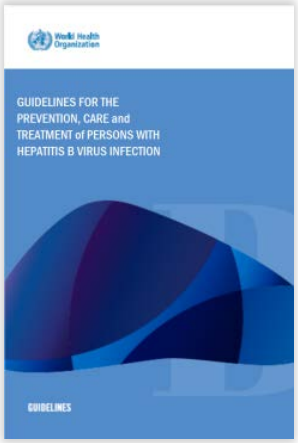
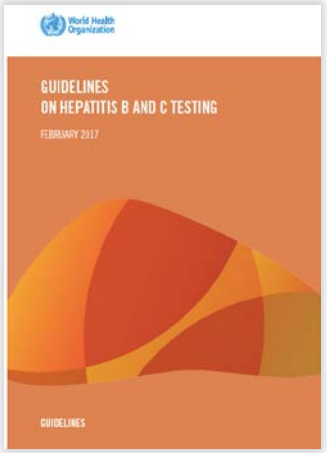
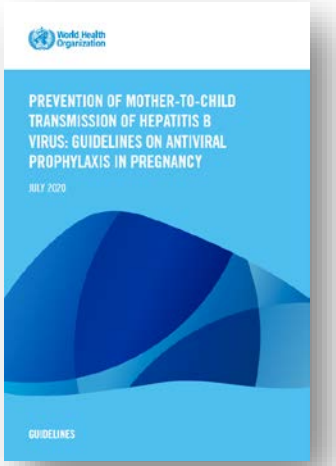
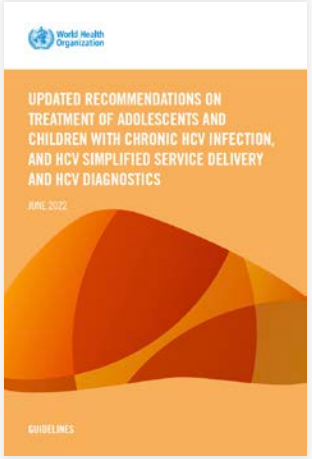
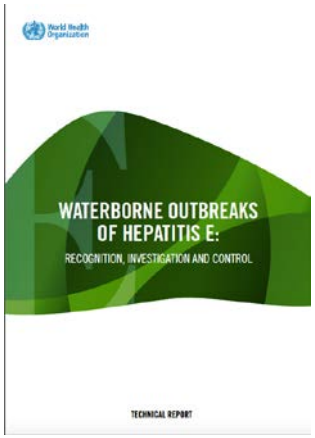
Update on viral hepatitis B and C – diagnostics and treatment



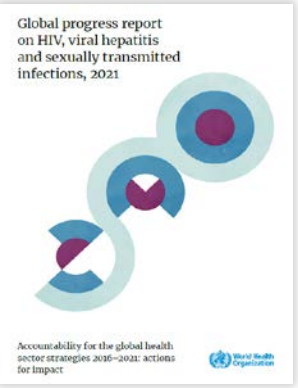






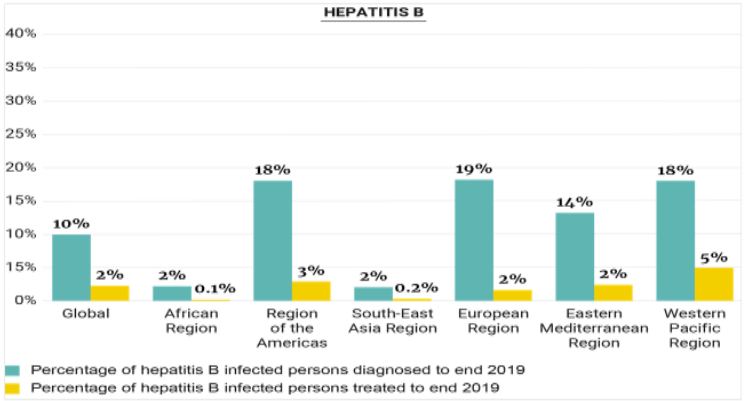


Philippa Easterbrook, Global Hepatitis Programme,
Global HIV, Hepatitis, STI Programmes
WHO HQ, Geneva



Cascade of care - major gaps in testing and treatment uptake on path towards public health elimination *(2019 Global Progress Report)*

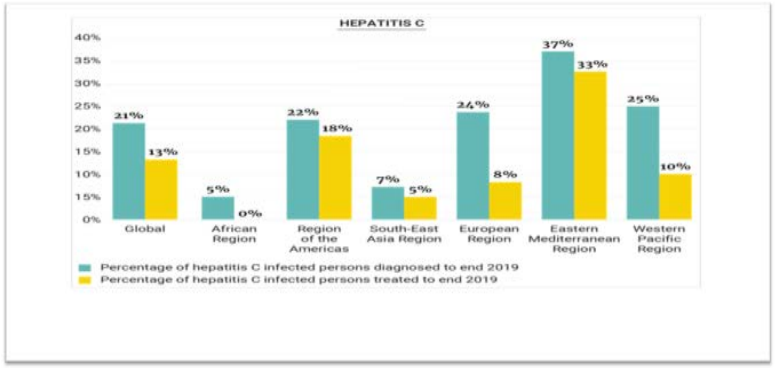
10% of estimated 296 million people with chronic HBV infection were diagnosed in 2019 with variation by regions



Data shows major gaps in path towards universal health access and public health elimination

Progress report on HIV, viral hepatitis and sexually transmitted infections 2021: accountability for the global health sector strategies, 2016–2021: actions for impact. Geneva: World Health Organization; 2021

21% of estimated 58 million people with chronic HCV infection were diagnosed in 2019 with variation by regions

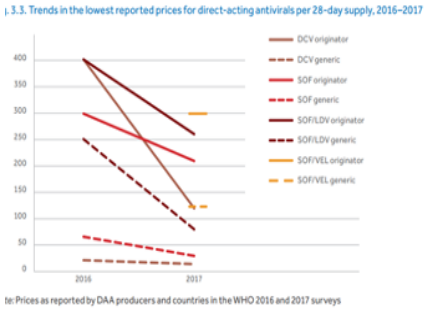


Data shows major gaps in path towards universal health access and public health elimination

