Prevention of Mother-to-child-Transmission of Viral Hepatitis

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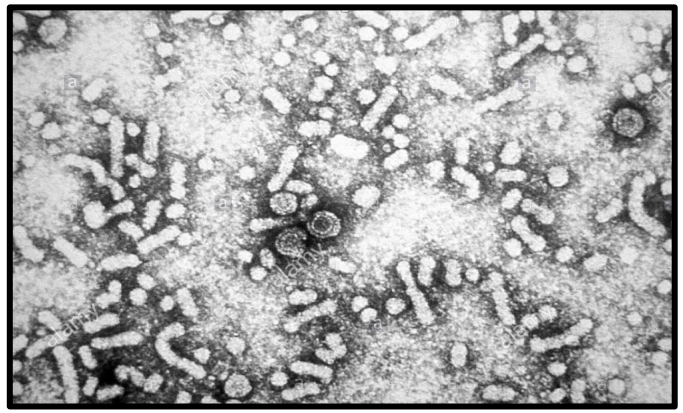
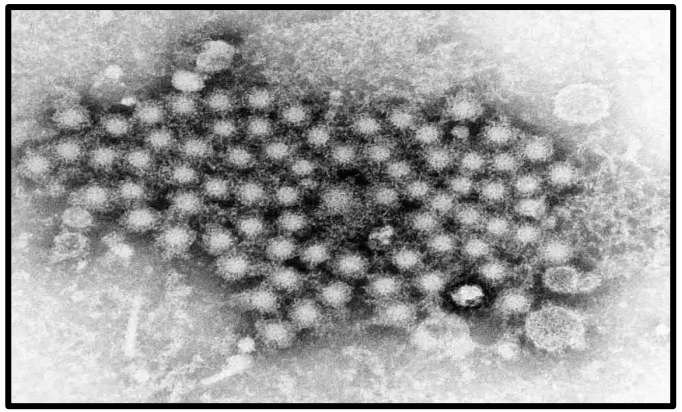
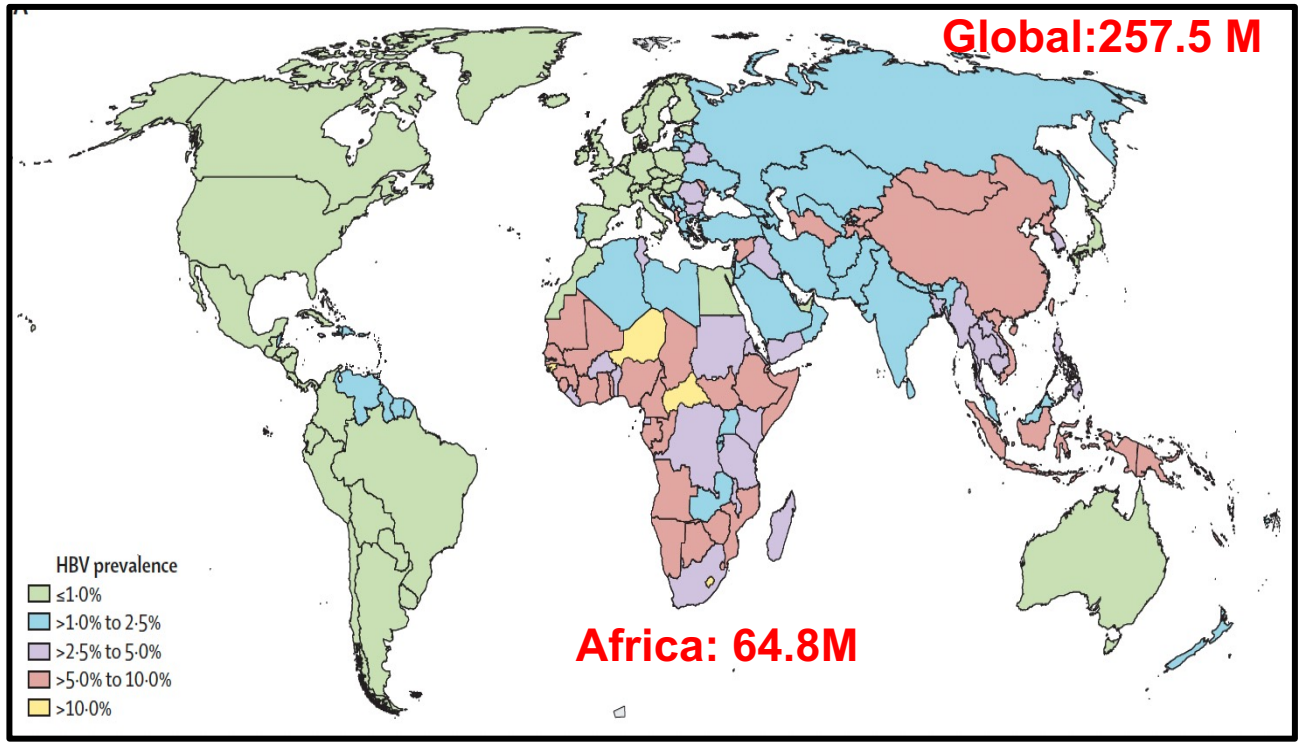




Hepatitis B in Africa

- **Hepatitis B is endemic: MTCT (90% chronic Infection), Early childhood (30-50%)**
- **HBsAg modelled prevalence in 2022: 5.4% (4.4-6.8%) in WHO AFRO region**
- **Lifetime risk of acquiring HBV infection in SSA is >60%**



WHO Africa 2022: 64.8 M (52.8-80.8 M) estimated to be HBV-infected

- No diagnosed: 2.61 M (4%)
- No eligible for Rx: 14.1 M
- No Treated: 142 000 (1%)

