Hepatitis B vaccination as an elimination tool
assessed in a paediatric cohort and simulated in a model

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ABBREVIATIONS

- 3TC - Lamivudine
- Anti-HBc – Antibody to hepatitis B core antigen (antibody mediated by exposure to infection)
- Anti-HBe – Antibody to hepatitis B envelope antigen
- Anti-HBs – Antibody to hepatitis B surface antigen (vaccine-mediated antibody)
- ART – Anti-retroviral therapy
- COSAC – Coinfection in South African children
- EPI – Expanded Programme on Immunisation
- FTC - Entecavir
- HBV – Hepatitis B virus
- HBcAg – Hepatitis B core antigen
- HBeAg – Hepatitis B envelope antigen
- HBsAg – Hepatitis B surface antigen
- HBlg – Hepatitis B immunoglobulin
- HIV – Human immunodeficiency virus (type 1)
- KReC – Kimberley Respiratory Cohort
- PMTCT – Prevention of mother to child transmission
- RTHB – Road to Health Book
- TDF – Tenofovir
- UN – United Nations
- WHO – World Health Organisation
ABSTRACT
Sustainable Development Goals set a challenge for the elimination of hepatitis B virus (HBV) as a public health concern by 2030. We evaluate the current and future role of HBV vaccination and prevention of mother to child transmission (PMTCT) as tools for elimination, through the combined scrutiny of a paediatric cohort in South Africa and a model to simulate transmission and prevention. Existing efforts have been successful in reducing prevalence of infection (HBsAg) in children to <1%. Our model anticipates that current combination efforts of vaccination and PMTCT can significantly reduce population prevalence (HBsAg) by 2030, but will reduce the prevalence of HBV e-antigen positive carriers more slowly, with potential implications for public health control. With strategies and resources already available, significant, positive public health impact is possible, although time to HBV elimination as a public health concern is likely to be longer than that proposed by current goals.
INTRODUCTION

The vaccine against hepatitis B virus (HBV) infection is widely regarded as robust, safe and immunogenic (1–3). As such, it is one of the cornerstone strategies through which the international community can work towards the target set by United Nations Sustainable Development Goals (SDGs) for HBV elimination as a public health threat by the year 2030 (4,5). In sub-Saharan Africa (sSA), a substantial burden of HBV transmission is likely to occur early in life, either vertically from mother to child, or through horizontal acquisition among young children (6). In this setting, the HBV vaccine has been progressively rolled out as part of the World Health Organisation (WHO) Expanded Programme on Immunisation (EPI) over the past two decades (6). In many countries, the first dose of vaccine is postponed until age six weeks, when it is given together with other routine immunizations; in South Africa, this is a hexavalent combination (HBV, Diphtheria, Tetanus, Pertussis, Haemophilus influenzae type B, Poliomyelitis) (7). Populations in sSA are particularly vulnerable to morbidity and mortality due to the high prevalence of HBV infection (≥8% in many regions) (8–10), co-endemic HIV infection (11), poor access to screening and diagnostics, limited deployment of antiviral therapy, stigma of HBV infection, and chronic neglect of education, research and resources (12,13).

Vaccine deployment can be difficult to measure; many children in sSA are born outside healthcare settings, there are no robust data regarding coverage of the three dose regimen (6), and different immunological correlates of protection have been applied (14,15). In order to accelerate progress towards elimination goals, a variety of approaches has been suggested, including shifting the first dose to be given at birth (16), additional doses in the context of HIV infection (17,18), booster doses in individuals whose antibody titre fails to meet a target threshold (14), and catch-up vaccination campaigns for adolescents and adults. However, there is a lack of robust data to inform which of these measures, individually or in combination, is most effective in shifting populations towards sustained elimination of HBV infection as a public health concern. Given the resource limitations of many settings in which HBV represents a public health challenge, there is an urgent need to underpin interventions with an evidence base derived both from careful observation of the existing impact of vaccination and from projections regarding future outcomes on both the incidence and prevalence of HBV infection.

On these grounds, we have set out to collect a detailed dataset to provide a snapshot of a population in South Africa in which HBV and HIV infections are co-endemic, first seeking evidence of the impact of the current immunization schedule on preventing HBV infection (indicated by hepatitis B surface antigen, HBsAg) in children with and without HIV infection,
and to examine the potential waning of immunity over time (with protective immunity assessed by vaccine-mediated antibody titres, anti-HBs). We then assessed the extent to which continuation of current practice could be predicted to achieve elimination targets within the timeframe set out by SDGs. Finally, we built on this framework by adding data assimilated from reference to the wider published literature to model the effects of different HBV vaccine deployment strategies, either alone or in combination with enhanced measures for prevention of mother to child transmission (PMTCT). PMTCT depends on antenatal screening to identify HBV positive mothers, deployment of antiviral treatment during trimester three, accelerated neonatal vaccination, and ideally the administration of HBV immune globulin (‘HBIg’) to high-risk babies immediately after birth, although the latter is rarely affordable in resource-limited settings (19).

The impact of HBV vaccination has been neglected in the modelling literature compared to other immunisations for infectious disease. To date, few studies have addressed this subject, with one study modelling the global prevalence of current intervention efforts (20), and another describing a modelling approach that scrutinizes the combined impact of broad HBV elimination strategies (21). Our study builds on these prior approaches in contributing to the development of robust insights into tackling the global burden of HBV. In this instance, we root our analysis within primary clinical data, single out the individual and combined impact of childhood vaccination and PMTCT strategies, and address the specific impact of co-endemic HIV infection. In so doing, we contribute to a growing body of evidence that can directly underpin practice in vaccination programmes, ensuring that clinical and public health resources are targeted in the best way to bring about HBV elimination, with particular reference to some of the world’s most vulnerable settings that overlap with the epicentre of the HIV pandemic.

Combining output from a clinical dataset together with a dynamic model provides a synergistic approach; in order to describe and understand the complete picture, both strands of evidence should be viewed together. Specifically, our paediatric cohort highlights the success and impact of the HBV vaccine programme in preventing new infections, while the model illustrates how simply continuing to pursue this strategy in isolation is not a reliable route to HBV elimination as a public health concern in the near future. Taking the evidence together, we conclude that while vaccination is a fundamental part of global elimination strategy and is highly effective in preventing infection in individual children, there is an urgent need for rigorous, enhanced deployment of parallel strategies including education, diagnostics, antiviral therapy, and the ongoing quest for a cure.
RESULTS

Serological evidence of exposure to HBV infection

From our cohort of 402 children in Kimberley, South Africa, three were HBsAg-positive (0.7%; Table 1). This HBsAg prevalence is significantly lower than in adults in a comparable study population (e.g. 11.1% in a previous study (9); p<0.0001). Exposure to HBV infection was measured using anti-HBc antibody; this was detected in three children (0.7%), one of whom was also HBsAg-positive. The other two were HBsAg negative, indicating previous HBV exposure and clearance.

