

The impact of the timely birth-dose vaccine on the global elimination of hepatitis B

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Article

Keywords: hepatitis B, birth-dose vaccination

Posted Date: April 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-370018/v1>

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Version of Record: A version of this preprint was published at Nature Communications on October 28th, 2021. See the published version at <https://doi.org/10.1038/s41467-021-26475-6>.

Abstract

Scaling-up timely hepatitis B birth-dose vaccination to 90% of new-borns in 110 low- and middle-income countries by 2030 could prevent 770,000 (600,000–1,060,000) deaths in the 2020 to 2030 birth cohorts compared to status quo, with the greatest benefits in Africa. Maintaining this could lead to elimination by 2032 in the Americas, but not before 2059 in Africa. Drops in coverage due to disruptions in 2020 may lead to 17,000 additional deaths, mostly in South-East Asia and the Western Pacific. Delays in planned scale-up could lead to an additional 630,000 deaths globally in the 2020 to 2030 birth cohorts.

Background

Nearly 40 years since the hepatitis B (HBV) vaccine was introduced in the 1980s, HBV infection continues to pose a significant public health threat, which disproportionately affects low and middle-income countries (LMICs). Nearly 250 million people are estimated to be living with chronic HBV infection globally and the virus causes nearly 900,000 deaths a year due to hepatocellular carcinoma (HCC) and cirrhosis¹.

In 2016, the World Health Assembly endorsed a World Health Organization (WHO) strategy to eliminate HBV as a public health threat by 2030^{2,3}, measured by the reduction of HBV surface antigen (HBsAg) prevalence in five-year-olds to 0.1% by 2030. Accordingly, targets were established that included scaling up coverage of infant HBV vaccine series, which reduces horizontal transmission, and the timely birth dose (TBD: a dose of monovalent vaccine administered within 24 hours of birth), which primarily reduces mother-to-child transmission (MTCT)⁴⁻¹⁰, each to 90% by 2030.

This is close to being achieved for the infant HBV vaccine series, which is usually integrated within the Expanded Programme on Immunization schedule and is funded by Gavi, the Vaccine Alliance (GAVI) in many low-income settings (<https://www.gavi.org/programmes-impact/our-impact/countries-approved-support>, accessed in March 2021): globally, coverage was 85% of infants in 2019 (https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html, accessed in July 2020). However, despite the targets and although the WHO has recommended since 2009 that all new-borns receive the TBD vaccine, scale-up of the TBD has been slow, coverage heterogeneous, and there has not been the same funding support from GAVI. By 2019, only an estimated 43% of new-borns had received TBD vaccine (~6% in the WHO AFRO region) and only 95 countries were administering the TBD vaccine to new-borns as part of their national policy (https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html, accessed in July 2020). There are concerns that the TBD is difficult to implement and not necessary for reducing the hepatitis burden to very low levels^{11,12}.

In 2019, GAVI re-evaluated extending their funding to provide catalytic support for introducing the HBV TBD vaccine (<https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy>, accessed in January 2021). However, the COVID-19 pandemic and the response to it have created additional barriers

to scaling up TBD coverage, both due to disruptions in healthcare facilities¹³⁻¹⁶, which have affected routine immunization and facility-based births^{17,18}, and indirectly due to changes in priorities and funding.

The aim of this study was to determine the impact of scaling up TBD vaccine on HBV cases, related deaths, and the trajectory towards the WHO elimination targets. We also evaluate the potential impact on the HBV epidemic of COVID-19 pandemic disruptions to TBD coverage where it is already routinely used, and of the delay in scale-up in countries that are yet to introduce it into their national policy.

Results

We use a set of models representing the HBV epidemic in each of 110 LMICs, which together represent all six WHO regions and include all current GAVI-eligible countries (Fig. S1). Each country model was calibrated to data on HBsAg (Table S1) and HBeAg seroprevalence, HBV-related deaths due to cirrhosis and HCC, and national data on coverage of vaccinations and treatment (Figs. 1a–d). We apply a set of scenarios for the future coverage of the TBD in each country (Table 1) and quantify impact with reference to the infections and deaths that would occur in a scenario in which the coverage of TBD remains at the level recorded for each country in 2019. These results were aggregated across country-level simulations to generate results for the six WHO regions (Fig. S1) and global results. Figs. 1e–f show the global coverage of infant and TBD vaccination (aggregated over country-level coverage values, weighted by population size in 2025) under a selection of these scenarios (Fig. S2 gives the breakdown by WHO region for status quo).

The Impact of Scaling Up the Timely Birth dose

Fig. 2 shows the modelled impact of scaling up TBD vaccination to $\geq 90\%$ by 2030 (scenario 2) on HBV disease burden globally. The scale-up results in immediate reductions in chronic HBsAg incidence and the prevalence of HBsAg among five-year-olds relative to the status quo scenario (scenario 1), greatly accelerating the gradual reductions that would be expected otherwise (Figs. 2a and 2b). The WHO elimination target (less than 0.1% HBsAg prevalence in five-year-olds by 2030) cannot be reached globally in the countries modelled (before 2100) without the scale-up of the TBD. However, with the modelled fast and substantial scale-up of TBD, that target can be reached in 2053 (2051 to 2056; Fig. 2b). Scaling up TBD vaccination to $\geq 90\%$ by 2030 would avoid 43,000,000 (37,000,000 to 57,000,000) chronic infections relative to status quo between 2020 and 2100. This scale-up results in 770,000 (600,000 to 1,060,000) fewer deaths among those born between 2020 to 2030 globally (Table S3). However, this would not be recorded as a drop in deaths (Fig 2c) or DALYs (Fig 2d) in calendar-time until ~ 2050 . This is because HBV usually takes decades to progress from infection to death. The expected trend in deaths and DALYs is an increase until 2030-2040, followed by a fall due to the competing effects of population ageing and growth (and so more people in older cohorts reaching ages when they are at risk of death caused by HBV) and the effect of the infant HBV vaccine series (reducing infections in younger cohorts).

