Requirements for global elimination of hepatitis B: a modelling study

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Summary

Background **Despite the existence of effective prevention and treatment interventions, hepatitis B virus (HBV) infection continues to cause nearly 1 million deaths each year. WHO aspires to global control and elimination of HBV infection. We aimed to evaluate the potential impact of public health interventions against HBV, propose targets for reducing incidence and mortality, and identify the key developments required to achieve them.**

Methods **We developed a simulation model of the global HBV epidemic, incorporating data on the natural history of HBV, prevalence, mortality, vaccine coverage, treatment dynamics, and demographics. We estimate the impact of current interventions and scaling up of existing interventions for prevention of infection and introducing wide-scale population screening and treatment interventions on the worldwide epidemic.**

Findings **Vaccination of infants and neonates is already driving a large decrease in new infections; vaccination has already prevented 210 million new chronic infections by 2015 and will have averted 1·1 million deaths by 2030. However, without scale-up of existing interventions, our model showed that there will be a cumulative 63 million new cases of chronic infection and 17 million HBV-related deaths between 2015 and 2030 because of ongoing transmission in some regions and poor access to treatment for people already infected. A target of a 90% reduction in new chronic infections and 65% reduction in mortality could be achieved by scaling up the coverage of infant vaccination (to 90% of infants), birth-dose vaccination (to 80% of neonates), use of peripartum antivirals (to 80% of hepatitis B e antigen-positive mothers), and population-wide testing and treatment (to 80% of eligible people). These interventions would avert 7·3 million deaths between 2015 and 2030, including 1·5 million cases of cancer deaths. An elimination threshold for incidence of new chronic infections would be reached by 2090 worldwide. The annual cost would peak at US$7·5 billion worldwide ($3·4 billion in low-income and lower-middle-income countries), but decrease rapidly and this would be accelerated if a cure is developed.**

Interpretation **Scale-up of vaccination coverage, innovations in scalable options for prevention of mother-to-child transmission, and ambitious population-wide testing and treatment are needed to eliminate HBV as a major public health threat. Achievement of these targets could make a major contribution to one of the Sustainable Development Goals of combating hepatitis.**

Funding **Medical Research Council.**

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Lancet Infect Dis 2016

Published Online
September 13, 2016
http://dx.doi.org/10.1016/S1473-3099(16)30204-3

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(16)30214-6

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Introduction

In 2014, the World Health Assembly requested WHO to examine the feasibility of, and strategies needed for, the elimination of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.[1] This substantial political momentum is entirely proportionate to the estimated magnitude of the global burden, with viral hepatitis ranked as the seventh highest cause of mortality worldwide and responsible for 1·4 million deaths per year (roughly 687 000 deaths due to HBV and 704 000 due to HCV).[2] However, despite being similar in scale to the 1·29 million deaths annually due to HIV, 1·34 million annually due to tuberculosis, and 850 000 deaths annually due to malaria,[3] viral hepatitis has been a relatively neglected area.[4,5]

Fortunately, a wide range of interventions are now available to prevent and treat HBV infection. Early childhood transmission can be prevented with a highly effective infant vaccine.[6] Mother-to-child transmission at birth can be almost completely eliminated by the administration of birth-dose vaccination, intravenous hepatitis B immunoglobulin, and peripartum antiviral therapy for mothers with high viral load.[7,8] For individuals who are already chronically infected with HBV, treatment with antivirals can suppress viral replication and substantially reduce the risk of progression to liver cirrhosis and liver cancer.[9,10]

However, these interventions are not fully used. Coverage of infant vaccination is high in many regions such as east Asia and north Africa and the Middle East (92–96% in 2013), but continues to lag behind in others, most notably central Africa (56% in 2013).[11] Birth-dose vaccine coverage is generally lower than infant vaccination worldwide, although a few countries, including China, have achieved over 95% coverage.[11] Treatment coverage is low in most high-burden settings (eg, sub-Saharan Africa)

Research in context

Evidence before this study

We searched PubMed for studies published up to Sept 4, 2015, with the terms "hepatitis B", "HBV", or "CHB", and "modelling", "modeling", or "model". Previous hepatitis B virus (HBV) modelling and epidemiological analyses have focused on the evaluation of the potential future impact of infant vaccination strategies. These studies have mainly been done at a country level, concentrated on prevalence and incidence outcomes, rather than morbidity and mortality, and have not examined costs of intervention. Only one study presented an HBV model on a global level, which examined the relationships between vaccination coverage and projections of deaths due to cirrhosis and liver cancer. However, this model did not include prevention of mother-to-child transmission (PMTCT) or treatment interventions, and the model was based on assumptions of a linear response between vaccination and disease incidence, which could underestimate the intervention impact.

Added value of this study

Our study is unique in providing a worldwide view of the hepatitis B epidemic and the potential impact and costs of a comprehensive set of interventions (vaccination, PMTCT, screening, and treatment). Furthermore, our study incorporates the latest data and understanding of HBV disease progression and treatment eligibility, as well as all available data on HBV prevalence and mortality and programme coverage indicators. Our results show that although much progress has been made through vaccination, a scale-up of both prevention and treatment interventions is needed to reduce HBV as a public health threat.

