# Towards Accelerating HBV Clinical Research in Africa

## Friday, April 12, 2024

## Culturgest Lisbon

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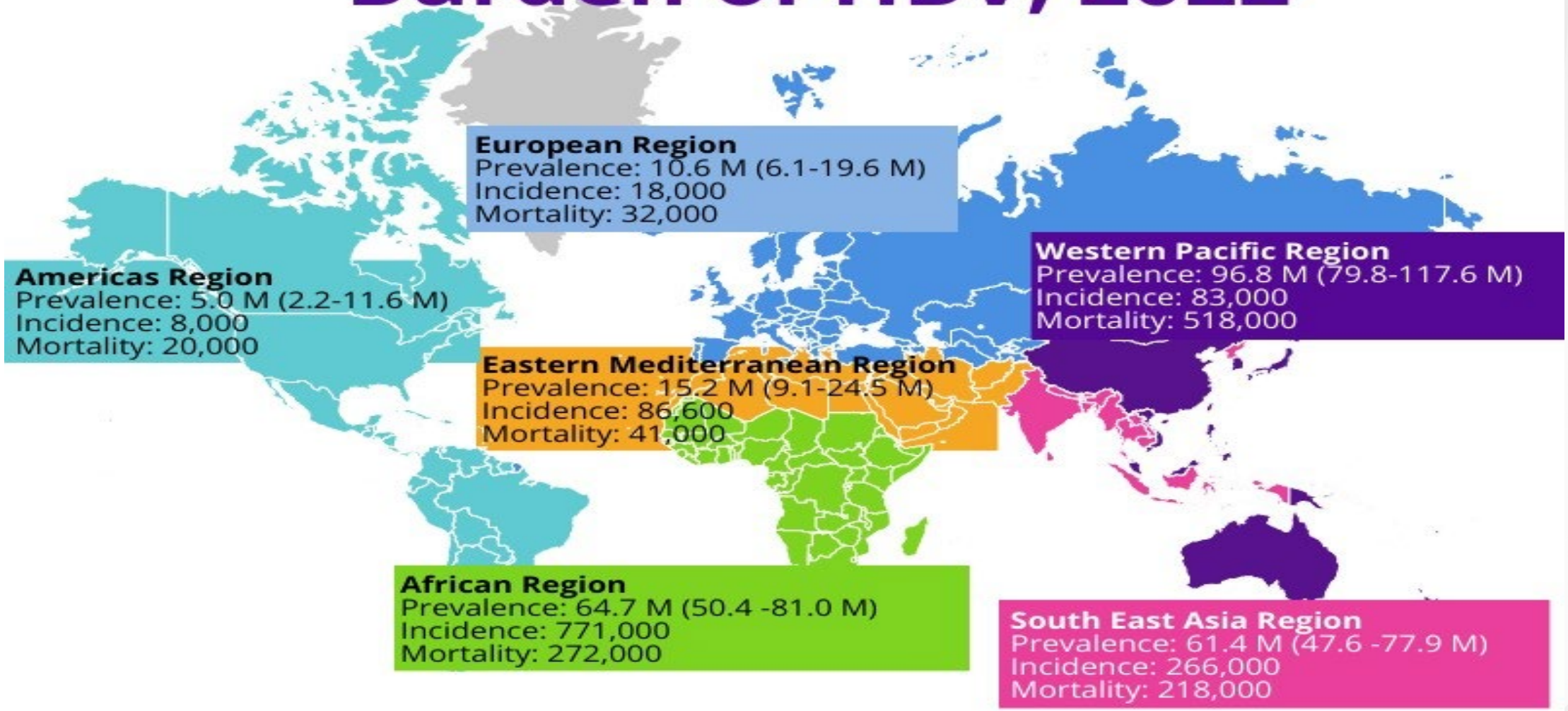
# Burden of HBV, 2022




Source: WHO, 2024. *Global Hepatitis Report*

www.who.int

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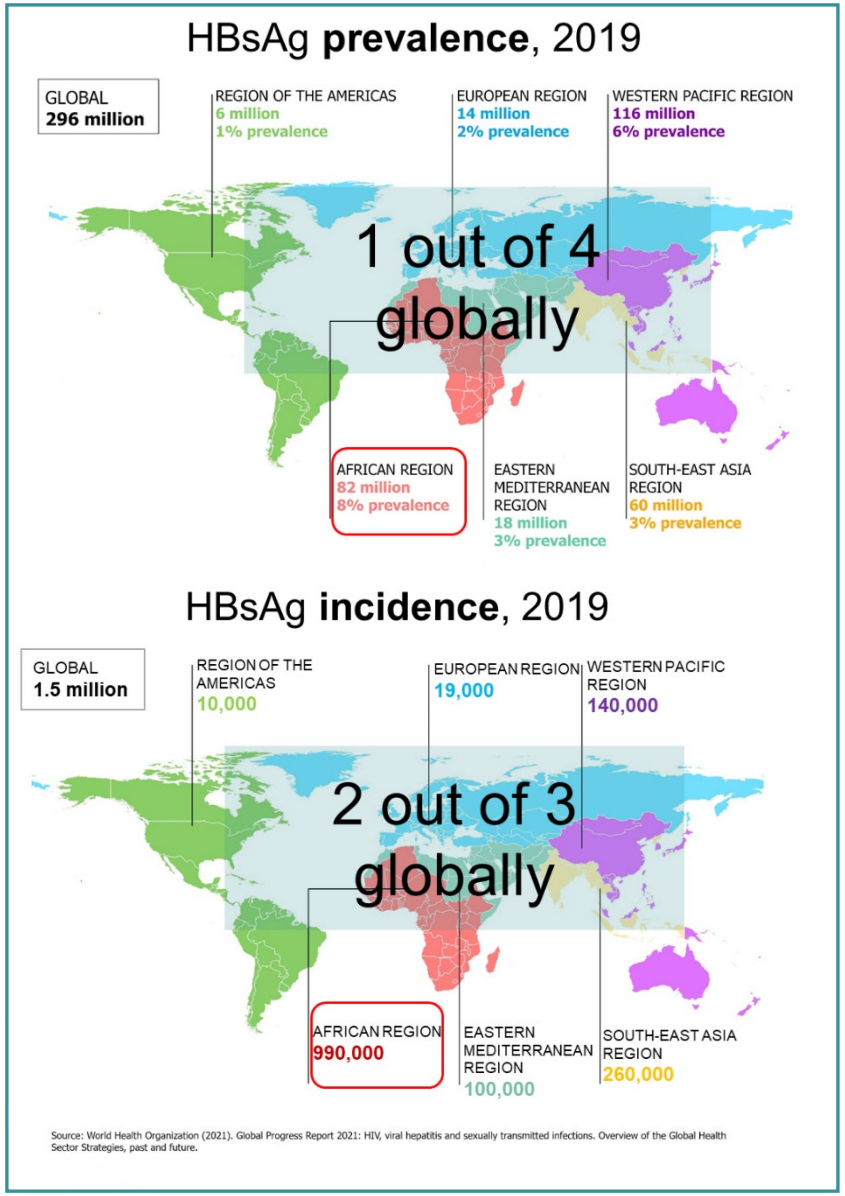
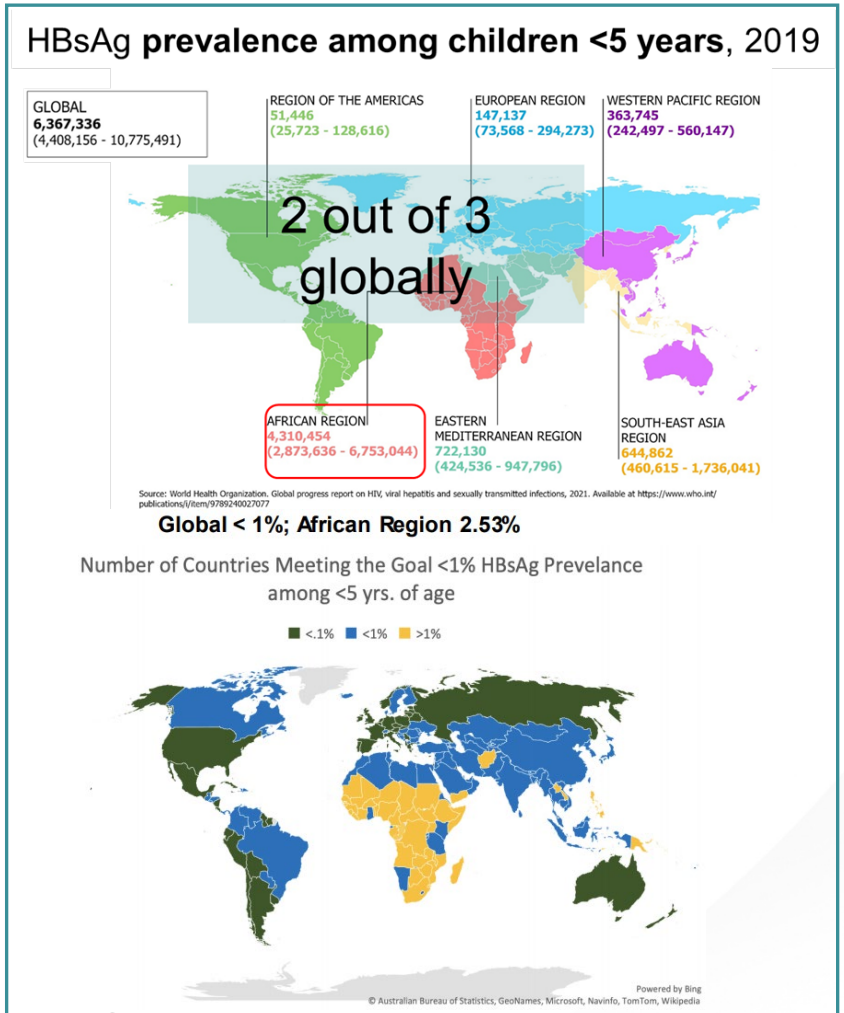
# Africa Has Highest HBV Burden and Majority of New Infections Occur Among Children




Africa has not met 2020 interim targets for hepatitis elimination

- Vertical (mother-to-child) common mode of HBV transmission in Africa
- Up to 25% of HBV infected infants will die prematurely from liver failure, cirrhosis and liver cancer

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St. Paul's Hospital Millennium Medical College