Table 1: Profiles of five children from Kimberley, South Africa, with serological evidence of current or previous infection with HBV (based on positive HBsAg (n=3) or anti-HBc (n=2))

| Subject | K306 | K405 | KReC51 | KReC151 | K093 |
|---------|------|------|--------|---------|------|
| Cohort  | HIV positive age ≤60 months | HIV positive age ≤60 months | KReC | KReC | HIV positive age >60 months |
| Sex     | F | F | F | M | F |
| Age (months) at time of sampling | 18 | 37 | 20 | 15 | 118 |
| HIV infection | Positive | Positive | Negative | Negative | Positive |
| ART* (if HIV positive) | Yes | Yes | NA | NA | No |
| Number of doses of HBV vaccine | NK | NK | NK | 3 | NK |
| HBsAg result** | Detected | Detected | Detected | Not detected | Not detected |
| Anti-HBc result*** | Not detected | Not detected | Detected | Detected | Detected |
| HBeAg result**** | Not done | Not done | Detected | Not done | Not done |
| Anti-HBs result***** | Not detected | Not detected | Not detected | Detected | Not detected |
| Interpretation | Active infection | Active infection | Active infection | Immunised, infected and cleared | Infected and cleared |

*ART indicates the participant was receiving anti-retroviral therapy to treat HIV infection; **Hepatitis B surface antigen test; ***Hepatitis B core antibody test; ****Hepatitis B envelope antigen test; *****Hepatitis B surface antibody test (vaccine mediated response). KReC = Kimberley Respiratory Cohort. NA = not applicable. NK=not known. HBV viral loads were not tested in any of these children.
Documented evidence of vaccination and serological evidence of immunity to HBV in children aged ≤60 months

We collected written evidence of immunisation from the Road to Health Book (RTHB) in 90.8% HIV-negative (KReC) subjects and 6.3% of HIV positive subjects (total 41.3% of cohort). None of the HBsAg-positive children attended with a written vaccination record (RTHB). Due to missing vaccination records, in the absence of a detectable anti-HBs titre we cannot reliably distinguish between children who are unimmunized, and children who are immunised but fail to mount an antibody response. However, among those with a RTHB record, 81.3% of HIV-negative and 100% of HIV-positive children were recorded as having received three HBV vaccine doses.

Among all children age ≤60 months, 238/310 (77%) had an anti-HBs titre ≥10 mIU/ml suggesting some degree of vaccine-mediated immunity. The median anti-HBs titre in HIV-negative children was significantly higher than among the HIV-positive group (196 mIU/ml, vs. 11 mIU/ml, respectively, p<0.0001) (Fig 1A). There was no detectable anti-HBs antibody in 3.4% of HIV-negative vs. 47.8% of HIV-positive children (p<0.0001). Irrespective of the antibody titre used as a threshold for immunity, anti-HBs was higher in HIV-negative compared to HIV-positive children (Fig 1B). There was no significant difference in anti-HBs titres between male and female participants, either with or without HIV infection (p=0.49 and 0.31 respectively, data not shown).

Waning of vaccine response with age

HIV-positive children with anti-HBs titres ≥100 mIU/ml were significantly younger than those with lower antibody titres (median age 17 months vs. 31 months, p=0.0008), while no such difference was observed within the HIV-negative group (Fig 2A). Using the lower threshold of ≥10 mIU/ml, we found no significant difference by age in either the HIV-positive or the HIV-negative groups (p=0.17 and 4.48 respectively, data not shown). To expand our view of the HIV-positive group, we also added analysis of an older cohort (92 children aged >60 months), and demonstrated that anti-HBs titres were significantly lower in this older group (p<0.0001), with only 2/92 subjects (2.2%) achieving an anti-HBs titre of ≥10 mIU/ml (Fig 2B). Anti-HBs titres waned significantly with age up to age 60 months in HIV-positive children (Fig 2C; p=0.004). We observed a similar trend in the HIV-negative cohort, but this did not reach statistical significance (Fig 2C; p=0.07). The proportion of HIV-positive subjects with a detectable anti-HBs titre declined steadily with age in the cohort, contrasting to the trend in HIV-negative subjects, where individuals maintained protective anti-HBs titres despite a trend towards decreasing mean titres (Fig 2C). Although the numbers of children in this cohort are small, and we did not collect longitudinal data, these results support previous literature reports.
that HBV vaccine-mediated immunity wanes over time independently of HIV serostatus, but faster for HIV positive individuals (22,23).

Stratification of vaccine responses by anti-retroviral therapy (ART) among HIV-positive children

For HIV-positive children aged ≤60 months, ART treatment data were available for 79% of subjects. Within this group, 71% were receiving ART at the time we tested for anti-HBs, and had received a median of 20 months of treatment (IQR 6-33 months). Comparing anti-HBs titres between ART-treated vs. untreated children, we found no significant difference (p=0.72; 76 ART-treated, median anti-HBs 13.3 mIU/ml and 31 untreated children, median anti-HBs 14.1 mIU/ml, data not shown). There was also no difference between anti-HBs titres of children treated for ≤12 months vs. >12 months (p=0.50, data not shown). We did not examine the effect of ART on anti-HBs titres in children >60 months due to the low numbers of subjects with a detectable anti-HBs titre (n=2).

Odds of developing an anti-HBs response

We used an odds ratio (OR) analysis to identify factors associated with vaccine-mediated protection (Fig 2D). HIV-positive status was associated with lack of protection, for antibody titres of both <10 mIU/ml (OR 26.2, 95% CI 11.2-58.6), and <100 mIU/ml (OR 11.6, 95% CI 6.7-20.4). In contrast, younger age (<24 months) was protective, (for anti-HBs <10 mIU/ml OR 0.3, 95% CI 0.2-0.5 and for anti-HBs <100 mIU/ml OR 0.3, 95% CI 0.2-0.4). Other characteristics analysed including gender, ART, CD4+ count, CD4+ ratio and HIV viral load were not found to be significantly predictive of anti-HBs titres at either threshold.

Fitting of a dynamic model to local HBV epidemiology

We set out to use our clinical data to inform the development of a dynamic model to provide insights into the long-term outcomes of sustained immunization, and to suggest how prevention strategies can be optimized, for example by enhancement of PMTCT or extended vaccination campaigns targeting older age groups.

In summary, the model takes into consideration the susceptible proportion of the population (S), the chronic (C) and acute (I) carriers, the immune (R) and the vaccinated (V) (Fig 3A). To be able to parameterize HBV or vaccine-related epidemiological traits in age, such as age-specific probability of chronicity or decay of vaccine-induced protection, susceptible (S) and vaccinated (V) individuals are divided into three subgroups representing infants (i, <1 years of age), children (c, 1-6 years of age) and older individuals (comprising older children, adolescents and adults, a, >6 years of age). Chronic carriers, C, are divided into HBeAg-
positive (C+) and HBeAg-negative (C-) to further allow for different parameterization between these two biologically distinct states.