Progress report on HIV, viral hepatitis and sexually transmitted infections 2021: accountability for the global health sector strategies, 2016–2021: actions for impact. Geneva: World Health Organization; 2021

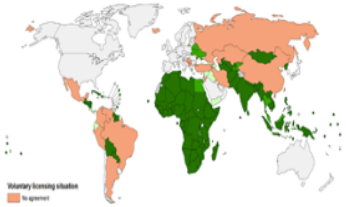
Massive Price reductions for DAAs (and now diagnostics)

ntensifying competition to reduce prices

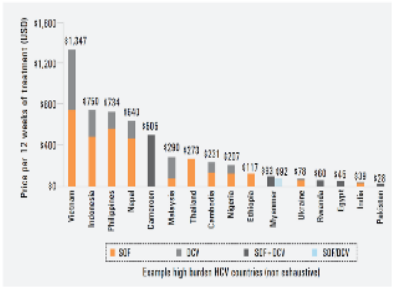


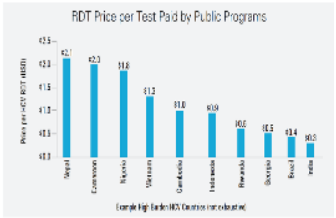
62% of people with HCV live in countries which have access to generic DAAs for as low as US$50-$150 (in green)

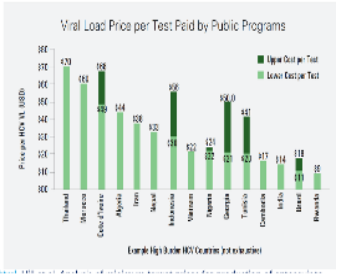
- Generic competition and local production
- Overcoming patent related barriers
  - Voluntary licensing and Patent pools (MPP)
- Price transparency and price negotiation
- Registration of DAA's in countries



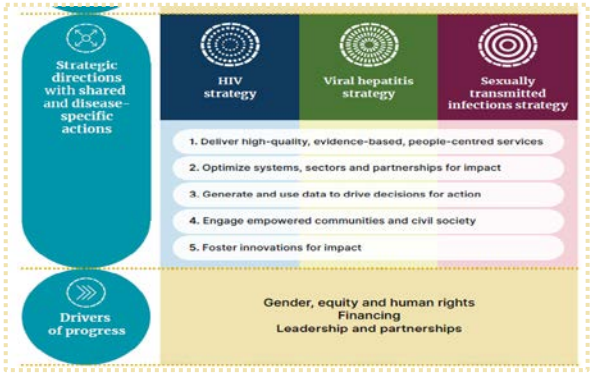
In reality, the price of a 3-month course of generic DAA and also viral load prices varies greatly by location







May 2023: CHAI announces generic manafacturers (Viatris and Hetero) ceiling prices of sof/dac of **$60 per patient course of HCV treatment**; and for Tenofovir (TDF) **$2.4 for 30 tablets ($30 per year).**



The VISION: Reaching elimination of viral hepatitis B & C by 2030 by implementing the 5 Strategic Directions of the HIV, VH, STI GHSS (2022-2030)

Key shifts required to end the AIDS by 2030

- Renew the **focus on primary prevention including** through primary health care
- Address the **major causes of HIV related deaths**, including tuberculosis, cryptococcal meningitis, and severe bacterial infections
- **Close gaps in service access for children** and adolescents
- Leveraging **antiretrovirals for prevention**
- Address the barriers faced by **key populations**
- Apply differentiated approaches to service delivery to meet the specific needs of populations and settings
- **Leverage innovations**, including new treatment regimens, new prevention approaches, support vaccine and effective cure agendas, supported by research that includes the needs of resource-limited settings

Key Shifts from the GHSS – Areas for prioritization in 2023

Key shifts required to end the epidemic of viral hepatitis by 2030

- **Greater public awareness** of the importance of viral hepatitis B and C prevention, testing and treatment
- **Strengthened community and civil society engagement**
- Scale-up of **universal access to hepatitis B birth dose vaccine** and improved services for prevention of vertical transmission
- Continuous investment in primary prevention
- **Greatly increased access to hepatitis B and C virus testing and treatment**
- **Simplified and decentralized service as well as integrated service delivery**
- Development of curative drug regimens for hepatitis B virus
- **Increased visibility and financial resources allocated**

Key shifts required to end STIs as a public health threat by 2030

- Increased **visibility and partner engagement** at all levels
- Vastly scale up **primary prevention**
- Increase **integration** of sexually transmitted infection services with **primary health care**, sexual and reproductive health, and HIV services for access to care
- Increase accessibility of **people-centred services** through public and private sectors
- **Close gaps in international and national funding**
- Facilitate adoption of **point-of-care diagnostics and other new cost-effective technologies**
- Invest in and facilitate research

2022 updated WHO hepatitis C guidelines:

Expanded treatment to children and adolescents, simplified diagnostic pathways and service delivery

Continued Evolution of WHO HCV Guidelines Towards simplified Treatments + Simplified HCV Service Delivery

Topic	2014	2016	2018	2022
Who to treat?			Treat All	Treat All
Genotyping	Yes	Yes	No	No
Regimens	PEG-IFN+RBV	DAAs preferred	Pan-genotypic DAAs	Pan-genotypic DAAs
	8 options - PEGIFN+RBV - SOF+RBV - SIMP or TELAP or BOCEP /PEGIFN+RBV -	6 options DAAs preferred by GT or cirrhosis	3 options SOF/DAC SOF/VEL G/P PEGIFN phase out	3 options SOF/DAC SOF/VEL G/P Paeds formulations
Age group	Adults ≥18yrs	Adults≥ 18yrs	Adults ≥18yrs and adolescents ≥12 yrs	Adults, adolescents and children≥3 yrs
Service Delivery			8 Good Practice Principles for Simplified Service	Decentralization Integration Task-shifting
HCV NAT diagnosis		Laboratory-based NAT	Core Ag	-HCV Self-testing (2021) -POC NAT assay -Reflex NAT testing (lab or clinic-based)

