### 4.1. WHO to test HBV?

**Decision-making tables – PICO 1**

What is the impact, cost, and cost–effectiveness of different HBV testing approaches and scenarios?

<table>
<thead>
<tr>
<th>Population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Risk-based screening in different high-risk populations</strong>: Injecting drug users (IDUs), men who have sex with men (MSM), immigrants, recipients of blood transfusion and blood products, sex workers, and health-care workers (HCW), HIV-infected persons</td>
</tr>
<tr>
<td>2. <strong>General population</strong> (excluding blood donors) or selected subpopulations of general population (women during pregnancy, those with raised alanine aminotransferase [ALT], Infants, schoolchildren and adolescents)</td>
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<tr>
<td>4. <strong>One off screening</strong> vs repeat screening every five years</td>
</tr>
</tbody>
</table>

**Intervention**: Testing strategies for HBV in different populations (risk based and general population and birth cohort); and at different prevalence thresholds

**Comparator**: No testing or current practice or comparison of different testing strategies

**Outcomes**: Benefits, harms and costs, and cost–effectiveness with different screening strategies for different target populations

- **Individual patient outcomes**: No. of cases detected, overall mortality, liver-related mortality, cirrhosis, end-stage liver disease, rate of hospitalizations, serious adverse events, quality of life

- **Prevention**: New infections (mother to child, horizontal [IDUs needle sharing and sexual; and sexual, esp MSM])

- **Cost–effectiveness**: Cost and incremental cost per case diagnosed; cost and incremental cost per case screened and treated; cost and incremental cost per life saved; cost and incremental cost per infections averted; quality-adjusted life years (QALYs) gained
Background:

Epidemiology:
Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more – is a major public health problem. Worldwide, there are an estimated 250 million chronically infected persons, particularly in low- and middle-income countries (LMICs). Universal hepatitis B immunization programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction.

The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20% and 30% of those who become chronically infected will develop these complications, and an estimated 650 000 people will die annually due to CHB.

The risk of developing chronic HBV infection decreases with age at infection, from about 90% when infected perinatally up to 6 months of age to 20–60% between the ages of 6 months and 5 years. Of those who acquire HBV as children 25% will develop primary liver cancer or cirrhosis as adults.

Routes of transmission worldwide: In sub-Saharan Africa and east Asia, transmission predominantly occurs in infants and children by the perinatal and horizontal routes (i.e. resulting from close contact that is not parenteral, perinatal, or sexual in nature) whereas in more industrialized countries, rates of new infection and acute disease are highest among young adults and transmission predominantly occurs via injecting drug use and other high-risk behaviours. Worldwide, the majority of infections are acquired at birth or in early childhood.

Low rates of diagnosis: The majority of people are unaware of their HBV infection, and therefore often present with advanced disease. At present, there is a massive burden of undiagnosed and untreated hepatitis B and C, with 40–85% of infected persons undiagnosed, but varies greatly by setting. By contrast, the estimated awareness of status among people living with HIV (PLHIV) is within 40%–60% range for two thirds of countries, but varies significantly (CHAI, UNAIDS Info).

Based on still limited studies, overall <15% of the estimated 180 million who are chronically infected with HCV are aware of their diagnosis, based on data from higher-income setting – United States, Europe and China.

And from a survey in the US, a similar proportion of those with chronic HBV infection are aware of their diagnosis.

The proportion in low-income settings is even higher, with only a tiny fraction diagnosed and aware.

Reasons for low uptake of testing are multifactorial, and include lack of awareness at all levels, lack of clear guidelines, competing health-care priorities, limited health-care budgets and political will.
This leads to many people remaining undiagnosed until the later stages of the disease, when prognosis is poor.

In addition to the very low access to and uptake of testing, there is also further attrition in the care cascade with very poor linkage to care and therefore treatment, among those who test positive.

**Hepatitis B and C testing and diagnosis are at the core of entry to both the prevention and treatment cascade.**

- Testing is required to *identify those with are positive*, linking them with care, counselling them on measures to reduce transmission to others then assessing who needs treatment, initiating treatment, achieving treatment response (sustained virological response [SVR] for hepatitis C) or long-term viral suppression for HBV and retaining in care for HBV.

- Hepatitis testing is also needed to *identify those who are negative*, to provide hepatitis B vaccination, and the opportunity to implement individual or facility-level prevention measures, counsel to reduce risk behaviours, or institute facility-level prevention measures on measures to acquisition.

