Requirements for global elimination of hepatitis B: a modelling study.

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### Abbreviations:

| Abbreviation | Description                        |
|--------------|-----------------------------------|
| CHB          | Chronic Hepatitis B               |
| CC           | Compensated Cirrhosis             |
| DC           | Decompensated Cirrhosis           |
| HBV          | Hepatitis B virus                 |
| HBsAg        | Hepatitis B Surface Antigen       |
| HBeAg        | Hepatitis B e Antigen             |
| HCC          | Hepatocellular Carcinoma          |
| LIC          | Low Income Country                |
| LMIC         | Lower-middle Income Country       |
| HIC          | High Income Country               |
| WHO          | World Health Organization         |
| BD           | Birth Dose                        |
| PPT          | Peripartum antiviral treatment    |

### Key words: Hepatitis B, Elimination, Global, Modelling Interventions, Vaccination, Treatment
**ABSTRACT**

(Word count: 353)

**Background**
Despite the existence of effective prevention and treatment interventions, hepatitis B virus (HBV) infection continues to be the cause of nearly one million deaths annually. The World Health Organization aspires to the global control and elimination of (HBV) infection. We evaluated the potential impact of public health interventions against HBV, proposed targets for reducing incidence and mortality and identified 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 demography. We used the model to estimate the impact of current interventions and the impact of scaling up of existing interventions for prevention of infection and introducing wide-scale population screening and treatment interventions.

**Findings**
Vaccination of infants and neonates is already driving a large decrease in new infections; it has averted 210M new chronic infections by 2015 and will have averted 1.1M deaths by 2030. However, without scale-up of existing interventions, there will be a cumulative 63M new cases of chronic infection and 17M HBV-related deaths between 2015 and 2030 due to ongoing transmission in some regions and limited access to treatment for those already infected. A target of a 90% reduction in new chronic infections and 65% reduction in mortality could be achieved with a scale-up of infant vaccination (90% of infants), birth-dose vaccination (80% of neonates), peripartum antivirals (80% of HBeAg positive mothers), and population-wide testing and treatment (80% of those eligible). These interventions would avert 7.3M deaths between 2015 and 2030, including 1.5M cancer deaths. An elimination threshold for incidence of new chronic infections would be reached by 2090 globally. The annual cost would peak at $7.5billion globally ($3.4 billion in low and lower-middle-income settings) but decline 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 ‘combatting hepatitis’.

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Research in context

Evidence before this study

We searched Pubmed for studies up to September 4, 2015 using the terms ‘Hepatitis B’, ‘HBV’ or ‘CHB’ and ‘Modelling’, ‘Modeling’ or ‘Model’. The focus of previous HBV modelling and epidemiological analysis has been on evaluating the potential future impact of infant vaccination strategies. These have mainly been performed at a country level, concentrated on prevalence and incidence outcomes, rather than morbidity and mortality and have not examined costs of intervention. Only Goldstein et al. have previously presented a global level HBV model, and this analysis 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 or treatment interventions and the model was founded on assumptions of a linear response between vaccination and disease incidence, which could under-estimate intervention impact.

Added value of this study

Our study is unique in providing a global view of the hepatitis B epidemic and the potential impact and costs of a comprehensive set of interventions (vaccination, PMTCT, screening and treatment). Furthermore, it 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 program coverage indicators. Our results show that although enormous progress has been made through vaccination, a step-change in scale-up of both prevention and treatment interventions is needed in order to reduce HBV as a public health threat.

Implications of all the available evidence

This study frames and quantifies all the major issues that will be addressed as momentum increases to tackle HBV globally. It proposes targets around which strategies can develop and identifies the main implementation research priorities and innovations needed in order to achieve this goal. This directly responds to the World Health Assembly resolution that calls for an evaluation of feasibility of global elimination and control of Hepatitis, as well as one of the new Sustainable Development Goals of ‘combatting hepatitis’.