Informed by the cohort data described above, natural decay and the effects of HIV sero-status on vaccine-induced protection are also taken into account. We used a Bayesian Markov-chain Monte Carlo (bMCMC) approach to fit the dynamic model to the local demographic and epidemiological setting of Kimberley before projecting the impact of interventions. We used informative priors for model parameters for which robust literature support exists, and uninformative (uniform) priors otherwise. For full details on the model and fitting approach, see the Methods section.

The dynamic model was able to closely reproduce the target (fitted) variables – HBV prevalence (HBsAg), prevalence of HBV exposure (anti-HBc) (Fig 3 B1), and relative proportion of HBeAg-negative and HBeAg-positive among chronic carriers (Fig 3B2). For parameters for which little or no support was found in the literature (Fig 3C), the resulting posteriors were well behaved. For parameters using informative priors taken from the literature (Fig 3 D, E), the resulting posteriors matched well. Overall, the obtained bell-shaped posteriors highlighted no identifiability issues with the fitting approach (Fig 3 C, D, E).

The posterior for the rate of seroconversion from HBeAg-positive to HBeAg-negative (θ) suggested slow progression, with a median period of ~18.5 years (95% CI [14.3, 21.9]). We note here that although we used an uninformative (uniform) prior for θ, its posterior with median ~5.3% a year, here not accounting directly to age-specificity, is compatible with empirical estimations (24) of yearly rates of less than 2% for <3 years of age and 4-5% for older children (25), with ~90% of individuals acquiring HBV early in life remaining HBsAg-positive at the ages of 15-20 years (26). Spontaneous clearance of chronic HBV infection (loss of HBsAg) (ρ) was estimated to be even slower, close to 0.3% a year (95% CI [0.04, 0.84]), slightly lower than reported rates of 0.7-2.26% previously observed in the literature (27–29), although there remains a lack of data for the African subcontinent.

Model projection of the impact of routine neonatal vaccination and PMTCT alone
Based on Sustainable Development Goals (SDGs) for the year 2030 set out in the WHO’s Global Health Sector Strategy on Viral Hepatitis (5), we have considered the impact of HBV interventions using two targets: (i) 90% reduction in HBsAg incidence (total new chronic HBV cases) relative to the pre-control era, and (ii) reduction of HBeAg-prevalence to 1 in 1000 individuals in the population (0.1%) in the post-control era (see Materials and Methods for further details). In our projections of the impact of HBV interventions, we addressed the time
required to achieve these goals separately. Fig 4 shows the results of numerical simulations for varying coverage of neonatal vaccination and PMTCT. Variation presented is from the stochastic nature of the simulations, including demographic stochastically and parameter (posterior) sampling.

As expected, both HBsAg incidence (Fig 4 A1) and HBeAg-positive prevalence (Fig 4 B1) reduce faster with increasing neonatal immunization coverage, resulting in shorter times to reach the elimination targets (Fig 4 A2, B2). Importantly, even immunization of 100% of neonates is predicted to take ~99 years (95% CI 61 - 186) for the HBsAg incidence target to be achieved (Fig 4 A2), and ~175 years (95% CI 103 - 278) for the HBeAg-positive prevalence target (Fig 4 B2). Such long timeframes are supported by a previous modelling study (21).

When simulating PMTCT intervention, both HBsAg incidence (Fig 4 C1) and HBeAg-positive prevalence (Fig 4 D1) reduced faster in time for increasing efforts, resulting in shorter times to reach the elimination targets (Fig 4 C2, D2). However, the impact of PMTCT was smaller than neonatal vaccination for similar coverage, resulting in significantly longer times to reach the target thresholds. In fact, for the majority of PMTCT effort levels simulated, the targets could not be reached within 500 years (beige areas in Fig 4 C2, D2). For HBeAg-positive prevalence, only when PMTCT effort was 1 (i.e. complete elimination of vertical transmission), was the reduction target attainable within 500 years. These results reflect the impact of a control strategy that can be highly successful at preventing infections at a particular time-point in an individual's life (perinatally) but does not necessarily translate into sustained long-term protection.

The model suggests that reaching either of the elimination targets will require different intervention coverage and different time scales. In particular, the target for reducing HBsAg incidence is easier to achieve than reducing HBeAg-prevalence. This implies that for a certain vaccination coverage or PMTCT effort, reductions in HBsAg incidence must be interpreted with caution, as such positive trends will potentially mask the fact that HBeAg-positive prevalence, critical for public health, will not be responding at the same rate.

Modelling progress towards HBV elimination by the year 2030 based on combinations of neonatal vaccination and PMTCT

Based on the premise that interventions in the South African population have been most consistently deployed since roll-out of the HBV vaccine in infancy since 1995 (6), we used our model to determine the impact of combined interventions by the year 2030 (Fig 5 A1, B1), and to predict the year at which the 90% reduction in HBsAg incidence and 0.1% HBeAg-positive
prevalence targets would be reached (Fig 5 A2, B2). Strikingly, HBsAg incidence could already have been reduced by >90% (Fig 5 A1) if both neonatal vaccination and PMTCT had been deployed at 100% coverage since they became widely available in 1995 (mean predicted year of elimination 2017; Fig 5 A2). In reality, complete coverage of such interventions is not possible, and we therefore projected outcomes based on <100% intervention coverage. For example, combining neonatal vaccination and PMTCT with 90% coverage of each since 1995 is projected to achieve the HBsAg incidence target by 2028; if this is reduced to 80% coverage then goals will be attained by 2044. To achieve the target reduction in HBeAg-positive prevalence, the projected years are 2072 and 2096 (modelled on 90% coverage and 80% coverage of interventions, respectively, Fig 5 B1, B2). Again, these results suggest that setting goals based on HBsAg incidence obfuscates the difficulty of achieving targets based on HBeAg-positive prevalence on similar time scales.

Projecting the probability of achieving elimination targets based on combinations of neonatal vaccination, PMTCT and enhanced vaccination

We simulated the impact of combining neonatal vaccination and PMTCT with additional vaccine deployment in other population groups (Fig 6 A1, A2), namely the routine vaccination of older children (at the entry point of 6 years of age), and one-off catch-up vaccination of children (<6 years) and others (>6 years).

Overall, the highest probability of achieving elimination targets is through a combination of 100% neonatal vaccination coverage and PMTCT (Fig 6 A1, red line). Again, such high intervention efforts are realistically not attainable. We therefore also modelled an ambitious combination of 90% coverage of both neonatal vaccine and PMTCT (Fig 6 A1, A2, green line) as proposed in WHO’S Global Health Sector Strategy on Viral Hepatitis (5). Such intervention resulted in only 50% probability of reaching the HBsAg incidence target by 2030, and approaching 100% probability only by 2050. For the target based on HBeAg-positive prevalence, the probabilities of achieving the goal were pushed forward by approximately four decades.