HBV is vaccine preventable BUT

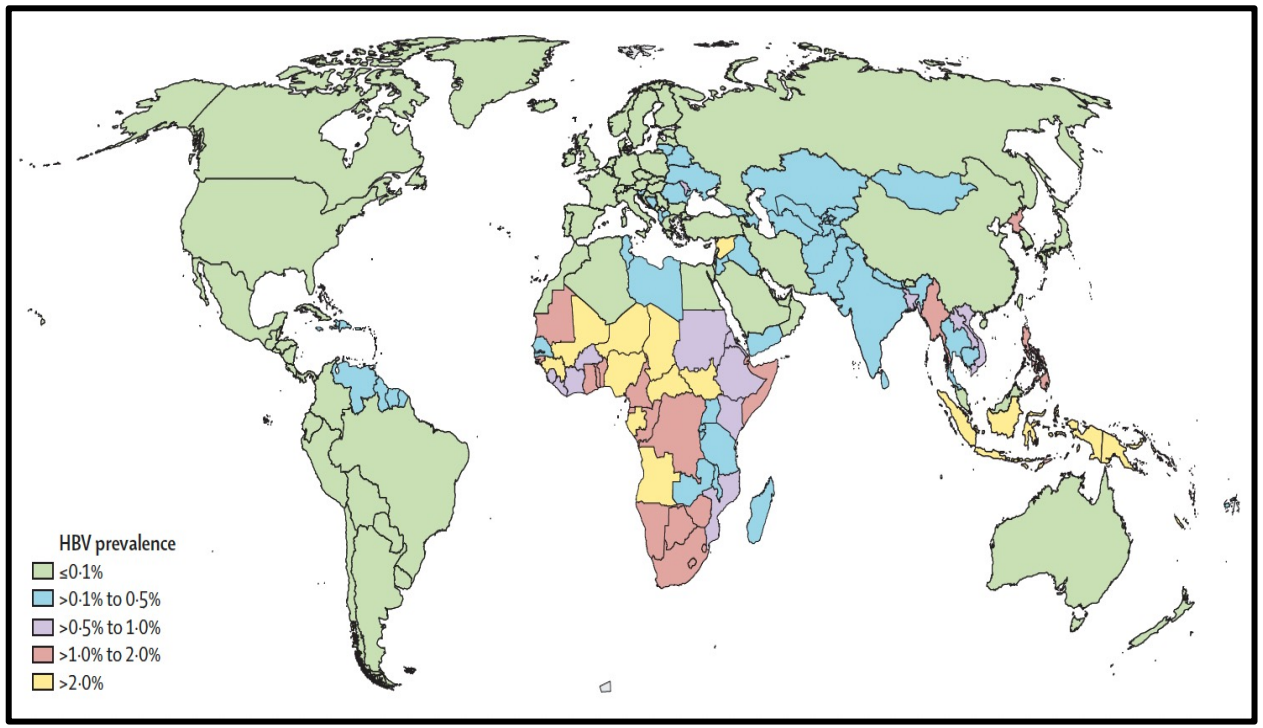
- Only 14 (29%) African countries have implemented HB Birth dose vaccine
- Full HBV vaccine coverage: 82%

Lancet Gastroenterol Hepatol 2023;8:879;
https://immunizationdata.who.int/pages/coverage/hepb.html

Hepatitis B in Africa: Children <5years old

Global: 2020 target: <1.0% 2030 target: ≤0.1%

- **WHO AFRO 2020 target: <2%**



HBsAg positive children <5 years: 2022

Global: 5.6 M (4.5-7.8)

- 0.7% (0.6-1.0) prevalence

WHO AFRO: 3.6 M (2.9-4.9)

- **1.7% (1.3-2.3) prevalence**

Highest prevalence in WHO AFRO region

- 64% of all children living with chronic HBV reside in WHO AFRO

Lowest coverage of timely birth dose vaccination globally: 14%

Lancet Gastroenterol Hepatol 2023;8:879

South Africa: Hepatitis B

2022 Total Population: 59 893 885

2022 Adult Population: 39 746 725

Rural population: 32.15%

World Bank Classification: Upper middle income

HBV Infections (2022)‡
2,825,000
5%

Diagnosed	Annual Treated	Annual Deaths	Deaths per hour
20%	3 000	10,778	1

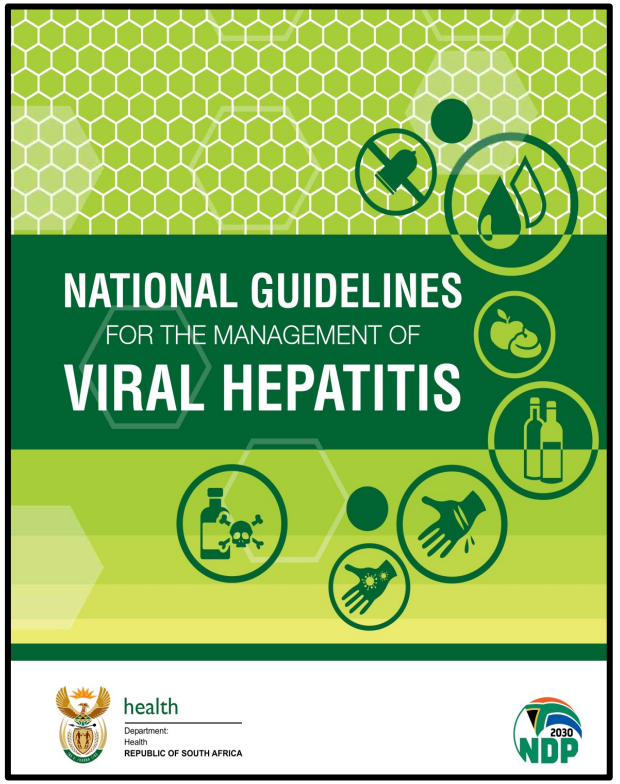
Birth Dose	3+ Dose	HBIG	Tx Pregnant Women
<1%	86%	<1%	5%

Polaris-CDA Observatory: https://cdafound.org/polaris/

South Africa: Hepatitis B

National Viral Hepatitis Guidelines: WHO Africa 2015

- Adopted December 2019
- Costed but no dedicated funding
- COVID-19 halted implementation
- Revitalized January 2023



South Africa's EPI schedule

Universal HBV Vaccination: April 1995

- HBV vaccine as part of the Hexavalent vaccine
  - 6, 10 and 14 weeks with booster at 18 months
- No birth dose vaccination
- No catchup HBV vaccination programme
- No vaccination of high-risk groups except for HCWs

