WHO Session

Hepatitis Delta: making a difference in low- and middle-income countries

3rd *DeltaCure Conference*

October 2024, Milano, Italy

World Health Organization

Niklas Luhmann
Technical Officer
Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
WHO Headquarters

New Global Health Sector Strategy for HIV, VH and STIs

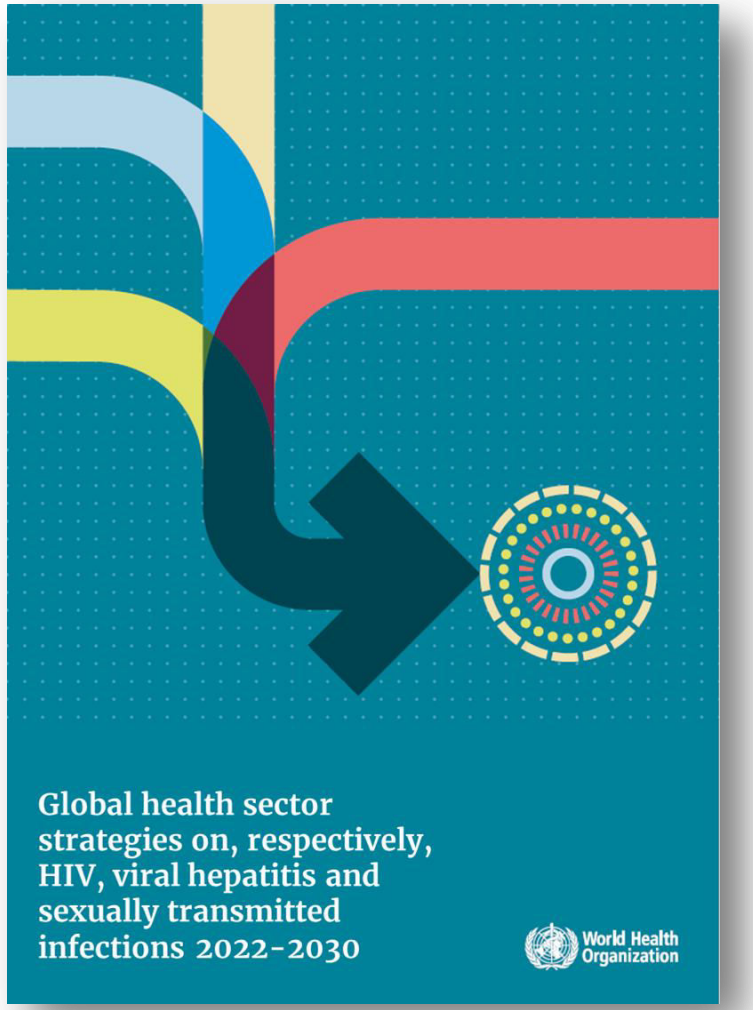
World Health Organization

Table 5.1. **Impact and coverage indicators, targets and milestones for viral hepatitis by 2030**

	Indicator	Baseline – 2020[a]	Targets – 2025	Targets - 2030
Impact	Hepatitis B surface antigen (HBsAg) prevalence among children younger than 5 years old[b]	0.94%	0.5%	0.1%
	Number of new hepatitis B infections per year	1.5 million new cases 20 per 100 000	850 000 new cases 11 per 100 000	170 000 new cases 2 per 100 000
	Number of new hepatitis C infections per year	1.575 million new cases 20 per 100 000	1 million new cases 13 per 100 000	350 000 new cases 5 per 100 000
	Number of new hepatitis C infections per year among people who inject drugs per year	8 per 100	3 per 100	2 per 100
	Number of people dying from hepatitis B per year	820 000 deaths 10 per 100 000	530 000 deaths 7 per 100 000	310 000 deaths 4 per 100 000
	Number of people dying from hepatitis C per year	290 000 deaths 5 per 100 000	240 000 deaths 3 per 100 000	140 000 deaths 2 per 100 000
Coverage	Hepatitis B – percentage of people living with hepatitis B diagnosed / and treated	30%/30%	60%/50%	90%/80%
	Hepatitis C – percentage of people living with hepatitis C diagnosed / and cured	30%/30%	60%/50%	90%/80%

[a] Latest data for end 2020. Some targets use data from 2019 because of COVID-19 related service disruptions in the data reported for 2020. COVID-19 is not currently expected to affect the targets for 2025. All data will be disaggregated by age, sex and when relevant the focus populations specific to the disease.