Implications of all the available evidence

This study frames and quantifies major issues that should be addressed as momentum increases to tackle HBV globally. It proposes targets around which strategies could develop and identifies the main implementation research priorities and innovations needed to achieve this goal. This study responds directly to the World Health Assembly resolution that calls for an evaluation of feasibility of global elimination and control of hepatitis, and Sustainable Development Goal 3.3 that aims to combat hepatitis and other infectious diseases.

and, where available, is typically provided to patients presenting for care with advanced disease and is not accompanied by active outreach or routine testing.[12]

Action on HBV worldwide will need the scale-up of these interventions, but the magnitude of impact that is achievable, the budgetary implications of scaling up interventions, and the emphasis with which these different approaches should be promoted and developed in the different regions is not yet clear.

A number of useful definitions of elimination exist. The 2015 Sustainable Development Goals (SDGs) include goals for the elimination of HIV, tuberculosis, and malaria, each of which uses a threshold definition of what constitutes elimination as a public health threat. Using this approach, we chose to adopt a threshold approach of fewer than ten per million people for incidence and fewer than 50 per million HBV-related deaths, which is intermediate to the levels used for tuberculosis and HIV.

See Online for appendix

Using a mathematical model, we aimed to evaluate the projected future course of the global epidemic of HBV infection and evaluate the impact of historical interventions. We also aimed to assess the impact of scaling up available public health prevention and treatment interventions on incidence, prevalence, and mortality due to HBV, set potential targets for elimination, and identify key developments needed to achieve them.

Methods

Model structure

We constructed a dynamic, deterministic mathematical transmission model of the global hepatitis B epidemic structured by age, sex, and region. The model is composed of 21 Global Burden of Disease world regions, and is fitted to data on hepatitis B surface antigen (HBsAg)[13] and hepatitis B e antigen (HBeAg)[14] prevalence, at two timepoints, and liver cancer deaths[15] for each region independently. The model incorporates region-specific demographic data on population size, mortality, and fertility schedules,[16] coverage of existing interventions (infant vaccination,[11] birth-dose vaccination,[11] and treatment availability[12]), and assumptions about the natural history of HBV. In the model, mother-to-child transmission, transmission between children, and transmission across the whole population (which includes other forms of transmission including sexual and iatrogenic) are included, the relative strengths of which are inferred through the calibration procedure (appendix p 35). We did not explicitly model the relative contribution of different routes of iatrogenic transmission (eg, blood transfusion, unsafe injection practices) because this is a relatively small proportion of all transmission of HBV worldwide at present and infection in adulthood is less likely to lead to chronic infection.

We did a literature review, which informed the HBV natural history scheme in the appendix (p 36). Briefly, we used twelve mutually exclusive health states, which includes seven untreated chronic hepatitis B stages: immune tolerant, immune reactive (HBeAg-positive chronic hepatitis), inactive carrier, HBeAg-negative chronic active hepatitis, compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma.[17,18] Immune reactive and HBeAg-negative chronic hepatitis B are states of chronic active hepatitis, with high or

fluctuating viral load, elevated transaminase concentration, and evidence of fibrosis. Along with compensated cirrhosis and decompensated cirrhosis, these stages are considered eligible for treatment, as per international guidelines.[18,19]

Costing model

A costing model was developed to estimate total intervention costs, which assigned region-specific, time-constant costs to each of the intervention components. The cost package included consumables plus delivery of the intervention and relevant outreach costs (appendix p 26). Cost inputs were based on costing data from published literature and databases. Primary cost results are presented in US$ (2014) to allow comparison with existing literature. An alternative approach, using purchasing power parity adjustments for non-traded resources was also done to correct for distortions in direct gross domestic product comparisons (presented in international$). Full costing methods are provided in the appendix. Antiviral drug price was based on observed global minimum pricing, assuming price reductions and in anticipation that costs can fall to these levels worldwide. The costs avoided through care costs for cirrhosis and cancer were not included because global-level data on these costs are scarce. A discount rate of 3% per year was applied when computing present values of a stream of future costs.[20]

Interventions scenarios

Five scenarios were used to quantify the effect of scaling up available interventions from 2015 (table). Additionally, we include a status quo scenario, in which the coverage of all interventions remains at their current levels, and a no historical intervention scenario, in which the impacts of all interventions are removed. In the infant vaccination scenario, coverage of infant vaccination is scaled up linearly over 5 years to 90% (or maintained at higher than 90%, if already achieved), consistent with the WHO Global Action Vaccine Plan targets for vaccination coverage of 90% or higher by 2020.[21] Addition of birth-dose vaccination involves a linear scale-up over 5 years of birth-dose vaccination coverage in neonates with HBsAg-positive mothers to 80% (or maintained at current levels if coverage higher than 90% has already been achieved) and the scenario with addition of peripartum antivirals involves a scale-up over 10 years so that 80% of HBeAg-positive mothers receive peripartum antivirals in the last trimester of pregnancy by 2025. The addition of test and treat includes testing, linkage, and adherence interventions necessary to provide successful treatment with durable viral suppression to 80% of people becoming eligible,[19] a value that signifies universal health coverage across a range of essential health services, and has commonly been used as a target for universal access to HIV treatment.[22] Treatment is assumed to be based on either tenofovir or entecavir and includes monitoring and adherence as is sufficient for patients to maintain viral suppression. Adverse events and contraindications are rare and were not considered in the model. We also included a hypothetical curative strategy whereby patients on treatment can be given a one-time intervention that results in sustained viral suppression or loss of HBsAg. Assumptions used to represent the efficacy of each intervention are outlined in the appendix (p 5).