INTRODUCTION

In 2014, the World Health Assembly requested the World Health Organisation (WHO) to examine the feasibility of, and strategies needed for the elimination of hepatitis B and hepatitis C. This significant political momentum is entirely commensurate with the estimated magnitude of the global burden, with
viral hepatitis being ranked as the 7th highest cause of mortality globally and estimated to be responsible for 1.4 million deaths per year (approximately 687,000 deaths due to HBV and 704,000 due to HCV). However, despite being comparable in scale to the 1.29 million, 1.34 million and 850,000 deaths annually due to HIV, TB and malaria,³ respectively, viral hepatitis has been a relatively neglected area.⁴,⁵

Fortunately, a wide range of tools are now available to prevent and treat HBV. Early childhood transmission can be interrupted with a highly effective infant vaccine.⁶ Mother-to-child transmission at birth may be virtually eliminated by the administration of birth dose (BD) vaccination, intravenous Immunoglobulin (HBIG) and peri-partum antiviral therapy (PPT) for mothers with high viral load.⁷,⁸ For those who are already chronically infected with HBV, treatment with antivirals can suppress viral replication and significantly reduce the risk of progression to liver cirrhosis and liver cancer.⁹,¹⁰

However, these tools are not fully utilized. Coverage of infant vaccination has reached high levels in many regions such as East Asia and North Africa & The Middle East (92-96% in 2013), but continues to lag behind in others, most notably Central Africa (56% in 2013).¹¹ Birth-dose coverage is generally lower worldwide, although a few countries, including China, have achieved over 95% coverage.¹² Treatment coverage is low in most high-burden settings (e.g. sub-Saharan Africa (SSA)) 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 global HBV will require the scale-up of these interventions but it has been unclear what magnitude of impact is achievable, what the budgetary implications of scaling-up interventions would be and with what emphasis these different tools should be promoted and developed in the different regions.

A number of useful definitions of elimination exist. The recently adopted Sustainable Development Goals (SDGs) include goals for the elimination of HIV, TB 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 for incidence and HBV-related deaths, of fewer than 10 and 50 per million population, respectively, which is intermediate to the levels used in TB and HIV.

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

**METHODS**
A dynamic age, sex and region structured deterministic mathematical transmission model of the worldwide hepatitis B epidemic was constructed. The model is composed of 21 Global Burden of disease (GBD) world regions, and is fit to data on HBsAg and HBeAg prevalence, at two time points, and liver cancer deaths for each region independently. The model also incorporates region-specific demographic data on population size, mortality and fertility schedules, coverage of existing interventions – infant vaccination, birth-dose vaccination and treatment availability, and assumptions about the natural history of HBV. In the model, transmission is represented from mother-to-child, between children, and across the whole population (which includes other forms of transmission including sexual and iatrogenic), the relative strengths of which are inferred through the calibration procedure (Figure S1, Appendix, page 36). We did not explicitly model the relative contribution of different routes of iatrogenic transmission (blood transfusion, unsafe injection practices etc) as this is a relatively small proportion of all transmission of HBV worldwide currently and infection in adulthood is less likely to lead to chronic infection. Furthermore global data on these routes are lacking.

The representation of HBV natural history is informed by a literature review (Figure S2, Appendix, page 37). In brief, we use twelve mutually exclusive health states, which includes seven untreated chronic hepatitis B (CHB) stages: immune tolerant (IT), immune reactive (IR) (HBeAg positive chronic hepatitis), inactive carrier, HBeAg negative chronic active hepatitis (EAN CHB), compensated cirrhosis (CC), decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). IR and EAN CHB represent states of chronic active hepatitis, with high or fluctuating viral load, elevated transaminases and evidence of fibrosis. Along with CC and DC, these stages are considered eligible for treatment, as per international guidelines.