**There are three key approaches to screening:**

1. **Population- or community-based screening (including antenatal).** This means that all members of the population have access to the screening programme under consideration. It may also include home-based testing (house to house); campaigns (e.g. HTC plus – malaria, safe water, noncommunicable diseases e.g. diabetes and hypertension); outreach (mobile) in general and key populations; workplaces and schools; and health-care facility-based screening.

2. **Health-care facilities.** Testing could also be offered in special dedicated clinics, e.g. HIV, STI clinics. Screening at health-care facilities may include primary care settings, inpatient and outpatient settings, and may involve screening on the basis of clinical presentation or focus on only those with abnormal liver function tests, abnormal ultrasound scan, family history of liver disease or other clinical suspicion of liver function test.

3. **Targeted risk factor-based screening.** This refers to screening of specific groups including key populations, who are generally at higher risk of being infected than the general population. This includes people who inject drugs (PWID), people in prisons and other closed settings, migrant populations, some indigenous populations, MSM and sex workers, but may also include health-care workers. People attending services providing care and treatment for viral hepatitis or HIV can be encouraged to bring their partners to be tested.

4. **Birth cohort screening** for HBV and HCV.

**Existing guidelines: what are countries doing?**

1. Most countries have based their list of high-risk groups as defined by the Centers for Disease Control and Prevention (CDC), and are largely based on known modes of transmission. Generally they include recommendations for three main screening approaches: (Apata, MMWR Morb Mortal Wkly Rep. 2014;63:613–19; Weinbaum, Hepatology. 2009;49:S35–S44; Han, Vaccine.
Population-based screening that includes antenatal clinic screening

- Screen those with high-risk behaviours, exposures and other conditions
  - Family members and household contacts of hepatitis B patients
  - MSM
  - PWID
  - HIV-positive patients
  - Patients on immunosuppression or chemotherapy
  - Persons with liver disease of unclear etiology
  - Health-care workers.

- Birth cohort for HCV screening in US and Japan.

2. At present, there is no universally accepted recommended screening programme. There is widespread testing of blood donors (but not necessarily universal), and widespread antenatal screening and infant vaccination in Asia. In addition, there is a risk factor-based testing in high-risk groups in Asia (PWID, liver disease, renal dialysis) and use of a birth cohort approach in the US and Japan.

Survey of guidelines (Surjo De)

Evidence: systematic reviews of prevalence of HbsAg

1. General population: systematic review (Ott, Lancet 2015)

161 countries included.

High endemicity (>5%): Most countries in Africa were of higher–intermediate endemicity (HbsAg prevalence 5–7.99%), or highly endemic for HBV (HbsAg prevalence ≥8%. The Western Pacific Region was also a high–intermediate endemicity region (5–7.99%), especially in the Pacific Island States such as the Solomon Islands.

Intermediate endemicity (2–5%): The Eastern Mediterranean Region was of lower–intermediate endemicity (2.00–4.99%), but Djibouti, Somalia and Sudan showed a higher prevalence of HbsAg than other countries in the region such as Iran.

Low endemicity: Countries in the Americas, such as Mexico, Guatemala, and the USA had mostly low endemicity levels (HbsAg prevalence <2%), ranging from 0.01% (95% CI 0.01–0.01) in the UK to 10.32% (8.56–12.38) in Kyrgyzstan. Overall, the South-East Asia Region had low endemicity levels but on country level, an HbsAg prevalence below 2% was only noted in India, Indonesia and Nepal.
Summary of prevalence across risk groups