We first used the model to generate predictions about the incidence of new chronic HBV carriage, prevalence of people living with chronic HBV, and deaths due to

	Infant vaccination coverage	Birth-dose vaccination coverage	Coverage of peripartum antivirals for HBeAg-positive mothers*	Access to treatment†	Cure expected
No historical intervention	None	None	None	None	No
Status quo	Continues at current levels‡	Continues at current levels‡	No coverage	Continues at current levels (categorised by region)§	No
Infant vaccination	90%¶||	Continues at current levels‡	No coverage	Continues at current levels (categorised by region)§	No
Infant vaccination + birth-dose vaccination	90%¶||	80%¶||	No coverage	Continues at current levels (categorised by region)§	No
Infant vaccination + birth-dose vaccination + PPT	90%¶||	80%¶||	80%**	Continues at current levels (categorised by region)§	No
Infant vaccination + birth-dose vaccination + PPT + treatment	90%¶||	80%¶||	80%**	80%†† (linear scale-up 2015–25)	No
Infant vaccination + birth-dose vaccination + PPT + treatment + cure	90%¶||	80%¶||	80%**	80%†† (linear scale-up 2015–25)	2025

Assumptions used to represent the efficacy of each intervention are outlined in the appendix (p 5). HBeAg=hepatitis B e antigen. PPT=peripartum antiviral therapy (given to HBeAg-positive mothers). *Peripartum antivirals are given to HBeAg-positive mothers only. Hepatitis B immunoglobulin not implicitly modelled because data were not available, but continues at current levels. †Includes case finding and treatment. ‡WHO data[11] on vaccination coverage up to 2013. §Global Policy report[12] on viral hepatitis and expert opinion. ¶If the regional coverage is already above the target level, it remains at current high level. || Linear scale-up 2015–20. **Linear scale-up 2015–25. ††80% incorporates a strategy of 90% case finding, 95% linked to care, 95% durable viral suppression.

Table: **Intervention strategies modelled, coverage levels, and scale-up times**

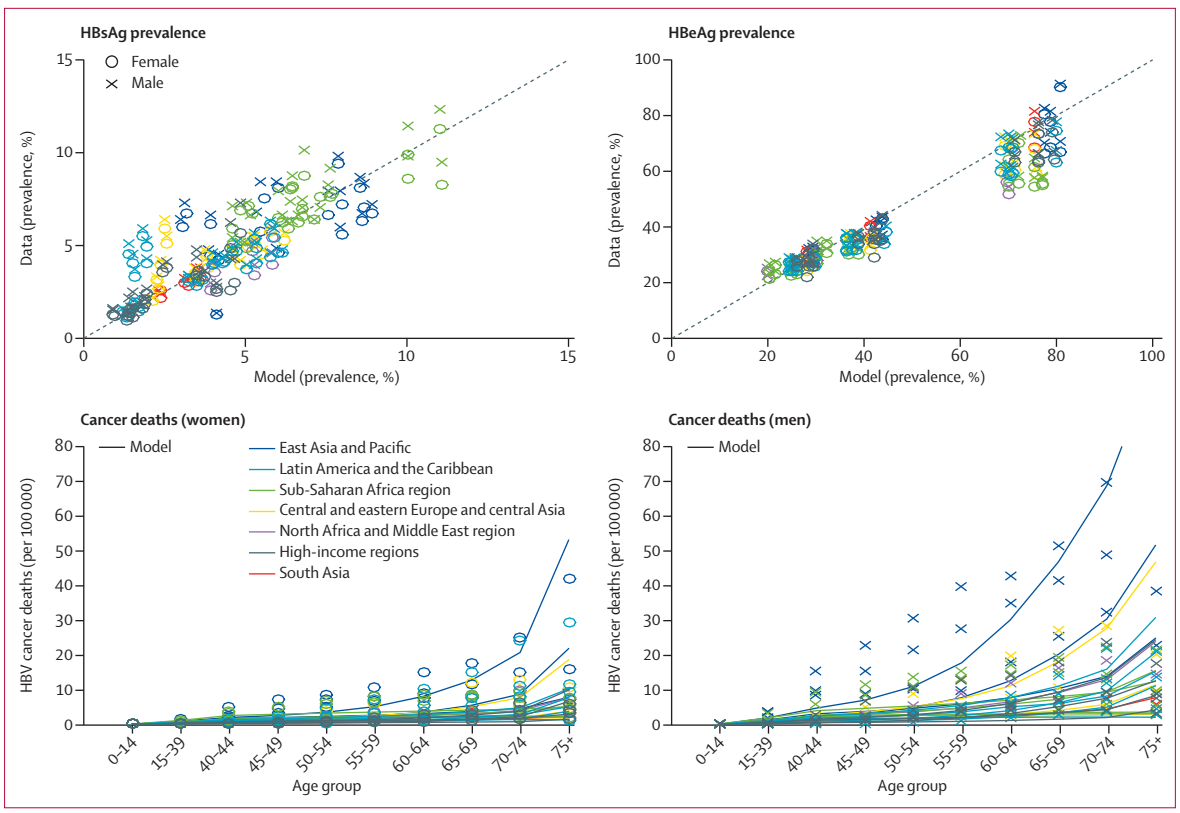

***Figure 1*: Model calibration (data *vs* modelled results)**
Calibration of the model outputs to available epidemiological data from each of the 21 world regions. Data versus modelled results by region for HBsAg prevalence (ages 5–70 years), HBeAg prevalence in HBsAg-positive people (from birth to age 40 years), and HBV-related cancer deaths (all ages in 2012). For HBsAg prevalence, individual data points are presented for each of the 21 regions, both sexes, and three age groups (5–10 years, 10–40 years, and 40–70 years) at two timepoints (1990 and 2005). For HBeAg prevalence, individual data points are presented for each of the 21 regions, both sexes, and three age groups (0–10 years, 20–30 years, and 30–40 years) at two timepoints (1990 and 2005). The lines are colour-coded to represent the seven different continent groupings. Individual regional calibration figures are in the appendix (p 45). HBsAg=hepatitis B surface antigen. HBeAg=hepatitis B e antigen. HBV=hepatitis B virus.