Project ECHO
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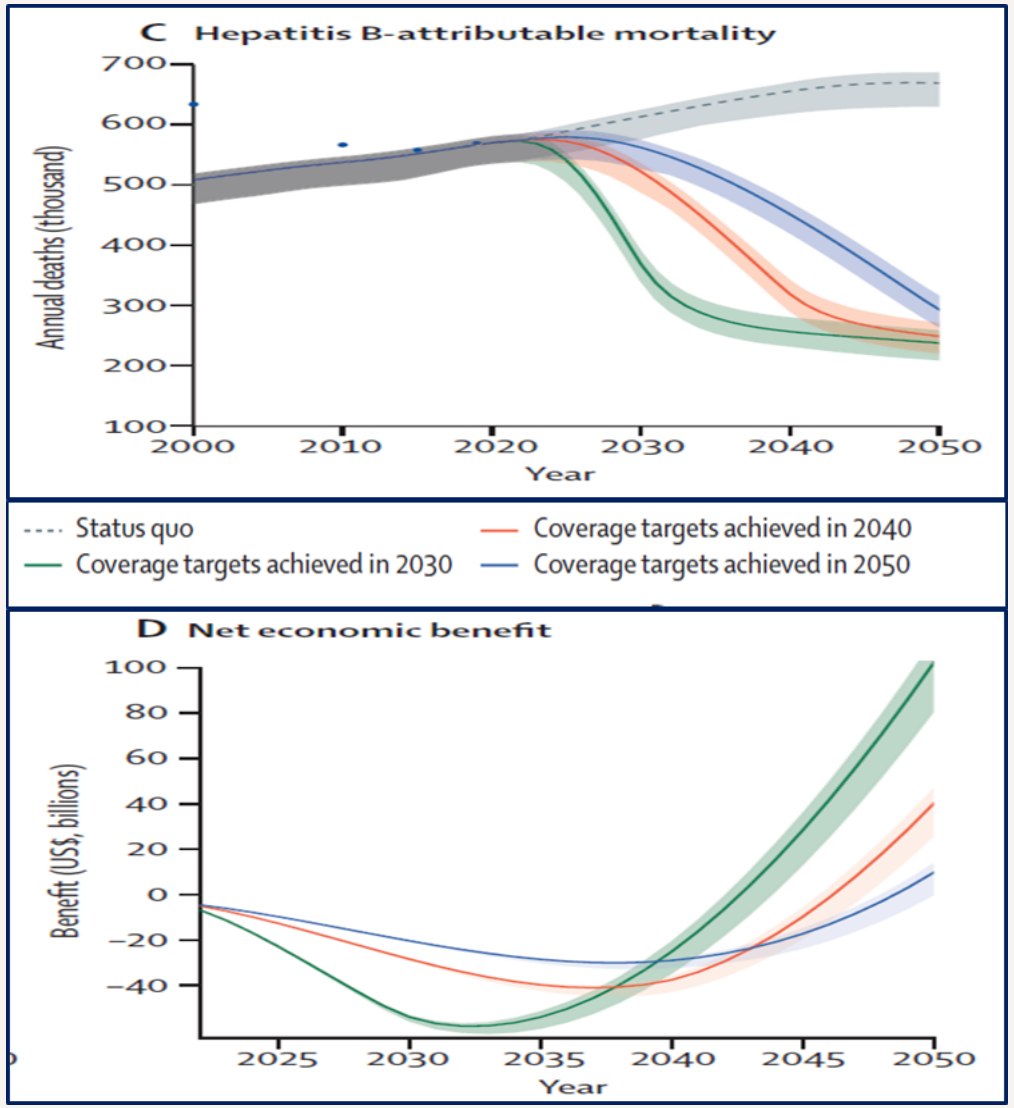
# Health and Economic Benefits of Hepatitis B Elimination




- **Prevent 25.6M infections**
- **Avert 8.6M deaths (by 2050)**

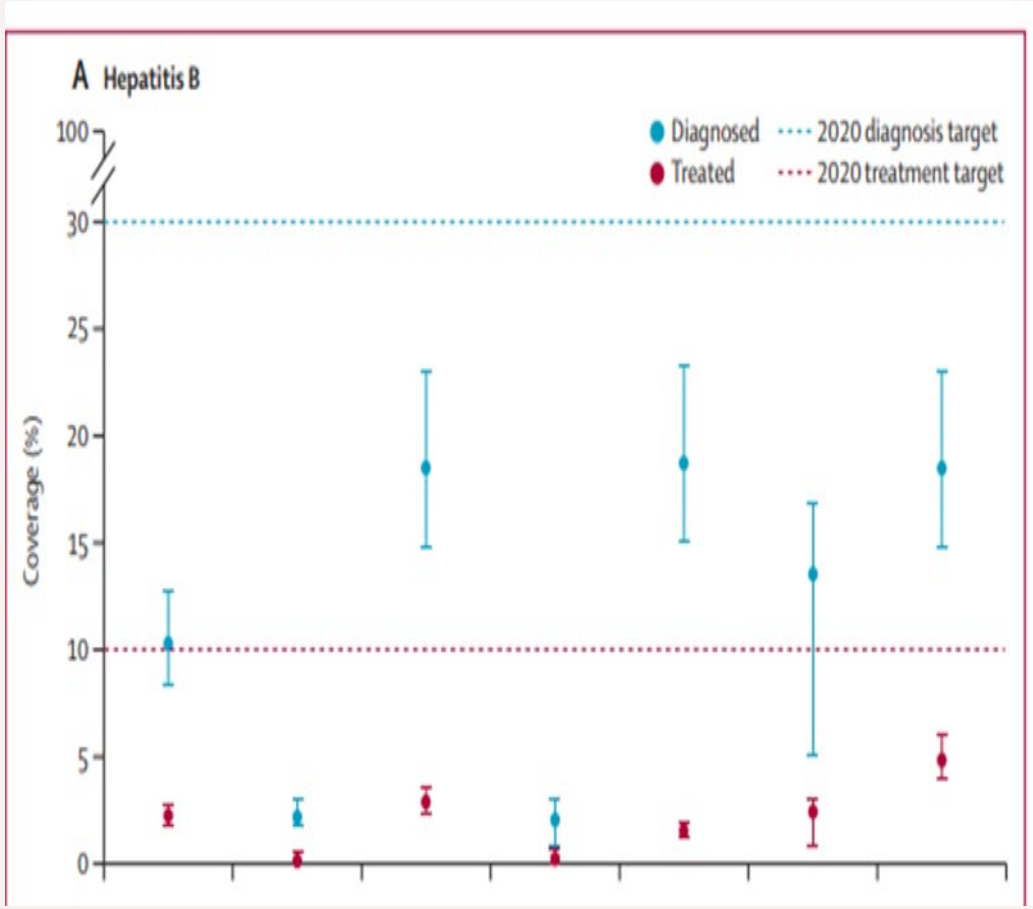
- **$141b program costs**
- **$240b productivity gains**
- **$99b economic benefit (by 2050)**

Elimination coverage: 90% infant vaccination, 90% diagnosis; 80% on appropriate treatment

Seaman CP, Lancet GastroHep 2023

World Hepatitis Summit 2024

# Reaching Goals for Reductions in Hepatitis B related Mortality
# Low HBV Diagnosis and Treatment Coverage B by Region, 2019




| Region | Percent of persons living with HBV diagnosed | Percent of persons living with HBV on treatment (among those eligible) |
|---|---|---|
| Global | 10% | 2.1% (22% diagnosed) |
| WPRO | 18.5% | 18.5% |
| SEARO | 2.1% | 2.1% |

World Hepatitis Summit 2024

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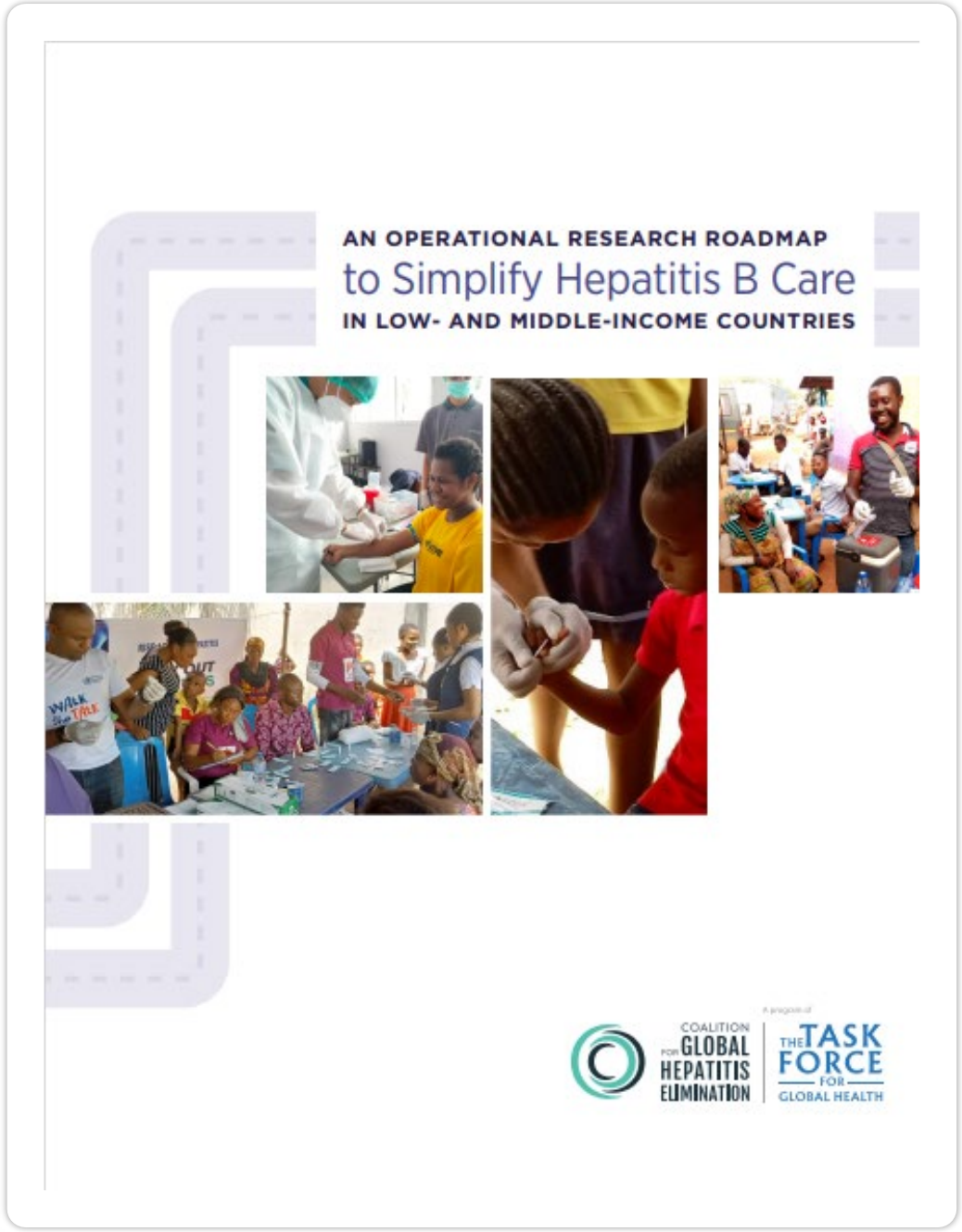
Lee KN, Clin Infect Dis. 2014 Jan;58(1):40-9; Abara WE, Ann Intern Med. 2017;167(11) Cui F et al 2023[:




# Objectives

- **Identify evidence gaps** in the implementation of hepatitis B testing, linkage to care, and treatment in LMICs
- **Propose high-priority operational research** to fill key evidence gaps
- **Develop actionable pathways** to conduct this research
- **Catalyze funding** to support LMIC researchers

**Download the full *HepB Operational Research Roadmap* Report**

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# Evidence on HBV care delivery is extremely limited in LMICs

- CGHE scoping review identified limited number of operational research for HBV care delivery in LMICs
- WHO global systematic review of models of care
- Research funding for HBV remains highly limited when compared to other global health threats