SIMPLER TREATMENTS

TREATMENT OF CHILDREN AND ADOLESCENTS

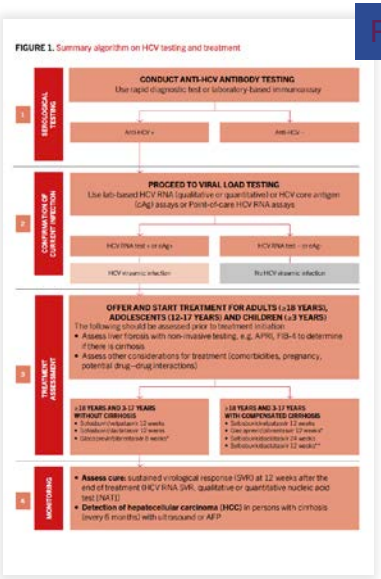
SIMPLIFIED SERVICE DELIVERY

DIAGNOSTIC INNOVATIONS

NEW

CHAPTER 6. SIMPLIFIED SERVICE DELIVERY FOR A PUBLIC HEALTH APPROACH TO TESTING, CARE AND TREATMENT FOR HCV INFECTION

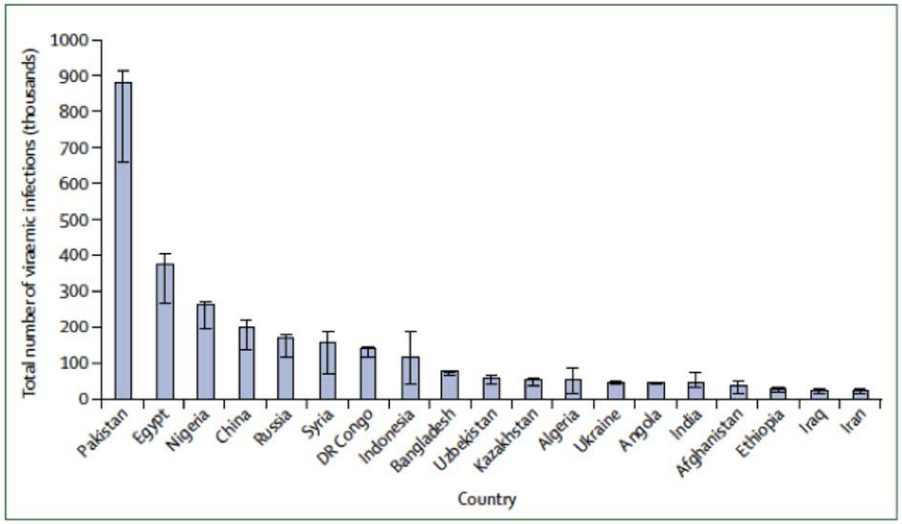
Five key steps



sofosbuvir/daclatasvir: SOF/DAC
sofosbuvir/velpatasvir: SOF/VEL
glecaprevir/pibrentesvir: G/P

Recommendations to promote treatment for HCV infected adolescents and children

- Estimated 3.26 million children and adolescents living with HCV
- 20 countries account for 80% of cases – esp Pakistan, China, India, Nigeria and Egypt



Reconciling DAA regimens across adults, adolescents and children

Age groups	Recommended pangenotypic DAA regimens			Non-pangenotypic DAA regimen (in settings with minimal GT3 infection)[2]
	SOF/DCV[1]	SOF/VEL[2]	G/P	SOF/LED
Adults (18 years and above)	12 weeks	12 weeks	8 weeks	12 weeks
Adolescents (12–17 years)	12 weeks	12 weeks	8 weeks	12 weeks
Older children (6–11 years)	12 weeks	12 weeks	8 weeks	12 weeks
Younger children (3–5 years)	12 weeks	12 weeks	8 weeks	12 weeks

**** Inclusion of Case-finding, testing, care and treatment of children and adolescents in national plans and guidelines**




Evolution in Hepatitis C testing and diagnostic recommendations

Topic	Recommendation in 2017 testing recommendation
Who to test?	• **Focused testing** for most affected populations*, those with a clinical suspicion of chronic viral hepatitis, family members/children, and sexual partners (HBV), healthcare workers. • **General population testing:** In settings with ≥2% or ≥5% (intermediate/high) HBsAg or HCV Ab prevalence.
How to test?	• A **single** serological assay (**EIA or RDT**) that meets minimum performance standards with prompt NAT testing + linkage to care
Confirmation of HCV viraemia	• **Lab-based Nucleic acid testing (NAT) (quantitative or qualitative RNA)** or **core HCV antigen assay,** with comparable clinical sensitivity
Promoting uptake and linkage	• **Use of DBS specimens for virology ± serology** • **On-site or immediate RDT testing + same day results** • Trained peer and lay health workers • Clinician reminders to prompt provider initiated, facility-based testing • Testing as part of integrated services at a single facility

2021 and 2022 Updates

How to test - serologic
- 2021 HCV self-testing guideline

Use of POC HCV RNA NAT
- For detection of viraemia
- For test of cure

Linkage to care
- Dried blood spots (HCV serology and virology) manafacturers protocols
- **Reflex viral load**

https://www.who.int/publications/i/item/9789241549981

2022 recommendations
Decentralization, Integration and Task-shifting
Moving treatment and care out of speciality clinics

Decentralization:
We recommend delivery of HCV **testing** and **treatment** at peripheral health or community-based facilities, and ideally at the same site, to increase access to diagnosis, care and treatment.
These **facilities** may include **primary care, harm reduction sites, prisons and HIV/ART clinics as well as community-based organizations** and outreach services.