HBV under assumptions that interventions remain at current levels (status quo). We then compared this scenario to a scenario when all historical interventions were removed to estimate how the epidemic would have unfolded if nothing had been done previously. We then used the model to estimate the impact of scaling up prevention and treatment interventions by considering the five alternative strategies. Incidence refers to incidence of new chronic HBV carriage, rather than acute infection, throughout this Article.

Sensitivity analysis

Sensitivity analysis was done by varying the main efficacy parameters (first value representing the lower limit used for the sensitivity analysis and the second value representing the default value used in the model); efficacy of infant vaccination against chronic carriage of 88–95%,[6,23] efficacy of birth-dose vaccination against mother-to-child transmission if maternal HBeAg negative of 85–96%,[7] efficacy of birth-dose vaccination against mother-to-child transmission if maternal HBeAg positive of 75–83%,[24–28] and efficacy of antiviral treatment on prevention of mother-to-child transmission (PMTCT) of 85–99% and adherence to antiviral treatment of 65–90%. These lower limits of ranges of efficacy parameters were chosen to represent what could happen in a worst-case situation and are based on conservative assumptions.

Role of funding source

The funder had no role in data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The model reproduces the global epidemiology of HBV well (figure 1) and several key epidemic patterns are noted: prevalence of HBsAg (a marker of chronic infection) is highest in west Africa, prevalence of HBeAg tends to be higher in east Asian regions than in African regions, and the number of cancer deaths increases sharply with age and is highest in east Asia,

where prevalence is high and treatment is not widely available.

The modelled global estimate of HBV-related mortality (850 000 deaths in 2010) and the number of people living with HBV (290 million people in 2010) are both consistent with previously published sources.[1,3,29] Modelled incidence of new chronic infections in 2010 is 6·7 million. In 2010, 30% of the HBV-related deaths, 40% of the people living with HBV, and 70% of new chronic infections occurred in the five regions with most of the low-income countries.

The model projects that at status quo, there will be 4·3 million new chronic infections, 270 million people living with HBV, and 1 million deaths due to HBV in the year 2020 (figure 2). Between 2020 and 2050, the number of new infections per year will drop by 70% to 1·3 million infections per year, as a result of sustained vaccination coverage. By 2050, the number of people living with infection will decrease by 40% to 165 million, because of reducing incidence and the continued death of individuals infected with HBV. The number of HBV-related deaths per year will increase in the coming years, reaching 1·14 million deaths per year in 2034, because of ageing cohorts of infected people. HBV-related deaths will then decline to 1·06 million deaths per year by 2050.

Vaccination scale-up is already having a large effect on the epidemic (figure 2). Without any infant or birth-dose vaccination, there would be 25 million new cases in 2020; meaning that interventions have already reduced new cases by 83% and cumulatively averted 310 million new cases between 1990 and 2020. The impact is largely mediated by the effects of infant vaccination (appendix p 37). By our definition, some regions with high infant vaccination coverage are projected to reach elimination of new infections between 2060 and 2070, even with status quo coverage levels (eg, east Asia, central Asia, eastern Europe, and the Caribbean). Infant vaccination is highly effective at reducing chronic HBV carriage in children, but does not directly affect the risk of acquisition in neonates. A consequence of that is the proportion of new chronic cases that arise through mother-to-child transmission is set to increase substantially, from 16% in 1990 to 50% in 2030 (figure 2). Therefore, in most regions, additional interventions will be required to further reduce infection rates.

Furthermore, existing interventions have not yet substantially reduced the number of individuals living with chronic infection (30% reduction in 2020 *vs* no intervention) or HBV-related deaths (4% reduction in 2020 *vs* no intervention), because treatment has not been scaled up to a global level, which is needed to reduce the risk of death in people already infected. Also, the long interval between acquisition of chronic carriage of HBV and death