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</thead>
<tbody>
<tr>
<td>East Asia and Pacific 5-7.99%</td>
<td>Southeast-Asia and East Asia 29-19.5%</td>
<td>Albania 18%</td>
<td>Azerbaijan 3.3%</td>
<td>East Asia and Pacific 11.3%</td>
<td>South Asia Region 4.6%</td>
<td>Central and Eastern Europe and Central Asia Region 5.8%</td>
<td>Europe 0.1(Spain)-4.4% (Slovakia)</td>
<td>East Africa 6-11%</td>
</tr>
<tr>
<td>South Asia Region 2-4%</td>
<td>South Asia 5.8 - 17.3%</td>
<td>Croatia 0.90%</td>
<td>Bosnia 1.4%</td>
<td>South Asia Region 4.6%</td>
<td>Central and Eastern Europe and Central Asia Region 5.8%</td>
<td>Central and Eastern Europe and Central Asia Region 5.8%</td>
<td>West, Central Africa 6-15%</td>
<td>Tanzania tertiary hospital 5.6-7% (Mueller et al. 2015)</td>
</tr>
<tr>
<td>Central and Eastern Europe and Central Asia Region 2-4%</td>
<td>Central Asia 7.9%</td>
<td>Georgia 10%</td>
<td>Serbia 1.8%</td>
<td>Europe 0.1(Spain)-4.4% (Slovakia)</td>
<td>Latin America 0.6-2%</td>
<td>South East Asia 1-2%</td>
<td>Uganda tertiary hospital 8.1% (Ziraba et al. 2010).</td>
<td></td>
</tr>
<tr>
<td>North Africa and Middle East Region 2-4%</td>
<td>Eastern Europe 0.5-21.3%</td>
<td>Serbia (incl. Kosovo) 8.70%</td>
<td>Turkey 2.4%</td>
<td>Europe 0.1(Spain)-4.4% (Slovakia)</td>
<td>Latin America 0.6-2%</td>
<td>South East Asia 1-2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa Region 5-7.99%</td>
<td>North Africa and Middle East 0.0 - 18.5%</td>
<td>Turkey 3.60%</td>
<td>Ukraine 9.1%</td>
<td>Europe 0.1(Spain)-4.4% (Slovakia)</td>
<td>Latin America 0.6-2%</td>
<td>Dollar East Asia 1-2%</td>
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<tr>
<td>Latin America</td>
<td>Central Africa 3.8 - 9.0%</td>
<td>Ukraine 9.80%</td>
<td></td>
<td></td>
<td>Latin America and Caribbean Region 1.7%</td>
<td>Eastern Mediterranean 10%</td>
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<td></td>
<td>Andean Latin America 2.3 -</td>
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2. PWID: Systematic review ([Nelson et al. 2011])

PWID are a key population who are at particularly high risk of HBV, HCV and HIV infection. In many high-income countries and some developing countries, ongoing HCV transmission is driven mainly by PWID populations. A review of global prevalence data from 77 countries estimated that exposure to HCV (anti-HCV positive) among PWID is estimated to be between 60% and 80% in 25 countries, and over 80% in 12 countries. Similarly, of 59 countries where data were available, prevalence of HBsAg...
among PWID ranged from 5% to 10% in 21 countries and over 10% in 10 countries. PWID data are global by 20 Global Burden of Disease regions
Southeast Asia and East Asia: 2.9–19.5%
South Asia: 5.8–17.3%
Central Asia: 7.9%
Eastern Europe: 0.5–21.3%
Central Africa: 3.8–9.0%
Andean Latin America: 2.3–8.6%

3. **MSMs and sex workers: systematic review** ([Hope et al. 2014])
MSM can acquire HBV and HCV sexually. In many populations, there are higher rates of HBV infection among MSM, requiring targeted HBV screening and vaccination. MSM who are HIV positive are at significantly higher risk of acquiring HCV infection than HIV-negative MSM.

   Sex workers are a key population who are at high risk of acquiring HBV and HCV infection. Multiple factors may contribute to this vulnerability, including unsafe working conditions, barriers to negotiating consistent condom use, and difficulties accessing health-care services.

**MSM (12 countries), sex workers (5 countries)**

<table>
<thead>
<tr>
<th>Country</th>
<th>MSM</th>
<th>Sex workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Croatia</td>
<td>0.9%</td>
<td>1.4% (Bosnia)</td>
</tr>
<tr>
<td>Georgia</td>
<td>10%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Serbia (incl. Kosova)</td>
<td>8.7%</td>
<td>18.3%</td>
</tr>
<tr>
<td>Turkey</td>
<td>3.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Ukraine</td>
<td>9.8%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

4. **Migrants and refugees: systematic review** ([Rossi et al. 2012])
sub-Saharan Africa Region: 10.3%
East Asia and Pacific: 11.3%
Central and Eastern Europe and Central Asia Region: 5.8%

5. **HIV-infected persons: systematic review** ([Easterbrook et al. 2015])
HIV/HBV (483 estimates from 75/193 (39%) countries
HBsAg prevalence based on a total of 170 estimates in HIV-infected persons, based on population type (general population, PWID, MSM, heterosexual, and pregnant women) and by eleven geographical regions.