[b] Please note that the targets in this table are global targets and should be adapted to set targets for countries in relation to the national context. For example, in some countries a target for hepatitis B surface antigen prevalence among children younger than five years may be less than 0.1% or 0.2%, although the overall global target should be 0.1%.

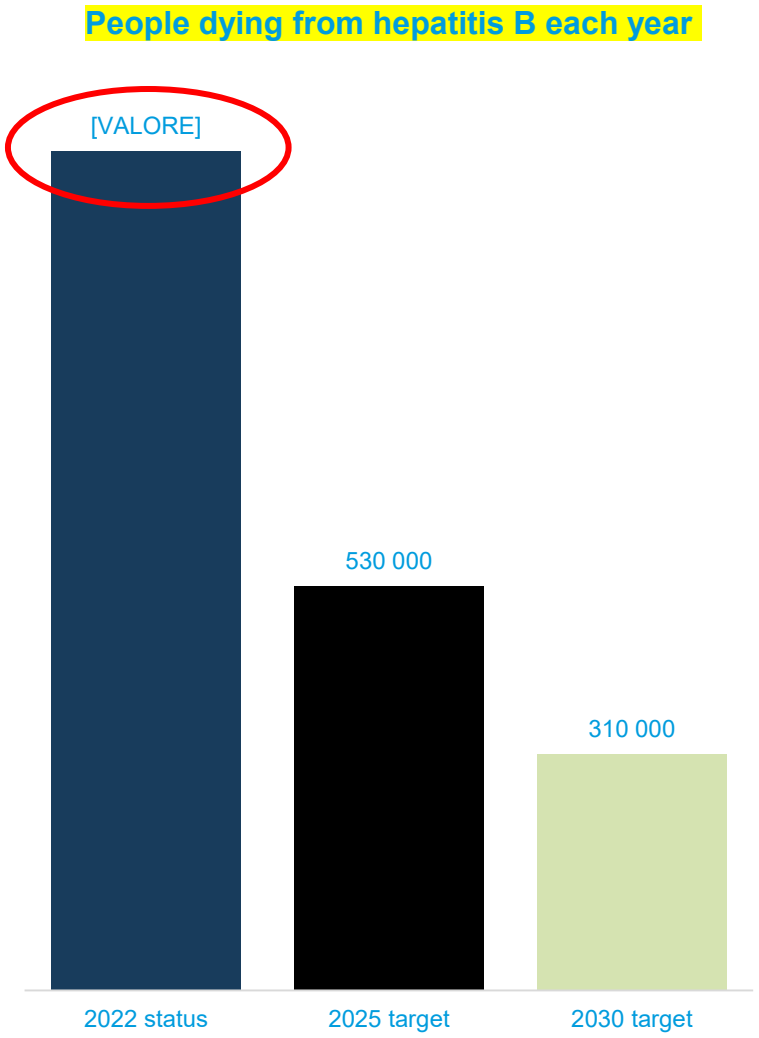


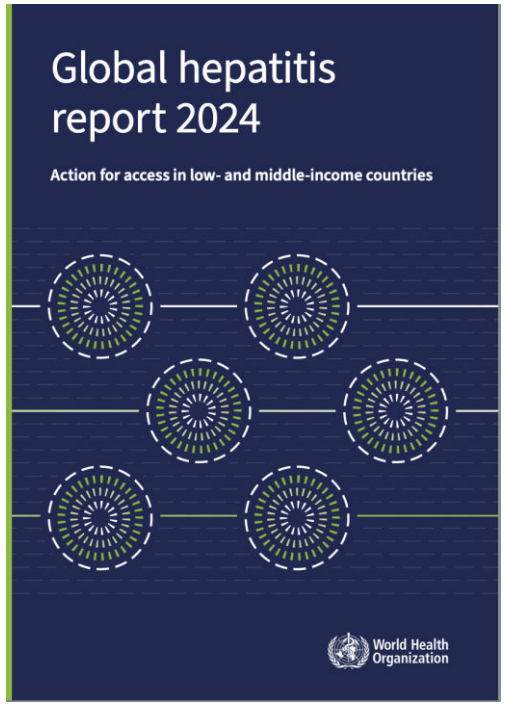
Link to GHSS: [9789240053779-eng.pdf]