A costing model was developed to estimate total intervention costs, which attached region-specific, time-constant costs to each of the intervention components. The cost package included the consumable plus delivery of the intervention, and relevant outreach costs (Table S5 & S6, Appendix, page 26). Cost inputs were based on costing data from review of published literature and databases. Primary cost results are presented in USD $ 2014 and allow for greater comparability with existing literature. An alternative approach, using purchase power parity (PPP) adjustments for non-traded resources was also performed, to correct for distortions in direct Gross Domestic Product (GDP) comparisons (presented in International $). Full costing methodology is provided in the appendix. Antiviral drug price was based on currently observed global minimum pricing, assuming price reductions and in anticipation that costs can fall to these levels globally. The costs averted through care costs for cirrhosis and cancer were not included as global data on these are limited. In computing present values of a stream of future costs, a discounting rate of 3% per year was applied.
Five scenarios were used to quantify the impact of the scale-up of available interventions from 2015 (Table 1). In addition, there is a status quo scenario where the coverage of all interventions remains at their current levels, and a ‘no historic intervention’ scenario, where the effects 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 a higher level if already achieved), consistent with the WHO Global Action Vaccine Plan targets of ≥90% vaccination coverage by 2020. The addition of BD vaccination involves a linear scale-up over 5 years of BD vaccination coverage among HBsAg mothers to 80% (or maintains it at higher level if already 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 such testing, linkage and adherence interventions as would be necessary to provide successful treatment with durable viral suppression to 80% of persons becoming eligible, 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. Treatment is assumed to be based on either tenofovir or entecavir and include such 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 representation of a hypothetical curative strategy whereby patients on treatment can be provided with a one-time intervention that results in their sustained viral suppression or loss of HBsAg. Assumptions used to represent the efficacy of each intervention are outlined in the appendix (Table S2, Appendix, page 5).

We first used the model to generate predictions regarding the incidence of new chronic carriage, prevalence of people living with chronic HBV and deaths due to HBV under assumptions that interventions remain at current levels (‘status quo’). We then compared this to a scenario when all historical interventions were removed to estimate how the epidemic would have unfolded if nothing had been done to date. 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 carriage, rather than acute infection, throughout the manuscript.

Sensitivity analysis was performed by varying the main efficacy parameters as follows (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 88% - 95%, efficacy of BD vaccination against MTCT if maternal HBeAg negative 85% – 95.6%, efficacy of BD vaccination against MTCT if maternal HBeAg positive between 75% - 83%, and efficacy of antiviral treatment on PMTCT 85% - 99% and adherence to antiviral treatment 65% - 90%. These lower ranges of efficacy parameters were chosen in order to represent what could happen in a ‘worst-case’ situation and are based on conservative assumptions.
Role of funding source

With the exception of coauthors, the WHO had no further 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; the prevalence of HBeAg tends to be higher in East Asian regions than African regions; and, the number of cancer deaths increases sharply with age and is greatest in East Asia, where prevalence has been high and treatment is not widely available.

The modelled global estimate of HBV-related mortality (850 000 deaths in 2010) and the number of persons living with HBV (290M in 2010) are consistent with previously published sources. Modelled incidence of new chronic infections is 6.7M. For the year 2010, 30% of the HBV-related deaths, 40% of the persons living with HBV and 70% of new chronic infections occurred in the five regions encompassing the majority of the low-income countries.

The model projects that at status quo, there will be 4.3M new chronic infections, 270M people living with HBV and 1M deaths due to HBV, in the year 2020 (Figure 2(A)). Between 2020 and 2050, the number of new infections per year will drop by 70% to 1.3M per year, as a result of sustained vaccination coverage. By 2050, the number of persons living with infection will decrease by 40% to 165M, due to reducing incidence and the continued death of those infected with HBV. The number of HBV-related deaths per year will increase in the coming years, reaching 1.14M deaths per year in 2034, due to cohorts of infected persons reaching older ages when the risk of HBV-related death is greater, and then decline slightly so that by 2050 there will be 1.06M deaths per year.