Annual investment into research and development (R&D) for new products and technologies, 2021 (Millions, USD)[5]

# *Operational Research Roadmap to Simplify HBV Care in LMICs*: Logic Model

## Project Activities

- Key informant interviews and focus group (APASL)
- Scoping review of operational research in LMICs
- Expert workshop (Atlanta, May 2023)

## Project Outputs

- Proposed operational research to improve HBV coverage in LMICs
- Roadmap to guide development and coordination of high-priority research

## Long-term outcomes

- Funded operational research projects intended to increase coverage of HBV services
- Multilateral stakeholder engagement in research roadmap

## Impact

- Improved coverage of HBV services
- Reduced global morbidity and mortality due to HBV

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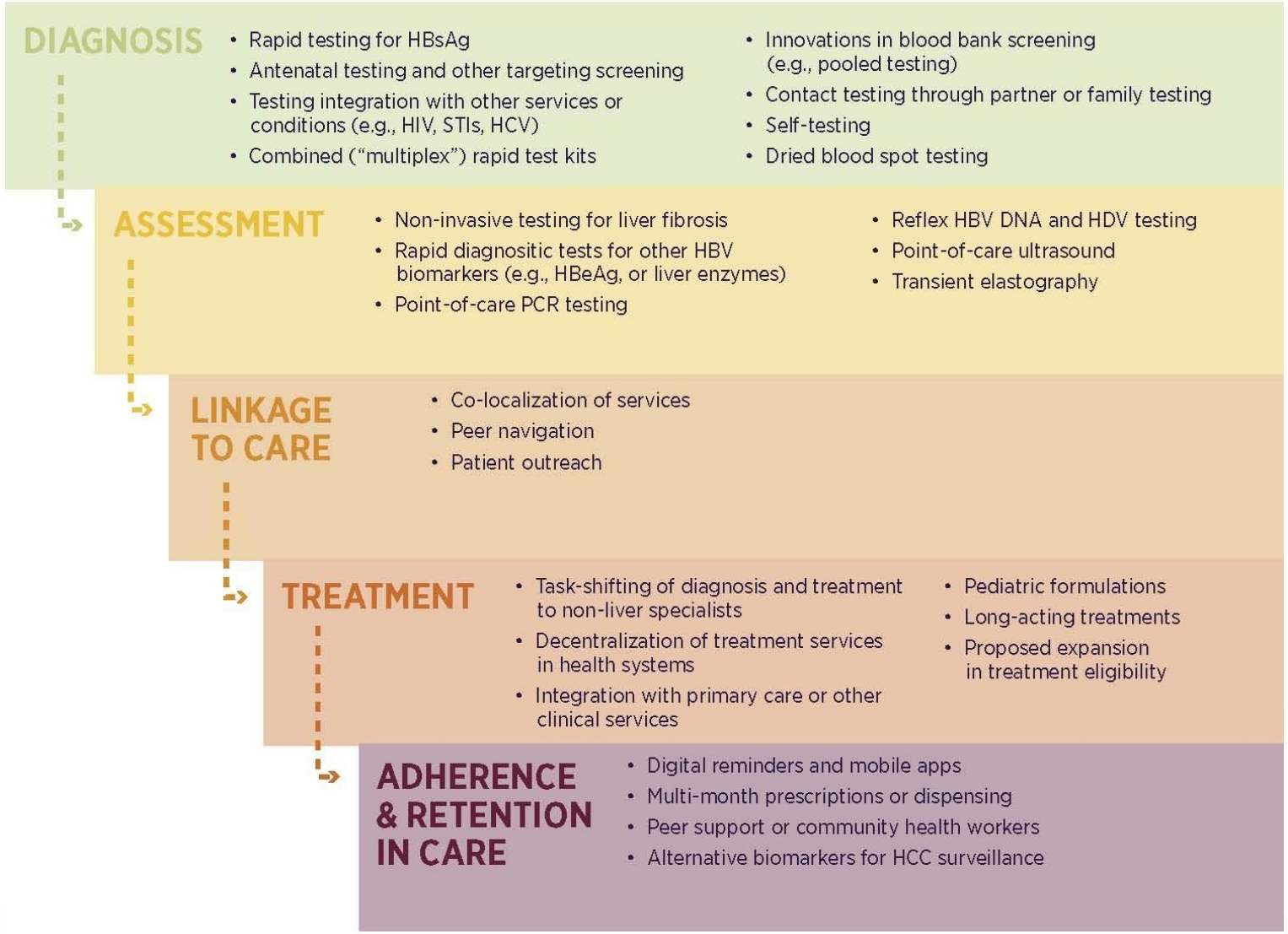
# Implementation Strategies to Improve HBV Care




- We have strong examples of intervention strategies to simplify care from HIV and HCV.
- Strong evidence-based models of care delivery are urgently needed for HBV.
- Operational research is needed so we can "learn while doing."
- Operational Research: The search for knowledge on interventions, strategies, or tools that can enhance program quality, effectiveness, or coverage.

# II. PRIORITY AREAS FOR OPERATIONAL RESEARCH TO EXPAND ACCESS TO HEPATITIS B PREVENTION, TESTING, AND TREATMENT

**PRIORITY 1:**
Simplify delivery models to assure decentralized, equitable access to hepatitis B testing and treatment

**PRIORITY 2:**
Improve interventions to eliminate mother-to-child transmission of HBV that protect the health of both mother and newborn, as well as their families

**PRIORITY 3:**
Develop and operationalize technologies for simplified hepatitis B diagnosis, treatment, and monitoring

**PRIORITY 4:**
Detect persons living with hepatitis B at highest risk for progression of fibrosis and development of HCC

# III. IMPLEMENT THE ROADMAP TO EXPAND ACCESS TO HEPATITIS B CARE AND SAVE LIVES: A LEARNING-BY-DOING APPROACH

**ACTION 1:** Implement studies to fill evidence gaps limiting effective delivery of hepatitis B care in LMICs

- **Establish a center** to solicit funding and coordinate research studies
- **Conduct request for proposals** for operational research
- **Monitor and evaluate** research activities

**ACTION 2:** Engage national programs in hepatitis B care research

- **Strengthen existing infrastructure,** e.g., health IT, laboratories
- **Study integration of hepatitis B care** with other programs
- **Estimate cost-effectiveness** of models of care

**ACTION 3:** Strengthen centers to conduct studies of hepatitis B care in LMICs

- **Invest in research infrastructure**
- **Support staff training** in operational research and evaluation
- **Promote a community of practice** to share lessons learned

**ACTION 4:** Disseminate findings and advocate for policy change

- **Communicate research findings** to stakeholders
- **Build local coalitions** to promote policy change
- **Guide policy development**

**IMPROVED HEPATITIS B SERVICE DELIVERY**

**DISABILITY AND DEATHS AVERTED**

A program of

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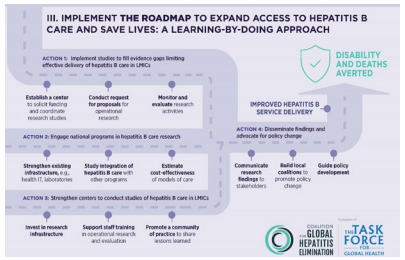


# Action 3: Strengthen centers to conduct studies of hepatitis B care in LMICs

➔ **Invest in research infrastructure**

➔ **Support staff training in operational research & evaluation**

➔ **Promote a community of practice to share lessons learned**

**Implementation considerations:**

- Each site will receive funding for capacity building for research and program evaluation (e.g., trainings, workshops, implementation tools)

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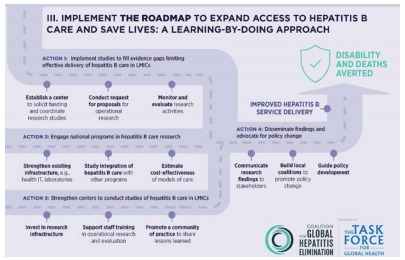


# Action 2: Engage national programs in hepatitis B care research

- → **Strengthen existing infrastructure, e.g.** health, IT, laboratories
- → **Study integration of hepatitis B care with other programs**
- → **Estimate cost-effectiveness of models of care**

**Implementation considerations:**

- Funding to begin and sustain engagement of the national government and other key stakeholders in strategic planning, community awareness, and integration of hepatitis B within existing health systems (e.g., facilities, IT systems, patient education).
- Cost-effectiveness modeling study of interventions evaluated in the research studies.

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# Operational Research Roadmap Funding Request

- 16 research studies over 4 years across 10 study sites, including:
  - National program engagement
  - Research center strengthening for long-term sustainability
  - Dissemination and policy change
- Total budget estimation: $24-35M USD over 4 years
- See Funders' Addendum

**An Operational Research Roadmap to Simplify Hepatitis B Care in LMICs FUNDERS' ADDENDUM**

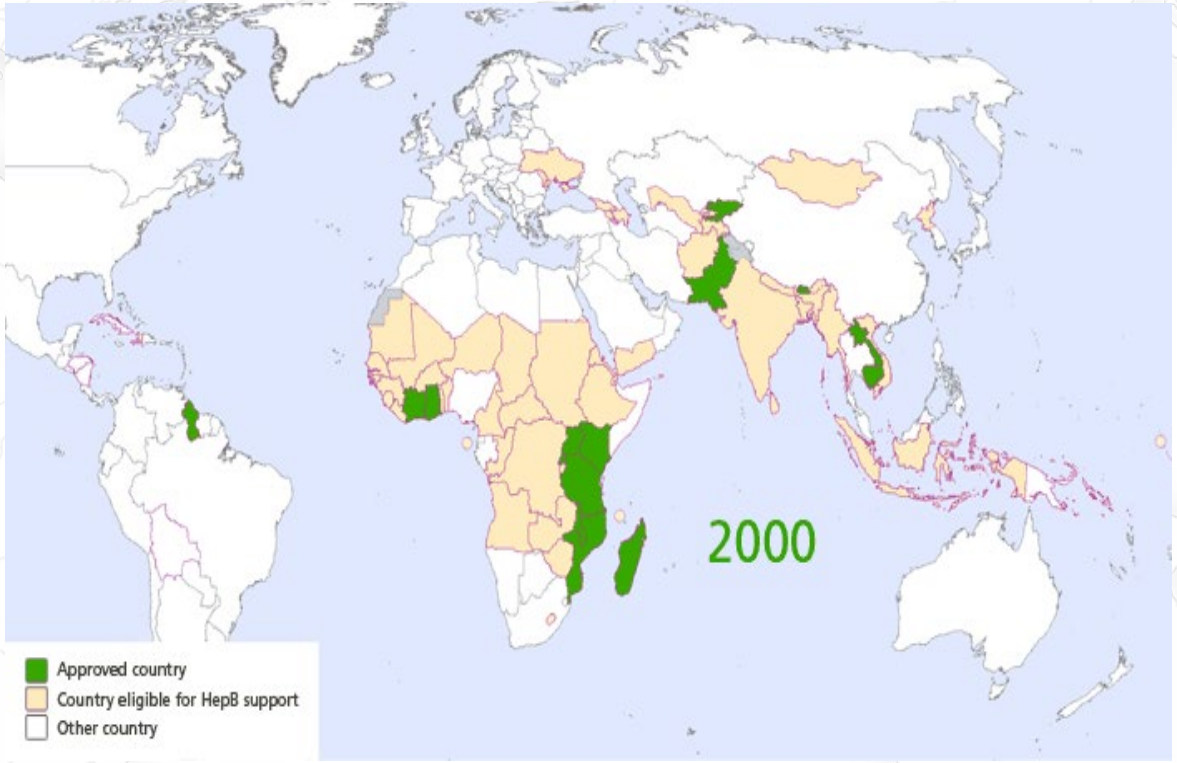
**Table 2. Budget Estimates for the *Operational Research Roadmap to Simplify Hepatitis B Care in Low- and Middle-Income Countries*, by Key Action and by Year of Implementation (USD)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Total |
|---|---|---|---|---|---|
| **Action 1:** Implement studies to fill evidence gaps limiting effective delivery of hepatitis B care in LMICs | 3.6-6.3 M | 3.3-5.8 M | 3.3-5.8 M | 1.7-2.6 M | 12.0- 20.5 M |
| **Action 2:** Engage national programs in hepatitis B care research | 1.1 M | 1.1 M | 1.4 M | 1.1 M | 4.6 M |
| **Action 3:** Strengthen centers to conduct studies of hepatitis B care in LMICs | 0.5 M | 0.5 M | 0.5 M | 0.5 M | 2.2 M |
| **Action 4:** Disseminate research findings and advocate for policy change | - | 0.5 M | 0.5 M | 0.5 M | 1.0-1.5 M |
| **Coordinating Center** | 1.0-1.5 M | 1.0-1.5 M | 1.0-1.5 M | 1.0-1.5 M | 3.8-6.2 M |
| **Total** | **6.1-9.4 M** | **6.5-9.5 M** | **6.7-9.8 M** | **4.8-6.3 M** | **24.2-35.1 M** |

