Annex 5.1

PICO 1 - Who to test (HBV)

Literature review on cost-effectiveness of HBV screening, treatment strategies and applicability to LMICs


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1. Background

Hepatitis B virus (HBV) infection is highly prevalent worldwide, with a disproportionately high burden in low- and middle-income countries (LMICs). There is mounting evidence regarding the efficacy of antiviral therapy in the reduction of disease progression to cirrhosis and hepatocellular carcinoma (HCC). However, this impact is not fully translated into practice as many people still remain unaware of their infection status, even in high-income countries (HICs), and this value is likely to be even lower in LMICs. For example, in the Gambia, only 0.4% of screening participants in PROLIFICA had been tested in the past. Wilson and Jungner criteria have been used to assess whether a disease should screened. However, despite fulfilling most of these criteria, screening for HBV is not performed systematically. The reasons surrounding this are likely multifactorial, including 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 later stages of the disease, when prognosis is poor. Furthermore, even if diagnosed, access to appropriate antiviral therapy and ongoing clinical management is lacking.

Clarifications of terminology used in this report

1.1.1. High-risk group

For the purposes of HBV screening in LMIC, the categorisation of populations into “high-risk” groups is not helpful or informative in guiding policy. In most LMICs, the adult population prevalence (unvaccinated) falls into the intermediate- to high-endemicity categories. Furthermore, within countries HBsAg prevalence is more homogenous within the population, than for example, with hepatitis C virus (HCV) infection. In this report, we therefore only refer to “high-risk” groups when referring to literature from HIC settings.

1.1.2. General population screening

This is used to refer to the fact that all members of the population have access to the screening programme under consideration. This can include community outreach screening, health-care facility-based screening, etc.
1.1.3. **Targeted screening**

This refers to screening of specific groups, e.g., pregnant women. Targeted groups are not necessary at higher risk of being infected than the general population.

2. **Overview of the report**

The purpose of this report is not to represent the results of a full systematic review. It is meant to serve as a summary of existing studies on cost-effectiveness of screening and treatment for HBV, with an analytic summary of key considerations. It was envisaged that there was a lack of relevant literature in LMICs, so existing studies from HICs are described and their potential uses and limitations when drawing conclusions are discussed.

3. **Search strategy**

We searched the bibliography of two previous systematic reviews on the cost-effectiveness of HBV screening by Hahné et al. and Gueue et al. (unpublished, shared by WHO team) and included these in the discussion, where appropriate. Hahne and Gueue searches were performed up to 2011 and 2012, respectively. We therefore performed an updated search using PubMed to retrieve any further relevant articles to be included in this report. We searched PubMed for articles published between January 2000 and September 2015, with terms incorporating “hepatitis B”, “HBV”, or “CHB” and “cost” or “economic” and “screen”, “test” or “Diagn”. We excluded studies prior to 2000, as older studies were mainly studying cost-effectiveness of pre-vaccination screening, rather than screening for consideration of antiviral therapy. Furthermore, Gueue et al. reports the low methodological standards of cost-effectiveness analyses in older studies. We selected articles published in English only. We did not search any databases other than PubMed, nor did we search the grey literature. However, we attempted to include any known ongoing HBV screening programmes in LMIC by consulting colleagues at WHO, in order to include any unpublished studies in this report.

We excluded studies that considered screening in the following groups, unless the study reported further linkage into care and treatment – blood banks and health-care workers. We excluded evaluations that included screening prior to vaccination, unless the analysis also considered antiviral therapy for the person found to be HBsAg-positive. We also excluded studies around screening for HBV prior to chemotherapy, as this was only likely to be relevant to higher income settings and would only concern a small subset of the populations in LMIC. We also excluded studies looking at coinfection with HIV and comparing diagnostic methods.

The PubMed search retrieved 32 studies, many of which overlapped with the bibliographies of the existing reviews. All studies were performed in HICs. We were unable to find any previous studies describing cost or cost-effectiveness of screening for HBV in LMICs. Due to the lack of published literature in LMICs, to better inform the report, we also included
data from the PROLIFICA study (forthcoming). Finally, eight published studies and one unpublished study met inclusion criteria and are discussed in further detail below.