Integration:
We recommend integration of HCV **testing** and **treatment** with existing care services at peripheral health facilities.
These **services** may include **primary care, harm reduction** (needle and syringe programme (NSP)/opioid agonist maintenance therapy (OAMT) sites), **prison and HIV/ART services**.

Strong recommendation/ moderate certainty of evidence (PWID/prisoner) low (general population, PLHIV)

Task-sharing: We recommend delivery of HCV **testing, care and treatment** by trained **non-specialist doctors and nurses** to expand access to diagnosis, care and treatment.

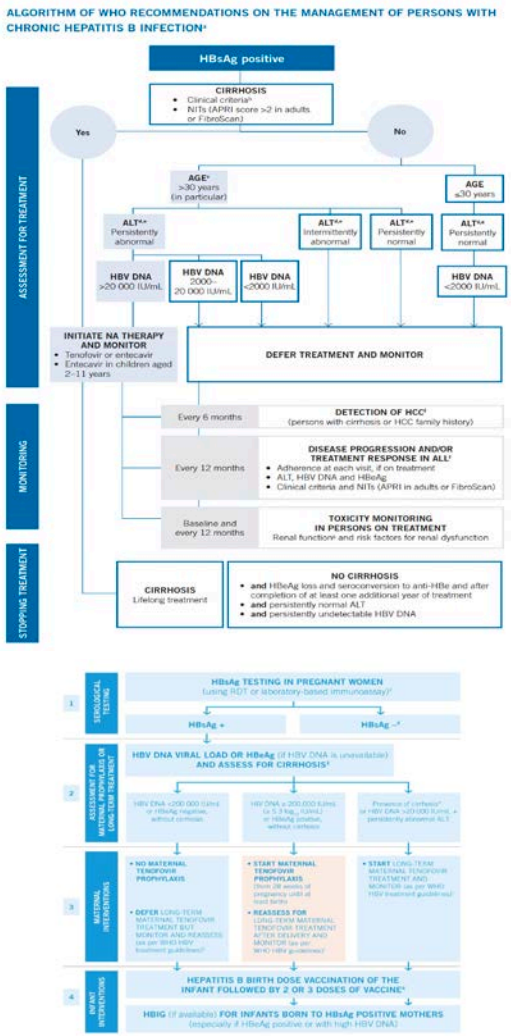
Strong recommendation/ moderate certainty of evidence

https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/hcv-guidelines-2022-presentations_25-7-2022.pdf?sfvrsn=733703ef_3

New directions for WHO hepatitis B guidelines:

Expanded treatment criteria, simplified diagnostic pathways and service delivery

HBV Guideline Recommendations (2015) and PMTCT update (2020)



TOPIC	RECOMMENDATION
Staging/ non-invasive test (NIT)	▪ APRI preferred NIT to assess for the presence of cirrhosis
Who to treat *HBV DNA not available:* Persistently abnormal ALT levels alone, regardless of HBeAg status	▪ Decompensated cirrhosis or cirrhosis (clinical criteria or APRI score >2), regardless of ALT levels, HBeAg, or HBV DNA. ▪ No cirrhosis but persistently abnormal ALT levels +/- ongoing HBV replication, (HBV DNA >20,000 IU/mL *or* HBeAg +ve).
First line treatment	▪ Drugs with a high barrier to resistance (TAF vs. TDF or ETV). ▪ ETV in children aged 2-11 years.
Treatment failure	▪ Switch to TDF if evidence of resistance to 3TC, ETV, ADF, TBV.
Treatment discontinuation	▪ Never discontinue in persons with cirrhosis. ▪ If no cirrhosis, discontinuation on case-by-case basis (persistent HBeAg and/or HBsAg loss or undetectable HBV DNA)
Monitoring (treatment response/toxicity)	▪ *On or pre-treatment:* ALT + HBV DNA (HBsAg, HBeAg + APRI pre-treatment) annually. More frequent monitoring with cirrhosis. ▪ Assessment of baseline renal function prior to treatment initiation.
Monitoring for HCC	▪ Ultrasound + AFP every 6 months in persons with cirrhosis and/or family history of HCC.
PMTCT antiviral prophylaxis (2020)	▪ TDF prophylaxis in those with HBV DNA >200,000 IU/mL from 3rd trimester or HBeAg positive (if HBV DNA not available)

Why the need for updated WHO HBV guidelines?

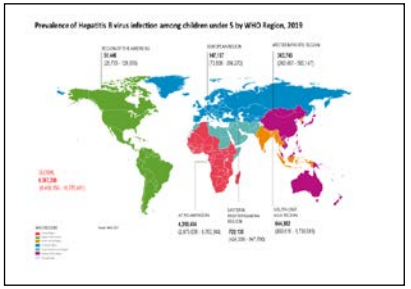
Addressing regional differences, especially for sub-Saharan Africa

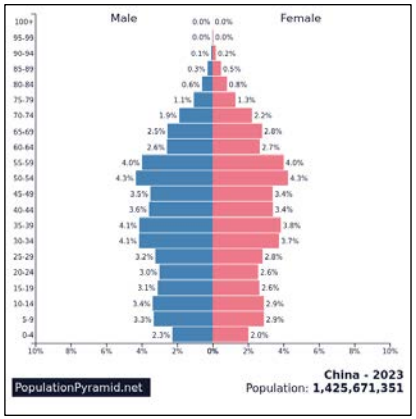
In sub-Saharan Africa

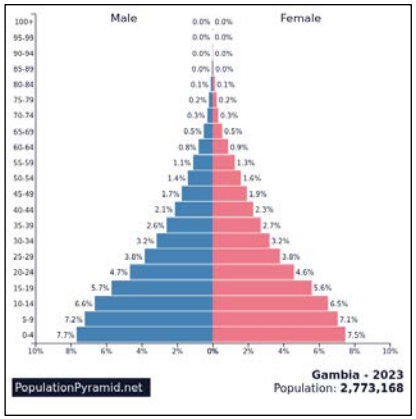
- **Significant rate of ongoing new chronic infections, mainly due to vertical mother-to child transmission (MTCT)**
  - Low uptake of HBV birth dose vaccination (12/47 countries and administered <24 hours in only 10%).
- **Regional Demographics and epidemiology**:
  - High birth rate and high proportion of population <20 years
  - 25% of all HBsAg+ve in Africa are in those <20 years vs. few % in China
  - Liver cancers at younger age
  - 75% of HBsAg+ve have HBV DNA <2000 IU/mL vs. 50% in Asia
- **Access challenges:** Limited access to HBV DNA
- **Limited data available from SSA** in 2015: Now HEPSANET