Current vaccination scale-up is already having a large impact on the epidemic (Figure 2(A)). Without any infant or birth-dose vaccination, there would be 25M new cases in 2020; that is, interventions have already reduced new cases by 83% and cumulatively averted 310M new cases between 1990 and 2020. The impact is largely mediated by the effects of infant vaccination (Figure S3, Appendix, page 38). By our definition, some regions with high infant vaccination coverage are projected to reach elimination of new infections, between 2060 and 2070, even at status quo coverage levels (eg East Asia, Central Asia, Eastern Europe and The Caribbean). Infant vaccination is highly effective at reducing chronic carriage among children but does not directly impact on the risk of acquisition among 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(B)). Therefore, in most regions, additional interventions will be required to drive infection rates to lower levels.

Furthermore, these existing interventions have not yet led to substantial reductions in numbers living with chronic infection or in HBV-related deaths (30% and 4% reduction, respectively, in 2020 compared to no intervention), due to the lack of global scale-up of treatment which is needed to reduce the risk of death for those already infected. Also, the long interval between acquisition of chronic carriage and death means that the pool of persons living with HBV changes slowly in response to intervention.

Without further scale-up of interventions, the number of persons living with HBV is going to remain at the same high levels for 40-50 years and there will still be a cumulative 63M new chronic infections and 17M HBV-related deaths between 2015 and 2030.

However, a scale-up of existing interventions could lead to a worldwide 90% reduction in incidence of new chronic infections and 65% reduction in mortality by 2030 (Figures 3(A) & (B)).

In the first scenario, scaling-up infant vaccination to 90% globally would avert 4.3M new incident infections between 2015 and 2030 compared to status quo. The addition of scale-up of BD vaccination and PPT to 80% enhances this impact, averting a further 19.3M new infections, with the majority of that incremental impact achieved by birth-dose alone (18.7M new cases averted). The large incremental impact due to PMTCT intervention is due to 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 the addition of a ‘testing and treating’ intervention with 80% coverage could reduce deaths by 65%, and could avert 7.3M deaths, including 1.5M cases of cancer deaths, between 2015 and 2030, compared to status quo. The addition of a cure would not impact on incidence or mortality, if it is applied to those already on successful treatment.

Such a set of combined interventions would bring forward the date of elimination of new incident chronic infections, as well HBV-related deaths in all settings (Figures 3(C) & (D)). Half of the global regions would be 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 heterogenous, with some regions, like Western Europe, achieving this by as early as 2017, and regions in SSA 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, current 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 (see methods), the comprehensive package of interventions would still achieve significant health gains and avert 18.4M new incident chronic infections (versus 28M with our default assumptions) and 4.7M HBV-related deaths (versus 7.3M with our default assumptions) between 2015-2030, compared to continuing at
The projections of reductions in new HBV cases are most sensitive to a lower efficacy of infant vaccination, as determined by the modeled loss of impact when using assumed lower levels of efficacy. The lower efficacy of infant vaccination alone would result in 4.8M (14%) more infections between 2015-2030 compared to our baseline scenario. The next most influential parameters are a lower efficacy of BD vaccination on PMTCT in HBeAg positive and lower adherence rates to treatment which, when varied individually, would each result in around 1.8M (5%) more infections compared to the baseline scenario.

Adherence to treatment has an effect on the number of new cases, as, for some women, this is relied upon to reduce MTCT. The projections of reductions in HBV-related mortality are most sensitive to a lower rate of adherence to antiviral therapy. With a lower proportion of those on treatment successfully adhering of 65%, but no other assumptions changed, the projections indicate there would be 2.6M (27%) more deaths between 2015-2030, compared to the projection with our default assumptions. This large effect is because the effectiveness of treatment in reducing the progression to liver disease is closely linked to adherence. Other factors had did not have substantial impact on the projection of HBV-related mortality.