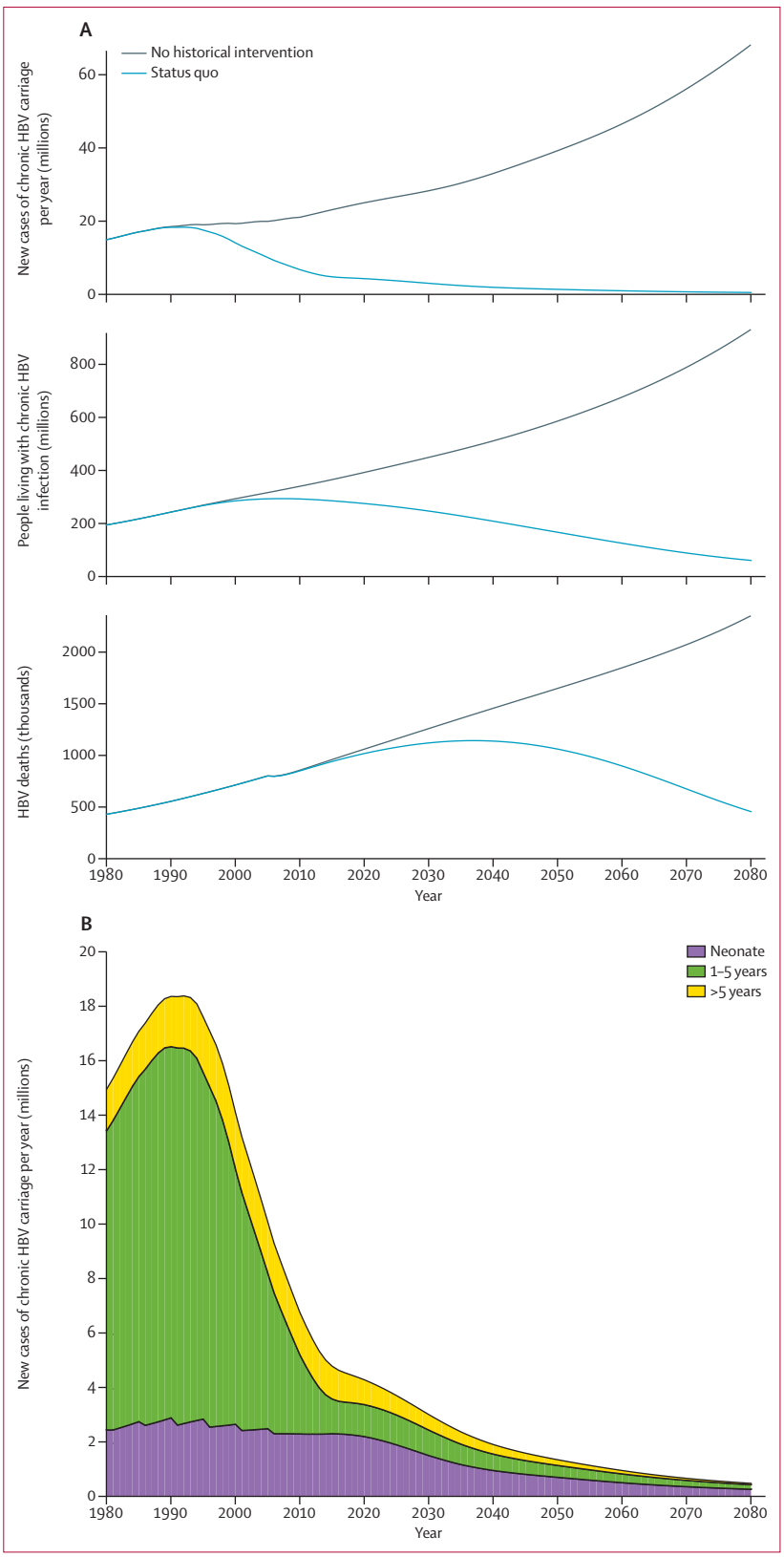

***Figure 2*: Epidemic projections for HBV**
(A) HBV incidence of new cases of chronic HBV, prevalence of HBV, and deaths caused by HBV in the status quo scenario (all interventions remain at current levels; blue line) and no historical intervention scenario (assumed no interventions have ever been applied; black line). (B) Ages of people in which new cases of chronic HBV occur in the status quo scenario. HBV=hepatitis B virus.

means that the population of people living with HBV changes slowly in response to intervention.

Without further scale-up of interventions, the number of people living with HBV is going to remain at the same high levels for 40–50 years and there will still be a cumulative 63 million new chronic infections and 17 million HBV-related deaths between 2015 and 2030. However, scaling up existing interventions could lead to a 90% reduction in incidence of new chronic infections and 65% reduction in mortality by 2030 worldwide (figure 3).

In the first scenario, scaling up infant vaccination to 90% globally would avert 4·3 million new infections between 2015 and 2030 compared with the status quo scenario. Addition of scaling up of birth-dose vaccination and peripartum antiviral therapy to 80% enhances this impact, preventing a further 19·3 million new infections, with most of that incremental impact achieved by birth-dose vaccination alone (18·7 million new cases prevented). The large incremental impact due to PMTCT intervention is because of the fact that vertical transmission increases in relative importance as other transmission routes are reduced. None of these prevention strategies reduce the prevalence or mortality in the short term, but addition of a testing and treating intervention with 80% coverage could reduce deaths by 65%, and could avert 7·3 million deaths, including 1·5 million cancer deaths, between 2015 and 2030, compared with status quo. Addition of a cure would not affect incidence or mortality, if applied to people already on successful treatment.

This set of combined interventions would bring forward the date of elimination of new incident chronic infections and HBV-related deaths in all settings (figure 3). Half of the world regions are projected to reach elimination of new incident chronic infections before 2060 with the scale-up of this set of interventions. Time to elimination of HBV-related deaths is more heterogeneous, with some regions, such as western Europe,