4. Summary of main literature
The existing published studies on the cost-effectiveness of screening and treatment for HBV have been performed in HICs where the prevalence in the general population is low. We have also included discussion of unpublished PROLIFICA data, which is the only study in a LIC setting.

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). We excluded studies of ANC screening as they did not consider antiviral therapy to the mother and only looked at the benefit of screening in order to guide vaccination strategies to reduce mother-to-child transmission. However, a brief summary is given below. The studies used different methods of screening the “high-risk” groups including, in the clinical setting, community outreach methods and overseas screening. Various outcome measures were used including cost per quality-adjusted life-year (QALY) gained, cost per life-year (LY) saved and cost per case screened. Many of the models were simulated using hypothetical cohorts.

4.1. General population level screening
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.

Eckman et al. looked at the cost-effectiveness of HBsAg testing of asymptomatic outpatients in primary care settings in the USA, using a hypothetical cohort (35-year-old male) with a general population prevalence of 2%. Screening was then followed by treatment with one of four regimens and compared to a no screening strategy. Screening and treatment were found to be cost-effective with an incremental cost-effectiveness ratio (ICER) of US$ 29 230/QALY. The ICER remained below their willingness to pay (WTP) threshold of US$ 50 000/QALY gained, even down to a population prevalence of 0.3%.

The feasibility of large-scale screening and treatment in sub-Saharan Africa (SSA) has been demonstrated by the ongoing “Prevention of liver fibrosis and liver cancer in Africa” (PROLIFICA) 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 US$ 705/LY gained (other outcome measures also calculated: US$ 476/QALY gained or US$ 575/DALY averted). The 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 = US$ 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.

4.2. Screening of “high-risk” groups in HIC

There were six studies looking at the cost-effectiveness of screening and treatment in migrant or refugee populations in HICs, and one looking at screening all groups classified as “high-risk” in Italy.

The study by Wong and colleagues in 2011 looked at the cost-effectiveness of screening and treatment of immigrants for chronic hepatitis B (CHB) in Canada. They considered a screen and treat strategy and a screen, treat or vaccinate strategy, with status quo (no screening). Screening was offered by the primary-care physician at a visit scheduled for another reason, described by the authors as a “case-finding” strategy. They used a hypothetical cohort (35-year-old male) with a baseline HBsAg prevalence among the immigrant population of 4.81%. The screen and treat strategy had an ICER of US$ 69 000/QALY gained. The authors acknowledge the uncertainty around WTP thresholds, but quotes range from US$ 50 000 to US$ 120 000 for Canada, implying a cost-effective intervention. This model is more clinically representative than many of the other models; however, it uses high and probably unrealistic uptake and adherence rates.

Another Canadian study by Rossi et al. (2013) looked at combinations of scenarios involving screening, treatment and vaccination among newly arrived immigrants and refugees. The screen and treat scenario was found to be the most cost-effective with an ICER of US$ 40 880/QALY gained. This strategy exceeds the Canadian WTP threshold adopted in this study of US$ 50 000/QALY, when HBsAg prevalence is less than 3%. A societal perspective for the analysis was used. A hypothetical cohort of 250 000 immigrants was used, with baseline assumptions of 70% acceptance of screening, 60% linkage to care, 75% of those eligible will have treatment and annual cost of antiviral drugs at US$ 8089.

An earlier study by Hutton et al. looked at the cost-effectiveness of screening and vaccination of Asian Pacific Islander adults for HBV by using a hypothetical cohort of 20–60 years old with a HBsAg prevalence of 10%. They compared four strategies of combinations of screening, treatment and vaccination, similar to the study described above. The screen and treat strategy was the most cost-effective with an ICER of US$ 36 000/QALY gained (compared to no screening), even down to an HBsAg prevalence of 1%. This study used a societal perspective.

Another, more recent, US study by Jezwa and colleagues compared the cost-benefits of two overseas programmes for reducing HBV infection among refugees. They compared two strategies: (i) vaccination only, and (ii) screening and vaccination; and suggested onward
treatment on arrival in USA if HBsAg was positive. The strength of this study was the use of original data sets of refugee populations in two US states. Their baseline assumptions included a prevalence of 6.8%, 100% adherence with screening, 60% of those tested positive for HBsAg will link to specialist care and that 90% will adhere to treatment.