The global cost required to meet these targets is forecast to peak at $7.5bn annually and averaging $5.5bn p.a. between 2015 and 2030 (Figure 4(A)). The majority of the total cost would be for the screening (39%) and treatment components (59%) in 2025 (Figure S4, Appendix, page 39). Costs reduce rapidly to $4.7bn p.a in 2030 due to an initial period of screening completing and would decline further after 2030 as there would be progressively fewer persons becoming in need of treatment due to the impact of the prevention interventions and with a cure, the costs reduce more rapidly. The total present cost to 2030 of this strategy would be $88.7bn, reduced to $83.7B if a cure was developed. The countries which may be most reliant on international financing are the low-income countries (LIC) and lower-middle income countries (LMIC). The costs in these regions, represent 45% of the global costs and peak at $3.4 B annually.

The feasibility and method of scale-up may vary between regions. In SSA, the number of people estimated to require treatment for HBV under this strategy is of similar order of magnitude to those requiring treatment for HIV (Figure 4(B)); whereas in Asia, those requiring 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 where we will start reaping the rewards in reduced HBV deaths. However, a maintenance of a ‘business as usual’ approach will not end the epidemic and will lead to 17 million avertable deaths over the next 15 years.
A comprehensive and ambitious package of interventions which tackle prevention and treatment could lead to a 90% reduction in incidence of new chronic infections and 65% reduction in mortality globally by 2030. This could be achievable with a global investment that peaks at $7.5bn p.a. In high and upper-middle income countries, programme costs may 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 persons with advanced liver disease and are likely to provide positive return on investment, especially, once productivity gains are considered. In those settings where patients bear the cost of that treatment, these interventions would also significantly reduce the risk of persons suffering catastrophic health expenditure. On the other hand, international financing will likely need to supplement resources required for combatting HBV in low and lower-middle income countries, estimated here to represent a peak annual cost of $3.4bn/year. This is of comparable or significantly smaller magnitude to recent forecasts for HIV funding requirements, which were estimated to be $8.1bn/year from donor governments in 2013, with a projected requirement of $18.4bn in LIC & LMICs needed in 2020 to end the AIDS epidemic. In the case of 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. Firstly, the need to prioritise a reduction in MTCT presents a significant operational challenge as available interventions require the mother attending pre-natal care and the neonate being administered with a vaccine within 24 hours of birth. However, in SSA and SE Asia, an estimated 77% of women have at least one antenatal visit and only 50% and 68% of deliveries, respectively, are attended by skilled health staff. An additional challenge is that the birth-dose (monovalent) vaccine is not funded by GAVI, which does fund other important vaccines. New highly scalable strategies will be needed to reach mothers in time to administer these interventions. One promising approach may be to follow the lead of HIV’s “PMTCT Option B and B+”, whereby antivirals to the mother (which may be continued indefinitely) are provided following an antenatal assessment, but an evaluation into the effectiveness and feasibilities of such an approach is needed.

Secondly, 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, especially in SSA, which have developed infrastructure and trained personnel for delivery of HIV care, vertical programmes may be expanded to also deliver HBV interventions (Figure 4(B)). The global success of 15 million persons on HIV antiviral treatments demonstrates that such an ambition is feasible and further specific trials and demonstration projects of large-scale screening and treatment programs, such as PROLIFICA in West Africa (Lemoine et al, under review), will show how such operations could be delivered most effectively. The issue of linkage between testing and treatment centres and of 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’.

Thirdly, progress towards development of a cure for HBV infection could be a significant 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 major barrier in the successful development of a curative treatment for HBV, but new drugs are
being developed that promise to overcome this.26

Earlier mathematical models have investigated the burden of HBV-related morbidity and mortality at the
global level1 and in particular high37 and low prevalence countries.38,39 However, these do not fully reflect
current understanding of the clinical behaviour of HBV and did not include testing and treatment
interventions. Also in comparison with previous analyses, the dynamic and mechanistic structure of our
model means that we can examine the current and historic burden of disease under different
counterfactual conditions, and make projections forward in time that take appropriate account of feedback
between treatment, infection and vaccination impact.