Fig. 3 identifies the populations in which the effect of TBD scale-up in reducing deaths is most strongly concentrated. For cohorts born before 2030, the number of deaths averted rises in line with the assumed increases in coverage of the TBD. Later cohorts benefit somewhat less, as the risk of infection to them is lower as a result of the declining HBV prevalence among women of child-bearing age. Most (>70%) of the deaths averted in the 2020 to 2030 birth cohorts are in the WHO Africa region (AFRO), where HBV prevalence is very high in many countries (Fig. 1a) and current TBD coverage is the lowest of all the WHO regions (~7%: see Fig. S2). In fact, 26% of all deaths averted globally in the 2020 to 2030 birth cohorts would be in a single country—Nigeria—which has a large and rapidly growing population with very low TBD coverage currently (0% in 2019). Large numbers of deaths averted would also be expected in the Middle East (WHO's EMRO region) and South-East Asia (WHO's SEARO region), which also have relatively low TBD coverages (~34% and ~55%, respectively; Fig. S2), but lower HBV prevalence than AFRO (Fig. 1a). Reflecting their large sizes, 9% and 8% of deaths averted globally in the 2020 to 2030 birth cohorts would be in India and Pakistan, respectively (Fig. 3b). Results for each region and country individually are presented for selected scenarios in Tables S3 to S6.

Achieving HBV Elimination

Fig. 4a shows the year by which the WHO elimination goal would be achieved for the combined populations within each region under status quo (scenario 1) versus if the TBD is scaled up to $\geq 90\%$ by 2030 (scenario 2). Without any TBD scale-up, elimination would be reached first in the Europe (WHO's EURO region) in 2038, followed by the Western Pacific (WHO's WPRO region) in 2042, in both of which there is already high TBD coverage and low prevalence of HBV. In contrast, in the WHO regions of EMRO and AFRO, elimination would not occur before 2100. The TBD scale-up would bring the date of elimination earlier in all regions (with the exception of EURO, where TBD is already at high scale) and make it possible in EMRO (in 2051) and AFRO (in 2059). With the TBD scale-up, by 2040, the regions EURO, PAHO and WPRO would all have reached the elimination target; and by 2050, all regions except AFRO would have reached the elimination target. Results for each country are given in Table S4.

Fig. 4b shows the relationship between the annual rate of scale-up of the TBD and the year by which elimination is reached in the populations within each of the WHO regions. Faster scale-up results in earlier elimination—especially where TBD coverage is lowest, in the AFRO, EMRO and SEARO regions—but no amount of accelerated scale-up would feasibly result in elimination being reached in any region by 2030 (the WHO's target). Indeed, even an infeasibly high rate of scale-up in Africa (9% per year) would not bring the date of elimination to before 2060. This is because many countries in the region have either a very low TBD coverage (e.g. Nigeria), a very high HBV prevalence (e.g. South Sudan (22% prevalence among all ages), Sierra Leone (19%) Liberia (15%); <http://whohbsagdashboard.com/#hbv-country-profiles>, accessed in January 2021), or both. The Americas (WHO's PAHO region) has the best chance of reaching the 2030 target—here moderate TBD coverage is combined with low overall HBV, so that an accelerate scale-up of TBD could have an effect quickly.

The Indirect Effects of the COVID-19 Pandemic

Fig. 5a shows that a temporary drop in TBD coverage in 2020 could result in 17,000 (13,000 to 23,000) additional HBV-related deaths, concentrated in the SEARO and WPRO regions, which have large population sizes and normally relatively high TBD coverage levels (55% and 91% in SEARO and WPRO, respectively; Fig. S2). The additional deaths occur mostly among those born in 2020 when the disruptions occurred, but also, to a lesser extent, to unprotected children (unvaccinated or vaccination failed) born in earlier and later years, who become infected following contact with a child born in 2020 (Fig. S5). The effect of the temporary disruption is long-lived—the additional deaths occur mostly from 2050 onwards (Fig. S6). However, the impact does not affect the year by which elimination is achieved (Tables S4 and S6).

Fig. 5b shows the effect that delays in scale-up of TBD could have (scenarios 4a to 4c) compared to the scale-up of TBD (scenario 2). The nature of these disruptions could be large: at worst (in scenario 4c), 630,000 (490,000 to 850,000) additional deaths globally in the 2020 to 2030 birth cohorts, concentrated mostly in AFRO. Even if TBD is scaled up faster after a period of delay between 2020 and 2023 (as is the case in scenario 4a), there would remain a significant excess number of deaths in the cohorts that missed out on vaccination. Delays in the scale-up of TBD lead to additional deaths that would occur mostly from 2060 onwards (Fig. S7).

Sensitivity analyses

Our results are sensitive to the assumptions made about other aspects of the HBV programme—the infant HBV vaccine series and treatment. Firstly, in the foregoing analyses it was assumed that infant vaccine series coverage levels will be maintained at the levels recorded in each country for 2019 as our primary aim was to explore the impact that TBD scale-up alone could have. However, increasing infant vaccine series coverage levels to 100% in every country leads to fewer infections (reduction of 35% globally) and deaths (reduction of 20% globally) being averted between 2020 and 2100 as a result of scaling up TBD to $\geq 90\%$ by 2030 (scenario 2) and an earlier year of elimination being reached overall (2048 versus 2053; Table S4). This is because a somewhat higher coverage of infant vaccine series would result in a lower risk of infection for those who did not receive the TBD. The effects are strongest in the countries for which infant vaccination is currently lower (Tables S5 and S6). For example, in Nigeria, which has an infant vaccine series coverage of 57% in 2019, there are 28% fewer deaths averted in the 2020 to 2030 birth cohorts in scenario 2 relative to scenario 1 if infant vaccine series coverage is scaled up to 100% compared to if infant vaccine series coverage is maintained at status quo levels.