Adding catch-up vaccination campaigns makes no impact on the probability of reaching either of the elimination targets (Fig 6 A1, A2, blue and cyan lines). Routine vaccination at 6 years of age as an alternative for PMTCT, even when delivered at 100% coverage, is markedly less effective than any other projected intervention (Fig 6 A1, A2, magenta line).

Projecting the impact of HIV on the probability of achieving elimination targets
As our clinical cohort is centred in South Africa, at the epicentre of the HIV pandemic, we also used our model to investigate the impact of co-endemic HIV on the success of interventions for HBV. We considered a baseline scenario defined by the epidemiological setting fitted by our model in the context of Kimberley, in which local HIV prevalence was taken into consideration for each of the modelled age groups (Fig 6 B1, B2, solid line). We then performed a sensitivity exercise, considering alternative scenarios in which HIV prevalence was altered to zero or higher prevalence, projecting HBV interventions into the future. Overall, when compared to a scenario with no HIV (Fig 6 B1, B2, dotted line), the presence of HIV infection at the prevalence seen in Kimberley (Fig 6 B1, B2, solid line) has a relatively modest impact on the probability of achieving the HBV targets, adding an estimated four years to the time taken to achieve a 50% chance of reaching the goals (Fig 6 B1). We also simulated the effect of higher population HIV prevalence (x2, x3 and x4 baseline data for Kimberley) to investigate the potential impact of coinfection in high-risk populations. Increasing HIV prevalence, as expected, has a negative impact on the success of combined interventions for HBV, but the effects are relatively modest. In particular, doubling HIV prevalence would shift the 50% probability endpoint into the future by ~4 years for the HBsAg incidence target, and ~7 years for the HBeAg prevalence target. With increasing HIV prevalence, the negative impact on HBV interventions increases, particularly with respect to reduction in HBeAg prevalence. Encouragingly, as ART is now offered at the point of HIV diagnosis and uptake is consistently increasing, any detrimental impact of HIV coinfection is likely to diminish over time, with more of the HIV-infected population retaining near intact immunity.

**DISCUSSION**

This is a unique study in which we capitalize on detailed clinical cohort data collected in South Africa, represented here and also in our previous publications (9,30), in order to (i) form a robust view of the dynamics of HBV epidemiology, and (ii) develop a mathematical model of HBV transmission and prevention. Overall, we demonstrate that the optimum population intervention is high coverage neonatal vaccination, and that this can be strengthened by robust deployment of PMTCT. However, we project long time-scales to achieve elimination targets, congruent with the large established reservoir of chronic HBV infection, lack of curative therapy, infection that can persist for the entire life-span of the host, and interventions that target only a small proportion of the population. Developing an evidence-based understanding of the most effective approaches to control and elimination is key in light of the Sustainable Development Goals, and is a particular priority for resource-constrained settings that are often made particularly vulnerable by the high prevalence of both HIV and HBV infection. The
outputs from this model could be of direct influence in informing ongoing public health strategies in high-prevalence settings.

Rationale for combining clinical data and modelling
Importantly, by assimilating the results of the clinical cohort and the model, we develop a much more complete picture than either individual approach would provide in isolation. Standing alone, the clinical study could provide false reassurance that vaccination campaigns will be adequate to bring about control or elimination; conversely, in the absence of the cohort, the model could be mistakenly interpreted to suggest that vaccination offers limited benefits to population health in the short-medium term. Only by viewing the two conclusions together can we correctly infer that vaccination is of profound importance in protecting individual children and significantly reducing the burden of infection in paediatric cohorts, but also that continuing to pursue this strategy alone is not sufficient to bring about HBV elimination, or even robust control, within the desired time-scale. Although vaccination is a powerful strategy, it is not the short or medium term route to elimination of this pathogen.

Comparison with other published models
Compared to published models of other vaccine-preventable diseases (31), there is a marked deficit in the existing literature for HBV, with few other modelling efforts represented in the peer-reviewed literature (32,33). Reassuringly, our findings are consistent with those of another recent simulation of HBV prevention (21); we concur in concluding that current vaccine-based interventions will result in a modest reduction in HBV prevalence by the year 2030. However, there are also some important differences that distinguish our work from previous efforts:

i. Our evaluation provides the advantages of both clinical data and a mathematical model, with close links between our cohort and simulations, and strengths in interpretation of data derived through different approaches. In so doing, we have also been able to specifically address the impact of co-endemic HIV that has not been factored into previous evaluations, using unique cohort data to implement a data-driven approach into the dynamic model.

ii. In contrast to approximating model behaviour to a wide range of epidemiological settings across many geographical regions, we focus on a particular population for which we derive unknown epidemiological parameters and apply a robust data-driven approach to others. Our Bayesian framework therefore stands alone (as a tool) that can be applied to any population for which empirical support of key HBV epidemiological parameters is missing. By supplying the model’s code, we can facilitate the use of the tool by other academics.
As outputs, we have used targets for reductions in both HBsAg incidence and HBeAg-positive prevalence, and have projected the impact of interventions based specifically on the WHO proposal for 90% vaccination of neonates and 90% PMTCT coverage by 2030. Previous studies (20,21) have focused instead on ad hoc control thresholds or impact on the public health problem through reduction of HBV-related deaths. By focusing on two alternative control targets for HBV, we conclude that different intervention efforts and time scales are required to achieve these. Goals based on HBeAg-positive prevalence levels are harder to achieve when compared to reductions in new infections, and reflect important epidemiological and public health traits of chronic infections; our results thus contribute to an ongoing discussion regarding which goals should be set, and their underlying public health implications.

HBV model projections

Although a high coverage of neonatal vaccination combined with robust PMCTC shows potential promise to reach elimination targets, the projected time-frame is currently substantially beyond the 2030 milestone. Furthermore, optimal intervention levels have not been in effect since 1995 and the real time-frame to achieve the goals is therefore expected to be considerably longer. We did not address elimination (extinction) in our projections, but it is clear from our main results that an elimination time-frame is far beyond reach with the interventions currently available, and efforts should, for now, be focused on planning for control of HBV as public health issue rather than elimination of the pathogen.

The model we have developed is statistically robust based on the parameters we have included for this population, and we believe this is an important parsimonious, data-driven tool, offering the potential to scrutinise different strategies independently from one another. The determinants of an equilibrium in any population depend on a number of factors, which may be determined by characteristics and behaviours of the host population (34) as well as potentially by the genetics of the virus. However, where the relevant epidemiological parameters have been defined, we believe the model could robustly be applied to other settings.