1. First, reflecting the epidemiology of HBV in Africa whereby the majority of HBV infections are acquired perinatally or in childhood, the prevalence among key populations of HIV-infected PWID and MSM is not substantially higher than the background rate in the general population or among heterosexuals, especially in Africa,

2. Only in the South-East Asia Region is there a higher prevalence in among PWID and MSM.

6. Prisoners

The prevalence of HBV in prisons is often significantly higher than in the general population. Globally, the prevalence of HIV, STIs, hepatitis B and C and tuberculosis in prison populations is estimated to be two to ten times higher than in the general population, and in some settings, 50 times higher. People in prisons and closed settings may be at particular risk for HBV, HCV and HIV infection for a number of reasons. Most commonly, this is due to sharing of needles and syringes and other injecting equipment; often because prevention hardware such as clean needles and syringes are not accessible to prisoners.

7. Indigenous populations: In some settings, indigenous populations are also disproportionately affected by viral hepatitis infection, along with a number of other health problems. Contributing factors to these disparities may include higher rates of injecting risk behaviours among indigenous people who inject drugs and higher rates of incarceration.

Epidemic scenarios

The broad categories of “generalized” and “concentrated” epidemics are not necessarily helpful in determining how best to prioritize hepatitis testing services. But some general principles apply.

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<table>
<thead>
<tr>
<th>Region</th>
<th>Gen pop</th>
<th>PWID</th>
<th>MSM</th>
<th>Hetero</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mid-point co-infection prevalence (Interquartile range)</td>
<td>Number of studies</td>
<td></td>
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</tr>
<tr>
<td>East Africa</td>
<td>8% (6-11)</td>
<td>10</td>
<td>9%</td>
<td>1</td>
<td>6.5% (5-10)</td>
</tr>
<tr>
<td>West, Central Africa</td>
<td>11% (6-15)</td>
<td>11</td>
<td>22%</td>
<td>1</td>
<td>12% (8-20.5)</td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Latin America</td>
<td>1% (0.6-2)</td>
<td>3</td>
<td>27%</td>
<td>1</td>
<td>9% (6-11)</td>
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<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>South East Asia</td>
<td>2% (1-2)</td>
<td>2</td>
<td>18%</td>
<td>(10-20)</td>
<td>10</td>
</tr>
<tr>
<td>Eastern Europe and CAR</td>
<td></td>
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<tr>
<td>Europe</td>
<td>4% (3-7)</td>
<td>3</td>
<td>5%</td>
<td>(4-6)</td>
<td>9</td>
</tr>
<tr>
<td>East Med</td>
<td>10%</td>
<td>1</td>
<td>8%</td>
<td>(4-44)</td>
<td>10</td>
</tr>
<tr>
<td>East Asia</td>
<td>9.5% (2.5-37)</td>
<td>4</td>
<td>12%</td>
<td>(10-13.5)</td>
<td>10</td>
</tr>
<tr>
<td>Western Pacific</td>
<td></td>
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</table>
Recommendations

Guiding principles for hepatitis B and C testing:

1. Promotion of health equity and human rights in national hepatitis B and C testing so that: expanded testing and access is fair and equitable; priority for testing is on diagnosing the undiagnosed; identifying those in greatest need of treatment and those with ongoing risk of infection; and that testing is voluntary and care is provided in a supportive environment free of stigma and discrimination.

   *This is critical as many of the affected population are those who are systematically excluded from access to testing, treatment and care, such as sex workers, injection drug users, men who have sex with men, and prisoners.*

2. All persons who test positive for hepatitis B and C (in addition to HIV) should have access to and be linked to hepatitis care and treatment services.

3. Testing of key populations should be undertaken where possible in conjunction with other risk or harm-reduction services.

DRAFT recommendation(s): Existing recommendations on prisons, for sex workers and PWID on HBV vaccination

1. Prisons should have a comprehensive hepatitis programme, including the provision of free hepatitis B vaccination for all prisoners, free hepatitis A vaccination to those at risk, and other interventions to prevent, diagnose and treat hepatitis B and C equivalent to those available in the community (including condom, needle and syringe programmes and drug dependence treatment as needed).

2. Include sex workers as targets of catch-up hepatitis B immunization strategies in settings where infant immunization has not reached full coverage (Source: WHO, 2012).
3. It is suggested to offer people who inject drugs the rapid hepatitis B vaccination regimen.