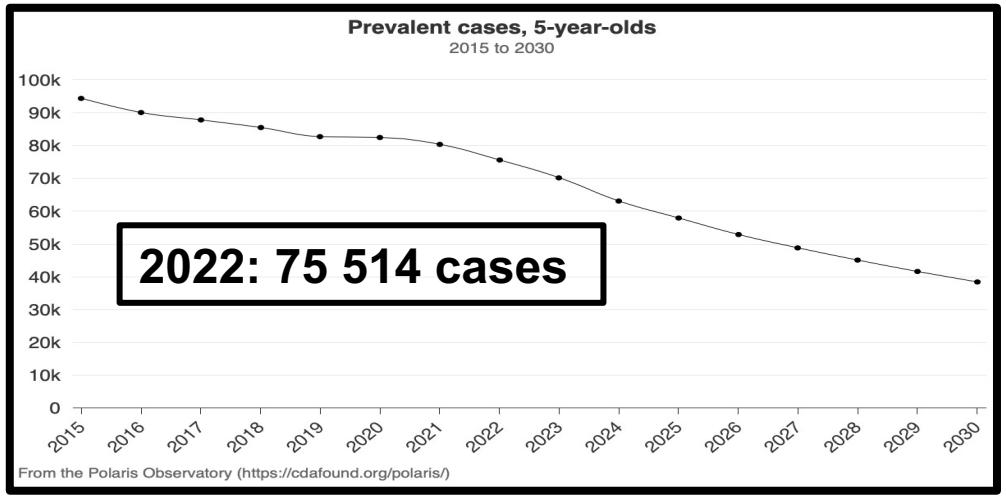
Impact of Universal Vaccination

1990: HBsAg 9% and in 2022: 5%

https://knowledgehub.health.gov.za/elibrary/national-guidelines-management-viral-hepatitis

South Africa: Prevention of HBV MTCT and Early Childhood Acquisition

Birth Dose	3+ Dose	HBIG	Tx Pregnant Women
-	86%	<1%	5%



HBsAg positive children <5-yrs

- **2022: 1.1%**

TARGETS

- WHO Africa 2020 target: <2%
- WHO 2020 target: <1.0%

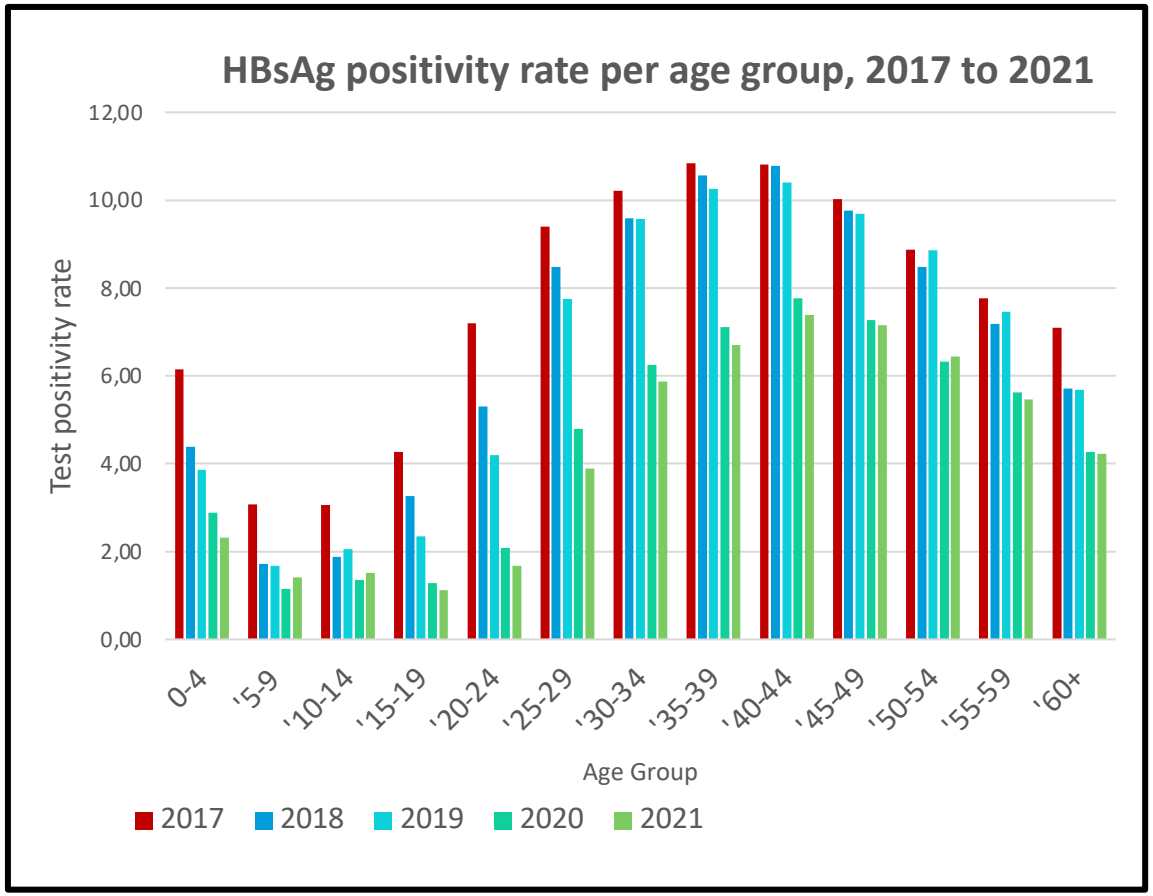
2022 modelled data

- **6 652 new chronic vertical infections**
- **6 063 new chronic horizontal infections**