Major gaps in HBV vaccination interventions in regions of greatest prevalence

	HBsAg prevalence in children <5	Incident cases (2019)	Coverage of childhood vaccination 2019	Coverage of childhood vaccination 2021	HBBD 2021	Births attended by skilled HCW (2015-2021)
AFRO	2.3	4,301,454	71	74	17*	65%
EMRO	0.8	722,130	81	82	33	75%
EURO	0.3	147,137	82	91	43	98%
PAHO	0.07	51,446	88	80	59	96%
SEARO	0.38	644,862	89	82	51	87%
WPRO	0.3	363,745	93	90	78	98%
Global	0.9%	6,387,336	84	80	42%	83.6%







New Directions – Updating WHO hepatitis B guidelines 2023

Who to treat?

- Expanding criteria for treatment (lower APRI score >0.5 and HBV DNA threshold >2000 IU/ml)
- Expanding treatment for adolescents

First-line treatment

- TAF and dual therapy (TDF/XTC) vs. TDF

PMTCT

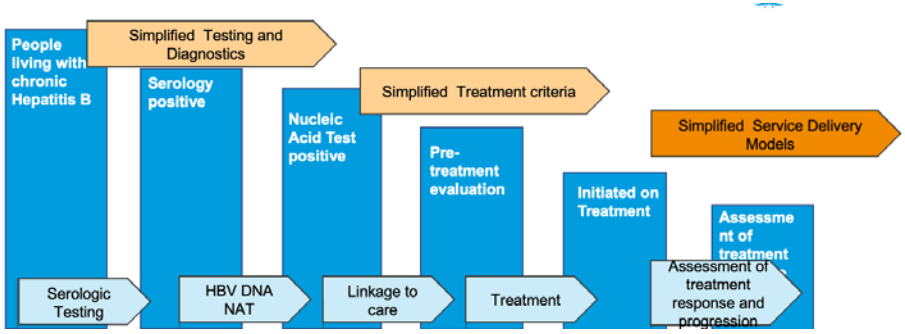
- Expanding criteria for use of antiviral prophylaxis to all HBsAg positive pregnant women

Simplifying diagnosis

- Use of PoC HBV DNA viral load and reflex viral load testing
- Delta virus testing – Who to test and how to test and reflex testing

Simplifying service delivery

- Good practice principles for promoting adherence and retention in care
- Decentralisation, integration and task-sharing



Key messages

Who to treat? Expanding treatment eligibility

– Recommendations now focus only on **who to treat**

– Inclusion of **<u>all</u>** age groups (adults and adolescents, including women of reproductive age (pregnant and non-pregnant)

  – Allows a common entry point for treatment, simplifying guidelines and implementation

  – Will mean many more pregnant and non-pregnant women will be on treatment for their own health.

– **Four <u>and/or</u> options for meeting treatment eligibility**

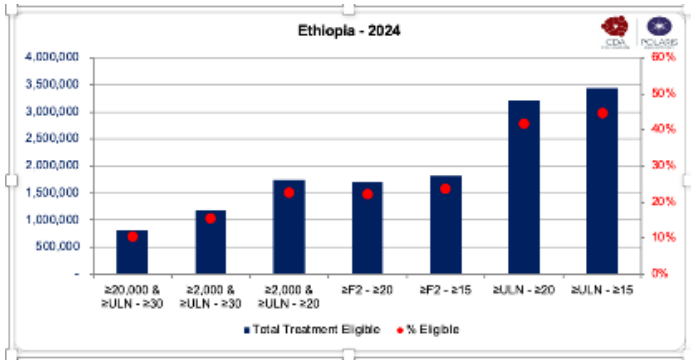
  – Will capture high proportion (≈ 50%) of all HBsAg.

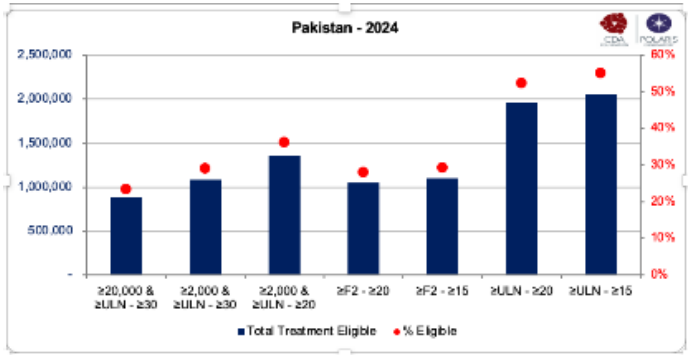
  – Applicable to all settings – where there is ready or limited or no access to HBV DNA assays.

  – Many HBsAg positive will meet criteria for treatment without need for HBV DNA assay.