**Summary and quality of evidence** *(see SR_Who to screen_HBV modelling report for references)*

**Summary of evidence base for different screening approaches**

The evidence base for these different screening approaches remains very limited, and largely relies on observational data and modelling.

- There are descriptive data showing that targeted testing and community-based screening programme approaches can increase uptake of testing and detection of cases, but very limited data to show impact on patient important outcomes (Pollack, Health Aff (Millwood) 2011;30:1974–83; Bryce BD, Yartel AK. Am J Prev Med 2014;47:23341).

  - Community-based: BFreeNYC screening program (~9000 people screened, 6 cases HCC + 22 end-stage liver failure diagnosed and managed)

- Lack of evidence and uncertainty as to whether risk-based targeted screening is reaching targeted populations.


- 32 studies all from high-income countries in settings with low HBV prevalence. No data on cost or cost–effectiveness of screening for HBV in LMICs was identified. Eight published studies, and one unpublished study (PROLIFICA screening study in Gambia) met inclusion criteria.

- Two studies evaluated HBV screening in the general population and seven studies in “high-risk” groups (all but one concerned screening in migrant or refugee populations). There was one previously published study in the USA and one forthcoming study in the Gambia, looking at the cost–effectiveness of offering screening and treatment to the general population.

- The studies used different methods of screening the “high-risk groups”
including, in the clinical setting (Wong, Rein), community outreach methods (Rein) and overseas screening (Jezwa). Various outcome measures were used, including cost per quality-adjusted life year (QALY) gained, cost per LY saved and cost per case screened. Many of the models were simulated using hypothetical cohorts.

- Overall, data show that offering screening to the general population with subsequent antiviral treatment strategy is cost–effective in HICs (Eckman), as well as LICs (Nayagam), even down to a population prevalence as low as 0.3% and 2%, respectively, in these studies.

- **PROLIFICA study of HBV community-based screening in Gambia:** the feasibility of large-scale screening and treatment in sub-Saharan Africa (SSA) has been demonstrated by the ongoing PROLIFICA (Prevention of Liver Fibrosis and Liver Cancer in Africa) study in West Africa (Lemoine et al., forthcoming). This implementation study has screened nearly 10,000 adults for HBsAg at the community level in the Gambia and Senegal using an active outreach method. This is followed by full clinical assessment of those found to be HBsAg positive and antiviral treatment if meeting eligibility criteria. A cost–effectiveness analysis of this community-based screen and treat strategy in the Gambia (Nayagam et al., forthcoming), compared to status quo, revealed an incremental cost–effectiveness ratio (ICER) of $705/LY gained (other outcome measures also calculated: $476/QALY gained or $575/DALY averted). The authors acknowledge that willingness to pay (WTP) thresholds levels, and their use, are highly debated in LMICs. However, it can be regarded as cost-effective if using the WHO WTP threshold of three times the country’s GDP per capita to define a cost–effective intervention (3 times GDP per capita = $1460 in the Gambia). This is the only cost–effectiveness study of screening and treatment we have found in LMIC settings. Furthermore, it is furnished with real-life cost and effectiveness data from a large-scale screening and treatment intervention programme. Furthermore, screening also has benefits that extend beyond the person screened to also others, for example, prevention-of-mother to child transmission.

**Conclusions:** The data on the cost–effectiveness of screening for HBV is lacking, especially in LMICs. Difficult to draw conclusions regarding the best screening strategy, in terms of who to screen and where to screen, based on cost–effectiveness alone. Currently, there is not enough literature to make strong recommendations for screening based on cost–effectiveness arguments alone.

Relatively low screening costs, highly effective and relatively low-
cost antiviral therapy at generic price and a fraction of HBsAg-positive persons requiring antiviral therapy should help drive the cost–effectiveness of a test-and-treat strategy. However, this has to be balanced against long-term treatment and the fact that a high proportion with CHB will survive without treatment.

Limitations of comparing models/generalizability of results: WHO recommendations are primarily aimed for use in LMICs. All models were from HICs (except PROLIFICA); making generalizations of results from cost–effectiveness analyses between countries or regions with such differing health-care structures, costs, patient behaviours, disease prevalence profiles and willingness-to-pay thresholds can be misleading.