Impact of HIV on population interventions for HBV

Although previous studies in southern Africa have indicated that HBV infection is not significantly associated with HIV status (7,35,36), our data do highlight and corroborate a likely additional vulnerability of HIV-infected children based on lower anti-HBs titres and waning immunity over time. Impaired vaccine responses have previously been reported in HIV-positive individuals (18,37–40), but it is also possible that vaccine coverage is lower in HIV-
infected children (41). Waning of anti-HBs titres over time has been observed in both HIV-positive and HIV-negative subjects, but this does not necessarily correlate with loss of clinical protection; anamnestic responses are thought to occur in a proportion of those vaccinated (42), although this memory may be attenuated by HIV (43,44).

ART has previously been associated with improved HBV vaccine responses (45,46), although we did not replicate this finding in our cohort. This can potentially be explained by data from a previous study of Kimberley children, demonstrating that CD4+ T cell recovery takes a median of five years after ART initiation (47). Our current study is underpowered to detect any true effect, given both the relatively short durations of ART, and the small number of untreated children. Interestingly, despite the lack of direct association with ART, children with lower HIV viral loads had significantly higher anti-HBs titres, in keeping with previous studies (17,45). Based on current treatment guidelines, all HIV-infected children are now started on ART (48) and the immune reconstitution of this population over time is likely to reduce differences in vaccine responses between HIV-positive and HIV-negative groups.

**Changes required to meet 2030 sustainable development goals**

The model suggests long time-lines, enumerated in centuries rather than decades, before control targets (focused on either HBsAg incidence or HBeAg prevalence) are reached using vaccination or PMTCT alone. Combinations of these interventions show much shorter time scales. Based on currently available interventions, major scaling up of both neonatal vaccination and PMTCT efforts will be required to deliver the 2030 targets. Importantly, the prevalence of HBeAg-positive carriers, who are at an elevated risk of chronic liver disease and hepatocellular carcinoma, as well as being at higher risk of transmitting their infection, will decline at a slower rate. Setting a control target based on reduction in the number of new HBV cases (i.e. HBsAg incidence) can therefore lead to the most optimistic projections but distract attention from the importance of reducing HBeAg-positive prevalence which constitutes the bulk of the public health burden of HBV.

Our results also underscore that a major public health impact is possible even without achieving elimination. Careful adjusting of expectations and aims, according to the scale on which particular changes occur, may inform the setting of realistic targets (e.g. reduction in the prevalence of HBeAg-positive carriers could be the most informative outcome measure). The wrong choice of either target or timescale could result in unnecessary abandonment of a strategy that could have a major impact in a few decades. In addition to informing rational use of interventions that have a positive population impact, our study is also important in cautioning against the use of strategies that may have little or no lasting population impact. This is
illustrated by our results for catch-up HBV vaccination, which adds little in situations where high coverage of both neonatal immunization and PMTCT can be attained. Considerable political drive, investing in increased surveillance and reducing barriers to treatment access will also be required in order to accurately monitor progress towards the elimination targets (49).

**Impact of HIV and ART on achieving the 2030 sustainable development goals for HBV**

Our clinical cohort highlights the day-to-day challenges of drug provision and monitoring within this setting: we did not have access to detailed prospective ART treatment data, guidelines have changed numerous times since 2002, and 3TC was intermittently used as a substitute for nevirapine (NVP) due to supply issues. During the period covered by our study, ART was only introduced in children achieving certain immunological criteria (as per old treatment guidelines), while in future, infected children will be started on treatment as soon as diagnosed, which could restore vaccine responses to similar levels as seen in the HIV-negative population; further studies will be required to assess this over time. ART treatment is relevant to outcomes in individuals with HIV/HBV coinfection, as first line ART regimens include either lamivudine (3TC) or tenofovir (TDF), both of which have activity against HBV. Alternative approaches for HBV prevention in HIV-positive subjects, such as supplementing the current schedule with booster vaccinations and increased vaccine doses have been trialled with variable results (17). A promising recent study found that repeating the primary course of vaccination after establishing HIV-positive children on ART generated lasting protective immune responses (18).

We used cohort data to parameterize vaccine-induced protection depending on HIV serostatus and time since vaccination. As far as we know, this is the first data-driven approach to project the effects of HIV prevalence on HBV interventions using a dynamic model. Our projections propose that HIV does have a negative effect on HBV interventions, although HIV prevalence only marginally increases time to reach elimination targets, which may not be significant in light of the long overall time-frames that we project even in the absence of HIV. The high HIV prevalences modelled can occur in specific high-risk groups including sex workers and men who have sex with men (50) and it is likely that increased intervention will be required in these groups to minimise HBV transmission.

**Caveats and limitations**

Different approaches to recruitment of our HIV-positive and HIV-negative cohorts may have introduced unintentional bias. By using respiratory admissions to hospital for the KReC cohort, we were able to identify and recruit a sufficient number of HIV-negative children, but the KReC
children may be less healthy than a comparable group of HIV-negative children in the community, and this approach predominantly selected younger children (on average 9.4 months younger than the HIV-positive cohort).

We set out to focus on children aged <60 months in order to collect data from the RTHB. In practice, we did not capture good RTHB data and data collection from the RTHB is itself subject to bias, as families who attend with such records may be those who are most likely to have immunised their children. Numerous complex social factors are also relevant in determining whether children are immunised; babies born to mothers who have HIV and/or HBV are more likely to be in disadvantaged by poverty, and by illness and death in the family, such that they might be less likely to present for (or respond to) vaccination. However, in this setting (and others where antenatal HBV screening is not routinely deployed (12,51,52)), we deem it unlikely that there is a significant difference in vaccination rates between infants born to HBV-positive versus HBV-negative mothers. Vaccine immunogenicity may be altered by a variety of other factors which we did not measure in this study, including maintenance of cold chain, body site of immunization, vaccine preparation (in this case the monovalent HBV vaccine (Biovac Paed)), circadian timing of vaccine doses, and time of day when samples are collected (53), although existing data for HBV vaccine do not support this (54).

We relied on HBsAg to detect cases of HBV infection. HBV DNA is a more sensitive screening tool but was not practical due to high cost and lack of availability in this setting. The relatively small numbers in each age group and the lack of longitudinal follow-up for individual children puts limitations on the data showing anti-HBs waning over time, but the trends we observe here are biologically plausible and consistent with the existing literature (23,55).

We have not considered the influence of population migration on the success of HBV interventions to reach the elimination targets. Migration of non-immune and/or infected individuals into an area would delay the time to achieve the targets estimated by our modelling approach. In the absence of clear data to underpin population migration in southern Africa, we have currently addressed our questions in the assumption that populations are static, but the potential impact on HBV control is an important consideration for regions in which there is significant population flux.