  – Use of non-invasive tests (APRI/Fibroscan) (≥F2): greatest individuals benefit in reducing liver cancer, cirrhosis and liver related mortality

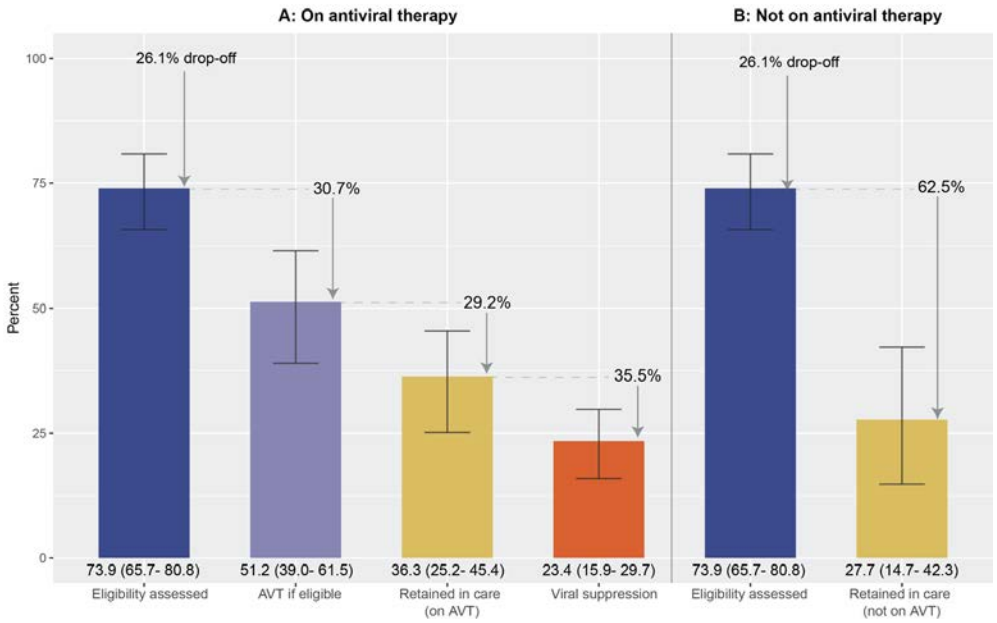
Proportion eligible according to different hypothetical treatment eligibility criteria



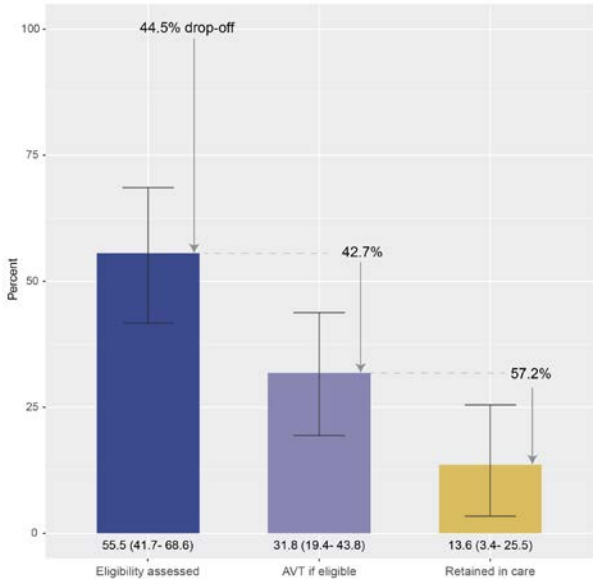


Cascade of care for general population shows low level of DNA suppression and retention in care, and importance of support for adherence and retention in care

Hospital/ specialist care models



Primary/mixed models



Implementation priorities for expansion of hepatitis B and C testing and treatment

1. Scale-up of testing and case-finding
2. Widespread education and awareness raising campaigns among community and healthcare workers
3. Promote wide access to training and capacity building of healthcare workers to provide adherence support and retention

TABLE 1. SUMMARY OF RECOMMENDATIONS ON TESTING FOR CHRONIC HEPATITIS B AND C VIRUS INFECTION

WHO TO TEST FOR CHRONIC HBV INFECTION	
Testing approach and population	**Recommendations***
General population testing	1. In settings with a ≥2% or ≥5%[1] HBsAg seroprevalence in the general population, it is recommended that all adults have routine access to and be offered HBsAg serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or health facility-based testing opportunities or programmes such as at antenatal clinics, HIV or TB clinics. *Conditional recommendation, low quality of evidence*
Routine testing in pregnant women	2. In settings with a ≥2% or ≥5%%[1] HBsAg seroprevalence in the general population, it is recommended that HBsAg serological testing be routinely offered to all pregnant women in antenatal clinics[2], with linkage to prevention, care and treatment services. Couples and partners in antenatal care settings should be offered HBV testing services. *Strong recommendation, low quality of evidence*
Focused testing in most affected populations	3. In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that HBsAg serological testing and linkage to care and treatment services be offered to the following individuals: • **Adults and adolescents from populations most affected by HBV infection[3]** (i.e. who are either part of a population with high HBV seroprevalence or who have a history of exposure and/or high-risk behaviours for HBV infection); • **Adults, adolescents and children with a clinical suspicion of chronic viral hepatitis[4]** (i.e. symptoms, signs, laboratory markers); • **Sexual partners, children and other family members, and close household contacts** of those with HBV infection[5]; • **Health-care workers:** in all settings, it is recommended that HBsAg serological testing be offered and hepatitis B vaccination given to all health-care workers who have not been vaccinated previously (*adapted from existing guidance on hepatitis B vaccination*[6]) *Strong recommendation, low quality of evidence*
Blood donors *Adapted from existing 2010 WHO guidance (Screening donated blood for transfusion transmissible infections[7])*	4. In all settings, screening of blood donors should be mandatory with linkage to care, counselling and treatment for those who test positive.