Secondly, whilst in the foregoing analyses it was assumed that the proportion of persons living with HBV that receive treatment remains at the same levels as those recorded in 2016 for each country, if instead treatment coverage were to increase to 40% or 80% of those eligible for treatment by 2030, then the impact of scaling up of the TBD to $\geq 90\%$ by 2030 on deaths is greatly reduced (globally by 42% or 77%,

respectively). Similarly, the effect of drops in TBD coverage relative to status quo is reduced (globally the effect of a 20% drop in TBD is reduced by 32% or 70%, respectively), as are the effects of delays in TBD coverage relative to scaling up the TBD to $\geq 90\%$ by 2030 (globally the effect of scaling up TBD to $\geq 90\%$ between 2025 and 2040 is reduced by 42% or 77%, respectively). This is because, with treatment, the risk of death following infection is reduced substantially.

Discussion

Infant HBV vaccine series coverage is already very high, having a global coverage of over 80%, protecting large numbers of infants in most countries from horizontal transmission of HBV. However, TBD coverage is still low in many places, especially in low and lower-middle income countries where the burden is concentrated, and this is the major impediment to eliminating HBV. Scaling up TBD is an effective way of reducing HBV burden in countries, and our results confirm the WHO's emphasis on the importance of scaling up the TBD. The scale-up consistent with the WHO target ($\geq 90\%$ TBD coverage by 2030) could reduce HBV-related deaths amongst the 2020 to 2030 birth cohorts globally by 770,000 (600,000–1,060,000). This impact is especially great in the AFRO region, which has the highest HBsAg prevalence and the lowest TBD coverage. However, TBD coverage is currently very low in countries in AFRO, and it may be a more realistic goal to scale up TBD to $\geq 25\%$ by 2030, which would avert 150,000 (110,000 to 230,000) deaths in AFRO in the 2020 to 2030 birth cohorts compared to status quo (Table S3 in supplementary materials).

The analyses show it will not be possible to achieve HBV elimination by 2030 (the WHO's stated ambition for HBV elimination) even with the TBD scale-up. Instead, 2040 is now a more realistic goal for the countries modelled in EURO, PAHO and WPRO, 2050 for EMRO and SEARO, and after 2060 for AFRO. Additional interventions such as increased testing (HBeAg, HBV DNA or HBsAg¹⁹) followed by the scale-up of antiviral treatment and the expansion of programmes to provide peripartum antiviral prophylaxis to HBsAg+ pregnant women with high viral loads²⁰, which are highly effective in reducing the risk of HBV MTCT²¹⁻²⁴, could potentially bring elimination into reach by 2030 in particular countries²⁵ or even some WHO regions.²⁶

Our findings are consistent with GAVI's conclusion on the favourability of expanding funding to provide catalytic support for introducing the HBV TBD vaccine (<https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy>, accessed in January 2021). However, we note that such an expansion has been delayed due, in part, to the circumstances created by the COVID-19 pandemic²⁷. This is deeply unfortunate, as delays in the scale-up lead to large numbers of additional avoidable deaths especially in Africa (Fig. 5b) that cannot be mitigated by an accelerated scale-up in later years. This indirect effect of the COVID-19 pandemic dwarves another type of effect—temporary disruptions in the on-going delivery of TBD (Fig. 5a)—which has attracted more attention hitherto²⁸. For example, a recent study²⁸ modelled the impact of disruptions caused by the COVID-19 pandemic on childhood immunization of several diseases in Africa, including the infant HBV vaccine series. That study found

that a suspension of childhood vaccination programmes for six months without any subsequent catch-up campaigns could cause 3,827 deaths in the unvaccinated children before the age of 5 years in Africa (although that is actually bound to be an underestimate of HBV-related deaths because HBV tends to take decades to progress from infection to death).

In addition to the COVID-19 pandemic, there are further challenges to scaling up TBD to 90% by 2030. Since the BD should be administered within 24 hours of birth to have maximum efficacy, home births, especially in rural settings, present challenges to vaccinating new-borns in this time-critical manner. Alternative solutions including outreach interventions or the use of HB-Uniject, which is a pre-filled, auto-disable injection device, could facilitate administration of TBD in these settings. Another challenge is that BD should be stored between 2°C and 8°C. However, provided that the vaccine is administered soon afterwards, the BD vaccine has been found to be heat-stable if it is exposed only once to high temperatures for a limited period of time^{6,29,30}. Integrating TBD with other vaccinations such as bacillus Calmette-Guérin tuberculosis and oral polio vaccines or other new-born interventions could facilitate and reduce the health opportunity cost of introducing an HBV TBD programme³¹.

Limitations of this current analysis include the paucity of historical and current prevalence and treatment data, which compromises the certainty with which projections can be made. Also, prevalence in Africa, particularly amongst children, is highly uncertain^{32,33}. Furthermore, models of HBV have to rely on assumptions for the natural history of infection from a variety of studies from different international settings, despite concerns population differences have a material effect on risk of transmission and disease progression³⁴⁻⁴⁰. Most notably, we have assumed an 70%–95% efficacy of TBD vaccination amongst those born to HBeAg+ mothers, which is based primarily on data from Asian studies. However, a systematic review¹⁰ found that in Africa, based on pooled data from a very limited number of studies, the TBD has much less effect on the risk of transmission. Therefore, our analysis might overestimate impact in the AFRO region if efficacy really is lower than in Asia. Another limitation of the study is that co-infections, such as with HIV and hepatitis D⁴¹, were not taken into account: if they had been, we would expect to estimate a greater number of deaths averted by TBD scale-up. Moreover, there is evidence that patients infected vertically with HBV remain highly infectious for longer due to slower HBeAg loss, and may have elevated risks of progressing to cirrhosis and/or HCC^{38,42-44}. This could result in more HBV-related deaths being averted by TBD scale-up than we have estimated. The scenarios for the disruptions due to COVID-19 (scenarios 3a to 3d and 4a to 4c) are non-specific out of necessity, although they are principled on reports that are available¹⁷. Drops in TBD coverage in a country could occur for a number of reasons: temporary disruptions to vaccine supplies, less availability of healthcare staff due to sickness or redeployment to provide COVID-19 relief or a reduction in the proportion of facility-births as a result of transport restrictions during lockdown or patients being fearful of catching COVID-19 in healthcare settings. Delays in the scale-up of the TBD vaccine in a country could be the result of prolonged transport disruptions (affecting international supply chain or local delivery systems) or funds being diverted away from routine vaccines and towards fighting the COVID-19 pandemic. Another limitation of these analyses is that we did not model high-income countries (Table S2). However, EURO and PAHO (which each

contain several countries that were not modelled), together contain less than 10% of global prevalent (HBsAg+) cases (<http://whohbsagdashboard.com/#hbv-country-profiles>, accessed in January 2021). Moreover, vaccine coverage tends to be higher in high-income countries (HICs) than in LMICs. Hence, our analysis is likely to only be a slight underestimate of global HBV-related deaths. Since HICs tend to have lower HBsAg prevalences than do LMICs, including all of the EURO and PAHO countries in the analyses would probably result in EURO and PAHO each reaching elimination sooner than was found in these analyses.