Key determinants of testing approach for countries (from cost–effectiveness review):

HBsAg prevalence:
HBsAg prevalence had a relatively small influence on cost–effectiveness in most of the studies. General population screening was found to remain cost–effective (i.e. ICER below the respective WTH threshold) down to HBsAg prevalence of 0.3% in the USA (Eckman) and 2% in the Gambia (PROLIFICA).

Costs:
Cost components that need to be considered in economic evaluations of screening and treatment for HBV include costs of screening, diagnostics, monitoring and drugs. This should involve both the cost of consumables, as well as other costs, including human resource costs (which are included to various extents between different studies). A key driver of cost–effectiveness of a screen-and-treat strategy reported in some studies is the cost of antiviral drug (Rossi, Hutton, PROLIFICA). Screening costs varied between the studies, and were only found to be drivers of cost–effectiveness in the Wong and PROLIFICA studies.

Linkage to care and adherence:
Adherence to treatment and linkage to care were reported as key drivers of cost–effectiveness in several studies (Rossi, Veld). In the PROLIFICA study, variation in treatment adherence was also a key driver of cost-effectiveness.

Uptake of screening is not reported to be a key driver of ICER in the studies; however, this does not imply that high participation levels in screening is not important, as when considering health impact alone, increasing uptake
is key. The implication of this result is that it is likely to be worthwhile performing screening and treatment, even if participation in screening is assumed to be low. This could be because screening costs are low, relative to the costs and health benefits of treatment for those who are infected.

**Distribution of patients between different disease states**

The proportion of people who would benefit from treatment in a population will guide cost–effectiveness, but by how much is difficult to quantify based on current evidence, and needs further research.

<table>
<thead>
<tr>
<th>Risks/benefits</th>
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<tbody>
<tr>
<td><strong>Community-based testing (outreach, mobile or venue-based)</strong></td>
<td></td>
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<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>• Leads to earlier diagnosis and access to treatment before development of cirrhosis</td>
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<tr>
<td>• Worldwide, the majority of infections are acquired at birth or in early childhood, and there is therefore generalized high prevalence throughout population, which requires population-based testing approaches.</td>
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<tr>
<td>• Highly acceptable with index partner testing, home-based and mobile outreach for HIV</td>
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<tr>
<td>• Generally good uptake</td>
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<tr>
<td>• Way of accessing missing populations, such as men, key populations and young women who are not pregnant</td>
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<tr>
<td>• Community-based testing is a critical approach for reaching people from key populations and vulnerable populations who are unlikely to go to a facility, particularly those who are asymptomatic.</td>
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<tr>
<td><strong>Risks</strong></td>
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<tr>
<td>• May lead to lower-than-expected positivity rates with home-based testing, testing within campaigns, key population outreach and testing of index partners.</td>
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<tr>
<td>• Suboptimal linkage to care is highly variable and may be problematic.</td>
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<tr>
<td>• Unit costs may be higher, but may be cost–effective.</td>
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**Provider-initiated testing and counselling (PITC) in health-care facilities**

**Benefits**

• 89/117 low- or middle-income countries recommend HIV PITC in all patient encounters
• High HIV PITC acceptance in antenatal care (ANC) and TB settings
• Introduction of PITC increased paediatric HIV testing
• Many clinical settings in generalized epidemic settings not offering hepatitis testing – e.g. STI clinics, primary care, and so many missed opportunities for HBV diagnosis in health-care facilities.

**Key and other populations targeted testing**

**Benefits**

• Key populations are disproportionately affected by hepatitis in all regions.
• Key populations are less likely to have received HBV vaccination and offer of HBV testing will facilitate higher rates of completion of vaccination.

**Partner testing**

**Benefits**

• Participating in couples and partner HBV testing has a number of benefits. These include adoption of prevention strategies by the couple (for example, condom use, safe injecting practices) and promotion of linkage to and retention in appropriate health-care services.
• Also applies to opportunistically offering HBV testing and vaccination to family members and other close household contacts of people diagnosed with CHB re access to vaccination and care.
• Couples and partner testing helps more people know their HBV and/or HCV status, particularly men, who in generalized epidemic settings may be less likely to test than women.
• Partners: <5% of people currently HIV test with their partners and similar low rates for HBV. Note: HIV serodiscordance is common (half to two thirds of HIV-positive adults with a co-habiting relationship have an HIV-negative partner
• Offering **partner testing** for persons with HBV and HCV – highest possible yield. Although risk of infection may be low, a negative test in the partner provides reassurance and the opportunity to provide counselling on reducing future risk including vaccination.