Polaris Observatory: https://cdafound.org/polaris/

South Africa: Hepatitis B: Different Age Groups

	HBsAg Positivity rate				
Age Group	2017	2018	2019	2020	2021
0-4	6.15	4.39	3.86	2.88	2.32
5-9	3.08	1.71	1.67	1.15	1.42
10-14	3.06	1.89	2.06	1.36	1.51
15-19	4.26	3.26	2.35	1.29	1.12
20-24	7.20	5.30	4.20	2.08	1.68
25-29	9.39	8.48	7.75	4.80	3.88
30-34	10.21	9.59	9.57	6.25	5.87
35-39	10.84	10.56	10.25	7.10	6.71
40-44	10.81	10.78	10.41	7.77	7.39
45-49	10.03	9.76	9.69	7.28	7.16
50-54	8.87	8.47	8.86	6.32	6.45
55-59	7.77	7.19	7.46	5.63	5.46
60+	7.10	5.71	5.68	4.27	4.23
Total	9.28	8.47	8.03	5.24	4.43



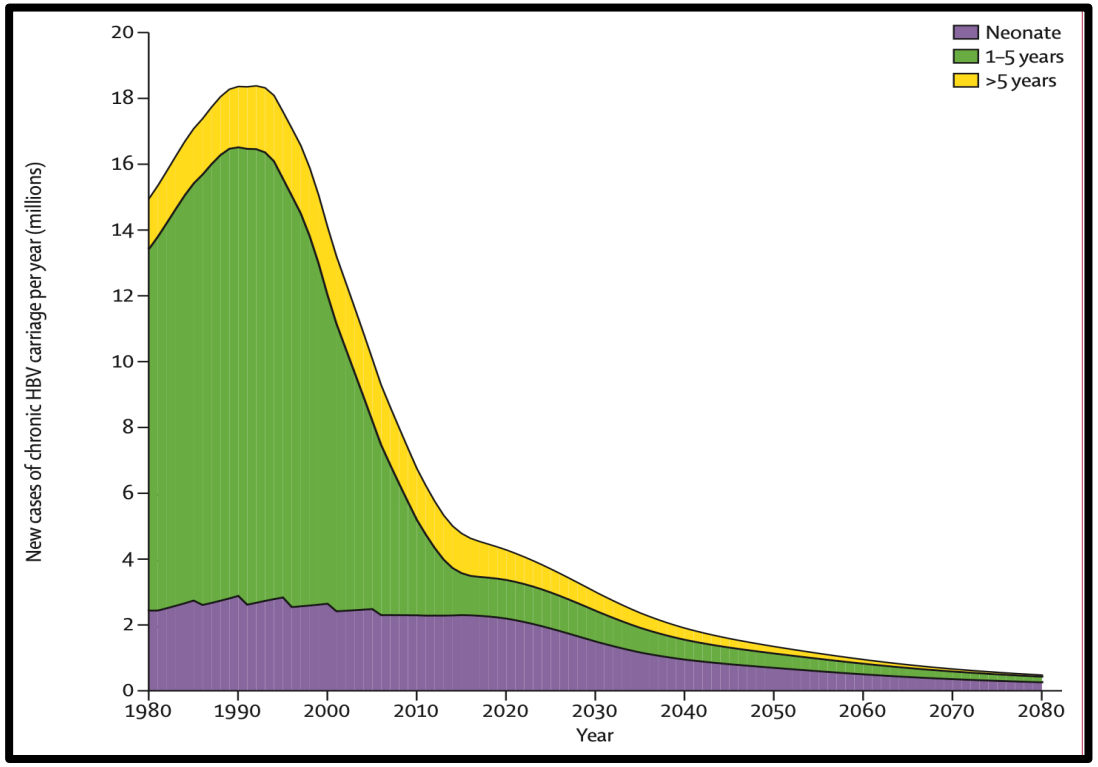
1990: HBsAg 9% and in 2022: 5%

Data obtained from Corporate Data Warehouse, NHLS, that is a repository of all results of tests conducted at NHLS labs, countrywide

Prevention of HBV Mother-to-child Transmission: Chronic HBV Infections

Cornerstone of strategies for global elimination of hepatitis B

- Protects the neonate
- Opportunity to optimise liver health for mother, her partner, siblings & other children



Universal HBV Infant vaccination

- **Highly effective at reducing chronic HBV carriage in children**
- Does not directly affect risk of acquisition in neonate
- Proportion of new chronic cases arising through MTCT is set to increase from 16% in 1990 to 50% in 2030