The study by Veldhuijzen et al.\textsuperscript{13} was the only European study which looked at the cost-effectiveness of HBV screening and early treatment of migrants. An active screening method was used, where the target population is identified using the municipal population registry and receives a postal invitation to attend screening. Compared to status quo, screening and treatment had an ICER of €8966/QALY saved and was therefore reported as cost-effective compared to the authors’ reported WTP threshold of €20 000/QALY. Their baseline HBsAg prevalence was 3.35%, 58% linkage to specialist care and 75% adherence.

A study by Rein et al.\textsuperscript{14} looked at different methods of screening for HBV among the Asian migrant population in the USA. This was a descriptive rather than a formal cost-effectiveness analysis, with outcome measures given as cost per person screened. The screening methods analysed included testing at a community clinic and other more active community outreach models, where screening was performed at various events in the Asian community. The costs per person screened ranged from US$ 40 to US$ 280 depending on the method used. Integrating screening into clinical services was found to be the least costly method, but reached the least people, whereas extending screening outside the clinical setting was more costly as it included costs of organizing events and volunteer time, but reached more people. This study provides useful insights into the relative costs of various screening methods and, unlike some of the other studies, it includes full costs including those associated with recruiting patients. However, it does not provide long-term outcomes following on from a positive screening test and is therefore limited in its generalizability.

Ruggeri et al.\textsuperscript{15} looked at screening of all groups defined as “high-risk” (according to local Italian guidelines), and compared the cost-effectiveness of screening followed by treatment for CHB using one of five alternative antiviral drugs. This was compared to the status quo strategy of no screening, but treatment for cirrhosis and HCC stages only. A hypothetic cohort of 100 000 individuals was considered and screening and treatment had an ICER of €17000/QALY.

### 4.3. Pregnant women

The screening of pregnant women for HBsAg (with or without HBeAg testing) in antenatal care (ANC) settings has also been considered in previous cost-effectiveness analyses. However, all these studies consider only the reduction in mother-to-child transmission and benefits to the child (using various outcome measures—cost per case detected, cost per infant carrier prevented or cost per LY gained). None of these ANC studies include onward linkage into care or treatment for the mother, to reduce her risk of progression of liver disease. A full discussion of these studies is therefore not included in this report. Furthermore, many of the studies are older studies published before 2000 (see Hahne review for summary of these
studies\textsuperscript{18} and performed in HICs (or one in upper-middle income category). They are also heterogeneous in terms of their research question and the baseline strategy under consideration, e.g. Barbosa study is comparing a comprehensive programme to a status quo which already includes screening and birth dose (BD), hepatitis B immune globulin (HBIG) and infant vaccination.\textsuperscript{19} Fan compares whether to screen for HBeAg or HBV VL in order to guide the use of PPT antiviral therapy in USA.\textsuperscript{20} Vimloket compared universal neonatal vaccination to screening for HBsAg and HBeAg to stratify whether HBIG is needed in Thailand, using cost per infection averted.\textsuperscript{21} A full discussion of these studies is therefore not included in this report, as they were unlikely to be useful in helping guide these current recommendations for HBV screening and treatment in ANC settings in LMICs, but would be relevant to consider for reduction of HBV mother-to-child transmission strategies.

5. Drivers of cost-effectiveness

From the studies reviewed, some of the main drivers of whether a HBV screening and treatment strategy will be cost-effective are discussed below. This is not meant to provide an exhaustive list of drivers of cost-effectiveness but a descriptive analysis of key considerations, which will hopefully be useful in informing discussions. The main factors influencing the cost-effectiveness result are usually presented as the results of one-way sensitivity analyses, meant to be performed over plausible parameter ranges. However, it should be noted that the contribution of each parameter depends on the underlying type of model used and its baseline parameters.