Although we have estimated and parameterized the impact of HIV status on HBV vaccine-induced protection, we have not modelled other factors related to HIV infection. Namely, we have not included the potential for increased susceptibility to HBV infection or increased risk of vertical transmission. These factors would have required further model classes and specific
parameterization, for which little literature support exists. It is likely that such HIV-related factors would have negative effects on our projections of impact, with time to reach elimination targets becoming longer. Including such factors is a possible path for future work once parametrization becomes possible from publically available data.

Conclusions
Our results affirm the success of the HBV vaccine programme in reducing the prevalence of HBV in children, with current prevalence rates of <1% underlining the importance of ongoing immunisation. However, we also highlight that cases of HBV transmission persist and that a proportion of children are potentially at risk of infection as a result of low anti-HBs titres, either as a result of missing or incomplete immunisation, or because of poor antibody titres following vaccination (especially in the context of HIV infection). We predict that current elimination targets, in particular when framed around reductions of HBeAg-positive prevalence, are unlikely to be achieved by 2030 based on existing interventions. Reaching the different proposed goals appears to be dependent upon different intervention efforts and thus can lead to very different levels of optimism and achievement, with important consequences on the future commitment of the players involved. For optimum impact, we suggest that elimination targets should be defined around HBeAg-positive carriers, which are a major proxy for the public health burden of HBV, and the target for which current interventions seem to have less impact. This highlights the essential need to collect better data that can help to inform progress towards targets, to optimize deployment of vaccination and PMTCT, and to invest substantially in education, case finding and treatment. The prospects of control would be substantially enhanced by improvements in therapy, and ultimately, the only route to elimination of HBV may be to develop a cure.

MATERIALS AND METHODS
Ethics Approval
Ethics approval for the study was obtained from the Ethics Committee of the Faculty of Health Science, University of the Free State, Bloemfontein, South Africa (HIV Study Ref: ETOVS Nr 08/09 and COSAC Study Ref: ECUFS NR 80/2014). Written consent for enrolment into the study was obtained from the child’s parent or guardian.

Study cohorts
Recruitment was undertaken in Kimberley, South Africa. A previous study of HBV serology in adults in the same setting found HBSAg prevalence of 9.5% (55/579) (7). Children were recruited as part of the Co-infection in South-African Children (COSAC) study as previously
The lower age limit of recruitment was 6 months in order to limit the
detection of maternal anti-HBs.

Children were recruited as follows:
1. HIV-negative children age 6-60 months (n=174), recruited through the Kimberley
Respiratory Cohort (KReC) as previously described (56). These children were admitted to
hospital between July 2014 and August 2016 with a clinical diagnosis of respiratory tract
infection. KReC children were confirmed HIV-negative in 163 cases (93.7%). A further 11
children did not have an HIV test result recorded, but were assumed to be HIV-negative based
on the clinical data recorded at the time of admission to hospital.
2. HIV-positive children were recruited primarily from HIV out-patient clinics between
September 2009 and July 2016 as previously described (30,56). We recorded date of
commencement of anti-retroviral therapy (ART), CD4+ T cell count and percentage, and HIV
RNA viral load using the time point closest to the sample that was analysed for HBV serology.

For the purpose of analysis, we divided these into two groups according by age:

i. Age 6-60 months; n=136. This group was selected to match the age range of
the HIV-negative group, and also included five children who were initially
screened for the KReC cohort but tested HIV-positive.

ii. Age >60 months (range 64-193 months); n=92.

Where possible, we recorded the number of HBV vaccine doses received based on the RTHB.
At the time of undertaking this study, children were immunised with three doses of a
monovalent HBV vaccine (Biovac Paed). The characteristics of the cohorts are summarised
in table 2 and all metadata can be found in Suppl. data 1 on-line (https://figshare.com/s/cd1e4f324606949d1680).

Table 2: Characteristics of three paediatric study cohorts, comprising 402 children,
recruited from Kimberley Hospital, South Africa.

| Cohort                      | HIV negative; KReC (age ≤60 months) | HIV positive (age ≤60 months) | HIV positive (age >60 months) |
|-----------------------------|-------------------------------------|-------------------------------|-------------------------------|
| Number of subjects          | 174                                 | 136                           | 92                            |
| Age range in months         | 8-58                                | 6-60                          | 64-193                        |
| Median age in months (IQR)  | 18 (12-26)                          | 29 (18-40)                    | 137 (122-154)                 |
| Sex (% male)                | 55.4                                | 44.9                          | 45.6                          |

KReC = Kimberley Respiratory Cohort. IQR = interquartile range.
Laboratory assessment of HBV status

Testing for Hepatitis B serum markers and DNA was performed as previously described; for HIV-positive children this is in keeping with recent implementation of HBV screening in Kimberley (30). Briefly, HBsAg testing was carried out in Kimberley Hospital, South Africa using the Magnetic parcel chemiluminometric immunoassay (MPCI; Advia Centaur platform). Confirmatory HBsAg testing was carried out by the UKAS accredited clinical microbiology laboratory at Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford, UK (Architect i2000). For all samples, anti-HBs and anti-HBc testing were carried out by the OUH laboratory (Architect i2000). Limit of detection of the anti-HBs assay was 10 mIU/ml.

Threshold for vaccine mediated immunity

An absolute threshold for vaccine-mediated immunity is difficult to define, and studies variably quote anti-HBs titres of ≥10 mIU/ml or ≥100 mIU/ml as a correlate of protection. UK recommendations for testing HBV immunity often rely on the more stringent criterion of an anti-HBs titre of ≥100 mIU/ml (14). However, early vaccine studies have highlighted that a titre of ≥10 mIU/ml is likely to be a clinically relevant threshold for protection; a study of children in The Gambia showed that children who attained an anti-HBs titre of ≥10 mIU/ml were most likely to be immune (15), and another study demonstrated increased risk of infection when antibody titres fell <10 mIU/ml (57). Due to the varying use of different thresholds, we have presented our results pertaining to both thresholds of ≥10 mIU/ml and ≥100 mIU/ml.

Statistical analysis

Data from the cohort was analysed using GraphPad Prism v.7.0. We determined significant differences between sub-sets within the cohort using Mann-Whitney U tests for non-parametric data, Fisher’s exact test for categorical variables and correlation between data points was assessed using Spearman’s correlation coefficient.

Mathematical model of HBV transmission and prevention

A mathematical model was developed using ordinary differential equations (ODE) and is shown in Fig 3. Parameterization of transmission and prevention was based both on our Kimberley paediatric cohort and current literature estimates. Mid-year population estimates from 2016 published by Statistics South Africa (11) were used to underpin assumptions about life expectancy, fertility rate and infant mortality.