**Risks**

• People may be reluctant to admit risk behaviours, or may be unaware they are at risk, and so a screening approach that relies on history may miss a substantial proportion of cases.
Acceptability, values and preferences

PITC
- High HIV PITC acceptance in ANC and TB settings

Partner testing
- Offering partner testing for persons with HBV and HCV – highest possible yield
- Need to overcome reluctance to provide partner testing/index partner testing

Community-based testing
- Community-based testing services would need to be made available in settings acceptable and convenient to people from key populations and vulnerable populations.
- Services need to be convenient and available, through flexible opening hours and/or walk-in or same-day appointments.
- Involving affected populations, including adolescents in design, delivery and evaluation of testing services is necessary to ensure that these programmes address their need.
- Need to address concerns that older relatives, neighbours or family friends will see them attending viral hepatitis/HIV services, including testing services.

Equity, ethics and human right implications

Will recommendation raise questions around equity?
- As for all testing services, programmes for key populations need to emphasize WHO’s “5 Cs” – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment.
- The use of community-based and hepatitis B and C rapid testing can increase the likelihood of some key populations, such as prisoners, receiving their results.
- Testing in certain populations, such as in prisons may increase the chances of stigmatization.

Are there ethical implications to this recommendation?
- No major concerns.

Resource use and financial implications
Resource use (see parameter matrix for sample HIV testing programme costs)

Estimating the costs associated with a given hepatitis testing approach can be challenging. Costs for similar hepatitis testing may differ significantly between countries and by programme type within a country. Differences in programme costs may be due to general cost differences between countries, in what specific services are provided (referral to clinic for those testing hepatitis-positive vs enhanced linkage support), cadre of staff employed (nurses vs community health workers), the ease of reaching different populations, the capacity of the health system, and the level of HIV testing coverage.

Standardized approach to costing of hepatitis testing: A common approach to estimating costs involves identifying and estimating costs incurred by the health-care provider within the following broad categories:

- personnel (for example, health-care providers at facilities, counsellors, other paid programme staff, volunteers);
- recurrent costs (for example, HIV test kits and commodities, printed materials, office supplies);
- capital expenses, often amortized over their useful life and discounted annually at 3% (for example, office space, transportation, equipment);

Materials:

- Cost of testing kits, buffer/reagents
- Cost of sterile lancets, pipettes, gloves, sharps-bins or other method of disposal of used-kits
- Cost of automated reading machine, if applicable
- Quality-control reagents, if applicable (some kits are supplied with positive and negative controls)

Training and supervision:

- Cost of training testing providers and appropriate assessment, validation and revalidation of their skills
- From included studies, excellent robust specificity of all tests is reassuring in terms of ensuring cost–effective initiation of algorithms for further investigation and treatment.
- If being utilized at the point of care, it will be the responsibility of the testing provider to record and report the result appropriately.

Other:

Are the resources required small?

- No
- Probably
- Uncertain
- Yes
- Varies
Creation of a database into which results obtained by POC can be recorded

Linkage to care, e.g. antenatal clinics.

**Possible test procurement cost:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost (US$) per test</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDT</td>
<td>0.3–0.95 (procurement cost)</td>
<td>WHO database</td>
</tr>
<tr>
<td>EIA</td>
<td>0.4–2.8 (procurement cost)</td>
<td>WHO database</td>
</tr>
</tbody>
</table>

**Costs**

In the PROLIFICA study, despite an active community-based screening campaign, screening costs were low ($7.43 per person offered screening) and the intervention remained cost–effective even if there was a 3-fold increase in screening costs. The Rein study in USA reported costs per person screened between $40 and $280, with the higher costs representing the more active outreach strategies.

**Feasibility and constraints to implementation**

*Are any major barriers expected for the implementation of this recommendation?*

The feasibility of large-scale screening and treatment in sub-Saharan Africa (SSA) has been demonstrated by the ongoing PROLIFICA (Prevention of liver fibrosis and liver cancer in Africa) study in West Africa (Lemoine et al., forthcoming). This implementation study has screened nearly 10 000 adults for HBsAg at the community level in the Gambia and Senegal using an active outreach method. This is followed by full clinical assessment of those found to HBsAg positive and antiviral treatment if meeting eligibility criteria.