The model is calibrated to existing estimates of prevalence (of HBsAg and HBeAg) and liver cancer
mortality. However, due to 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 SSA,40 estimates of HBV-related mortality also have to rely on
statistical adjustments. Due to limited data, and the availability of reliable region-specific estimates, the
model groups countries within a region together but this 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. In particular, concerns have been raised about reported birth-dose coverage values not
reflecting that often a dose is not administered within the required 24 hour period.41 Furthermore,
numbers of people receiving treatment for hepatitis B and regimens used worldwide are not collated at
country and regional levels, especially in LIC & LMICs, therefore, in the model, regions were classified using
available data and expert knowledge. Finally, we assumed a linear relationship between unit cost of the
interventions and intervention coverage levels, which could underestimate the true costs, because
accessing the hardest to reach populations 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 required 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 persons with chronic carriage that are diagnosed and
treated when eligible, as well as maintenance and expansion of infant vaccination programs. This will
require substantial new innovations but these can be synergistic with developments in many other parts of
the health-system – especially in mother and child health and screening for HIV and non-communicable
diseases, and HIV treatment delivery. These targets are well aligned with forward-looking development goals that emphasize cross-health system strengthening, chronic diseases and the alleviation of risk of catastrophic health expenditure. More generally, there should be significant momentum toward making the successes of the HIV response, like innovating to deliver large reduction in mother-to-child transmission and providing wide-scale treatment programs, the rule rather then exception in global public health.\(^{33}\)

Contributors
SN, TH and MT designed the study. SN and TH developed the model, carried out 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
M Thursz has accepted fees for advisory boards and lectures from Abbvie, BMS, Gilead, Janssen and Merck.

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Summary of figures

**Figure 1: Model Calibration.** These graphs represent 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), HBeAg prevalence among those HBsAg positive (birth-40 years old) and HBV related cancer deaths (all ages in 2012). The lines are colour coded to represent the seven different continent groupings. Males are represented by crosses and females by circles.

**Figure 2: Epidemic Projections for HBV. (A)** HBV incidence (of new chronic carriage), HBV prevalence and deaths under the status quo scenario (all intervention remain at current levels; blue line) and a counterfactual scenario (assumed no interventions have ever been applied; dashed black line). (B) Ages of persons in which cases of new chronic carriage occur under the status quo scenario. HBV=Hepatitis B Virus.
**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 1. In figures A & B, the yellow lines are nearly completely overlapped by the purple lines. In figure A, the green line is nearly completely overlapped by the light blue line. (C) Year of Elimination of incidence of new chronic infections under status quo scenario and with maximal interventions. (D) Year of Elimination of HBV-related deaths. *Elimination defined here as reduction of incidence of new chronic infection to lower than 10 per million population or reduction in HBV related deaths to below 50 per million population. Yellow bars represent the year of elimination at status quo and purple bars represents the year of elimination with maximal interventions (minus cure). If the bar is open ended, this means that elimination is not achieved by 2100. PPT = Peripartum antiviral therapy (for HBeAg positive mothers). BD = Birth Dose. Vacc = Vaccination.

**Figure 4(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 low and lower-middle income countries only (as defined by World Bank 2014). LIC = low-income country. LMIC = lower-middle-income country.

**(B) The ratio of those requiring treatment for HBV (modelled estimates for 2025) compared to number requiring treatment for HIV (HIV estimate from UNAIDS 2013).** HBV = Hepatitis B Virus. HIV = Human Immunodeficiency Virus.

**Table 1: Table of intervention strategies modelled, coverage levels and scale-up times.**

*If the regional coverage is already above these levels, it remains at current higher coverage. § Peripartum antivirals are given to HBeAg +ve mothers only. HBIG not implicitly modelled as data not available, but continues at current levels. † To include case finding and treatment. **80% incorporates a strategy of 90% case finding, 95% linked to care, 95% durable viral supression. HBeAg = Hepatitis B e antigen. BD = Birth Dose. PPT = peripartum antiviral therapy (given to HBeAg + mothers). ‡ WHO data on vaccination coverage upto 2013. § Assumption. ‡ Global Policy report on viral hepatitis & expert opinion.