Overall, the scale-up of the TBD could lead to major gains in health and is a necessary requirement for achieving HBV elimination. Even though the WHO recommends the scale-up and GAVI has indicated willingness to help fund it, delays in the scale-up of TBD are leading to future preventable deaths being accumulated, especially in Africa.

Methods

Data sources

We focus on 110 LMIC GAVI-eligible countries that together contain 92% of global HBsAg prevalent cases (Table S2) and capture all of the HBV burden in the low-income and lower-middle income countries globally. We classify these countries according to the six WHO regions (Fig S1).

The model was populated with country-specific demographic data (fertility rates, male-to-female sex ratios at birth, population size, migration rates, and all-cause mortality rates) from the United Nations' 2019 World Population Prospects (<https://population.un.org/wpp/Download/Standard/Population/>, accessed in October 2019). Country-specific historical vaccination coverage (1980 to 2019) of the infant HBV vaccine series and TBD vaccines were sourced from WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) released in July 2020 (https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveredtp3.html, accessed in July 2020) (Figs. 1e–f and S2). The exception to this is China, for which the WUENIC vaccination coverage values for 1980 to 2013 were replaced with vaccination coverage values from another study⁴⁵. The model was fit to country-specific, age-specific HBsAg prevalence data (Table S1) obtained from the Polaris Observatory, from the WHO HBsAg dashboard (<http://whohbsagdashboard.com/#hbv-country-profiles>, accessed in October 2019) and from another study⁴⁵ in the case of China, country-specific HBeAg prevalence in HBsAg+ pregnant women from the Polaris Observatory, as well as country-specific, age-specific HBV-related death rates (deaths per 100,000) from cirrhosis and HCC sourced from the Global Burden of Disease (GBD) Results Tool website in December 2018 (<http://ghdx.healthdata.org/gbd-results-tool>). Disability weights for calculating DALYs were obtained from⁴⁶.

The HBV model

We used a population-level, deterministic, dynamic transmission model^{26,47}, resolved according to sex and age, to determine the impact of scaling up TBD coverage and the impact of the COVID-19 pandemic on HBV disease burden. In the model, HBV is either transmitted vertically from infected mothers to their new-borns or horizontally from infected members of the population. The horizontal force of infection is determined by the proportion of infectious individuals in the population that are HBeAg+ and HBeAg-, as well as by the risk of transmission amongst young children, which is calibrated for each country. The risk of vertical transmission is also calibrated for each country. The probability of an acute horizontal infection becoming chronic is a function of age, falling from over 53% in one-year-olds to less than 5% in adults over 30 years of age, while the probability of a vertical infection becoming chronic is 88.5%. Individuals who do not develop chronic HBV clear the virus and become immune to HBV. The TBD (efficacy of 95% if the mother is HBsAg+ HBeAg-, and 83% if the mother is HBsAg+ HBeAg+) is administered to new-borns, and the third dose of the infant HBV vaccine series (efficacy of 95%) is administered at six months of age.

Model fitting

The model was fit to data from each country using the Approximate Bayesian Computation Sequential Monte Carlo algorithm⁴⁸, and 200 particles were sampled from the posterior distribution of each country⁴⁷. Vaccine efficacy was varied amongst the 200 particles, with infant HBV vaccine series efficacy varying between 90% and 100%^{49,50} and the TBD efficacy in the case of HBeAg+ mothers varying between 70% and 95%⁵¹⁻⁵⁵. Model results from the 200 particle runs were summarized as the mean or median, with the 2.5 and 97.5 percentiles used to construct 95% credibility intervals. Treatment data and modelling are outlined in the Supplementary Information.

Model Analysis

Analyses were performed by running the scenarios described in Table 1 until the year 2100. Analyses were done for each country-level model and then added up within WHO regions (regional estimates) as well as across WHO regions (global estimates), with 95% credibility intervals calculated for the summed model results under the assumption of independence between the individual country results.

Declarations

MJdV, SN and TBH gratefully acknowledge funding from the Vaccine Impact Modelling Consortium (VIMC; <https://www.vaccineimpact.org/>) based at Imperial College London, UK.

This award is jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and is also part of the EDCTP2 programme supported by the European Union.

SN is also supported by the NIHR Imperial Biomedical Research Centre (BRC; <https://imperialbrc.nihr.ac.uk/>).

The authors would also like to thank Meg Doherty, Niklas Luhmann and Fuqiang Cui at the World Health Organization for their contributions towards developing realistic scenarios for investigating the impact of possible COVID-19 pandemic disruptions on HBV disease burden.

Author Contributions

SN and TBH secured funding. SN, TBH and MJdV constructed the disease transmission model. SN and TBH designed the study. MJdV wrote computer code, conducted the analyses and prepared results. MJdV wrote the first draft of the paper, and the other authors reviewed drafts.

Competing Interests statement

The authors declare the following competing interests:

This work was supported, in whole or in part, by the Bill & Melinda Gates Foundation OPP1157270. Under the grant conditions of the Foundation, a Creative Commons Attribution 4.0 Generic License has already been assigned to the Author Accepted Manuscript version that might arise from this submission.

This work was carried out as part of the Vaccine Impact Modelling Consortium (www.vaccineimpact.org), but the views expressed are those of the authors and not necessarily those of the Consortium or its funders. The funders were given the opportunity to review this paper prior to publication, but the final decision on the content of the publication was taken by the authors.