# Priority Research Area 2: Improve interventions to eliminate mother-to-child transmission of HBV that protect the health of both mother and newborn, as well as their families - Research Questions

# GAVI Alliance Support for Hepatitis B Vaccination

- In 2008, 68 of 69 eligible countries approved for funding
  - 192 million persons vaccinated
- By 2014, all 74 eligible countries expected to have introduced infant hepatitis B vaccination
- HepB given in combination vaccines for infants
- Support does not include HepB vaccination at birth

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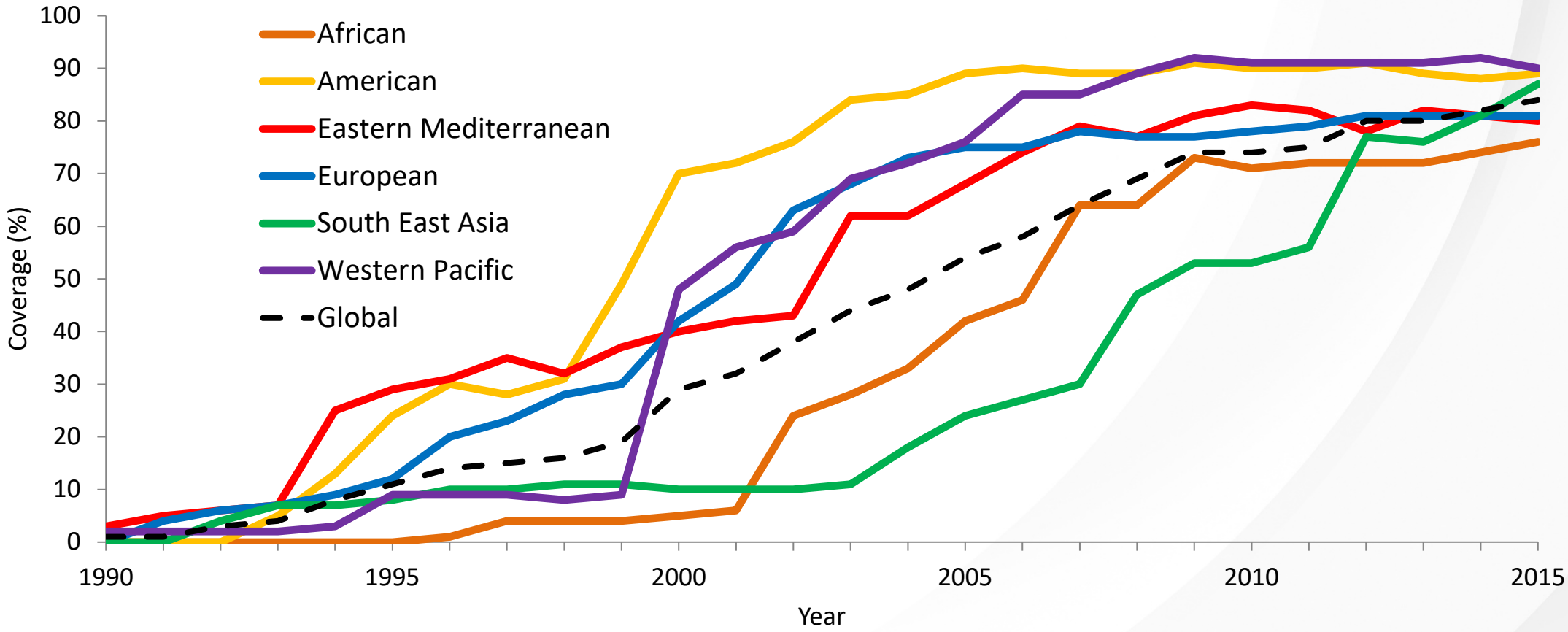
# Three Dose Hepatitis B Vaccine Coverage Among Children by WHO Region and Globally

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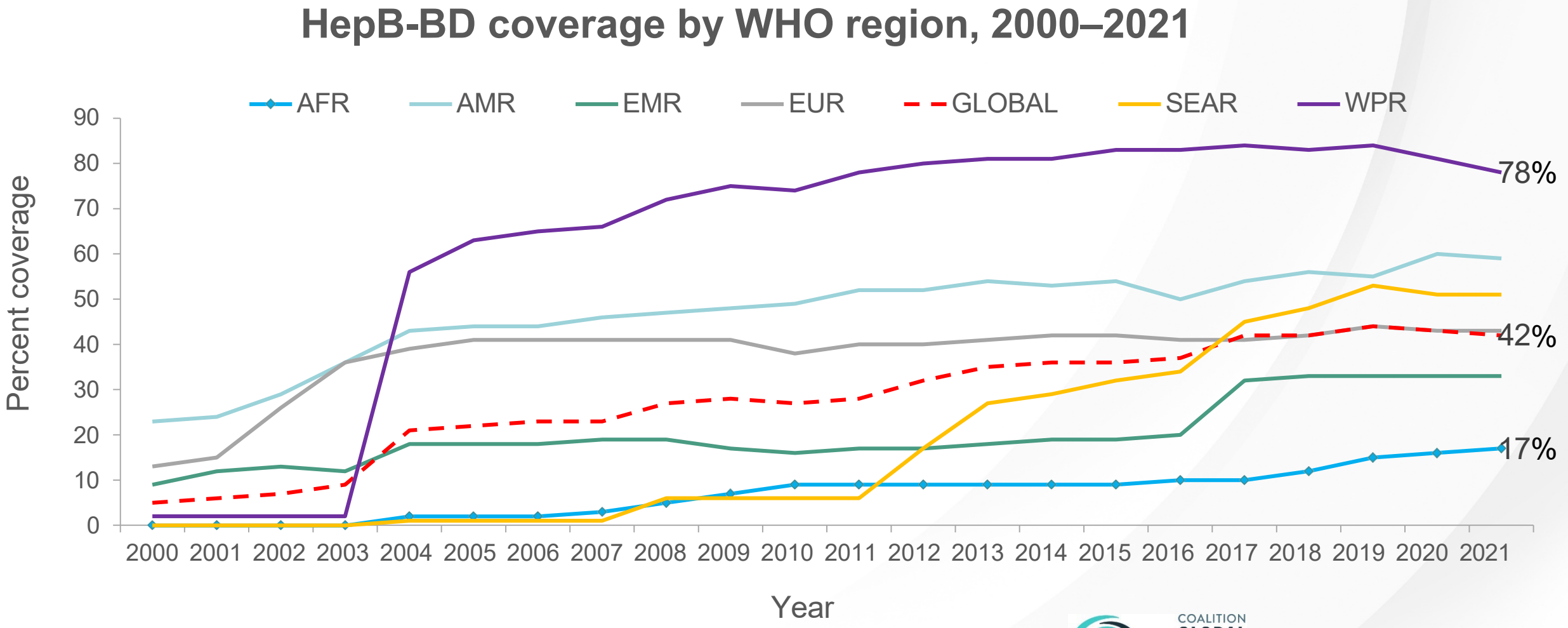
# Western Pacific has highest coverage of HepB-BD vaccine; Africa region the lowest

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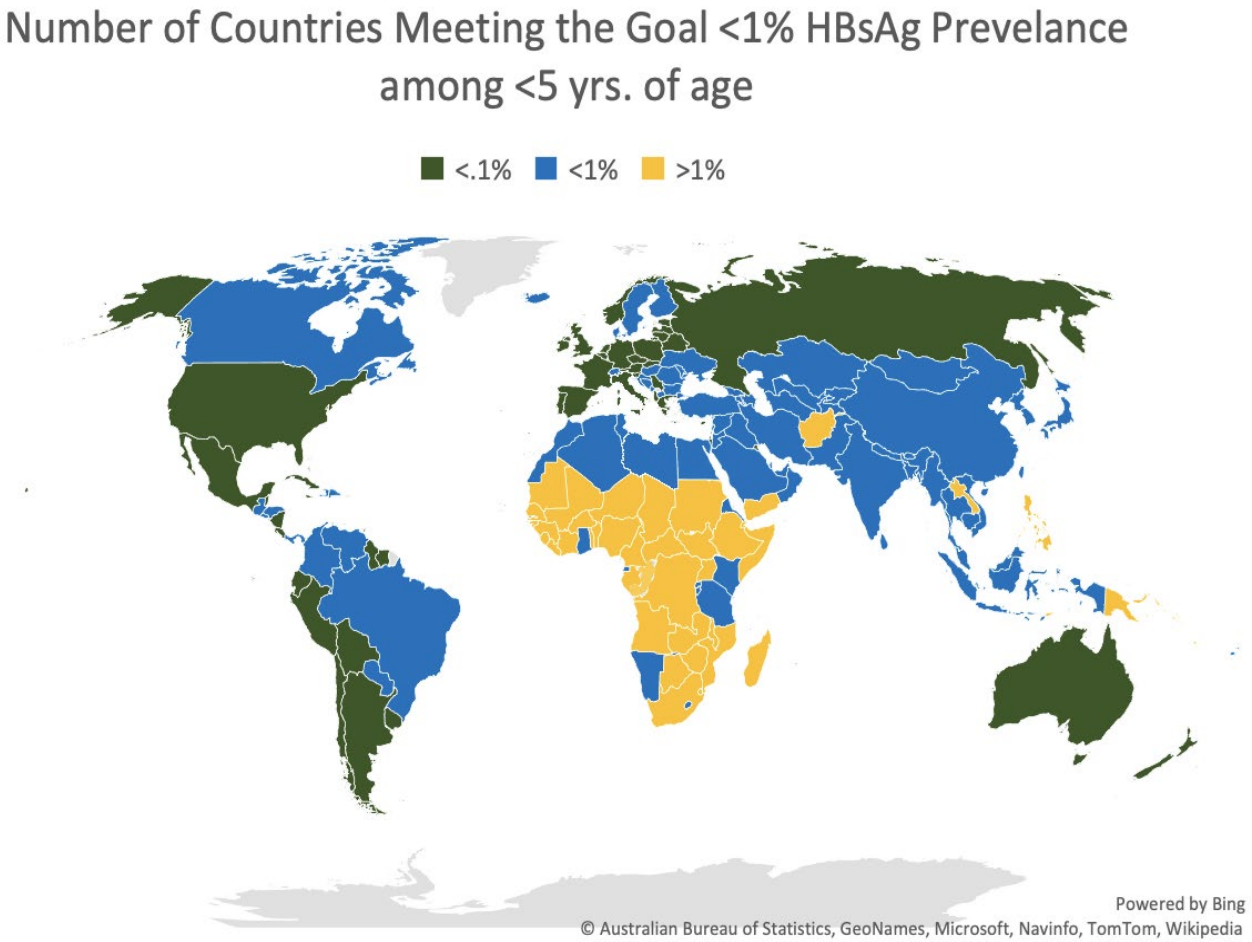
# Achievement of Interim Global Targets for HBV Elimination among Children