Global HBV related Mortality

World Health Organization

- **1.1 million people died from chronic HBV in 2022**
- **Viral hepatitis is the only communicable disease for which mortality is increasing.**
- **Report focuses on HBV and HCV infections and also addresses hepatitis D virus and important contribution of HBV/HDV co-infection to liver related morbidity and mortality**

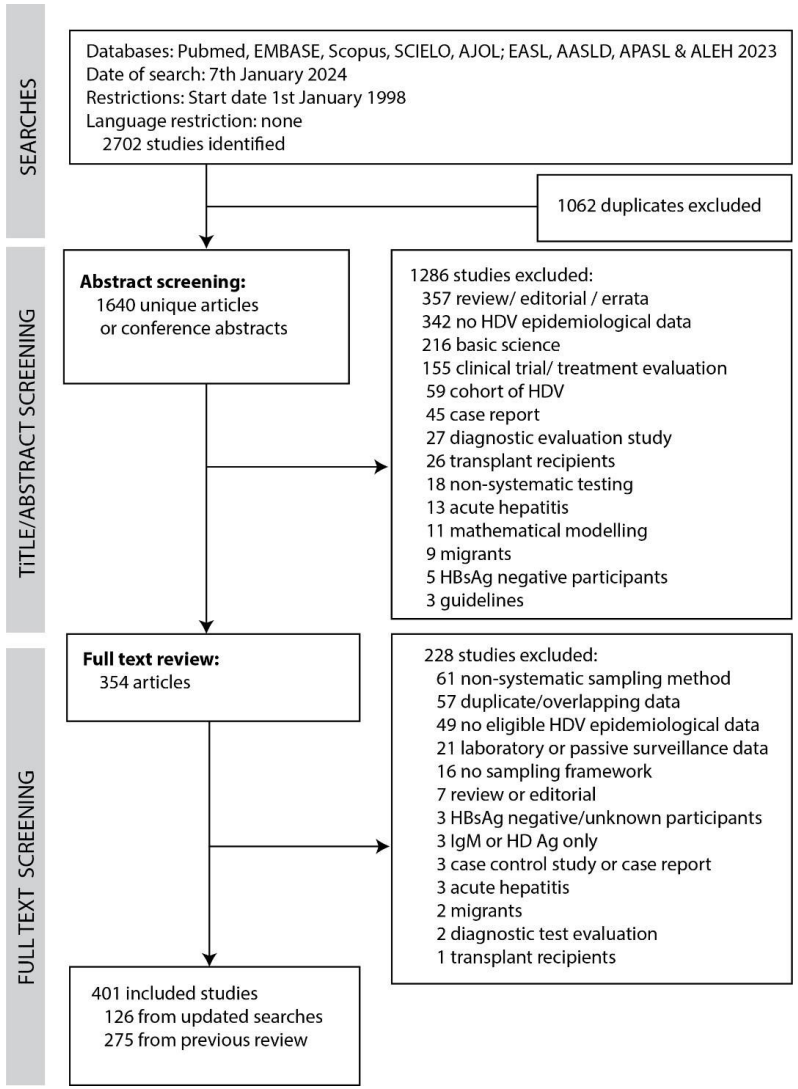




World Health Organization

https://www.who.int/publications/i/item/9789240091672

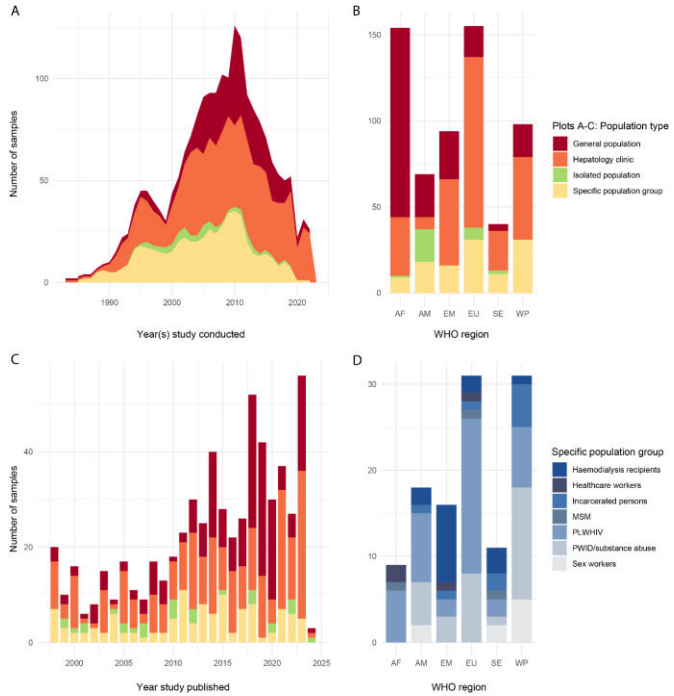
Updated epidemiology



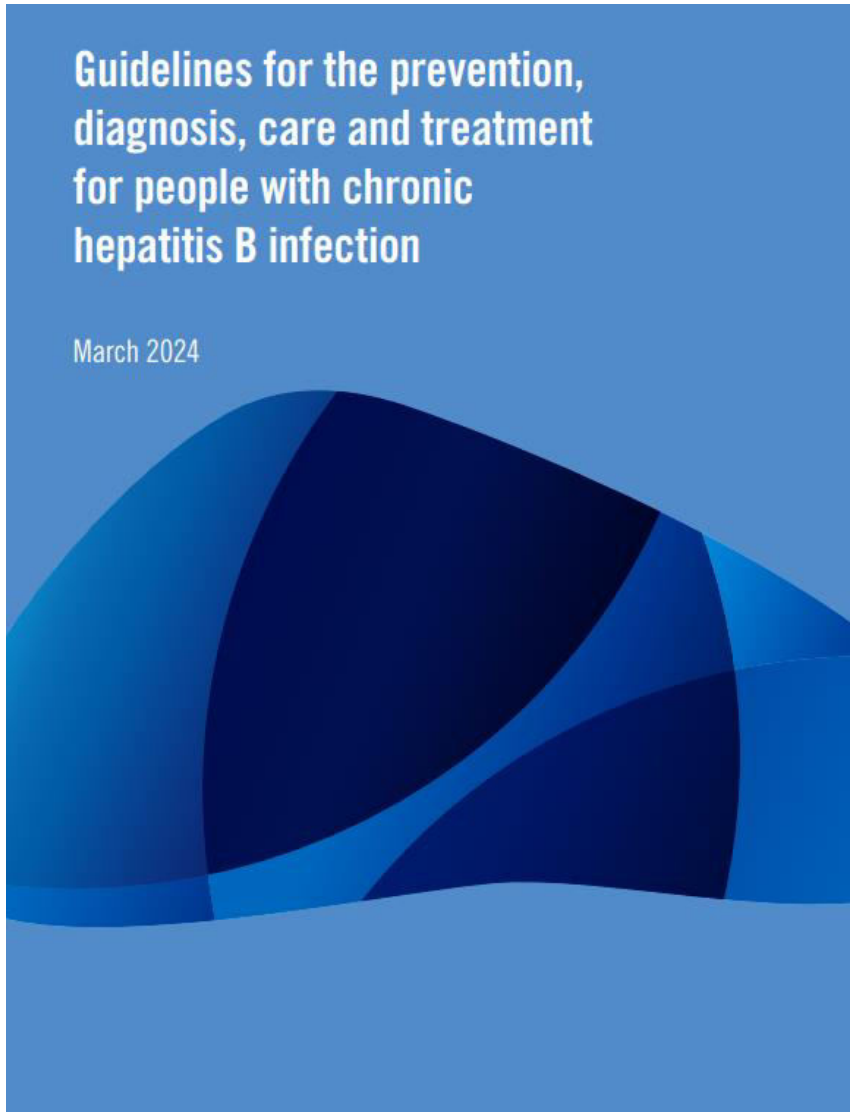
unpublished / with courtesy from A. Stockdale