Lancet Infect Dis 2016; 16: 1399–408

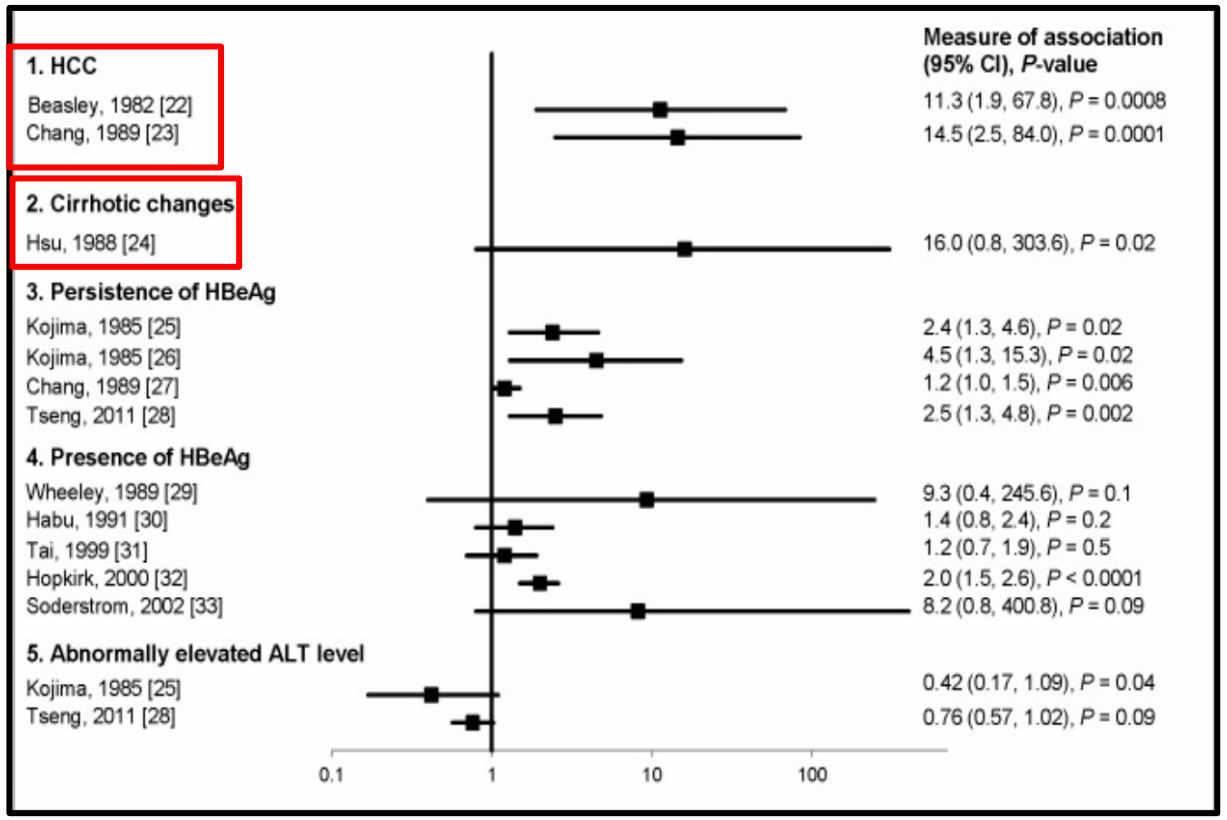
Prevention of Perinatal HBV Infection

Systematic review:

Earlier age at infection associated with:

- Increasing probability of chronic HBV infection
- Worse liver outcomes

Shimakawa et al;
PlosOne 2013; 8(7): e69430



Longitudinal study in The Gambia: HBV MTCT was a risk factor for:

- Persistent high viral replication
- Significant fibrosis
- HCC

Shimakawa et al; Gut 2016;65(12):2007

Prevention of MTCT of HBV

WHO, EASL, AASLD and APASL Recommendations: Functional funded infrastructure

- **Antenatal HBsAg screening: Requires point-of-care screening**
  - Identify highly viraemic pregnant women for TDF prophylaxis
    - HBV DNA >200 000 IU/ml or HBeAg positive
  - Vaccinate HBsAg negative pregnant women
  - Screen partners, siblings and children of HBsAg positive women
- **Tenofovir from 28 weeks pregnancy: HBV DNA >200 000 IU/ml until at least delivery**
- **Birth dose HBV vaccine within 24 hours of delivery ± HBIG**
  - Increased risk of HBV transmission if HB-BD given 7 days after delivery vs 1-3 days post delivery: Odds Ratio 8.6
- **Universal HBV vaccination as part of EPI**
  - Risk of chronic infection 3.74x higher (95%CI 0.97 - 14.39): Interval bet 1st & 2nd doses >10 wks
  - Incomplete vaccination is an important predictor for HCC
    - HR 2.52 after correction for maternal HBsAg status

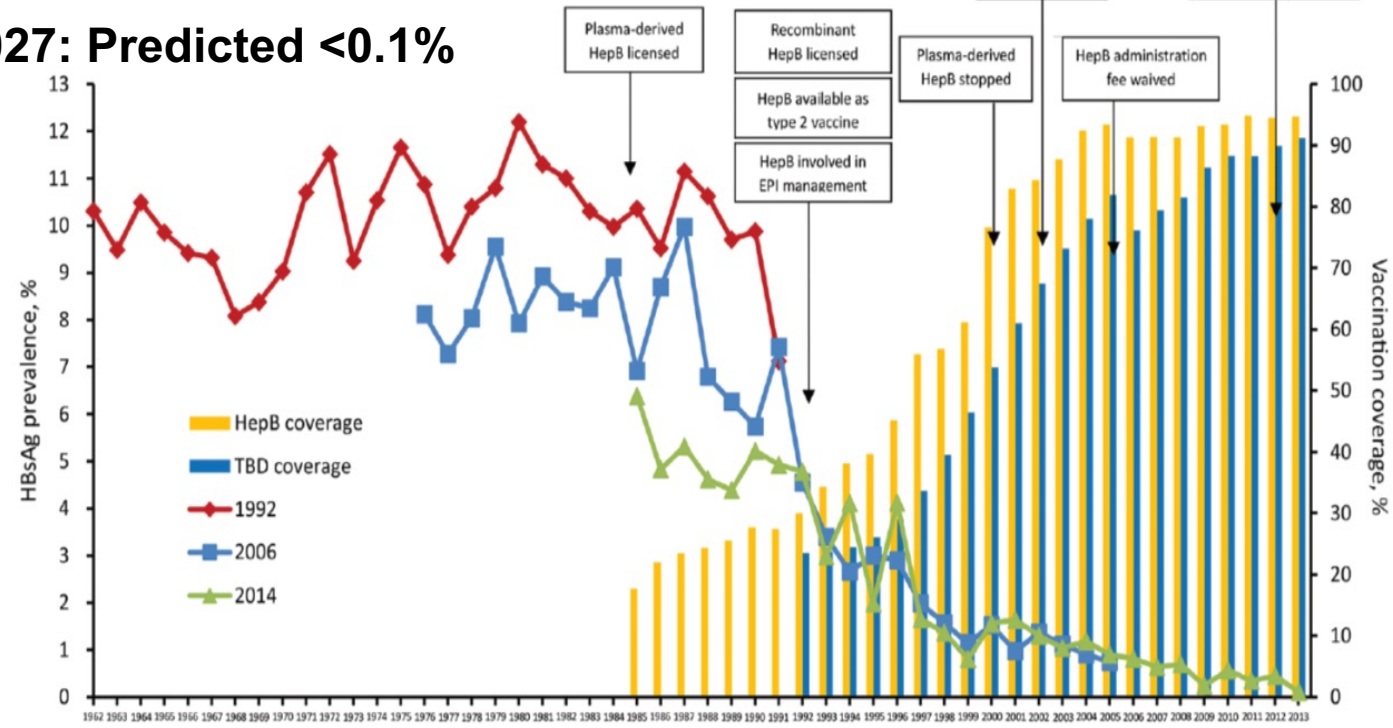
J Hepatol 2017;67:370; Hepatol 2018;67(4):1560; Hepatol Int 2021; 5(5):1031; Weekly Epidemiol Rec 2017; 92(27):369; Hepatol 2014;60:125