5.1. HBsAg prevalence

Although the studies varied in the baseline HBsAg prevalence used in the model, they reported how the cost-effectiveness of the intervention would change over wide HBsAg prevalence ranges. HBsAg prevalence was found to have a relatively small influence on cost-effectiveness over the wide ranges tested in most of the studies. General population screening was found to remain cost-effective, i.e. ICER below the respective WTP threshold down to a HBsAg prevalence of 0.3\% in the USA\textsuperscript{6} and 2\% in The Gambia (PROLIFICA). Screening of migrants in North America remained cost-effective down to a prevalence of 1–3\%.\textsuperscript{12,22} Other studies did not explicitly state a prevalence cut-off when the intervention is no longer cost-effective.\textsuperscript{10,15}

It is important to note that “cost-effectiveness” is assessed using differing scales of cost and WTP thresholds between these studies. Therefore, extrapolation of the HIC results to LMICs is difficult, and absolute threshold cut-off for HBsAg prevalence should not be decided on the basis of this literature from HICs. However, the fact that all analyses revealed that a
screen and treat strategy remained cost-effective down to low HBsAg prevalence in the groups analysed increases the confidence of this finding.

This has important implications for strategy choice when considering screening in other countries with different prevalence profiles to the study in question. Also, importantly, as prevalence begins to fall as vaccination coverage increases, will it still remain cost-effective to continue screening once prevalence is low, and down to what HBsAg prevalence level does it still remain cost-effective to continue?

5.2. 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 in different studies).

A key driver of cost-effectiveness of a screen and treat strategy reported in some studies is the cost of antiviral drugs.\(^9,11,12\) The Rossi study used a drug cost of US$ 8089/year to represent the average cost of tenofovir and entecavir and varied this between US$ 7000 and US$ 9100, changing ICER by US$ 10 000, while still remaining cost-effective. Other costs were less important drivers of cost-effectiveness in their study. In the PROLIFICA study, the generic price of tenofovir (US$ 48) available for use in HIV programmes in SSA\(^23\) was used as the base case. It should be noted that this price is not currently available for most countries to treat HBV mono-infection. Using the current pharmaceutical drug price of US$ 207\(^24\) was reported to increase the ICER to US$ 1042/LY saved, whilst still remaining below the WTP threshold.

Screening costs varied between the studies, and were only found to be drivers of cost-effectiveness in the Wong\(^10\) and PROLIFICA studies. In the PROLIFICA study, despite an active community-based screening campaign, screening costs were low (US$ 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\(^14\) study in USA reported costs per person screened between US$ 40 and US$ 280, with the higher costs representing the more active outreach strategies.

It should also be noted that in HICs there are different cost components incurred (and included in these studies) for the management of end-stage liver disease, e.g. liver transplant. The cost-effectiveness of screen and treat strategies in HIC settings is partly due to the fact that early management reduces the risk of long-term sequelae, which can incur significant costs, e.g. estimated costs of managing cirrhosis is US$ 9000 per patient per year (pppy) and HCC is US$ 15 000 pppy in the Canadian study by Rossi et al.\(^11\) However, in LICs, where there are currently limited options for management of end-stage liver disease (no transplant, limited endoscopy facilities, limited palliative care) and where patients often die at home, with the family as the primary care-giver, the costs of the intervention might not offset the cost avoided of end-stage liver disease. Furthermore, the annual costs of managing liver disease are variable and largely unknown.\(^25\) The addition of a societal perspective analysis might be more appropriate in these settings.
5.3. Patient behaviour

Adherence to treatment and linkage to care were reported as key drivers of cost-effectiveness in some of the studies. Veldhuijzen et al. reported that variation in rates of linkage to care and treatment adherence had the largest influence on ICER (ICER varied by about €3000 over the ranges tested—39–75%, 50–100%, for linkage and adherence, respectively). In the PROLIFICA study, variation in treatment adherence was also a key driver of cost-effectiveness. However, rates of linkage into care were reported to be less influential on ICER in this study. The baseline value of linkage into care was high at 81%, likely aided by re-imbursement of transportation fees, clinics held in rural sites to facilitate access to treatment, active reminders about appointments, as well as good sensitization and counselling of screened participants during the study.

Linkage into care and adherence rates being drivers of cost-effectiveness should be unsurprising if one considers that in order to gain the health benefits of a screening programme, the infected person needs to start antiviral therapy to reduce their chance of progression to end-stage liver disease. Furthermore, when people drop out at later stages of the care cascade, the impact is reduced, but the initial costs have already been incurred. This highlights the importance of educating patients on the need for continued treatment that has potential implications for successful programmatic implementation. Many barriers exist to successful linkage to care including both health service and patient factors – poor health infrastructure, distance from screening site to health facility, lack of education and patient fear.