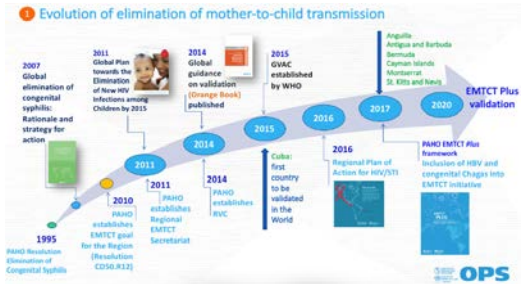
Online trainings and workshops

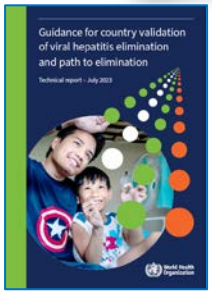
Online Training	Website Address	Key Source Institution, Country	Number of Modules	Covers HBV, HCV or Both
Hepatitis C Online	https://www.hepatitisc.uw.edu/	University of Washington, USA	6	HCV
Hepatitis B Online	https://hepatitisb.uw.edu/	University of Washington, USA	9	HBV
Liver Learning: Fundamentals of Liver Disease: • Hepatitis C 2.0 • Hepatitis B 2.0	https://liverlearning.aasld.org/	AASLD, USA	15	HBV, HCV
ASHM/iNHSU	lms.ashm.org.au/ https://www.inhsu.org/online-learning-modules/	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine, Australia International Network on Health and Hepatitis in Substance Users	Variable depending on the training. Max 9	HBV, HCV
HIV/HCV Co-Infection: An AETC National Curriculum	Aidsetc.org/hivhcv	AIDS Education and Training Center (AETC), USA	6	HCV, HCV/HIV
IAPAC • HBV Clinical Management • HCV Clinical Management	iapac.org/education/african-regional-capacity-building-hub/	International Association of Providers of AIDS Care (IAPAC), South Africa	11	HBV, HCV
CATIE • Hepatitis C Basics • Hepatitis C Treatment	https://www.catie.ca/education-publications-websites-education/self-directed-learning-0	Canadian AIDS Treatment Information Exchange, Canada	6	HCV
Health E Knowledge	http://healtheknowledge.org/course/view.php?id=100	Addiction Technology Transfer Center Network, USA	4	HCV
Know HBV and HCV	https://www.edx.org/course/know-hbv-and-hcv?index=product&queryID=5a5a485a4573afdb2b041b7f0eb3427f&position=1	Stanford University, USA	3	HBV

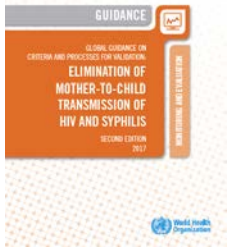
Tele-mentoring: ECHO platform

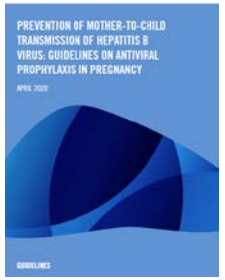
Triple Elimination of HIV, syphilis and Hepatitis B
Opportunity to advance the HBV EMTCT agenda

- A global community commitment to the elimination of mother-to-child transmission (EMTCT) OR vertical transmission of HIV, syphilis and hepatitis B virus (HBV) as a public health priority.
- Encourages countries to **simultaneously commit** to EMTCT of HIV, syphilis and HBV, further pushing the agenda for **integrated service delivery.**
- Focuses on a **harmonized approach** to improving health outcomes for mothers and children.
- Triple elimination of HIV, syphilis and HBV in PAHO and WPRO and now globally
- Multiple countries developing triple elimination framework and guidelines (WPRO/SEARO and PAHO regions)
- Validation criteria for elimination of viral hepatitis including Path to Elimination (June 2021 and Sept 2023)
- Update to the "Orange book" - *Global guidance on criteria and processes for validation of elimination of mother-to-child transmission of HIV and syphilis,* to include hepatitis B





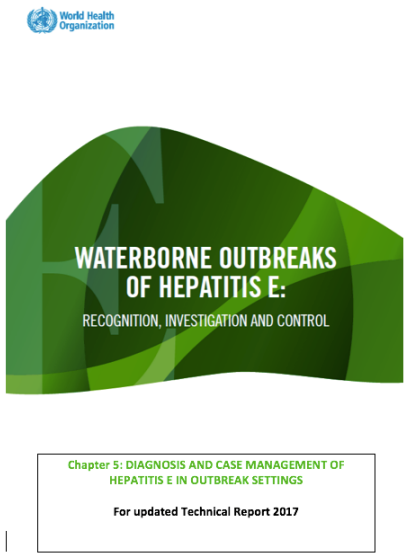







Existing WHO tools on HEV response and clinical management

- Responding to an outbreak
- Specimen collection
- Direct and indirect tests for HEV
- Water supplies and treatment
- Infection control and prevention
- Outbreak communication
- Outbreak investigation report
- Decision making steps on vaccine use



- Diagnosis and case definition/Differential diagnosis
- Assessment/triage for hospitalisation
- Management of ALF in hospital
- Outpatient management and monitoring
- Specific management issues in pregnant women

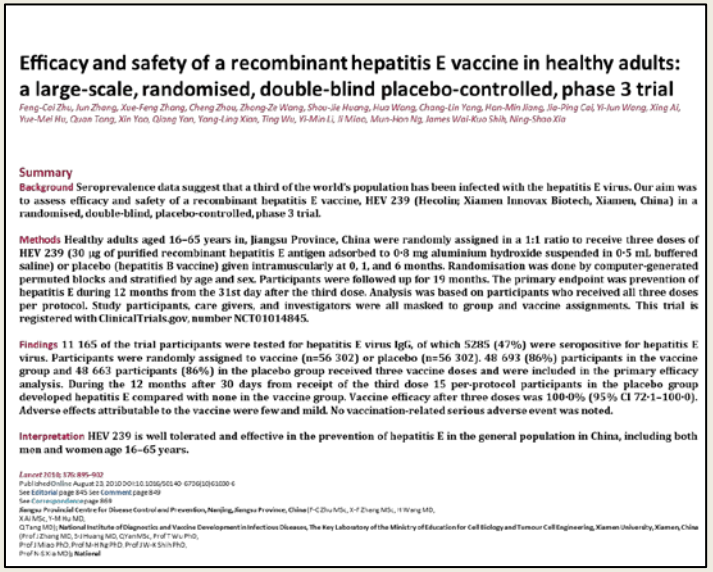
Hepatitis E vaccine

- Currently only one product available, licensed in China in 2012;
- 30µg HEV239 protein, arising from genotype 1;
- Schedule: 0, 1 and 6 months;
- For use in individuals aged 16 years and over;
- Limited data, in particular in pregnant women;
- To date, no WHO prequalification;
- Vaccine has not been used programmatically outside of China.