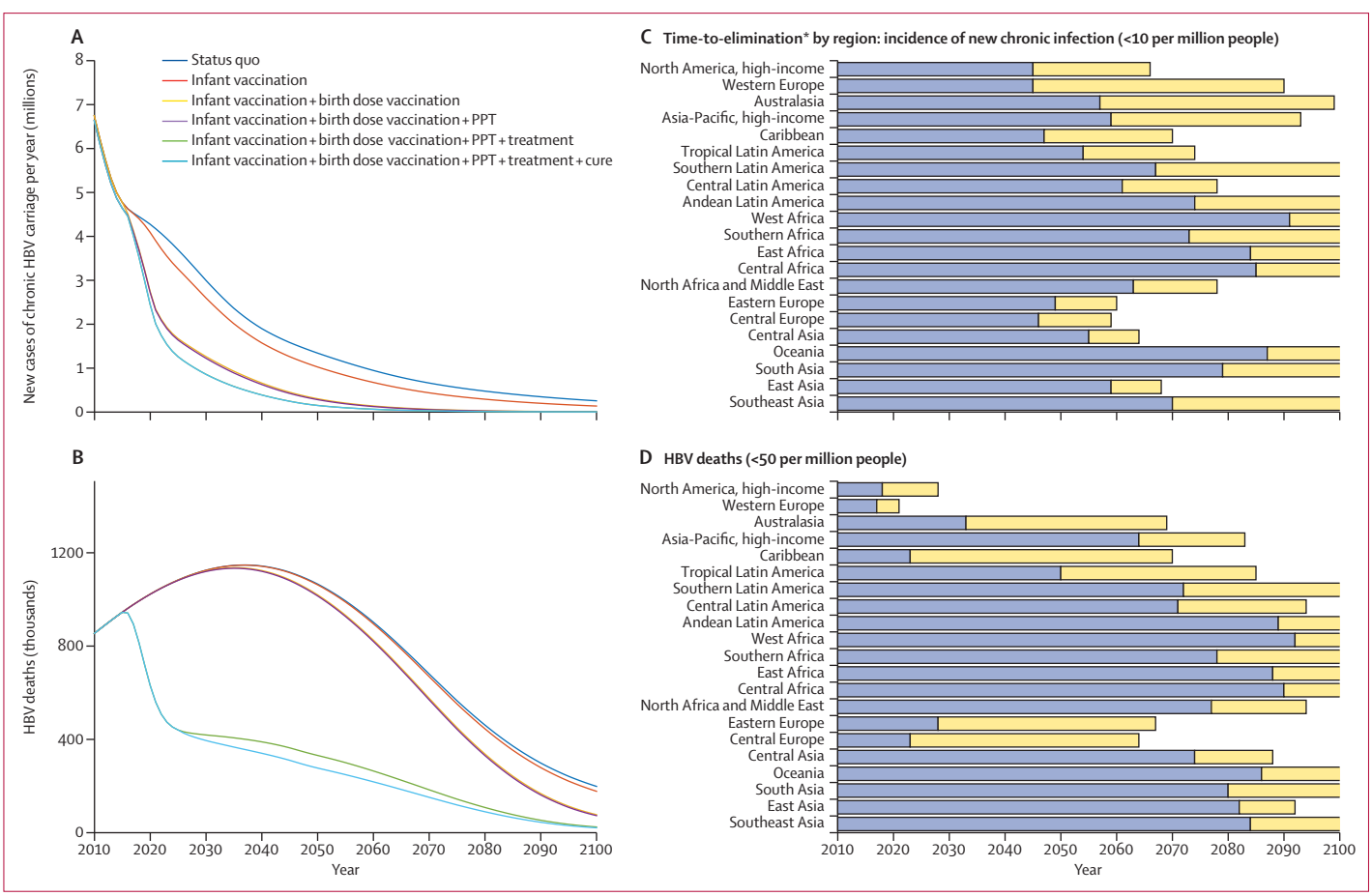

***Figure 3*: Global impact of interventions against HBV**

(A) Impact of interventions on incidence of new chronic infections. (B) Impact of interventions on HBV-related deaths. For description of intervention and targets see table. Yellow lines are overlapped by the purple lines in (A and B). Green line is overlapped by light blue line in (A). (C) Year of elimination of incidence of new chronic infections with status quo scenario and with maximal interventions. (D) Year of elimination of HBV-related deaths. *Elimination defined as reduction of incidence of new chronic infection to fewer than 10 per million people or reduction in HBV-related deaths to fewer than 50 per million people. Yellow bars represent the year of elimination at status quo and purple bars represents the year of elimination with maximal interventions (minus cure). Open-ended bars mean that elimination is not achieved by 2100. HBV=hepatitis B virus. PPT=peripartum antiviral therapy (for hepatitis B e antigen-positive mothers).

