African region:** high endemicity, relative low prevalence HBeAg among women, low vaccination and birth dose coverage, limited availability of testing and treatment commodities _ efforts should first focus on timely birth dose
 - **Region of the Americas:** low endemicity with pockets of high endemicity (f.e. indigenous populations) _ guidelines will support countries in scale up of antiviral prophylaxis
 - **Eastern Mediterranean region:** intermediate endemicity, vaccination coverage is high but birth dose coverage is low _ efforts to increase timely birth dose
 - **European region:** endemicity low in most countries, some intermediate, vaccination coverage is high. Some countries (HIC) test all pregnant women and provide birth dose to HBsAg+ women instead of universal birth dose.
 - **South East Asia region:** varies from low to high endemicity, high prevalence of HBeAg among women, high vaccination and intermediate birth dose coverage _ efforts can focus on implementation of current guidelines
 - **Western Pacific region:** rapid reduction from high to low prevalence due to high vaccination and birth dose coverage, already experience with antiviral prophylaxis _ guidelines will support countries in scale up of antiviral prophylaxis

In conclusion

- Early HBV infections, particularly perinatal infection, lead to more rapid development of advanced liver disease and liver cancer in (young) adults
- With these new recommendations, and many countries working towards dual elimination of perinatal HIV and syphilis infection there are opportunities for efficiency gains and integration to also include elimination of mother-to-child transmission of HBV
- Prevention of HBV infection at birth and in the first years of life requires a coordinated approach:
 - Immunization services
 - Maternal and child health /PMTCT of HIV and syphilis
- Different WHO regions require different implementation approaches

Acknowledgements

- Guidelines development group:

Indri Oktaria Sukmaputri, Ramatoulie Njie, Roger Chou, Rakesh Aggarwal, Benjamin Cowie, Manal El-Sayed, Fernanda Fonseca, Alice Guinane, Gonzague Jourdain, Elizabeth Mason, Hiromi Obara, Deborah Odoh, Huma Qureshi, Oliver Segeal, Sarah Schillie, Su Wang, Cihan Yurdaydin

- WHO Steering group:

Marc Bulterys, Philippa Easterbrook, Yvan Hutin, Judith van Holten, Morkor Newman, Shalini Desai, Melanie Taylor, Anne Brink, Naoko Ishikawa, Po-lin Chan, Julien Kabore, Lesi Olufunmilayo, Leandro Sereno, Antons Mozalevskis

- Evidence review teams:

Systematic review and meta-analysis: Yusuke Shimakawa, Pauline Boucheron, Anna Funk, Ying Lu, Tianshuo Zhao, Kyoko Yoshida

Modelling: Shevanthi Nayagam, Timothy Hallet

Immunization coverage with HepB birth dose, 2017