CHINA in partnership with GAVI: Control of HBV infection: 1962 - 2013 Birth cohorts

- Free birth dose vaccine
- Upscaling of full vaccine schedule, improved antenatal HBsAg screening
- Utilising village lay healthcare workers

HBsAg seroprevalence now 0.96% in children <5yrs (9.67% in 1992)

2027: Predicted <0.1%



Vaccine 2013;31(Suppl 9):J29 and J36

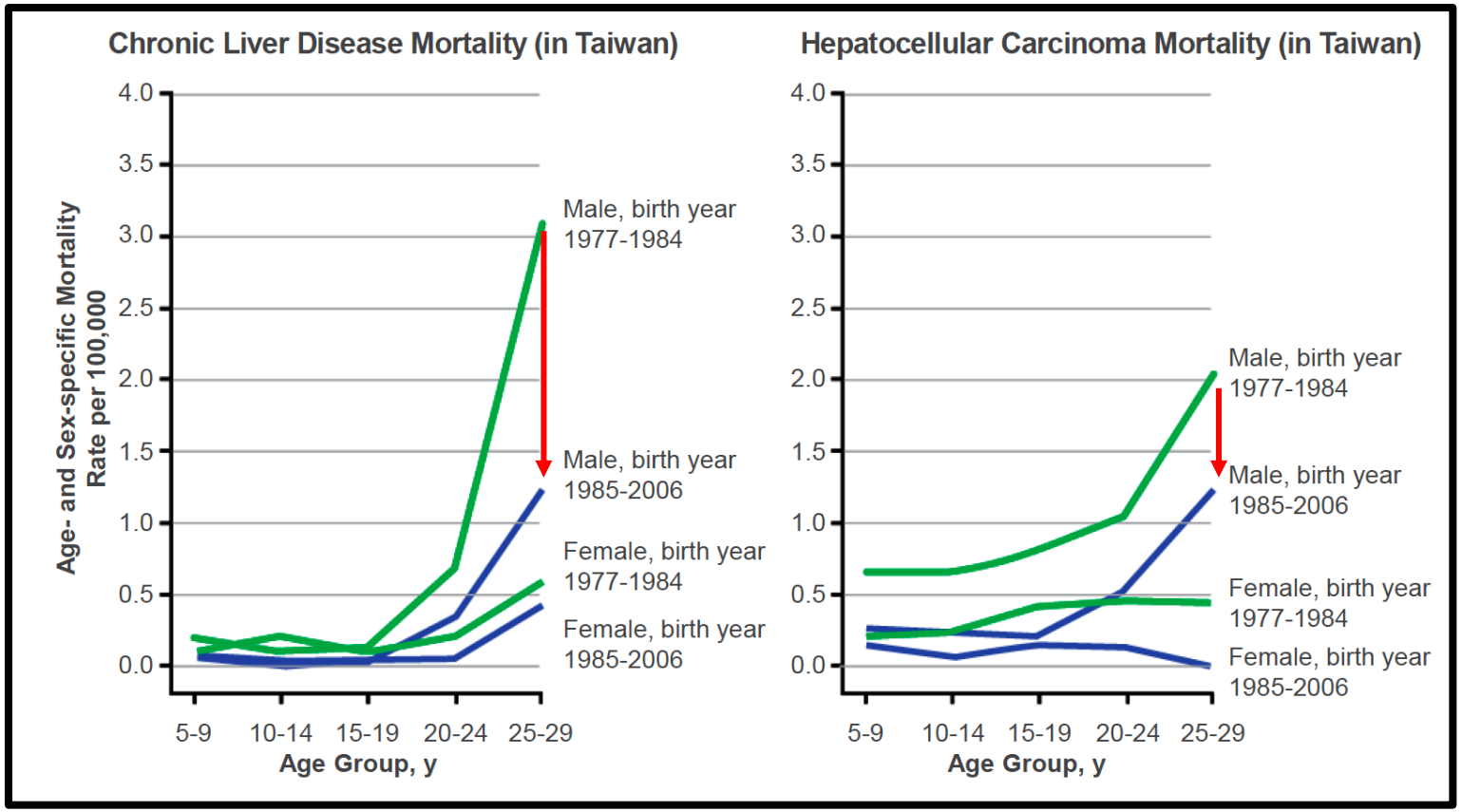
Taiwan: Impact of HBV immunisation programme on chronic liver disease and HCC

Universal vaccination in 1984 together with

- Improved antenatal HBsAg screening
- HBV Birth dose vaccination
- Catch-up vaccination programme

1984: HBsAg: 10%

2014: HBsAg: 0.5% in >30 yr-olds



- **Chronic liver disease and HCC mortality decreased by >90%**
- **HCC incidence decreased by >80%**

JAMA 1987;257:2597;JAMA 1988;260:2231; JAMA 1996;276:906; Ann Int Med 2001;135:796; JAMA 2013;10:974; Gastroenterology 2016;151:472

Prevention of HBV MTCT: Challenges in Africa

Screening and risk stratification: HBV DNA >200,000 IU/ml

WHO Africa

- 12.45% (5.81-24.68) HBsAg positive pregnant women: HBV DNA ≥200,000 IU/mL
- 15.09% (9.29-23.58) HBsAg positive pregnant women are HBeAg positive

HBeAg is a poor proxy for HBV viral load >200,000 IU/ml

- **West Africa: HBV GT E**, HBeAg negative with high viral load
- **Southern Africa: Subgenotype A1 loses HBeAg early**
  - 12-16% HBeAg-negative women have HBV DNA ≥5 $\log_{10}$ IU/mL
- **Ideally need HBsAg point of-care test with reflex POC HBV DNA quantification**
  - Risk stratify and for long-term follow-up of PLWHB

Lancet Inf Dis 2021;21:85; Lancet Inf Dis 2021;21:70; World J Hepatol 2021;13:1875; Hepatol Comm 2020;4:1781; JHEP Rep 2023;5(8):100777