SN and TBH have received personal fees for technical consultation work with the World Health Organization on Hepatitis elimination, surveillance and monitoring, and for the preparation of reports for guidelines committees on the prevention of mother-to-child transmission.

Data Availability

The data sets for running the scripts to generate the results are available at Zenodo.

Code availability

MATLAB scripts for running the analyses and generating the results are available at Zenodo.

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Tables

Table 1: Vaccination scenarios analysed. For all scenarios, TBD coverage and infant HBV vaccine series coverage reflects data from WHO/UNICEF Estimates of National Immunization Coverage (https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveredtp3.html, accessed in July 2020) through to the end of the year 2019, and the infant HBV vaccine series coverage is maintained at the level recorded for 2019 in each country from 2019 to 2100. TBD: timely birth dose; HBV: hepatitis B.

Scenario	Timely birth-dose vaccination
1) Status quo	Maintained at level recorded for 2019, throughout the period 2020–2100.
2) TBD expansion to $\geq 90\%$ ^[1] by 2030	Linear expansion from 2019 level to the target value ^[2] by 2030 and, maintained at that level until 2100.
3) Drop in TBD coverage in 2020 by a) 5%, b) 10%, c) 15%, d) 20% due to disruptions associated with COVID-19	Drop of target value in the year 2020 relative to the level recorded for 2019; maintained at level recorded in 2019 in the period 2021–2100.
4) TBD expansion delayed & $\geq 90\%$ coverage reached over the period a) 2023 to 2030, b) 2023 to 2033, c) 2025 to 2040	Maintained at level recorded for 2019 until starting year of expansion; linear expansion from the level recorded for 2019 to $\geq 90\%$ over the expansion period and maintained at that level until 2100.

^[1] Note that results from target values other than $\geq 90\%$ i.e. $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, are presented in the supplementary materials.

^[2] Expansion in coverage is always to the greater of the target expressed or the value recorded for each country in 2019.

Figures

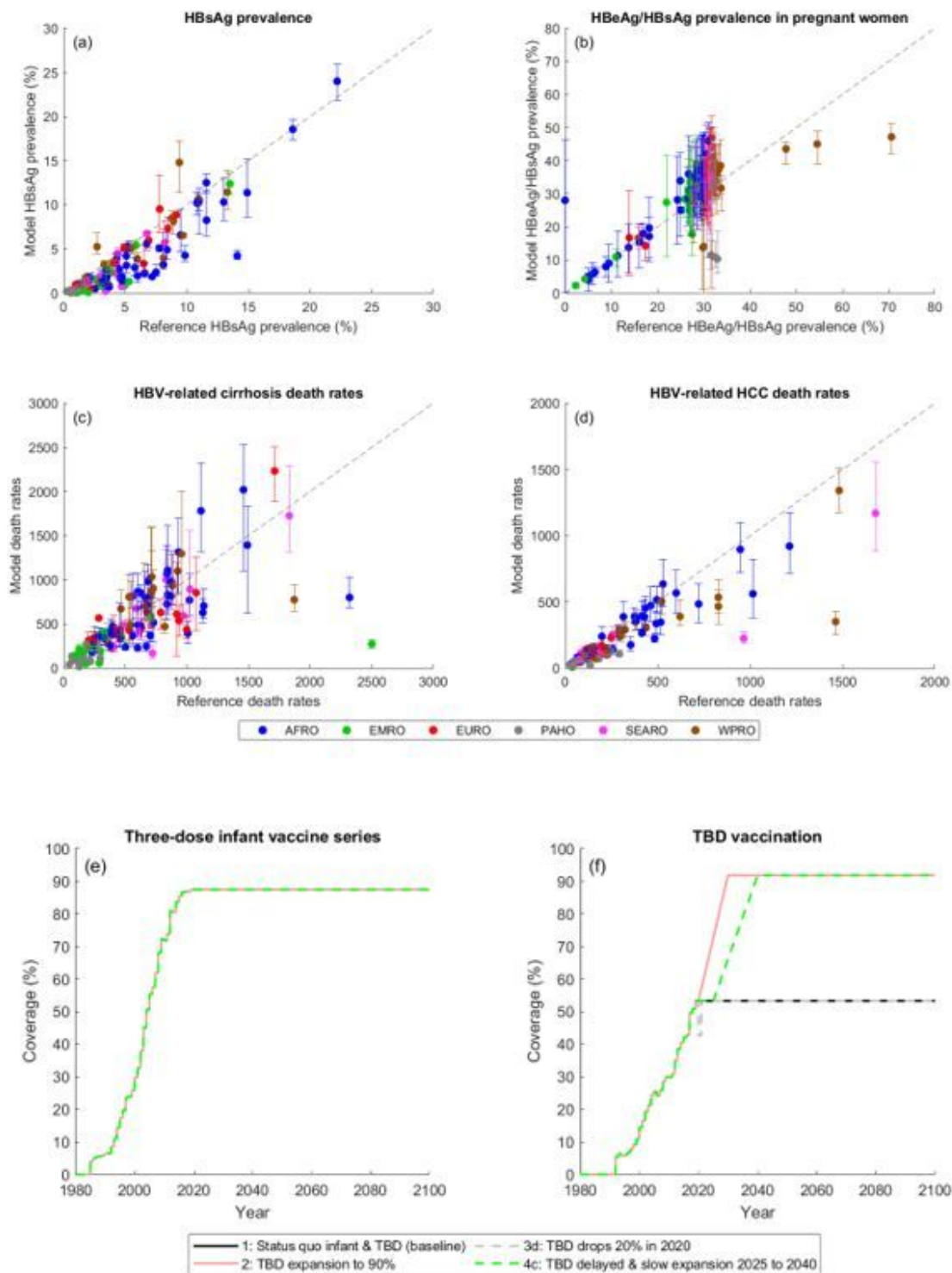


Figure 1

The model calibrations and the scenarios used. (a) HBsAg prevalence in all ages, (b) HBeAg prevalence in HBsAg+ pregnant women, and HBV-related death rates (deaths per 100,000) from (c) cirrhosis and (d) hepatocellular carcinoma, with 95% credibility intervals, in the 110 countries modelled compared to data from the literature in the year the data were collected. Countries modelled in the six WHO regions AFRO, EMRO, EURO, PAHO, SEARO and WPRO are given in Fig. S1. (e) Infant HBV vaccine series and (f) TBD

vaccination coverage globally in selected scenarios (see Table 1). HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B; HCC: hepatocellular carcinoma; TBD: timely birth dose.