**Interim Global Goal < 1%; achievement 0.97%**
**African Region 2.53%**

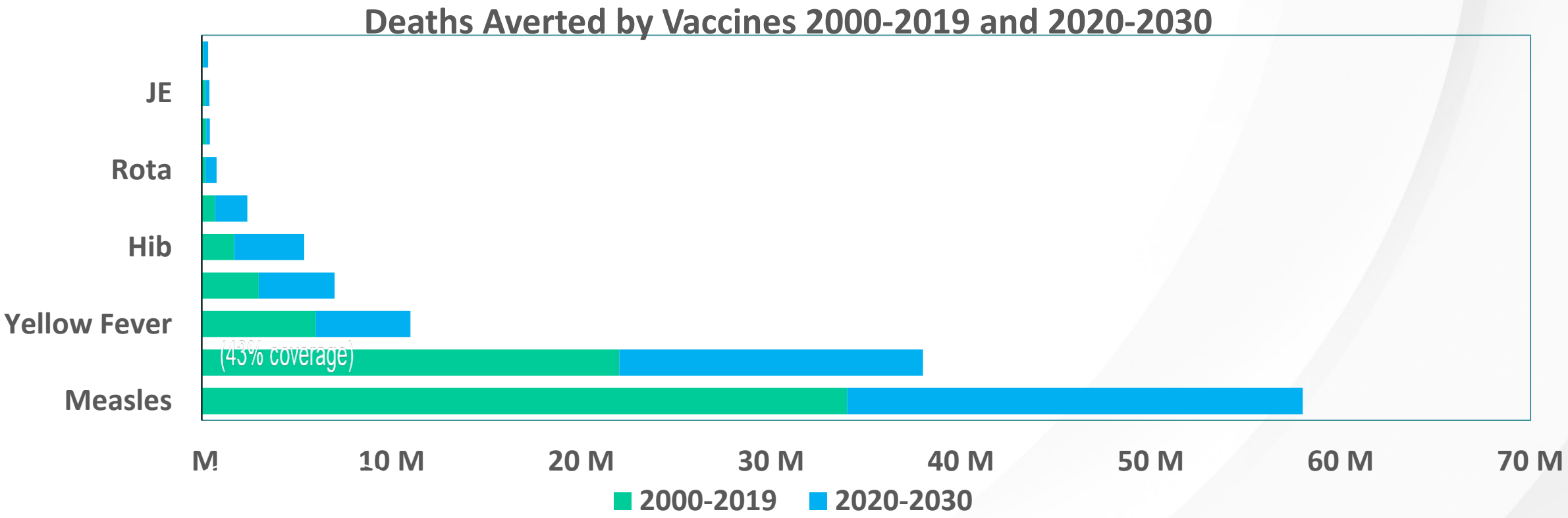



| Regions Currently Meeting the Goal <1% HBsAG Prevalence <5 | | |
|---|---|---|
| WHO Region | Number of Countries | Proportion of Region |
| PAHO | 35 | 100% |
| AFRO | 15 | 32% |
| EURO | 53 | 100% |
| EMRO | 16 | 76% |
| SEARO | 10 | 91% |
| WPRO | 18 | 67% |
| Total | 147 | 76% |

IHME 2019; WHO www.who.org

# WHO Hepatitis B Vaccination Averted 22 Million Deaths from 2000-2019 and Potential of 38 Million Deaths by 2030

*Progress toward elimination can begin before goals are set*




Achievement of Interim 2020 Goal
Global < 1.0 prevalence among children < 5 yrs.

Li X, et al Lancet 2021;39:398-408.

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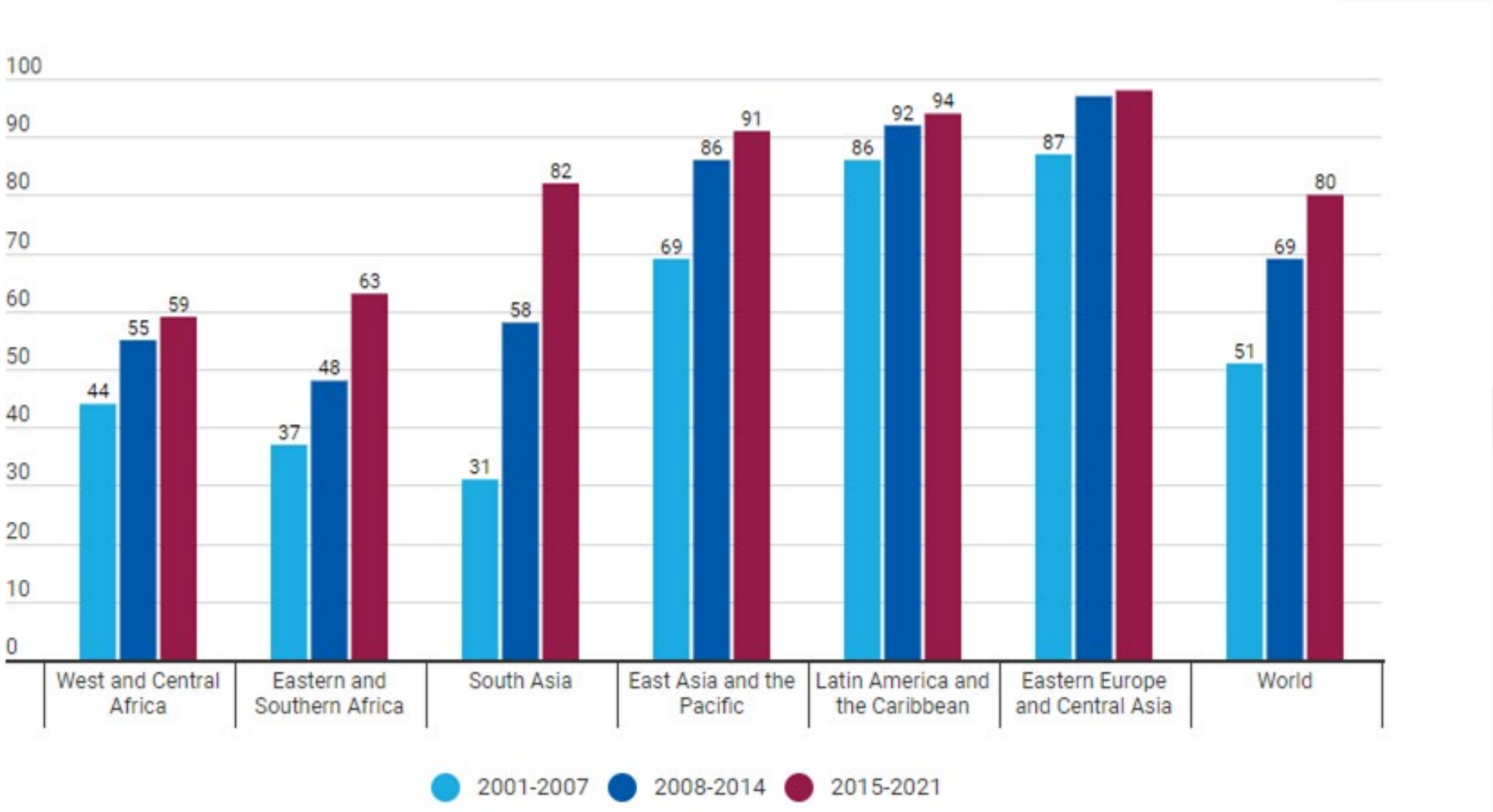
# Percentage of Births Taking Place in a Health Facility by UNICEF region, (historical trends 2001- 2021)




**Source**: UNICEF global databases, 2022, based on population based national household survey data and routine health systems.
**Note**: Data not shown for regions where population coverage is below 50%.
https://data.unicef.org/topic/maternal-health/delivery-care/