Efficacy of Prevention of HBV MTCT Strategies

Modelling study: 110 countries across all WHO regions: Assess impact & cost-effectiveness of universal TDF prophylaxis in all HBsAg positive pregnant women irrespective of HBV DNA level in settings without access to HBV DNA measurement

Scale up of HepB-BD vaccination had greatest incremental effect across all WHO regions

- **Could avert approximately 6·0 M** (95% UI 5·6 –6·5 M) **new neonatal HBV infections** and 2 969 DALYs (95% UI 2605–3371) from **2024 to 2030**
- Highest impact of scaling up HepB-BD will be in WHO AFRO region

Addition of TDF prophylaxis: HBsAg-positive pregnant women: HBV DNA ≥200 000 IU/mL

- **Could avert an extra 1·1 M** (95% UI 1·0 –1·2) **new neonatal infections by 2030** & approx. 3·2 M (3·0 –3·4) new neonatal infections & about 8·8 M (7·8 –9·7) DALYs by 2100
- Highest impact in Africa: Approx 1·9 M (95% UI 1·8 –2·1) new neonatal infections averted

Lancet Gastroenterol Hepatol 2023; 8: 635

Efficacy of Prevention of HBV MTCT Strategies

Modelling study: 110 countries across all WHO regions

Universal TDF prophylaxis to all HBsAg positive pregnant women

- **Approx 4·9 M (95% UI 4·7 –5·1) neonatal cases averted** & 13·5 M (12·3–14·6) DALYs averted relative to HepB-BD strategy in 110 countries modelled to 2100
- **75·7 M** (95% UI 72·1–79·0) vs 13·2 M (12·4 –14·1) **pregnant women potentially require TDF**
- **Relative cost-effectiveness** of PAP-universal and PAP-VL (each compared with HepB-BD) depended on **relative costs of antiviral drug used** and **cost of providing second diagnostic test**
- **Sustainable access to TDF**

Lancet Gastroenterol Hepatol 2023; 8: 635

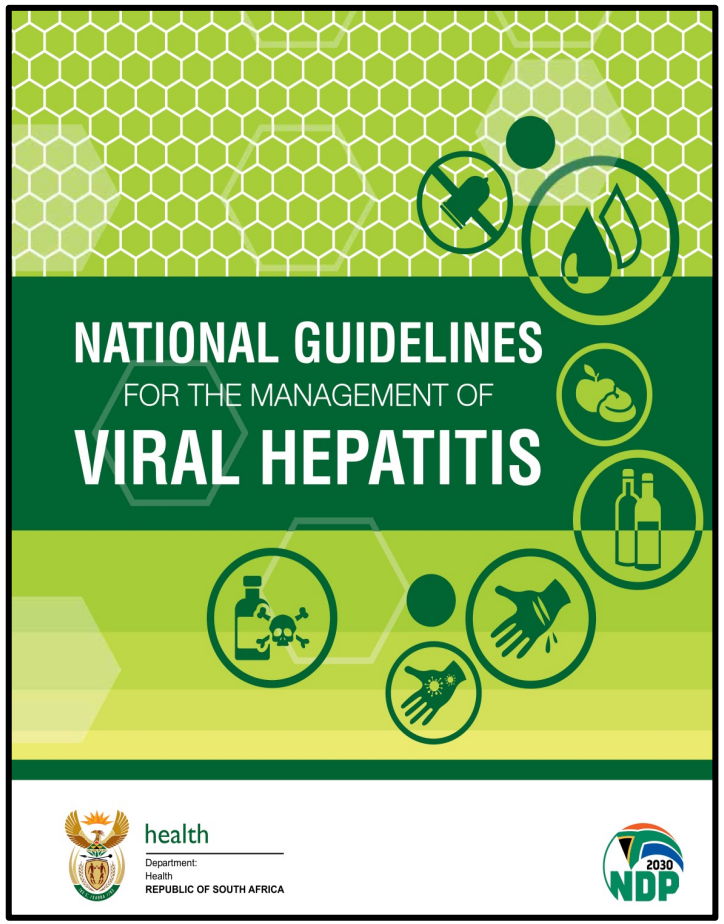
South Africa: Prevention of MTCT of HBV

April 2023: NDOH implementing the recommendations of the National Guidelines

- Antenatal HBsAg screening
- Tenofovir for HBsAg positive pregnant women
- HBV vaccination for HBsAg negative women
- HBV Birth dose vaccination to neonates of HBsAg positive mothers