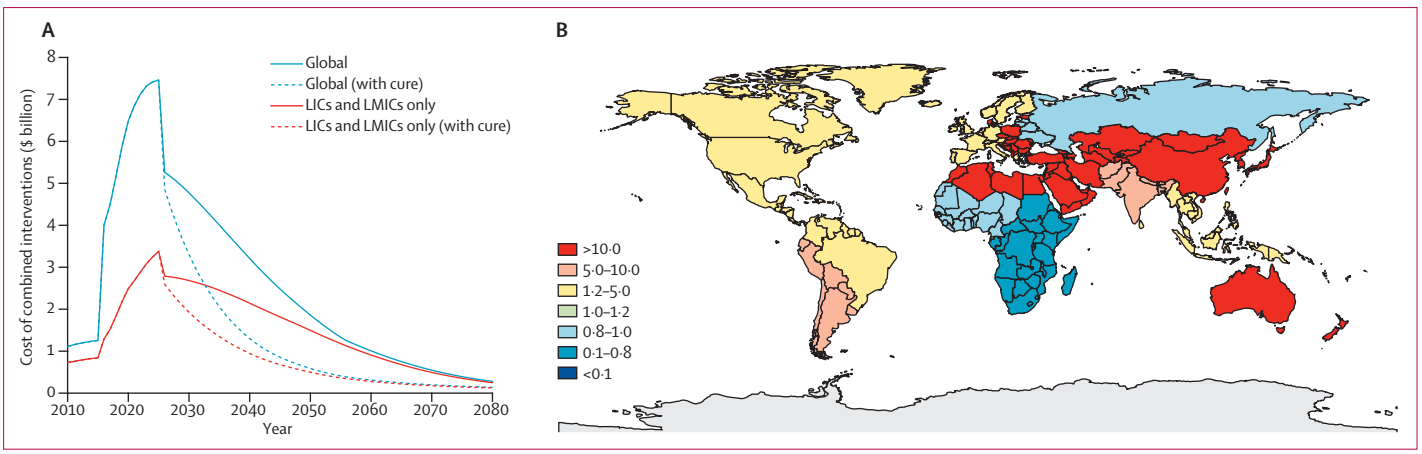

Figure 4: **Cost of combined interventions and ratio of HBV and HIV treatment need**
(A) Cost of combined interventions with and without cure. The solid lines represent the cost of the combined interventions in the absence of a cure. The dotted lines represent the costs with the introduction of a cure in 2025. The blue lines represent the total global cost. The red lines represent the costs incurred in LICs and LMICs only (as defined by the World Bank in 2014[30]). (B) Ratio of people requiring treatment for HBV (modelled estimates for 2025) to people requiring treatment for HIV (HIV estimate from UNAIDS 2013[31]). HBV=hepatitis B virus. LICs=low-income countries. LMICs=lower-middle-income countries.

achieving elimination of HBV-related deaths as early as 2017, and regions in sub-Saharan Africa and Asia not reaching this threshold until closer to 2090. In both cases, the region projected to achieve elimination last is west Africa, where the burden is high, coverage of interventions is low, and population growth will lead to proportionately more mother-to-child transmission.

Sensitivity analysis revealed that even when using lower efficacy rates of all interventions combined, the comprehensive package of interventions would still achieve substantial health gains and avert 18·4 million new incident chronic infections (*vs* 28 million with our default assumptions) and 4·7 million HBV-related deaths (*vs* 7·3 million with our default assumptions) between 2015 and 2030, compared with continuing at status quo (appendix p 44).

The projections of reductions in new HBV cases are most sensitive to a lower efficacy of infant vaccination, as determined by the modelled loss of impact when using assumed lower levels of efficacy. Reducing infant vaccination efficacy from 95% to 88% would result in 4·8 million (14%) more infections between 2015 and 2030 than our baseline scenario. The next most important parameters are a low efficacy of birth-dose vaccination on PMTCT in HBeAg-positive mothers and lower adherence rates to treatment which, when varied individually, would each result in around 1·8 million (5%) more infections than with the baseline scenario. Adherence to treatment has an impact on the number of new cases, because adherence is relied on to reduce mother-to-child transmission for some women. The projections of reduction in HBV-related mortality are most sensitive to a low rate of adherence to antiviral therapy. With a proportion of those on treatment successfully adhering of 65%, lower than our default assumption of 95% adherence, and no other assumptions changed, the projections suggest that there would be 2·6 million (27%) more deaths between 2015 and 2030 than the projection with our default assumptions. This large effect is because effectiveness of treatment in reducing the progression to liver disease is closely linked to adherence. Other factors did not have substantial effect on the projection of HBV-related mortality.

The global cost needed to meet these targets is forecast to peak at $7·5 billion annually and will average $5·5 billion per year between 2015 and 2030 (figure 4). Most of the total cost would be for the screening (39%) and treatment components (59%) in 2025 (appendix p 38). Costs reduce rapidly to $4·7 billion per year in 2030 due to an initial period of screening completing and would decline further after 2030 as progressively fewer people would be in need of treatment because of the impact of the prevention interventions. With a cure, the costs reduce more rapidly. The total net present cost to 2030 of this strategy would be $88·7 billion, which would reduce to $83·7 billion if a cure was developed. The countries that might be most reliant on international financing are the low-income countries (LICs) and lower-middle-income countries (LMICs). The costs in these regions represent 45% of the global costs and peak at $3·4 billion per year.

The feasibility and method of scale-up might vary between regions. In sub-Saharan Africa, the number of people estimated to need treatment for HBV under this strategy is similar to the number of people who need treatment for HIV (figure 4); whereas in Asia, the number of people who need treatment for HBV far exceeds that of HIV, with a ratio of greater than ten in some areas, and this intervention could bring a considerable challenge to health systems.

Discussion

Major progress has been made in the prevention of hepatitis B infection through vaccination, and we will

soon enter an era in which we will start reaping the rewards of a reduction in HBV deaths. However, maintenance of a business as usual approach will not end the epidemic and will lead to 17 million avoidable deaths over the next 15 years.

A comprehensive and ambitious package of interventions that tackle prevention and treatment could lead to a 90% reduction in incidence of new chronic infections and 65% reduction in worldwide mortality by 2030. This target could be achievable with global investment that peaks at $7·5 billion per year. In high-income and upper-middle-income countries, programme costs could be largely funded through domestic resources, given the low cost of the interventions. These costs would also be substantially offset by reduced costs of caring for people with advanced liver disease, and are likely to provide positive return on investment, especially once productivity gains are considered (unpublished). In settings where patients pay for cost of treatment themselves, these interventions would also substantially reduce the risk of people experiencing catastrophic health expenditure.[32,33] Conversely, international financing will probably need to supplement resources necessary for combating HBV in LICs and LMICs, which are estimated to represent a maximum annual cost of $3·4 billion per year. This investment is similar to or substantially smaller than forecasts for HIV funding, which were estimated to be $8·1 billion per year from donor governments in 2013,[34] with a projection of $18·4 billion in LICs and LMICs needed in 2020 to end the AIDS epidemic.[35] For HBV, the reduction in costs over time is assured because transmission is reduced by immunisation.