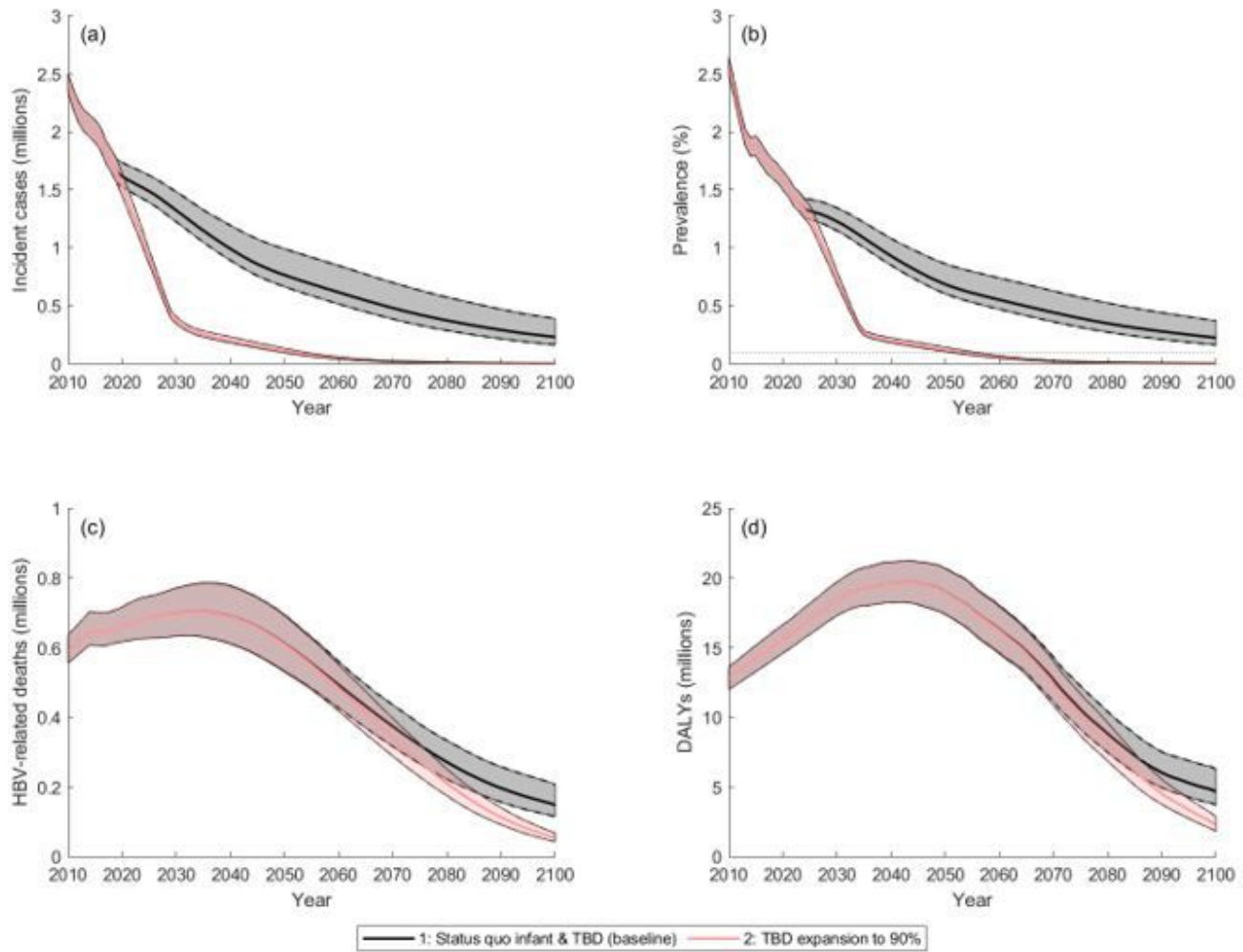


Figure 2

The overall impact of TBD scale-up on disease burden globally. (a) Incidence of new chronic carriage of HBV, (b) prevalence of chronic HBsAg among five-year-olds, (c) HBV-related deaths and (d) total DALYs incurred. Shown are the means (lines) and 95% credibility intervals (shaded areas), comparing the status quo (scenario 1; black line; grey shading) with a scenario in which TBD is given to $\geq 90\%$ of new-borns (scenario 2; red line and shading). Results are the sum from all modelled countries. The horizontal dashed line in Fig. 2b represents the WHO 'elimination threshold' of 0.1% HBsAg prevalence in five-year-olds. DALY: disability adjusted life years; HBsAg: hepatitis B surface antigen; HBV: hepatitis B; TBD: timely birth dose.