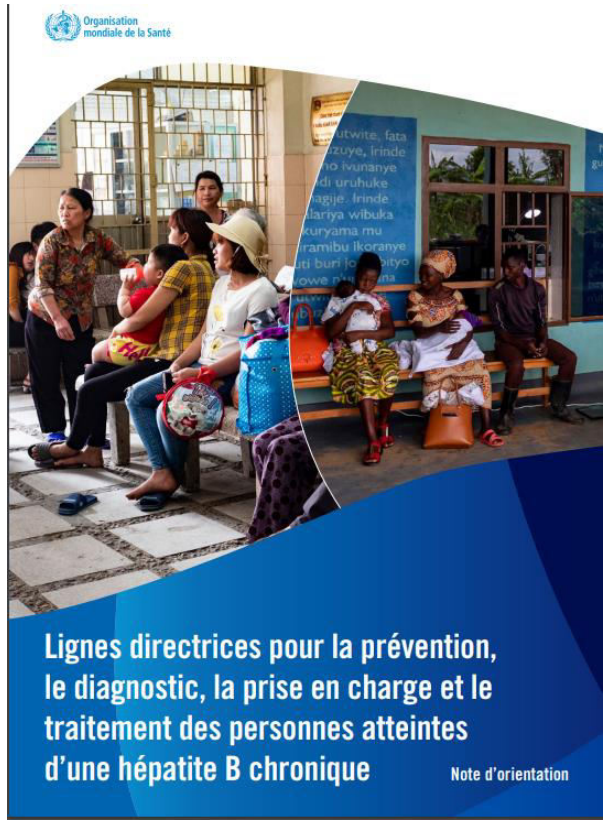
Updated provisional PAF estimates:

- Population attributable fraction (PAF) for cirrhosis from HDV among HBsAg-positive people was estimated using random effects models.
  - **46 studies, 25,330 patients**
  - **19.5% (95% CI: 13.1 – 28.9)**
- Population attributable fraction (PAF) for HCC from HDV among HBsAg-positive people
  - **19 studies, 10,480 patients**
  - **15.5% (95% CI 6.4 – 24.5)**



World Health Organization





https://iris.who.int/bitstream/handle/10665/377000/9789240095076-fre.pdf?sequence=1

RECOMMENDATIONS AND RATIONALE – HDV testing - Who to test?

World Health Organization

Universal testing approach

Serological testing for anti-HDV antibodies may be performed **for all individuals** who are HBsAg positive, as the preferred approach to scale up access to HDV diagnosis and linkage to care

(conditional recommendation, very-low-certainty evidence)

- No studies directly evaluated impact and cost-effectiveness of different anti-HDV testing approaches.
- Observational studies from high income settings **show poor testing uptake and case-finding based on risk-based approach**, and marked increase with laboratory-based universal anti-HDV testing

World Health Organization

Priority population testing approach

In settings in which a universal anti-HDV antibody testing approach is not feasible because laboratory capacity or other resources are limited, testing for anti-HDV may be given priority in specific populations of HBsAg-positive individuals:

- people born in **HDV-endemic** countries, regions and areas;
- people with **advanced liver disease**, those receiving hepB treatment; and those with features suggesting HDV infection (such as low HBV DNA with high ALT levels); and
- people considered to have **increased risk** of HDV infection (haemodialysis recipients, people living with HCV or HIV, people who inject drugs, sex workers and gay men and other men who have sex with men).

(conditional recommendation, very-low-certainty evidence)