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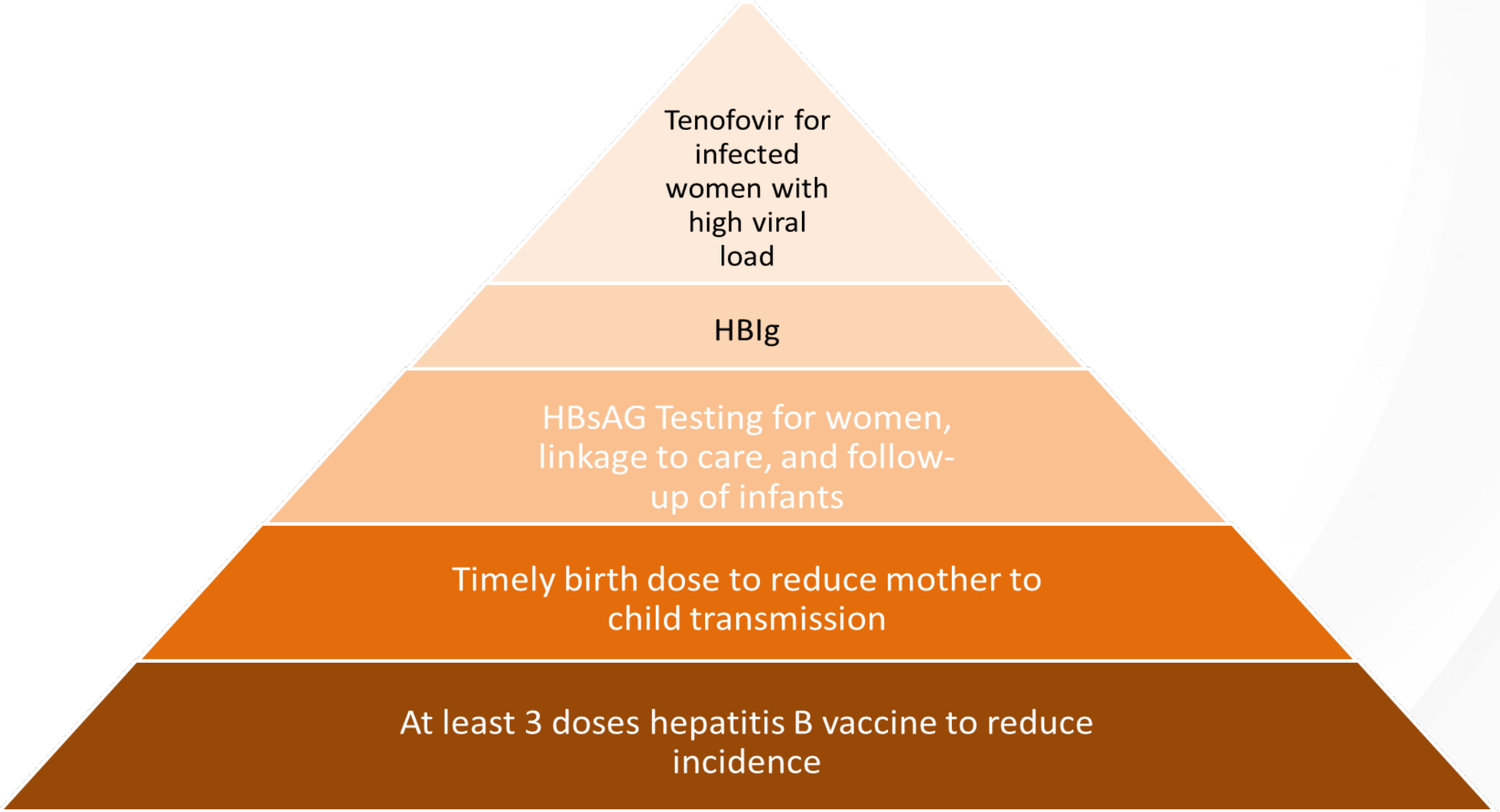
# Mothers with High Viral Loads at Greatest Risk of Perinatal HBV Transmission

- **All infants received vaccine and HBIG**
- **Infant with chronic HBV at ~ age 9 months**
  - 4/138 (3%) with maternal HBV DNA positive
  - 0/91 with maternal HBV DNA $<10^8$ copies/mL
  - 4/61 (7%) with maternal HBeAg positive
  - 4/47 (9%) with maternal HBV DNA $\geq 10^8$ copies/ml

E Wiseman, Aust J Med, 2009

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# The call for triple elimination of HIV, congenital syphilis, and Hepatitis B



- Global strategy for women's, children's and adolescents' health 2016-2030
- WHO recommendations on antenatal care (2016)
- Regional action plan for healthy newborn infants 2014-2020

- End the AIDS, STI epidemics and viral hepatitis as public health threats by 2030
- Regional action plan for viral hepatitis, 2016-2020

Common platform of maternal, neonatal and child health (MNCH) care and similar interventions across three infections

Currently,

- ➢ Services not always provided as a standard component of MNCH care
- ➢ Planning, implementation and reporting do not always occur in coordination, resulting in gaps or duplications

Result: Services less favorable and accessible to women, children and their family
→ **infants born with largely preventable infections**

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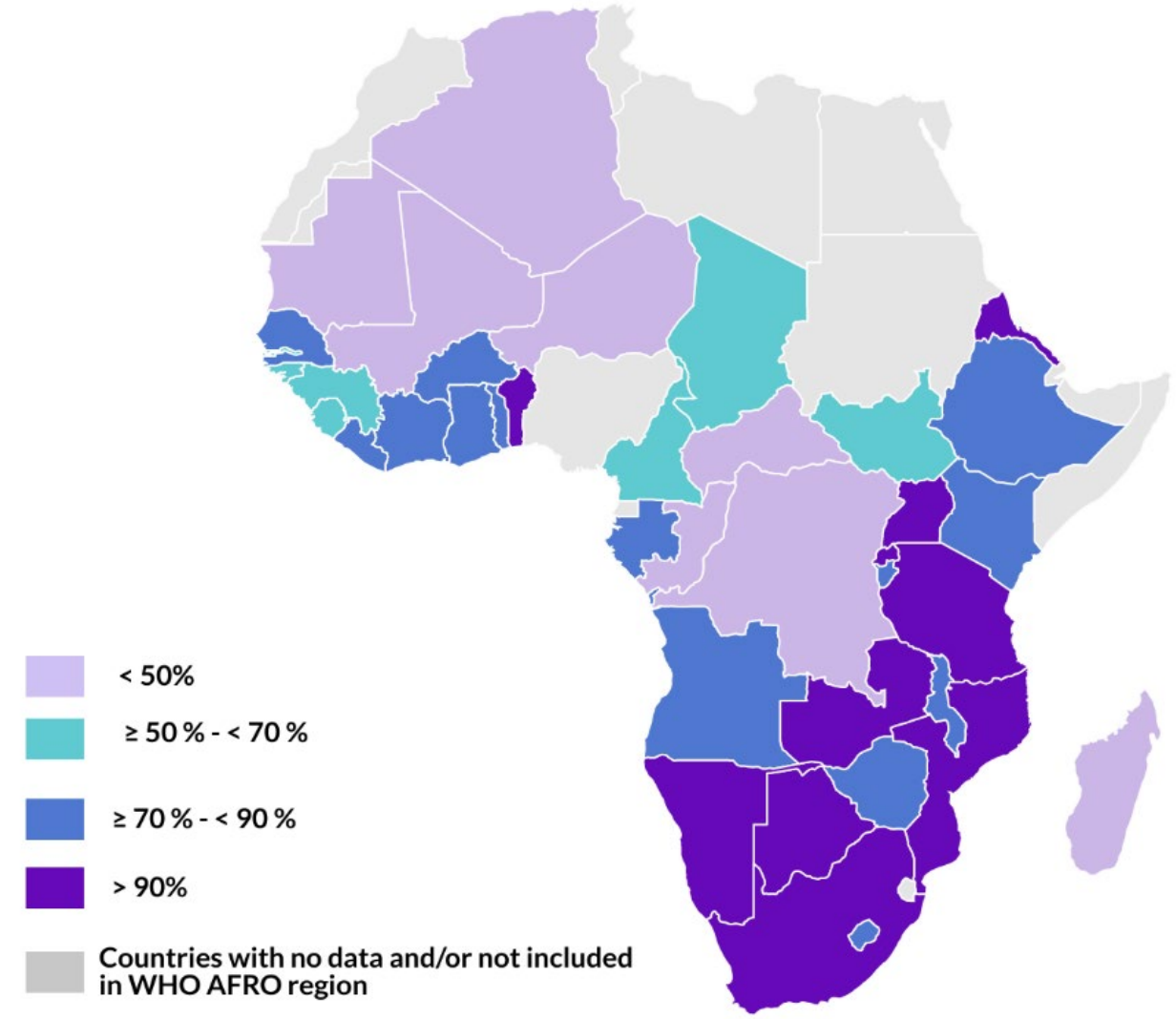
# Percent Coverage of Pregnant HIV + Women Receiving HIV Antiviral Prophylaxis for PMTCT




Source: UNAIDS https://aidsinfo.unaids.org?did=554c9070c904ab29709ecd44&r=world&t=2022&tb=m&bt=mnli&ts=0,0&ml=2&mt=1

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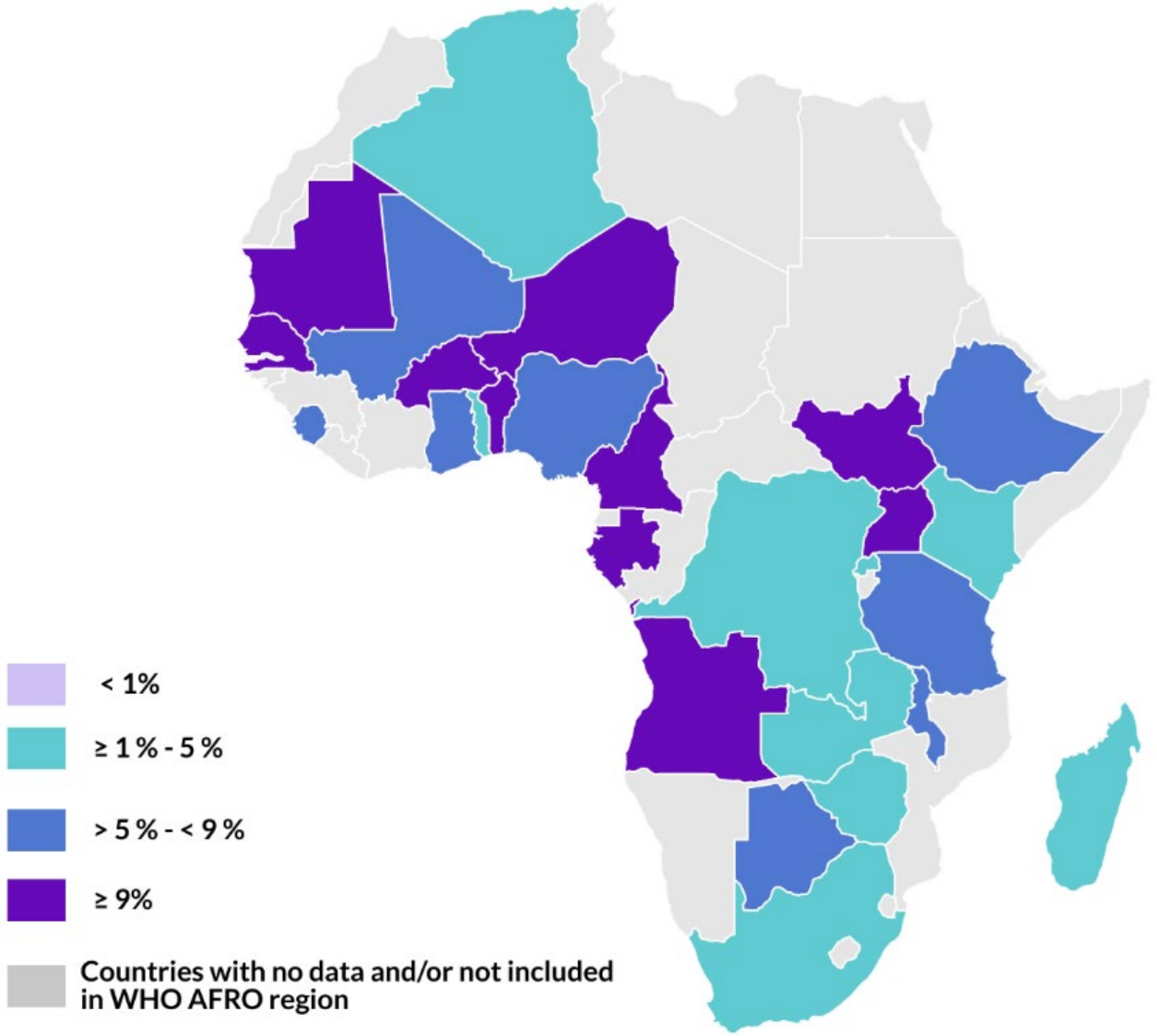
# HBsAg+ Prevalence among Pregnant Women in Africa