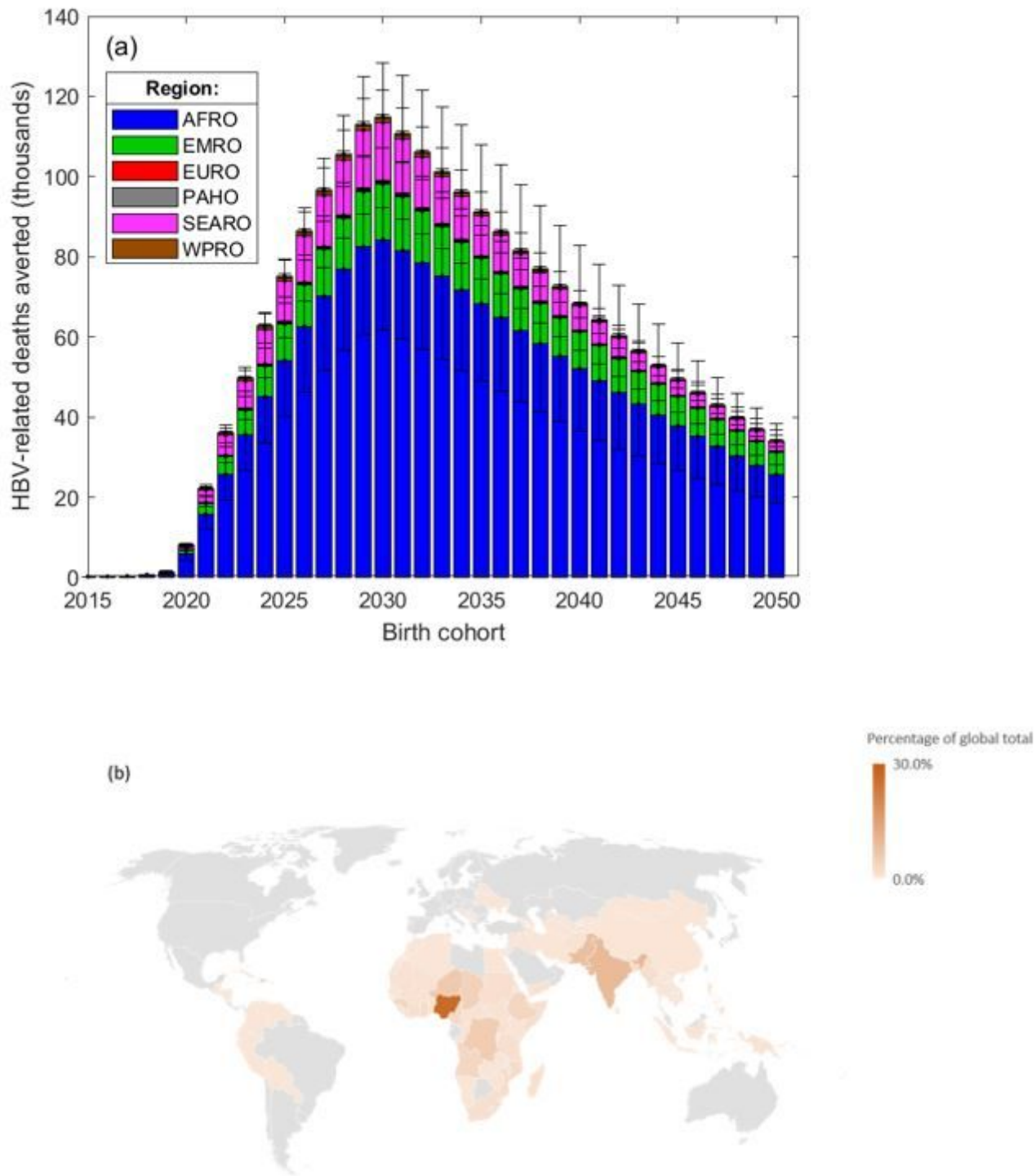


Figure 3

The impact of TBD scale-up on HBV-related deaths. (a): HBV-related deaths averted in each WHO region (mean and 95% credibility intervals) in the birth cohorts for years 2015 to 2050, in the scenario in which TBD coverage is scaled up to $\geq 90\%$ by 2030 in each country (scenario 2) compared to the status quo (scenario 1). (b): Percentage of global total HBV-related deaths averted in the 2020 to 2030 birth cohorts that occurs in each country if TBD coverage is scaled up to $\geq 90\%$ by 2030 (scenario 2) relative to the status quo scenario (scenario 1). HBV: hepatitis B; TBD: timely birth dose; WHO: World Health