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 the key. The implication of this result is that it is likely to be worthwhile performing screening and treatment even if participation 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.

5.4. Age of cohort

Age of the cohort screened was reported as a significant driver of cost-effectiveness in the Hutton and Wong studies. The former varied aged of screened cohort from 20 to 60 years, showing variation of ICER of US$ 23 000–US$ 58 000; the latter showed ICER between US$ 60 000 and US$ 136 000 over similar ranges, and Rossi found that the screen and treat intervention is no longer cost-effective if the cohort is over 55 years, with a non-linear relationship between ICER and age. However, despite the finding in HICs that it is more cost-effective to screen and treat younger, rather than older people, there are ethical
considerations around using age cut-offs and whether this should be used to guide these type of decisions.

5.5. Disease progression rates

Although the HBV models used slightly differing natural history structures and parameter assumptions, most of them showed that the cost-effectiveness was relatively sensitive to variations in disease progression rates used.

The Dutch study\textsuperscript{13} showed that varying parameters between a range representing fast to slower disease progression showed significant variation in ICER between €5000 and €60 000/QALY gained, respectively, a trend which was also seen in other studies.\textsuperscript{10,12} The Eckman study showed that the ICER was most sensitive to the rate of spontaneous HBeAg seroconversion assumed to be 5\% at baseline, but exceeded the WTP threshold if increased to 10\%. PROLIFICA study also showed that many of the transition rates were influential on ICER.

However, given the complex and heterogeneous natural history of HBV both within and between populations, and lack of natural history progression rate data specific to all populations, this is likely to remain an inherent limitation of all CE models for HBV. However, the ICER did remain below the WTP threshold used in the respective studies for most of the ranges used.

5.6. Effectiveness of antiviral therapy

Effectiveness of antiviral therapy was found to be influential on ICER in some studies.\textsuperscript{10,12} However, different antivirals and different efficacy assumptions (which have often been superceded with more current data) were used by different authors (the older studies often included low-barrier to resistance drugs like lamivudine or interferon, whilst the newer studies mainly used tenofovir or entecavir). Therefore, conclusions as to the influence of these parameters on the result, as well as comparisons between studies have to be interpreted with caution.

With the recommendation of the use of newer drugs like tenofovir and entecavir, with similar high efficacy rates and better data on efficacy, model inconsistencies regarding efficacy assumptions should be less of a problem with economic analyses in the future. It needs to be noted that this will be dependent on the assumption that efficacy of antiviral therapy will be the same in HBV infected populations in LMICs as in HICs where most of the efficacy literature originates from.
5.7. Distribution of patients between different disease states

The proportion of HBsAg-positive patients with “stable infection”, i.e. CHB not requiring treatment was seen as one of the drivers of cost-effectiveness in some studies. Rossi estimated that 50% of migrants diagnosed with CHB would be eligible for treatment, i.e. they had active chronic infection. They found that the ICER was sensitive to the proportion with stable infection, which when decreased from 70% to 30% increased ICER from US$ 37 000 to US$ 48 000/QALY saved. Veldhuijzen et al. assumed that 26% of HBeAg positive patients and 19% of HBeAg negative patients would be eligible for treatment according to Dutch HBV treatment guidelines, but did not comment on its influence on ICER. In contrast, within the PROLIFICA study, less than 10% of patients were considered eligible for treatment (in states of chronic active hepatitis, compensated cirrhosis or decompensated cirrhosis), and when a lower proportion of HBsAg positive people had stable CHB infection, the ICER decreased, i.e. the intervention became more cost-effective.

The explanation for the differences in eligibility criteria is beyond the scope of this current report, but might be partially explained by population characteristics (especially between HBV in Asian and African populations)\(^{26,27}\) and the use of different local guidelines to classify treatment eligibility. The natural history structures are different between models, therefore direct conclusions cannot be drawn from these studies. The proportion of people who would benefit from treatment in a population, is likely to guide cost-effectiveness, but by how much is difficult to quantify based on current evidence and needs further research.

5.8. Others

Other drivers of cost-effectiveness included factors that are inherent to some of the techniques used in economic analysis, e.g. health utility values used for QALY assumptions\(^{8-10}\) and discount rate used.\(^{10,16}\) However, these are not discussed further in this report.