"WHO recognizes the importance of hepatitis E as a public health problem in many developing countries, particularly among special populations such as pregnant women and individuals living in camps for displaced persons and in outbreak situations."

"…WHO does not make a recommendation on the introduction of the vaccine for routine use in national programmes in populations where epidemic and sporadic hepatitis E disease is common. However, national authorities may decide to use the vaccine based on the local epidemiology."

"Special groups and outbreak situations: There may be special situations such as outbreaks where the risk of hepatitis E or of its complications or mortality is particularly high. The current WHO position concerning routine programmes should not preclude the use of the vaccine in these specific situations. In particular, the use of the vaccine to mitigate or prevent outbreaks of hepatitis E should be considered as well as the use of the vaccine to mitigate consequences in high risk groups such as pregnant women."



Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial

Feng-Cai Zhu, Jun Zhang, Xue-Feng Zhang, Cheng Zhou, Zhong-Ze Wang, Shou-Jie Huang, Hua Wang, Chang-Lin Yang, Hon-Min Jiang, Jia-Ping Cai, Yi-Jun Wang, Xing Ai, Yue-Mei Hu, Quan Tang, Xin Yao, Qiang Yan, Yang-Ling Xian, Ting Wu, Yi-Min Li, Yi Miao, Mun-Hon Ng, James Wai-Kuo Shih, Ning-Shao Xia

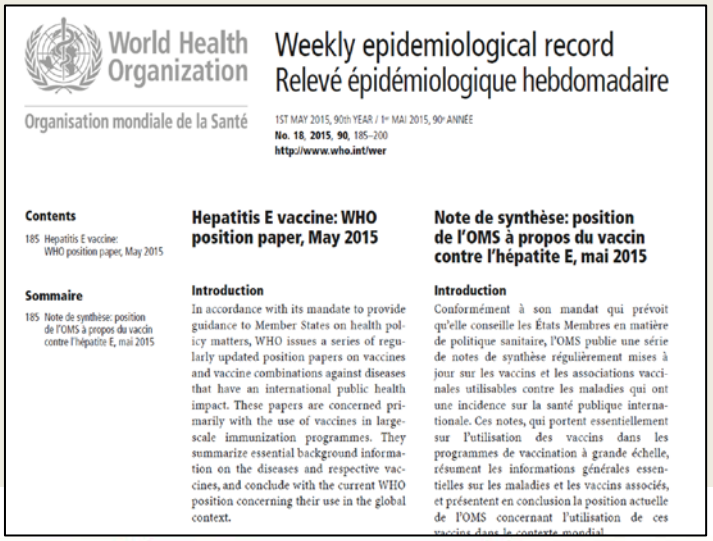
Summary

Background Seroprevalence data suggest that a third of the world's population has been infected with the hepatitis E virus. Our aim was to assess efficacy and safety of a recombinant hepatitis E vaccine, HEV 239 (Hecolin; Xiamen Innovax Biotech, Xiamen, China) in a randomised, double-blind, placebo-controlled, phase 3 trial.

Methods Healthy adults aged 16–65 years in, Jiangsu Province, China were randomly assigned in a 1:1 ratio to receive three doses of HEV 239 (30 µg of purified recombinant hepatitis E antigen adsorbed to 0·8 mg aluminium hydroxide suspended in 0·5 mL buffered saline) or placebo (hepatitis B vaccine) given intramuscularly at 0, 1, and 6 months. Randomisation was done by computer-generated permuted blocks and stratified by age and sex. Participants were followed up for 19 months. The primary endpoint was prevention of hepatitis E during 12 months from the 31st day after the third dose. Analysis was based on participants who received all three doses per protocol. Study participants, care givers, and investigators were all masked to group and vaccine assignments. This trial is registered with ClinicalTrials.gov, number NCT01014845.

Findings 11 165 of the trial participants were tested for hepatitis E virus IgG, of which 5285 (47%) were seropositive for hepatitis E virus. Participants were randomly assigned to vaccine (n=56 302) or placebo (n=56 302). 48 693 (86%) participants in the vaccine group and 48 663 participants (86%) in the placebo group received three vaccine doses and were included in the primary efficacy analysis. During the 12 months after 30 days from receipt of the third dose 15 per-protocol participants in the placebo group developed hepatitis E compared with none in the vaccine group. Vaccine efficacy after three doses was 100·0% (95% CI 72·1–100·0). Adverse effects attributable to the vaccine were few and mild. No vaccination-related serious adverse event was noted.

Interpretation HEV 239 is well tolerated and effective in the prevention of hepatitis E in the general population in China, including both men and women age 16–65 years.



World Health Organization

Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

1ST MAY 2015, 90th YEAR / 1er MAI 2015, 90e ANNÉE
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Hepatitis E vaccine: WHO position paper, May 2015

Introduction

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and vaccine combinations against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes. They summarize essential background information on the diseases and respective vaccines, and conclude with the current WHO position concerning their use in the global context.

Note de synthèse: position de l'OMS à propos du vaccin contre l'hépatite E, mai 2015

Introduction

Conformément à son mandat qui prévoit qu'elle conseille les États Membres en matière de politique sanitaire, l'OMS publie une série de notes de synthèse régulièrement mises à jour sur les vaccins et les associations vaccinales utilisables contre les maladies qui ont une incidence sur la santé publique internationale. Ces notes, qui portent essentiellement sur l'utilisation des vaccins dans les programmes de vaccination à grande échelle, résument les informations générales essentielles sur les maladies et les vaccins associés, et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation de ces