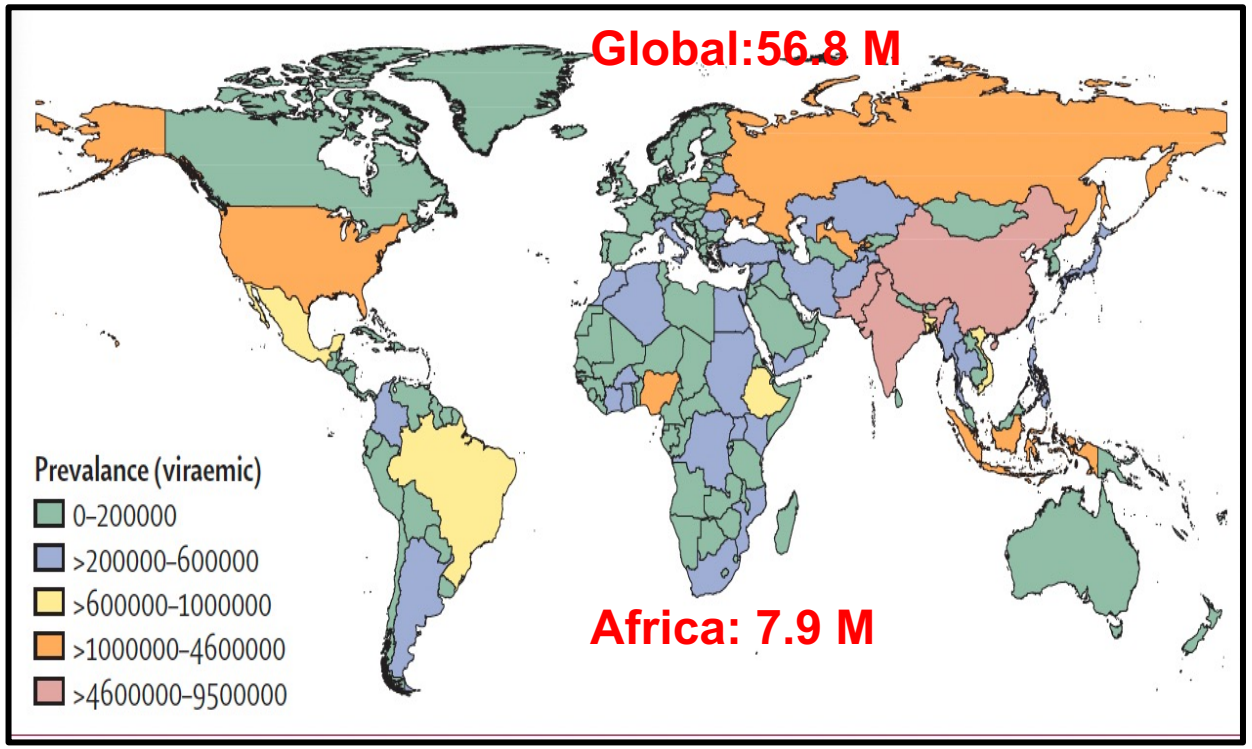
Indicators

- Number of pregnant women screened for HBsAg
- HBsAg positive rate in pregnant women
- Number of pregnant women HBV vaccinated



https://knowledgehub.health.gov.za/elibrary/national-guidelines-management-viral-hepatitis

Hepatitis C in Africa



Polaris Observatory: 2022: Modelling study: 110 countries or territories

WHO Africa 2022: 7.9 M estimated to be HCV-infected

- **No diagnosed:** 755 311 (9.6%)
- **No Treated:** 36 322 (4.8%)

HCV curable

- 8–12-week pangenotypic DAA regimen

Lancet Gastroenterol Hepatol 2022; 7: 396

South Africa: Hepatitis C

2022 Total Population: 59 893 885

2022 Adult Population: 39 746 725

265 000 (95% UI 205-519) HCV-infected and HCV Seroprevalence: 0.4% (0.3-0.9)

- **Pangenotypic: GT 1-5** **Bimodal distribution: 20 - 39 years and 50 - 70 years**

HCV Infections (2020)†
265,000
<1%

Diagnosed
22%

Annual Treated
<1%

Annual Deaths
2,177

Deaths per day
6

No routine HCV screening during pregnancy: Reserved for high risk: PWID/PWUD

- 46% anti-HCV positive, 75-80% are viraemic

Polaris Observatory: https://cdafound.org/polaris/; Lancet Gastro Hepatology 2022;7:396-415
J Viral Hepat 2016; 23: 881; MMWR Morb Mortal Wkly Rep 2020;69:399; BMC Infectious Diseases 2020;20:655

Hepatitis C: Mother-to-child Transmission

Steady rise in HCV RNA levels during pregnancy followed by slight or significant drop (>3 to 4 $\log_{10}$) in postpartum period

Hepatitis C MTCT occurs at an overall rate of 5% to 15%

- HCV mono-infection: 5%
- HIV/HCV coinfection increases risk: 11-15%
- No specific risk factor except for HIV/HCV co-infection predicts transmission

Risk of progression to chronic infection: 3% to 5%

BJOG. 2000;107(12):1503; Open Forum Infect Dis. 2015;2(2):ofv089; Am J Obstet Gynecol 2017;217(5):B2; J Med Virol. 2009;81(6):1024; J Infect Dis. 2005;192(11):1880; J Pediatric Infect Dis Soc. 2013;2(2):126

Hepatitis C: Mother-to-child Transmission

Prevention of HCV MTCT

No specific intervention has been demonstrated to reduce HCV transmission

- Except suppression of HIV replication in women with HIV/HCV coinfection

Advisable to avoid invasive procedures

- Preference for amniocentesis over chorionic villus sampling for invasive prenatal diagnostic testing
- Foetal scalp monitors during labour, forceps delivery, episiotomies

Breastfeeding not contraindicated

BJOG. 2000;107(12):1503; Open Forum Infect Dis. 2015;2(2):ofv089; Am J Obstet Gynecol 2017;217(5):B2; J Med Virol. 2009;81(6):1024; J Infect Dis. 2005;192(11):1880; J Pediatric Infect Dis Soc. 2013;2(2):126

Treatment of Hepatitis C in Pregnancy

No large-scale clinical trials evaluating the safety of DAAs in pregnancy

- Women of reproductive age with HCV should be counselled about the benefit of antiviral treatment prior to pregnancy

Small study evaluating pharmacokinetics of ledipasvir/sofosbuvir in pregnancy

- 100% SVR12 and no safety concerns

International case series: 15 pregnant women treated with ledipasvir/sofosbuvir

- 100% SVR12 and no early safety concerns in the women or their infants

Currently, no available data on use of pangenotypic regimens during pregnancy

Treatment can be considered during pregnancy on an individual basis after a patient-physician discussion about the potential risks and benefits

High index of suspicion for intrahepatic cholestasis of pregnancy: Pruritus

Hepatol Int. 2018;12(Suppl. 2):S292; Lancet Microbe [Internet] 2020;1(5):e200

Prevention of Mother-to-child-Transmission of Viral Hepatitis

Hepatitis B is vaccine preventable

- POC HBsAg screening of pregnant
- Risk stratification of HBsAg positive pregnant women: POC HBV DNA quantification
  - HBV DNA >200 000 IU/ml: Tenofovir from 2nd trimester
  - No HBV DNA quantification: Universal TDF prophylaxis
- Timeous HBV Birth dose vaccination
- Complete Universal HBV vaccination
- Opportunity to break cycles of infection: HBsAg screening of partners, siblings and children

Hepatitis C

- Anti-HCV screening of high-risk women of child-bearing age
  - Curative DAA therapy before pregnancy
- NO vaccine, NO Immunoglobulin and DAAs are contraindicated in pregnancy
- Avoid invasive monitoring during pregnancy