6. Limitations of comparing models/generalizability of results

WHO recommendations are primarily aimed for use in LMICs. Therefore, most of the studies summarized in this report have to be interpreted with extreme caution as they have mostly been conducted in HICs. The application of results from one setting cannot be translated into another setting. Conclusions drawn by making generalizations of results from cost-effectiveness analyses between countries or regions with such differing health-care structures, costs, patient behaviour, disease prevalence profiles and WTP thresholds can be misleading.
Comparison of model results are also hindered by differences in model structures, base-line scenarios used, populations under consideration, costs components included and varying assumptions around models parameters. The most useful health outcome measures to be used for cost-effectiveness analyses are also debated, and vary between studies, as do WTP thresholds.

In order to fully answer the question of what the most cost-effective approach is, ideally, a cost-effectiveness analysis is needed which is as specific as possible to the setting being considered as well as the strategies under consideration. However, this is obviously time and labour intensive.

7. Other considerations regarding place of screening

7.1. Community-level

Community-level screening could be considered the most active type of case-finding strategy with outreach components and therefore likely the most labour and resource intensive. However, within PROLIFICA, it has been found to be cost-effective, with low screening costs of US$ 7.43 per person offered screening. Various examples of community outreach programmes exist in the field of HIV,\textsuperscript{38} and comparable strategies could be considered for HBV, with the caveat that “high-risk” groups will not be as applicable to HBV infection.

7.2. Health-care facilities

Screening at health-care facilities could include primary-care settings, inpatient and outpatient settings. It could include testing everyone, regardless of the reason for 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. Testing could also be offered in special dedicated clinics, e.g. HIV, STD clinics.

A clinically guided testing approach is likely to reveal a higher proportion of people with HBV in highly endemic settings and therefore a lower cost per positive person found. Preliminary data from Mboup et al. (Senegal – verbal communication) where HBsAg screening is performed in the hospital guided by clinical reasons in the health facility (inpatient and outpatient settings), shows that out of 1000 people screened, 567 have been found to be HBsAg-positive (56.7% of those tested).

However, when considering performing a cost-effectiveness analysis of health facility-based screening, the difficulty arises in adjusting for background mortality among those seeking health care. It will depend on many factors, including underlying comorbidities and
age distribution and is likely to be highly heterogeneous between settings. Research into this is ongoing (Hess et al.).

7.2.1. ANC clinics

Cost-effectiveness of ANC screening, linkage into care and antiviral treatment for the mother (for the health benefit of the mother, rather than just the child), could be affected by the fact that women have been shown to have slower rates of progression to HCC and have lower prevalence of HBsAg than men. However, women attending ANC screening are likely to be of a younger age group than those reached by community-based screening, with a longer life expectancy, and therefore can potentially have more impact. The prevalence of HBsAg in women of childbearing age will also depend on the historical vaccination coverage in the country and the percentage of HBeAg-positive mothers will partly depend on the average childbearing age of the country and the rate of HBeAg loss in the region under consideration. However, most importantly, since screening of mothers for HBV has benefits to both the mother and child, this is likely to be cost-effective.

Since there is variable percentage of attendance to antenatal care depending on the world region (ref), with this being the lowest in sub-Saharan Africa (SSA) (77% of women have at least one ANC visit, only 48% have four ANC visits), this approach should also take into factors which will help strengthen ANC coverage in general and awareness campaigns.

7.2.2. Blood banks

Blood donor screening for HBV already forms part of WHO recommendations in order to prevent transmission of blood-borne viruses to the recipient. However, this is rarely accompanied by the HBsAg positive donor being informed of this positive result, counselled and linked into care for clinical evaluation and treatment.