https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf?sequence=1

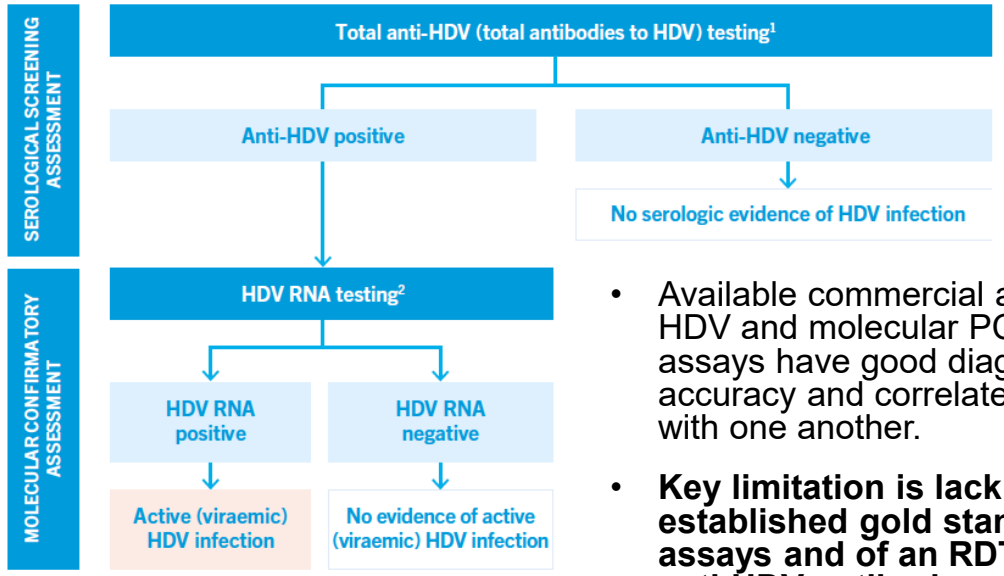
RECOMMENDATIONS – HDV testing

How to test?

People with CHB (HBsAg positive) may be diagnosed with hepatitis D by **using a serological assay to detect total anti-HDV followed by an NAT to detect HDV RNA and active (viraemic) infection** among those who are anti-HDV positive.

Assays should meet minimum quality, safety and performance standards.

(conditional recommendation, low-certainty evidence)



- Available commercial anti-HDV and molecular PCR assays have good diagnostic accuracy and correlate well with one another.
- **Key limitation is lack of established gold standard assays and of an RDT for anti-HDV antibody.**

Reflex testing

Reflex testing for anti-HDV antibody testing following a positive HBsAg test result and **also for HDV RNA testing** (where available) following a positive anti-HDV antibody test result, may be used as an additional strategy to promote diagnosis.

(conditional recommendation, low-certainty evidence)

Systematic review of reflex testing

- 11 studies of reflex anti-HDV Ab testing (3 had non-reflex comparator arm) in those HBsAg positive
- Increased uptake of serology testing (97% (95% CI: 92–100%) vs. 45% (95% CI: 0.3–98%) with non-reflex testing
- Very high uptake of reflex HDV RNA in those anti-HDV positive - 98% (95% CI: 77–100%) in 8 studies.

https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf?sequence=1

Research gaps

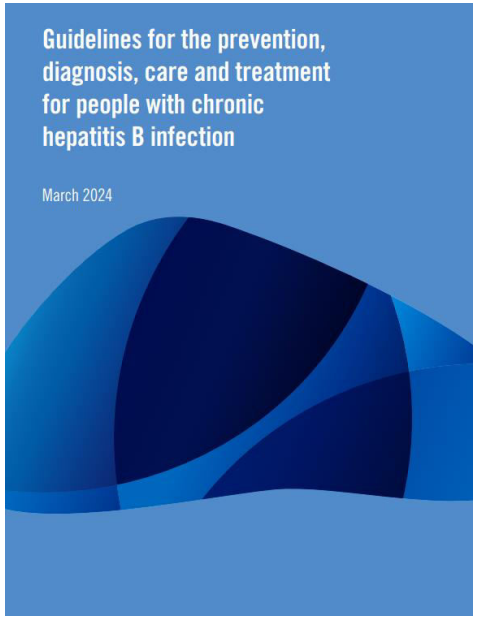
1. High-quality, well-defined and representative HDV epidemiological studies with quality assured diagnostics

2. Give priority to developing anti-HDV RDTs to facilitate decentralisation in LMIC

3. Developing a fully-automated NATs that enable more accurate and reliable quantification of HDV RNA for all genotypes

4. Cost-effectiveness modelling and feasibility studies of universal testing approaches in LMIC with different epidemiological scenarios

5. Impact, cost-effectiveness and feasibility studies of anti-HDV reflex testing in different epidemiological scenarios



https://iris.who.int/bitstream/handle/10665/376353/9789240090903-eng.pdf?sequence=1