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Figure 1: Model Calibration. These graphs represent 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), HBeAg prevalence among those HBsAg positive (birth-40 years old) and HBV related cancer deaths (all ages in 2012). The lines are colour coded to represent the seven different continent groupings. Males are represented by crosses and females by circles. HBsAg = Hepatitis B surface Antigen. HBeAg = Hepatitis B e antigen. Prev = Prevalence.
Figure 2: Global Epidemic Projections for HBV. (A) HBV incidence (of new chronic carriage), HBV prevalence and deaths under the status quo scenario (all intervention remain at current levels; blue line) and a counterfactual scenario (assumed no interventions have ever been applied; dashed black line). (B) Ages of persons in which cases of new chronic carriage occur under the status quo scenario. HBV = Hepatitis B virus.
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 1. In figures A & B, the yellow lines are nearly completely overlapped by the purple lines. In figure A, the green line is nearly completely overlapped by the light blue line. (C) Year of Elimination of incidence of new chronic infections under status quo scenario and with maximal interventions. (D) Year of Elimination of HBV-related deaths. *Elimination defined here as reduction of incidence of new chronic infection to lower than 10 per million population or reduction in HBV related deaths to below 50 per million population. Yellow bars represent the year of elimination at status quo and purple bars represents the year of elimination with maximal interventions (minus cure). If the bar is open ended, this means that elimination is not achieved by 2100. PPT = Peripartum antiviral therapy (for HBeAg positive mothers). BD = Birth Dose. Vacc = Vaccination.
**Figure 4(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 low and lower-middle income countries only (as defined by World Bank 2014). LIC = low-income country. LMIC = lower-middle-income country.

**Figure 4(B).** The ratio of those requiring treatment for HBV (modelled estimates for 2025) compared to number requiring treatment for HIV (HIV estimate from UNAIDS 2013). HBV = Hepatitis B Virus. HIV = Human Immunodeficiency Virus.
| Intervention Scenarios                      | Infant Vaccination Coverage | Birth Dose Vaccination Coverage | Coverage of Peri-partum antivirals for HBeAg+ mothers | Access to treatment ± | Cure |
|-------------------------------------------|-----------------------------|--------------------------------|------------------------------------------------------|-----------------------|------|
| No Historic Intervention                  | None                        | None                           | None                                                 | None                  | No   |
| Status Quo                                | Continues at current levels ¹ | Continues at current levels ¹ | No coverage currently ²                               | Continues at current levels (categorised by region) ³ | No   |
| Infant Vacc                               |                             |                                |                                                      |                       |      |
| Infant Vacc + BD Vacc                      |                             | 90%* (Linear scale-up 2015-2020)|                                                      |                       |      |
| Infant Vacc + BD Vacc + PPT               |                             | 80%* (Linear scale-up 2015-2020)|                                                      |                       |      |
| Infant Vacc + BD Vacc + PPT + Treatment   |                             | 80% (Linear scale-up 2015-2025) |                                                      |                       |      |
| Infant Vacc + BD Vacc + PPT + Treatment + Cure |                             | 80%** (Linear scale-up 2015-2025) |                                                      | 2025                 |      |

Table 1: Table of intervention strategies modelled, coverage levels and scale-up times.
*If the regional coverage is already above these levels, it remains at current higher coverage. § Peripartum antivirals are given to HBeAg +ve mothers only. HBIG not implicitly modelled as data not available, but continues at current levels. ± To include case finding and treatment. **80% incorporates a strategy of 90% case finding, 95% linked to care, 95% durable viral suppression. HBeAg = Hepatitis B e antigen. BD = Birth Dose. PPT = peripartum antiviral therapy (given to HBeAg + mothers). ¹ WHO data on vaccination coverage upto 2013. ² Assumption. ³ Global Policy report on viral hepatitis & expert opinion.