Sources:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7176112/
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https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-023-15710-y#:~:text=Our%20findings%20are%20consistent%20with,25%5D%20at%20approximately%2012%25
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https://www.researchgate.net/publication/336854332_Maternal_Hepatitis_B_Virus_Infection_Pregnancy_and_Infant_Health_Outcomes_in_Botswana

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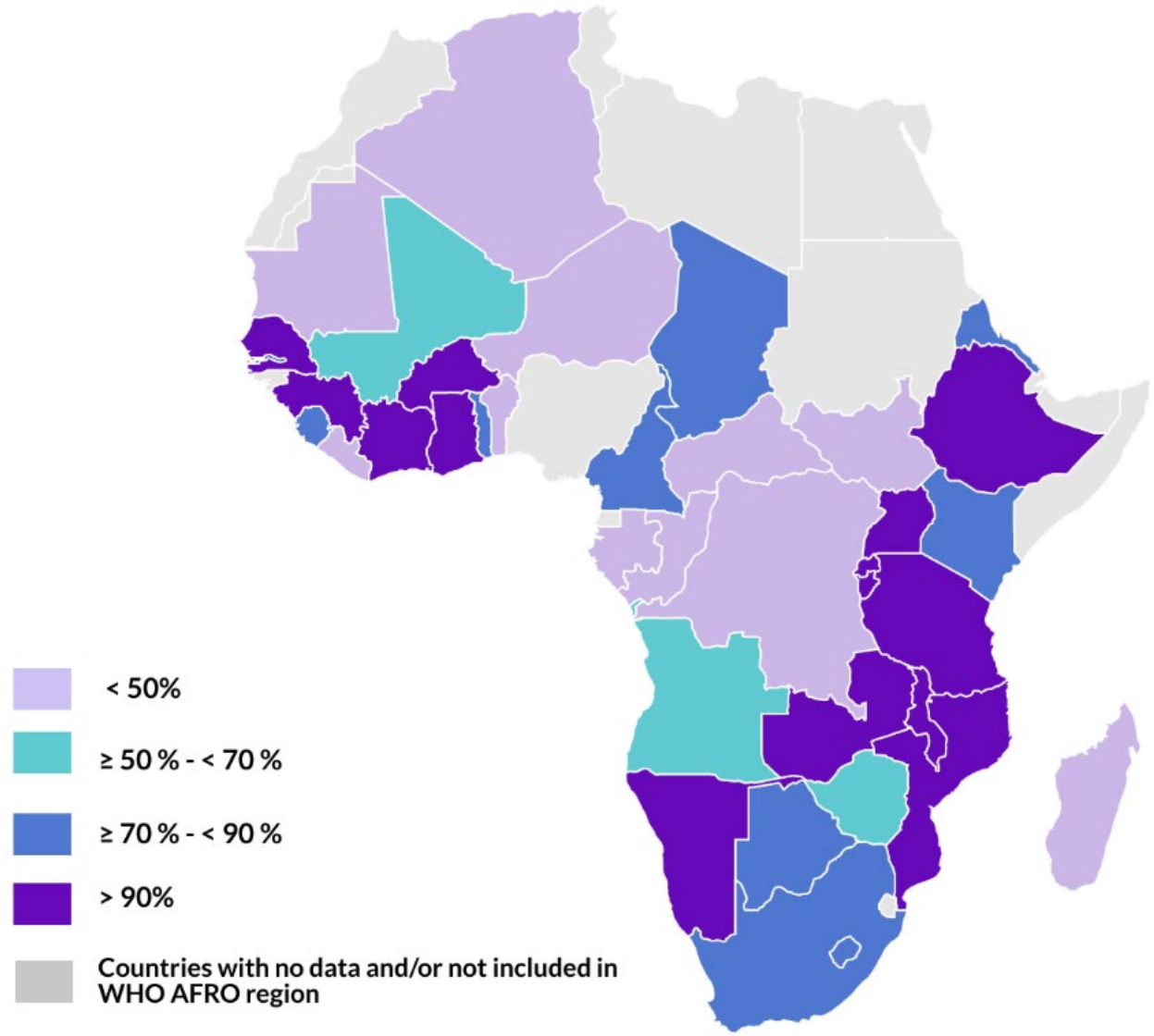
# Percent of Pregnant WomenTested for HIV




Source: UNAIDS https://aidsinfo.unaids.org?did=5b55166567e422581636f6ed&r=world&t=2022&tb=m&bt=mnli&ts=0,0&ml=2&mt=1

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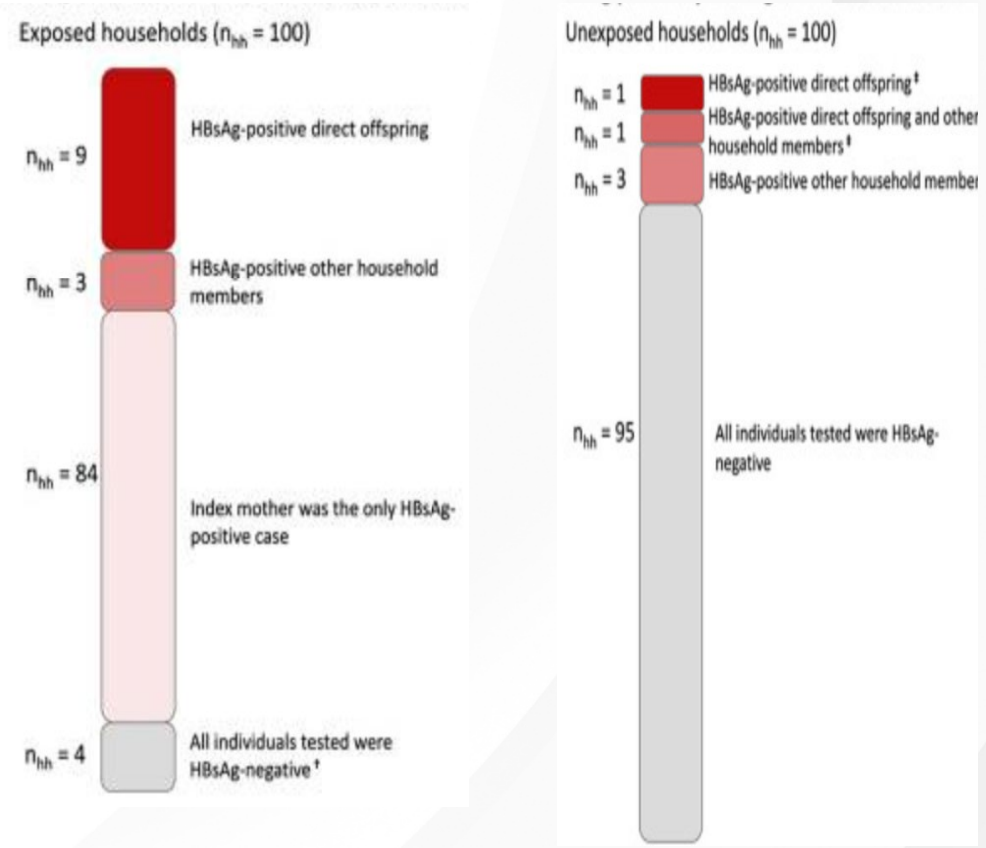
# Transmission in Households of HBsAg+ Pregnant Women- Kinshasa DRC

- 100 households of HBsAg- pregnant women ( n=422)
  - HBsAg+
  - All: 1.9% (95% CI 0.6, 3.2%)
  - Child: 1.3% (0.0%, 2.7%)
  - Other: 2.7% (0.4%, 5.1%)
- 100 households of HBsAg+ pregnant women (n=384)
  - HBsAg+
  - All: 5.0% (2.8%, 7.1%)
  - Child: 5.3% (2.4%, 8.2%)
  - Other 4.5% (1.2%, 7.7%)




HBV risk exposures ( horizontal)
No. sexual partners, sharing nail clippers, street salons, scarification,

CE Morgan medRxiv. 2024

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# Priority Research Area 2: Improve interventions to eliminate mother-to-child transmission of HBV that protect the health of both mother and newborn, as well as their families - Research Questions

- How can maternal HBsAg screening be integrated into antenatal care and with other screening tests (i.e., triple elimination of HBV, HIV, and syphilis)?
- How can HBsAg+ women be routinely screened to identify those at high risk of HBV transmission to their newborn?
- How can uptake and adherence to antiviral prophylaxis be optimized in pregnant women?
- How can HBsAg+ women be referred for appropriate hepatitis B care and when should antiviral prophylaxis be discontinued?
- How can partners and family members of HBsAg+ mothers be counseled and receive appropriate vaccination, testing, and treatment services?
- What strategies are needed to build awareness, understanding, and acceptance of HepB-BD among pregnant women, birth attendants, and communities?