We have provided targets for control and elimination that can frame and prioritise further innovation and operations research that will be required to address three main challenges. First, the need to prioritise a reduction in mother-to-child transmission presents a major operational challenge because available interventions require the mother to attend prenatal care and the neonate to be given a vaccine within 24 h of birth. However, in sub-Saharan Africa and southeast Asia, 77% of women are estimated to have at least one antenatal visit and only 50% of deliveries in sub-Saharan Africa and 68% of deliveries in southeast Asia are attended by skilled health staff.[36] An additional challenge is that the birth-dose (monovalent) vaccine is not funded by Gavi, the Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunizations), which does fund other important vaccines. New highly scalable strategies will be needed to reach mothers in time to give these interventions. One promising approach could be to follow the lead of HIV's PMTCT Option B and B+, whereby antivirals (which might be continued indefinitely) are provided to the mother after an antenatal assessment, but an assessment of the effectiveness and feasibility of such an approach is needed.

Second, the proposed strategy calls for an enormous scale-up of case finding and delivery of antiviral therapy. Targets can be achieved in different ways for different regions, according to existing engagement with health systems and health-system capacity. In countries that have developed infrastructure and trained personnel for delivery of HIV care, especially in sub-Saharan Africa, vertical programmes could be expanded to deliver HBV interventions (figure 4). The success of 15 million people worldwide on HIV antiviral treatments shows that achievement of such an ambition is feasible and further specific trials and large-scale screening and treatment programmes, such as PROLIFICA[37] in west Africa, will show how such operations could be delivered most effectively and cost-effectively.[38] Linkage between testing and treatment centres and long-term adherence to treatment should be investigated and, more generally, lessons should be drawn from the experience in HIV treatment scale-up, especially in monitoring and strengthening the cascade of care.

Third, progress towards development of a cure for HBV infection could be an important factor in reducing the scale of the projected costs. The ability of the virus to persist and integrate into the host genome has been the main barrier in the successful development of a curative treatment, but new drugs are being developed that promise to overcome this problem.[39]

Early mathematical models have investigated the burden of HBV-related morbidity and mortality at the global level[40] and in high prevalence[41] and low prevalence countries.[42,43] However, these models do not fully reflect current understanding of the clinical behaviour of HBV and did not include testing and treatment interventions. Furthermore, in comparison with previous analyses, the dynamic and mechanistic structure of our model means that we can examine the current and historical burden of disease under different counterfactual conditions, and make future projections that take appropriate account of feedback between the impacts of treatment, infection, and vaccination.

The model is calibrated to existing estimates of prevalence (of HBsAg and HBeAg) and liver cancer mortality. However, because of a paucity of data, especially in sub-Saharan Africa, published estimates of prevalence are based on extensive model-based extrapolation.[13] Similarly, due to incomplete cause-of-death and cancer registry data, especially in sub-Saharan Africa,[44] estimates of HBV-related mortality also rely on statistical adjustments. Because of a scarcity of data and availability of reliable region-specific estimates, our model groups countries within a region together, but this grouping is at the expense of obscuring between-country variation. We have used uncorrected vaccination coverage data reported to WHO, despite this being of unverified quality. Specifically, concerns have been raised about reported birth-dose vaccine coverage values not

reflecting the fact that often a dose is not administered within the required 24 h period.[45] Furthermore, the numbers of people receiving treatment for hepatitis B and regimens used worldwide are not collated at country and regional levels, especially in LICs and LMICs. Therefore, regions were classified using available data and expert knowledge in our model. Finally, we assumed a linear relationship between unit cost of the interventions and intervention coverage levels, which could underestimate the true costs, because access to populations that are hardest to reach is often more costly and scale-up costs would vary depending on existing country-level infrastructure.

The current global approach to tackle HBV—a reliance on infant vaccination—has brought enormous health gains, but a step-change in strategy will be needed to bring a target of HBV elimination within reach. This change must see a large increase in the proportion of births that benefit from a package of prevention interventions and in the proportion of people with chronic HBV carriage who are diagnosed and treated when eligible, as well as maintenance and expansion of infant vaccination programmes. This strategy will require substantial new innovations, but these innovations can be synergistic with developments in many other parts of the health system, especially in mother and child health, screening for HIV and non-communicable diseases, and HIV treatment delivery. These targets are well aligned with forward-looking development goals that emphasise cross-health system strengthening, chronic diseases, and the alleviation of risk of catastrophic health expenditure. Generally, there should be substantial momentum towards making the successes of the HIV response, such as innovation to deliver a large reduction in mother-to-child transmission and provision of wide-scale treatment programmes, the rule rather than exception in global public health.[34]

Contributors

SN, TBH, and MT designed the study. SN and TBH developed the model, did the analysis, and wrote the manuscript. ES prepared the costing estimates and LC assisted in the development of the economic analyses. All authors read and approved the final manuscript.

Declaration of interests

SN reports personal fees from WHO, during the conduct of the study and outside the submitted work. TBH reports personal fees from WHO, during the conduct of the study; grants from Bill & Melinda Gates Foundation, WHO, UNAIDS, World Bank, Rush Foundation; and personal fees from Bill & Melinda Gates Foundation, WHO, World Bank, University of Washington, The Global Fund to Fight AIDS, Tuberculosis and Malaria, New York University, outside the submitted work. ES, LC, SW, and DL-B declare no competing interests.

Acknowledgments

We thank the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) who jointly fund the clinical research fellowship that supports SN and WHO for funding support. All authors acknowledge the support of the UK National Institute for Health Research Biomedical Research Centre at Imperial College London (London, UK), for infrastructure support, and the European Commission FP7 (Prolifica grant reference 265994).

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