We used our mathematical model to simulate the transmission dynamics of HBV and the impact of interventions. Our approach is divided into three steps: fitting of demographic
background, fitting of HBV transmission background, and simulation of interventions. The following set of ordinary differential equations (ODE) is used to model the deterministic transmission of HBV under homogeneous mixing. Constant parameters informed by the literature and estimated parameters are described in further detail below.

\[
\begin{align*}
\frac{dS_i}{dt} &= Z - c S_i - \lambda S_i - \mu S_i \\
\frac{dS_c}{dt} &= (1 - \omega_c) c S_i - a S_c - \lambda S_c - \mu S_c \\
\frac{dS_a}{dt} &= (1 - \omega_a) a S_a - \lambda S_a - \mu S_a \\
\frac{dI}{dt} &= \lambda \gamma S_a + \lambda \epsilon S_c + \lambda \psi S_i \\
&\quad + \lambda(1 - \Delta) V_i + \lambda \gamma(1 - \Delta) V_a + \lambda \epsilon(1 - \Delta) V_c + \lambda \psi(1 - \Delta) V_i \\
&\quad - \sigma I - \mu I \\
\frac{dC^+}{dt} &= \sigma I + \rho C^- - \mu R \\
\frac{dC^-}{dt} &= \theta C^+ - \rho C^- - \mu C^- \\
\frac{dW}{dt} &= \psi(1 - \psi) S_i + \lambda(1 - \gamma) S_a + \lambda(1 - \epsilon) S_c \\
&\quad + \lambda(1 - \psi)(1 - \Delta) V_i + \lambda(1 - \gamma)(1 - \Delta) V_a + \lambda(1 - \epsilon)(1 - \Delta) V_c \\
&\quad - \theta C^+ - \mu C^+ \\
\frac{dV_i}{dt} &= Z' - c V_i - \lambda(1 - \Delta) V_i - \mu V_i \\
\frac{dV_c}{dt} &= \epsilon V_i + \omega_c c S_i - a V_c - \lambda(1 - \Delta) V_c - \mu V_c \\
\frac{dV_a}{dt} &= \omega_a a S_a - \lambda(1 - \Delta) V_a - \mu V_a
\end{align*}
\]

We take into consideration the susceptible proportion of the population \((S_i, S_c, S_a, V_i, V_c, V_a, eq. 1-3)\), the chronic \((C^+, C^-, eq. 6-7)\) and acute infections \((I, eq. 4)\), the recovered and immune \((R, eq. 5)\) and the vaccinated \((V_i, V_c, V_a, eq. 8)\). Susceptible and vaccinated subgroups are divided into 3 main classes representing infants \((S_i <1 \text{ years of age})\), children \((S_c, 1-6 \text{ years of age})\) and older individuals \((S_a, >6 \text{ years of age})\).

**Carriage and infection types**

Carriers are represented by two chronic infection states depending on HBe-antigen status (designated \(C^+\) for HBeAg-positive and \(C^-\) for HBeAg-negative), and \(I\) for acute infection. Individuals may acquire HBV at any of the age classes, developing chronic infection depending on age-associated risks: \((1 - \psi)\) for infants, \((1 - \epsilon)\) for children, \((1 - \gamma)\) for older ages. We assume that the probability of developing chronic infections decreases with age, with \(\psi=0.15, \epsilon=0.4, \text{ and } \gamma=0.95\) (58–60). When developing chronic infection, we assume that all individuals become HBeAg-positive but may lose this status and become HBeAg-negative at a rate \(\theta\) (61). HBeAg-negative carriers may clear infection spontaneously at a rate \(\rho\), entering the recovered class \((R)\). Acute infections \((I)\) are assumed to last 6 months (62) and are cleared at a rate \(\sigma\), entering the recovered class \((R)\).
**Force of Infection**

All carriers contribute to the force of infection ($\lambda$, eq. 11). It is assumed that chronic HBe-antigen positive infections ($C^+$) and acute infections ($I$) have a higher transmission rate ($\beta m$) than chronic HBe-antigen negative infections ($C$) ($\beta$) (9):

$$\lambda = \beta(C^- + \beta m(C^+ + I))$$  \hspace{1cm} (11)

**Births and Mortality**

The population is assumed to be of constant size with equal births ($b$) and deaths ($\mu$, $\mu'$). Due to HBV-associated mortality, the lifespan of chronic HBeAg-positive ($C^+$) individuals is taken to be lower (50 years) than the general lifespan (59 years (11)). In the absence of control, the total number of births ($b$) is divided into $Z$ (eq. 13), $W$ (eq. 14) and $Z'$ (eq. 17) depending on the probability of vertical transmission ($A_1$, $A_2$) and proportion vaccinated at birth ($\omega_n$). $W$ is the proportion of babies born to infected mothers acquiring infection at birth or shortly after, and $Z$ the proportion born susceptible.

$$b = \frac{\mu(S_e + S_r + S_t + I + R + V_e + V_r + V_t + C^-) + \mu' C^+}{S_e + S_r + S_t + I + R + V_e + V_r + V_t + C^- + C^+}$$  \hspace{1cm} (12)

$$Z = b(1-\omega_n)(S_e + S_r + S_t + I + R + V_e + V_r + V_t + V_c) + bC^+(1-\omega_n)(1-A_1) + bC^-(1-\omega_n)(1-A_2)$$  \hspace{1cm} (13)

$$W = bC^+A_1 + bC^-A_2$$  \hspace{1cm} (14)

**Vertical Transmission**

Vertical transmission takes place from mothers with chronic infections and is dependent on their HBe-antigen serostatus, with frequency of transmission $\alpha_1$ for HBeAg-positive ($C^+$) and $\alpha_2$ for HBeAg- ($C$). For interventions reducing vertical transmission, $\alpha_1$ and $\alpha_2$ are multiplied by $(1-\zeta)$, with $\zeta \in [0,1]$ being the impact of the intervention (eq. 15-16). For simplicity and lack of observations for appropriate parameterization, we assume that acute infections do not contribute to vertical transmission.

$$A_1 = \alpha_1(1-\zeta)$$  \hspace{1cm} (15)

$$A_2 = \alpha_2(1-\zeta)$$  \hspace{1cm} (16)

**Routine vaccination**

Routine vaccination is implemented under three general strategies: coverage of neonates ($Z'$, eq. 8, 17), coverage of 1-6 years old by vaccinating individuals leaving the susceptible <1 years old class (term $\omega_cS_i$ in eq. 9), and coverage of 6+ years old by vaccinating individuals leaving the susceptible 1-6 years old class (term $\omega_aS_c$ in eq. 10). In essence, we model vaccination occurring either at birth, or at particular ages (1 year, 6 years).
Catch-up vaccination

For simplicity, catch-up is modelled in a single event (time step $t_{cu}$), by moving a proportion of susceptible individuals into the age-corresponding vaccinated classes. In practice, this is an impulse event in the ODE system. Catch-up proportions are age-specific with parameters $K_i$ for <1 years old, $K_c$ for 1-6 years old, and $K_a$ for 6+ years old.