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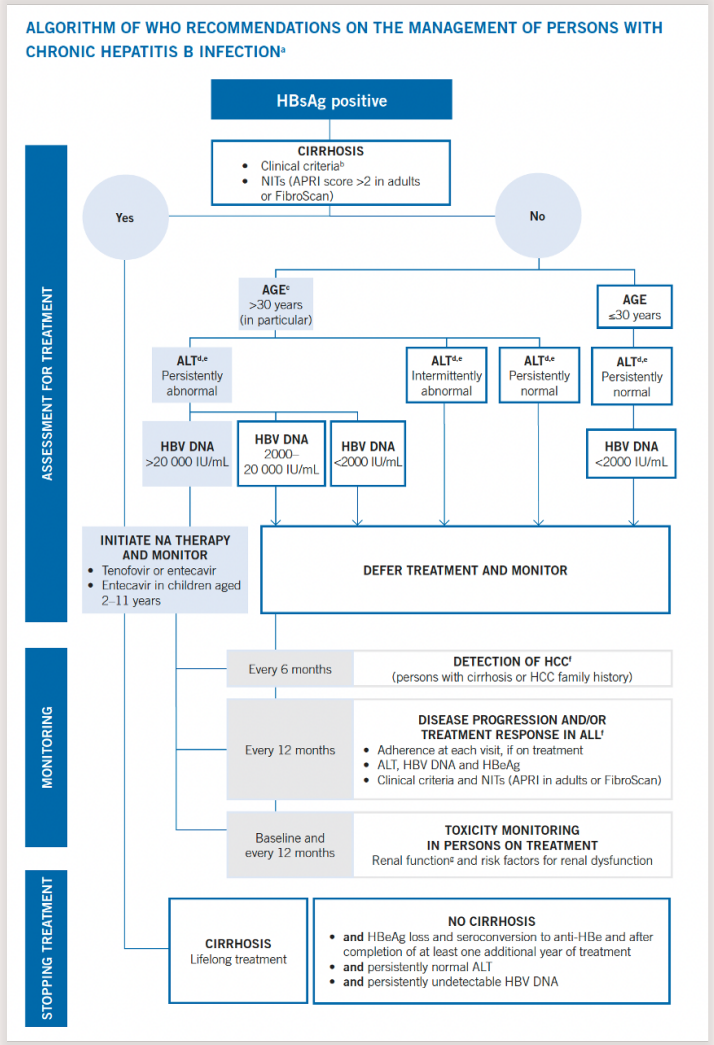
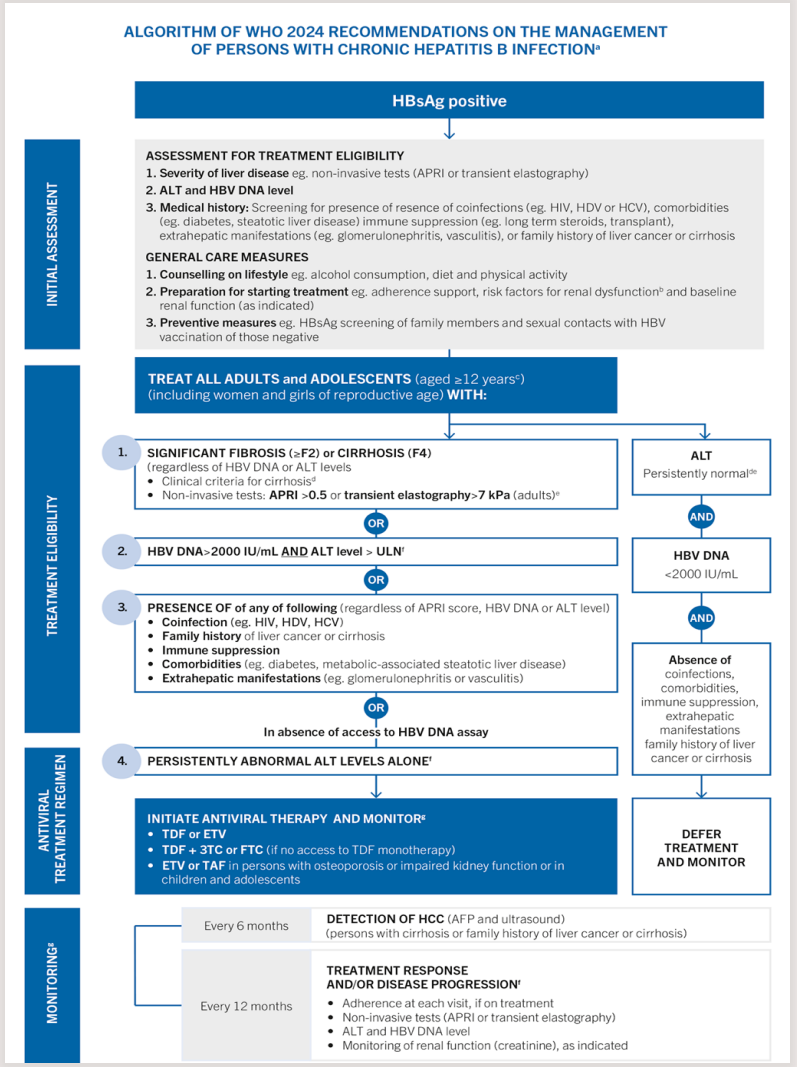
| Design Options | Study Examples | Outcomes of Interest |
|---|---|---|
| **Formative Research** (surveys, focus groups)<br>**Timeline:** Short<br>**Cost:** Low<br>**Potential Impact:** Low | 1. Provider perspectives on simplified delivery of HepB care delivery<br>2. Provider and patient perspectives on promotion of HepB screening, care, and treatment | - Inform study priorities<br>- Design HepB education for healthcare workers in non-specialist settings |
| **Implementation Science & Observational Studies**<br>**Timeline:** Medium<br>**Cost:** Medium<br>**Potential Impact:** High | 1. Feasibility of new or ongoing care models for EMTCT, referral of HBsAg+ women for care, counseling and care services for HepB exposed families<br>a. Coverage of maternal HBsAg testing, and appropriate antiviral prophylaxis and HepB-BD<br>b. Integration of test technologies and service delivery (triple elimination)<br>c. Strategies for counseling, testing, vaccination, and care for families of HBsAg+ women<br>d. Effectiveness of strategies for antiviral prophylaxis, linkage to care adherence, and postpartum follow up<br>e. Delivery of HepB care for mothers delivering infants in facilities and at home | - **Care cascade:** adherence to care, testing uptake, diagnosed, linked to care<br>- **Health system:** feasibility, cost, cost-effectiveness<br>- **Patient-reported:** preferences, acceptability |
| **Randomized Control Trials**<br>**Timeline:** Long<br>**Cost:** High<br>**Potential Impact:** High | 1. Evaluate comprehensive package of interventions for EMTCT and maternal care compared to the status quo<br>2. Evaluate EMTCT algorithms<br>a. stratified by indicators of high viral load, all HBsAg+ women<br>b. referral HBsAg+ women to care<br>c. follow up testing of HepB exposed infants<br>3. Evaluate maternal antiviral prophylaxis strategies and safety of discontinuation<br>4. Comparison of methods for family counseling and engagement in vaccination, testing, and treatment services | - **Care cascade:** adherence to care, treatment, and disease assessment<br>- **Clinical:** MTCT at six to nine months, maternal flare occurrence after discontinuation, indicators to adherence to long-term therapy<br>- **Patient-reported outcomes:** acceptability, satisfaction, quality of life<br>- **Health system:** feasibility, costs, cost effectiveness<br>- **Epidemiology:** MTCT and under-five prevalence |

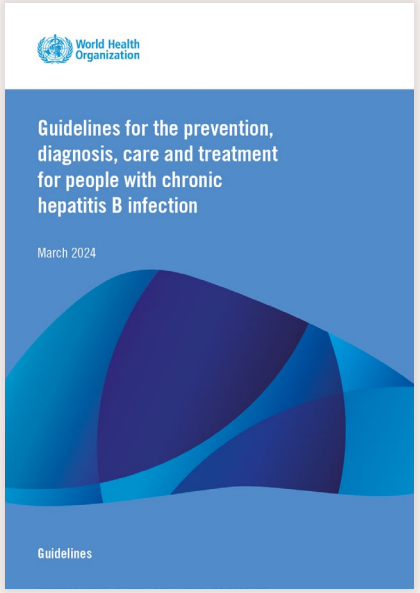
# Simplify Eligibility Criteria for HBV Treatment

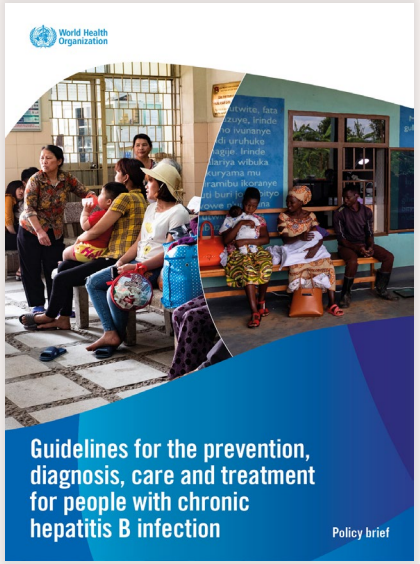
## 2015




## 2024 – NEW

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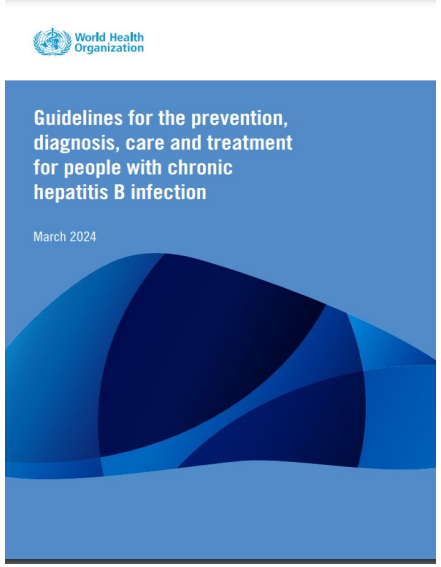
# 7. Preventing mother-to-child transmission of hepatitis B using antiviral prophylaxis




## 7.1 Recommendations

**Antiviral prophylaxis among pregnant women and adolescent girls** *(3)*

### Updated recommendation

**In settings where HBV DNA or HBeAg testing is available**, prophylaxis with tenofovir disoproxil fumarate (TDF) is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg[a] (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.

*(strong recommendation, moderate-certainty evidence)*

### New recommendation

**In settings where neither HBV DNA nor HBeAg testing[b] is available,** prophylaxis with tenofovir disoproxil fumarate (TDF)[c] for all HBV-positive (HBsAg-positive) pregnant women may be considered (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent MTCT of HBV.

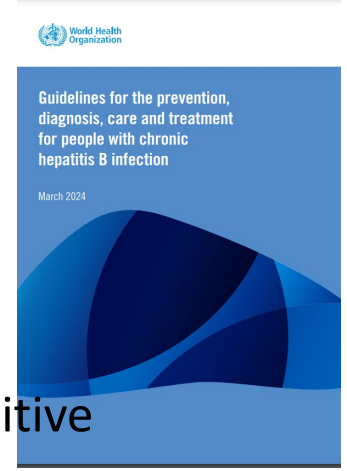
*(conditional recommendation, low-certainty evidence)*

All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose.

Note: All pregnant women and adolescent girls should be assessed first for eligibility for long-term treatment for their own health. For women of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice (Table 7.1).

Note: All pregnant women should be assessed first for eligibility for long-term treatment for their own health and then for antiviral prophylaxis to prevent mother-to-child transmission (if not eligible for treatment or pregnant mother declines).

# PMTCT of HBV
# Research Needs




- Evaluate maternal anti-viral prophylaxis (universal or high HBV DNA driven) for HBsAg-positive pregnant women, also in the absence of a timely birth dose, including home births.
- Study adherence to maternal peripartum antiviral prophylaxis and uptake of onward referral for assessing treatment eligibility among HBsAg-positive pregnant women.
- The optimal timing of TDF initiation/duration during pregnancy and postpartum treatment.
- Study benefits and potential harm of discontinuing versus continuing antiviral therapy
- Evaluate different models of integrated and simplified service delivery of antenatal hepatitis B care and treatment and triple elimination of HIV, syphilis and hepatitis B.

# Sample Research Questions

- How can maternal HBsAg screening be integrated into antenatal care and with other screening tests (i.e., triple elimination of HBV, HIV, and syphilis)?
- How can HBsAg+ women be routinely screened to identify those at high risk of HBV transmission to their newborn?
- How can uptake and adherence to antiviral prophylaxis be optimized in pregnant women?
- How maternal anti-viral prophylaxis (universal or high HBV DNA driven) for HBsAg-positive pregnant women, also in the absence of a timely birth dose, including home births?
- How to study optimal timing of TDF initiation/duration during pregnancy and postpartum treatment including studies of benefits and potential harm of discontinuing versus continuing antiviral therapy?

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# Sample Research Questions

- How can HBsAg+ women be best referred for appropriate hepatitis B care
  - What is the impact of referral to care for pregnant women?
- How can partners and family members of HBsAg+ mothers be counseled and receive appropriate vaccination, testing, and treatment services?
  - What the health impact  for family members receiving these services?
- What type of technical capacities and settings are needed to conduct research for decentralizing HBV care in Africa?
  - What are the types of study settings?
- What are the priority gaps in building this capacity?
- What is the role of communities in research to improve HBV care ?
  - Priority-setting;
  - Protocol development
  - Study implementation
  - Date analysis and , presentation
  - Who are key stakeholder

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