As part of the PROLIFICA study, linkage into specialist care for blood donors who had tested HBsAg-positive at the blood bank was performed (Lemoine et al., forthcoming). The main difference found between the cohort of blood donors and those screened in the community were a higher proportion who were tested HBsAg-positive, a majority of whom were males, of younger ages, with a higher proportion requiring treatment and a lower proportion who linked to care. A formal cost-effectiveness analysis has not yet been performed, but these factors are likely to make it even more cost-effective for this cohort, compared to the cohorts who were screened in the community. However, as blood donors form only a small fraction of the population, this strategy is likely to be limited in its reach and population level effectiveness and probably should be seen as a complementary, rather than as an alternative to a wider screening strategy.
7.3. Workplace

Other ongoing research in West Africa as part of the PROLIFICA programme includes HBsAg screening in workplaces in Senegal (Mboup et al., unpublished data). Epidemiological and cost-effectiveness studies are underway. Provisional data shows that compared to community screening, there is a higher HBsAg prevalence, higher proportion of males uptaking screening and a higher proportion requiring treatment.

7.4. Others

Although other methods of screening are used, to varying levels, worldwide, including screening of health workers, couples pre-marriage, military recruits or pre-employment screening, etc., implementation and guidance of these methods are highly heterogeneous between countries;\textsuperscript{35} and apart from the study in Iran (below), no data was found regarding their cost-effectiveness. Therefore, they will not be considered here in further detail. The study in Iran\textsuperscript{36} looked at premarital HBsAg testing, but this was in order to determine whether to offer the partner of someone who is tested HBsAg positive vaccination. This does not include linkage for treatment. Mandatory premarital testing is not policy in many countries and would therefore have limited reach and applicability.

8. Further research needed to fill this information gap

More implementational research in LMICs needs to be done to assess feasibility, impact and cost-effectiveness of different screening methods. Further research into the simplification of care, as well as health systems research into integration of hepatitis programmes with other health services (e.g. HIV services), could also help guide how impact can be maximised and cost-effectiveness improved.

Ongoing HBV cost-effectiveness screening analyses that are being conducted are as follows:

- Screening in OPD settings – Sarah Hess, WHO
- Screening in ANC – benefits to the mother, Sarah Hess, WHO
- Screening in ANC – benefits to the child, Jess Howell, Imperial College
- Screening in work places, Senegal – Shevanthi Nayagam, Imperial College.

9. Conclusions

The data on the cost-effectiveness of screening for HBV is lacking, especially in LMICs. Therefore, it is hard to draw conclusions regarding the best screening strategy in terms of who to screen and where to screen, based on cost-effectiveness alone. However, the data that is
available shows that offering screening to the general population with subsequent antiviral treatment strategy is cost-effective in HICs\textsuperscript{8} as well as LICs,\textsuperscript{9} even down to a population prevalence as low as 0.3% and 2%, respectively in these studies. Furthermore, screening also has benefits that extend beyond the person screened but also others, e.g. prevention of mother-to-child transmission.

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. Finite treatment courses in certain patient groups are showing promising results and this could help increase cost-effectiveness further.\textsuperscript{37} Improving country access to generic priced tenofovir for HBV mono-infection in all LMICs is vital to allowing adoption of wide scale HBV treatment programmes. Other strategies for reducing costs further include integration of HBV services into existing health-care structures, particularly in SSA where enormous progress has been made in the scale-up of HIV services, which may be expanded to also deliver HBV interventions using existing infrastructure, trained health-care professionals and field teams.

Although general guidance cannot be given based on the evidence, a pragmatic approach is to encourage screening anywhere that it is feasible within the country context, e.g. it can include ANCs, health-care facilities and blood banks. PROLIFICA has shown that population-level screening is feasible and cost-effective in The Gambia, but further research and large-scale implementation studies should be performed to evaluate this further in other high-endemic, low-income settings. Furthermore, HBV screening costs could be shared across other disease programmes, as there are overlapping benefits and synergies with maternal and child health goals and HIV infrastructure and experience.

This report aims to summarize key components of the existing literature which has highlighted that apart from the PROLIFICA study in West Africa, there is no data about the cost-effectiveness of screening and treatment in LMICs. Currently, there is not enough literature to make strong recommendations for screening based on cost-effectiveness arguments alone, and further research needs to be done to fill this gap, using similar real life screening data in LMICs like the PROLIFICA project. However, cost-effectiveness analyses form only a small part of guiding public health recommendations, and the overall health impact and key drivers should be considered.

References


7. Lemoine et al. Screen and treat as an intervention programme for hepatitis B virus infection in sub-Saharan Africa: the PROLIFICA experience in the Gambia (Manuscript in progress).