Summary

- Viral Hepatitis B/D is a significant public health problem with high yearly mortality
- HDV is increasingly highlighted by WHO and we have formal recommendations for HDV testing and diagnosis
- Stakeholders and countries are highlighting the need for additional recommendations for HDV treatment
- Need for developing diagnostics and treatment that are affordable and can be implemented in LMICs

Acknowledgements Guidelines Development Group and WHO Steering Committee

Co-chairs: **Saeed Sadiq Hamid** (The Aga Khan University, Pakistan), **Wendy Spearman** (University CapeTown, South Africa) and **GRADE methodologist:** **Roger Chou** (Oregon Health and Science University, Portland, USA).

GDG: **Danjuma Adda** (World Hepatitis Alliance), **Suna Balkan** (Médecins Sans Frontières, France), **Ajeet Singh Bhadoria** (All India Institute of Medical Sciences, Rishikesh, India), **Yap Boum** (Pasteur Institute of Bangui, Cameroun), **Maria Butí** (Hospital Universitario Valle Hebron, Spain), **Vladimir Chulanov** (National Medical Research Centre for TB and Infectious Diseases, Russian Federation), **Chari Cohen** (Hepatitis B Foundation), **Naranjargal Dashdorj** (Onom Foundation, Mongolia), **Hailemichael Desalegn Mekonnen** (St Paul's Hospital Millennium Medical College, Ethiopia), **Manal Hamdy El-Sayed** (Ain Shams University, Egypt), **Jordan Feld (**Toronto General Hospital, University of Toronto), **Jin-Lin Hou** (Southern Medical University, China), **Saleem Kamili** (Centers for Disease Control and Prevention, United States), **Patrick Kennedy** (Queen Mary's University, UK), **Giten Khwairakpam** (TREAT Asia, Thailand), **David Muljono** (Eijkman Institute for Molecular Biology, Indonesia), **Wongani Mzumara** (Ministry of Health, Malawi), **Edith Okeke** (Jos University Teaching Hospital, Nigeria), **Janus Ong** (University of the Philippines, Philippines), **Christian B. Ramers** (Clinton Health Access Initiative, USA), **Tânia Reuter (**Federal University of Espírito Santo, Brazil), **Cielo Yaneth Ríos-Hincapié** (Ministry of Health and Social Protection, Colombia), **Lewis Roberts** (Mayo Clinic, United States), **Cao Thi Thanh Thuy** (Clinton Health Access Initiative, Vietnam), **Su Wang** (Center for Asian Health and Viral Hepatitis, United States)

Paediatrics sub-group: **Alasdair Bamford (** Great Ormond Street Institute of Child Health, UK), **Mei Hwei Chang (**College of Medicine National Taiwan University and Children Hospital, Taiwan (China), **Geoffrey Dusheiko** (King's College Hospital, United Kingdom), **Giuseppe Indolfi (**Anna Meyer Children's University-Hospital of Florence, Italy), **Simon Ling (**The Hospital For Sick Children, Canada), **Fatima Mir (**Department of Pediatrics and Child Health, Aga Khan University, Pakistan), **Tammy Meyers** (School of Women's and Children's Health, UNSW, Sydney, Australia

Delta co-infection sub-group: **Segolene Brichler (**French National Reference Centre for Hepatitis B, C and Delta, France), **You Hong** (Capital Medical University, China), **Will Irving (**University of Nottingham, UK), **Francesco Negro (**University of Geneva, Switzerland), **Cirley Maria de Oliveira Lobato (**Faculdade de Medicina da Universidade Federal do Acre, Brazil), **Cihan Yurdaydin (**University of Ankara, Turkey)

WHO Steering Committee
WHO headquarters staff: (GHP) Philippa Easterbrook, Olufunmilayo Lesi, Niklas Luhmann, Sandi Myat Min, Catherine de Martel; and Meg Doherty, Nathan Ford, Morkor Newman, Marco Vitoria, Lara Vojnov
WHO regional office staff: Kiyohiko Izumi (WPRO), Casimir Mingiedi Mazengo (AFRO), Joumana Hermez (EMRO), Marcelo Naveira (EURO), Bharat Bhushan Rewari (SEARO), Leandro Soares Sereno (PAHO).