A cost–effectiveness analysis of this community-based screen and treat strategy in the Gambia (Nayagam et al., forthcoming), compared to status quo, revealed an ICER of $705/LY gained (other outcome measures also calculated: $476/QALY gained or $575/disability-adjusted life year [DALY] averted). They authors acknowledge that WTP thresholds levels, and their use, are highly debated in LMICs. However, it can be regarded as cost–effective if using the WHO WTP threshold of three times the country’s GDP per capita to define a cost-effective intervention (3 times GDP per capita = $1460 in the Gambia). This is the only cost–effectiveness study of screening and treatment we have found in LMIC settings.

**Couples and partners**

*Is the option feasible to implement?*
HIV testing for couples and partners has been conducted in various settings, including ANC and community-based TB services, through ART services and during premarital health visits.

Couples and partner HIV testing for the partners of women attending ANC, in particular, is a focus in the 21 priority eMTCT countries. These countries are all highly endemic for HBV, and this provides a unique opportunity to integrate concurrent HBV testing for partners of women with CHB, or chronic HCV infection if risk factors are present.

Relevance to different settings/populations

Will this recommendation be most relevant for particular settings (e.g. endemicity)?

Adolescents

In high HBV-prevalence settings there are two groups of adolescents (that is, people 10–19 years of age) who may need access to HBV testing: (1) undiagnosed adolescents who were exposed perinatally or in early childhood and; (2) adolescents who acquire HBV sexually (through early sex, sex with multiple partners or sex with a person with CHB), or through injecting drug use. Perinatally infected adolescents urgently need to be diagnosed so that they can be linked to HBV monitoring and care and start antiviral treatment if and when this is clinically indicated. In many highly endemic HBV settings, there are a significant number of undiagnosed perinatally infected adolescents. Perinatally exposed adolescents who do not have evidence of CHB need to be vaccinated if this has not yet been done. In many countries, adolescents and young adults may have missed out on HBV vaccination depending on the timing of introduction of universal infant vaccination.

Children

Universal HBV immunization, including a vaccine birth dose within 24 hours after birth, is key to preventing MTCT of HBV, but many countries have not been able to implement this crucial intervention, due to economic and logistic constraints.

Most infants whose mothers have been diagnosed with HBV or HCV should be followed-up and routinely offered EID, and those diagnosed with either with should be regularly monitored for signs of liver disease so that treatment can be offered when necessary. However, some infants are lost to follow-up, so additional pediatric case finding is important. This can be achieved through the routine offer of PITC in health facilities, particularly in high prevalence settings, and also through testing the family members of index cases where appropriate.

HBV testing services for infants should be implemented with the aim of identifying as many HBV-infected infants as early as possible. Although a conservative approach to treatment is usually indicated, children born to HBV-infected mothers should be screened early so that monitoring for progression of liver disease can be organized and so that testing and vaccination of household contacts can be carried out.

In high-prevalence settings: HBV and HCV testing of mothers and infants should be routinely
available through a variety of services – child health services, immunization clinics, under-5 clinics, malnutrition services, well-child services and services for hospitalized and all sick children, TB clinics, and services for orphans and vulnerable children.

**Testing the family members of index cases**
Gaps in HBV testing and in documenting the HBV status of children of HBV-positive parents constitute significant missed opportunities. These gaps can be closed by following up the families of cases identified in ANC or facilities offering HBV testing. In all settings all children with an HBV-positive parent or close household contact should be tested for HBV as a priority.

**Rationale for recommendation:**

**Strength of recommendation**

**Implementation considerations**
- As for all testing services, programmes for key populations need to emphasize WHO’s “5 Cs” – particularly consent, confidentiality and connection to comprehensive prevention, care and treatment.
- Need to overcome reluctance to provide partner testing/index partner testing
- Make use of lay providers/peer testing for outreach especially among key populations
- Viral hepatitis testing for key populations needs to be delivered alongside other key primary prevention interventions.
- Accessibility and coverage of testing would need to be high to have an impact on the prevalence of HBV among PWID and other key populations. Offering DBS testing for HCV to PWID attending drug treatment programmes increased uptake of testing services.

**Research gaps**
- Further research and large scale-implementation studies should be performed to evaluate this further in other high-endemic, low-income settings.
- What proportion of HBV- or HCV-positive cases will be missed by a testing policy based on screening for at risk behaviours and exposures?
- Evaluation of different testing approaches in terms of cost, impact and cost–effectiveness and evaluation of key drivers in a range of different settings.