Organization. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

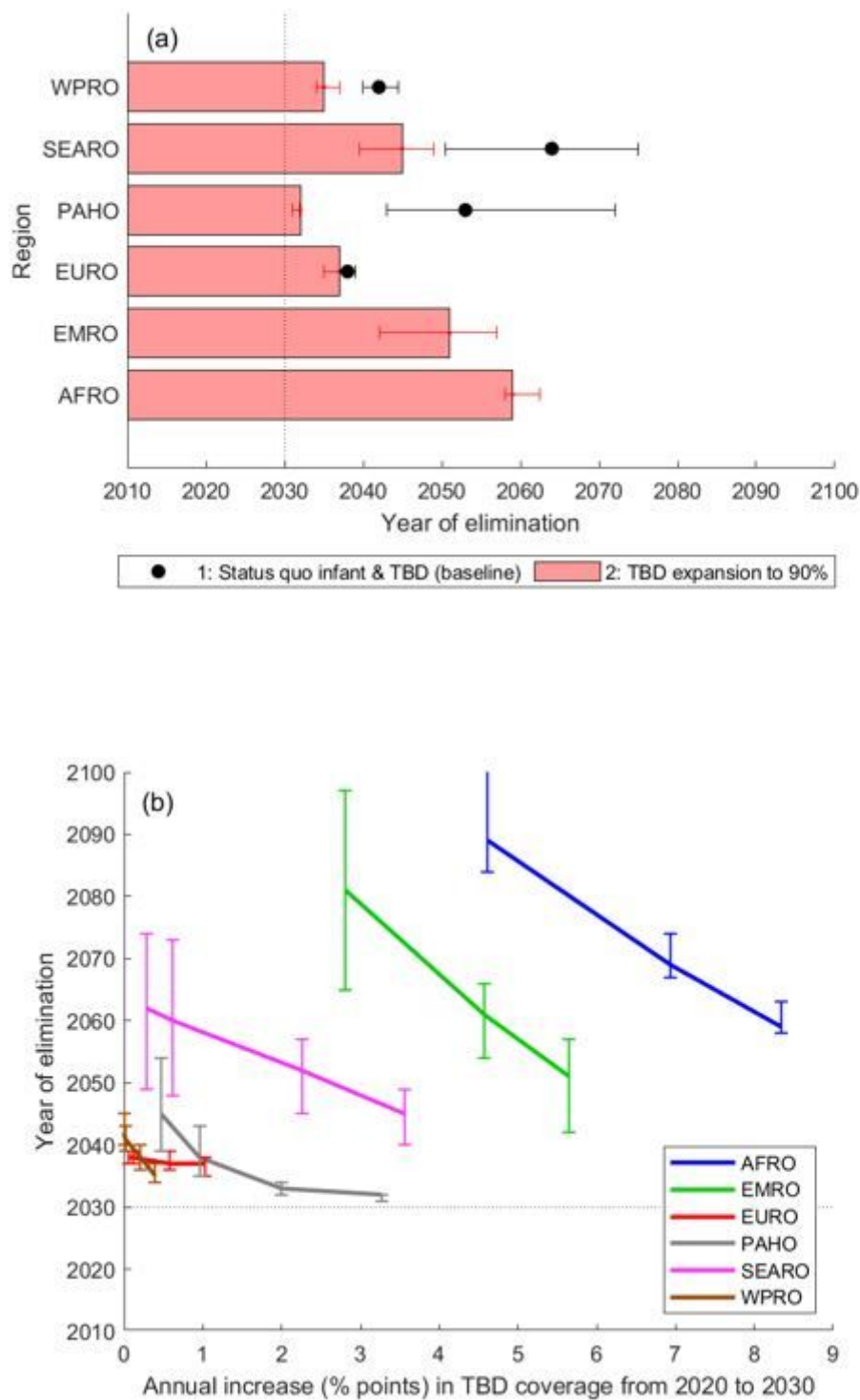


Figure 4

The impact of TBD scale-up on achieving WHO elimination targets. (a): Median year by which the elimination target (0.1% HBsAg prevalence in five-year-olds) is reached in the WHO regions, with 95% credibility intervals, in the status quo scenario (scenario 1; black dots) and the scenario in which TBD coverage is scaled up to $\geq 90\%$ by 2030 (scenario 2; red bars). (b): Median year of elimination, with 95% credibility intervals, for different levels of annual scale-up of TBD coverage (scenario 2) in the populations within each of the WHO regions. The dotted lines at the year 2030 are for reference purposes only. HBsAg: hepatitis B surface antigen; TBD: timely birth dose; WHO: World Health Organization.

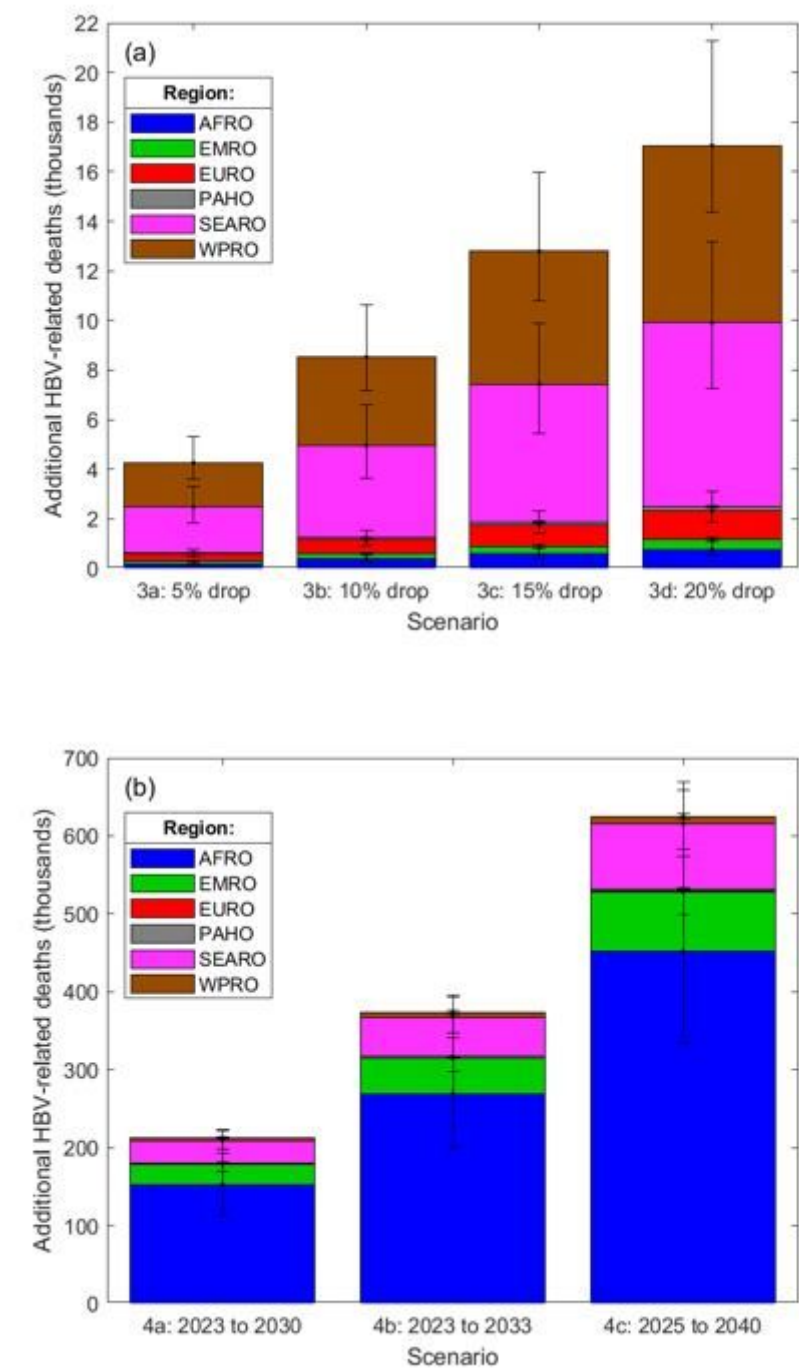


Figure 5

The impact of disruptions to the scale-up of TBD on HBV-related deaths. (a): Mean additional HBV-related deaths in the birth cohorts in 2020-2030 due to a drop in the proportion of new-borns receiving TBD in 2020 (scenarios 3a to 3d) relative to the status quo scenario (scenario 1), with 95% credibility intervals. (b): Mean additional HBV-related deaths in the birth cohorts in 2020-2030 due to delays in scaling up TBD coverage to $\geq 90\%$ (scenarios 4a to 4c) relative to scaling up TBD coverage to $\geq 90\%$ between 2019 and 2030 (scenario 2), with 95% credibility intervals. HBV: hepatitis B; TBD: timely birth dose.

Supplementary Files

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