$$K_i = \begin{cases} K_{i}, & \text{if } t = t_{cu} \\ 0, & \text{otherwise} \end{cases}$$

$$K_c = \begin{cases} K_{c}, & \text{if } t = t_{cu} \\ 0, & \text{otherwise} \end{cases}$$

$$K_a = \begin{cases} K_{a}, & \text{if } t = t_{cu} \\ 0, & \text{otherwise} \end{cases}$$

Markov-chain Monte-Carlo fitting approach

In two independent steps, we fit certain ODE model outputs to empirically observed variables in the South African population, to set demographic and transmission backgrounds before simulating intervention strategies. We apply a Bayesian Markov-chain Monte-Carlo (MCMC) approach, developed and used by us in other modelling studies (63,64). The proposal distributions ($q$) of each parameter are defined as Gaussian (symmetric), effectively implementing a random walk Metropolis kernel. We define our acceptance probability $\alpha$ of a parameter set $\Theta$ given model ODE output $y$ as:

$$\alpha = \min\{1, \frac{\pi(y|\Theta^*)p(\Theta^*)q(\Theta^*|\Theta^0)}{\pi(y|\Theta^0)p(\Theta^0)q(\Theta^0|\Theta^*)}\}$$

where $\Theta^*$ and $\Theta^0$ are the proposed and current (accepted) parameter sets (respectively); $n(y | \Theta^*)$ and $n(y | \Theta^0)$ are the likelihoods of the ODE output representing the (observed) variables by each parameter set $\Theta^*$ and $\Theta^0$; $p(\Theta^0)$ and $p(\Theta^*)$ are the prior-related probabilities given each parameter set.

For simplicity and because all fitted variables are proportions, the likelihoods $n$ were calculated as the product of conditional Gaussian probabilities ($Pr(...)$). The likelihood is the product the conditional probabilities of all variables. The likelihood can be formally expressed as:

$$\pi(y|\Theta) = \prod_{i=1}^{N} [Pr[y_i = d_i]]$$
**MCMC and model implementation**

The mathematical ODE model and MCMC approach were developed in C/C++ (available as additional material which will be uploaded on manuscript acceptance). Visualisations were implemented in R.

**Fitting demographic background**

Before considering transmission and interventions, we first fitted the model to a demographic background. This is done with the above described fitting approach without transmission (i.e. at \( t=0, \ I+C^+ +C^- = 0 \)), using as target variables (Gaussian with standard deviation 1) the expected mean proportions of infants <1 years old (\( S_i=0.022 \)), children 1-6 years old (\( S_c=0.11 \)) and older ages (\( S_a=0.868 \)) in the population of study (taken from Census 2011 (65)). We set the posteriors of the aging rates \( a \) and \( c \), with median \( a=0.1337 \) (95% CI 0.1330 - 0.1343) and median \( c=0.7536 \) (95% CI 0.7369 - 0.7709). We set the values of \( a \) and \( c \) to the median values of the posteriors for all other model results (fitting transmission background and simulating interventions).

**Fitting transmission background**

After fitting demographic parameters and before considering interventions, we fitted the model to a transmission background. This is done using the above described fitting approach, with fixed aging rates \( a \) and \( c \). The target variables are set to the percentage of the population that is HBsAg-positive (total carriers), percentage that are anti-HBc positive (\( R \)), and relative prevalences of chronic carriers HBeAg-positive (\( C^+ \)) and HBeAg-negative (\( C^- \)) for the population of study. We used target Gaussian distributions (standard deviation 1) with mean 30% for anti-HBc, mean 8.3% for total carriers, mean proportion of 73% for HBeAg-negative and 23% for HBeAg-positive (9,66). In this step, the posteriors of the parameters \( \beta, \rho, \alpha_1, \alpha_2, \theta \) and \( \beta_m \) are obtained.

**Fitted parameters and priors for transmission setting**

We fitted six parameters for the local transmission setting (\( \beta, \rho, \alpha_1, \alpha_2, \theta \) and \( \beta_m \)). Gaussian informative priors are used for three parameters: frequency of vertical transmission \( \alpha_1 \) for HBeAg-positive (\( C^+ \)) with mean \( M=0.8 \) and standard deviation \( SD=0.05 \), the frequency of vertical transmission \( \alpha_2 \) for HBeAg+ (\( C^- \)) with \( M=0.25 \) and \( SD=0.05 \) (59,60,67,68), and the increased transmission factor for chronic HBe-antigen positive infections (\( C^+ \)) and acute infections (\( I \)) \( \beta_m \) with \( M=10 \) and \( SD=2.5 \) (69–72). For \( \beta, \rho \) and \( \theta \) uninformative, uniform priors are used with ranges of 0 to 30 for \( \beta \) and 0 to 1 for \( \theta \) and \( \rho \). In the main results we demonstrate that the posteriors for \( \rho \) and \( \theta \) follow the scarce knowledge of these parameters.
Simulating deterministic interventions
After fitting demographics and transmission backgrounds, when simulating deterministic interventions, we fix $a, c, \beta, \rho, \alpha_1, \alpha_2, \theta$ and $\beta_m$ to the obtained posterior medians. We vary combinations of the intervention parameters $\omega_i, \omega_c, \omega_a$ (routine coverage for different ages), $K_i, K_c, K_a$ (catch-up coverages) and $\zeta$ (reduction in vertical transmission). The transmission dynamics without interventions are run until the population reaches equilibrium, effectively reproducing the desired proportions as used in Fitting transmission background, at which point interventions are started and the model is tracked for 1000 years.

Simulating stochastic interventions
A stochastic version of the model presented in equations 1-10 was developed by introducing demographic stochasticity in state transitions. This followed a previously used strategy, in which multinomial distributions are used to sample the effective number of individuals transitioning between classes per time step \((64,73,74)\). Multinomial distributions are generalized binomials – Binomial \((n,p)\) - where \(n\) equals the number of individuals in each class and \(p\) the probability of the transition event (equal to the deterministic transition rate). Simulations followed the same approach as described for deterministic simulations (see above). However, for each combination of parameters defining the intervention, \(N=50\) stochastic simulations are run by sampling \(N\) times the posteriors of the parameters obtained in Fitting transmission background \((\beta, \rho, \alpha_1, \alpha_2, \theta \text{ and } \beta_m)\). This approach effectively takes into account demographic stochasticity and parameter (posterior) variation.

Measuring impact of interventions
Sustainable development goals (SDGs) for the year 2030 have been set out in the WHO Global Health Sector Strategy on Viral Hepatitis \((5)\). Given the public health relevance of chronic infections, in particular of HBeAg-positive infections, we here set out to measure impact of interventions based on two targets set for the year 2030:

i. The WHO target for a 90% reduction in HBsAg incidence, based on the assumption that this applies to chronic infection. (WHO goals also use reductions in HBsAg prevalence, and we have included this approach in Figure Supplements).

ii. An additional target for reduction of HBeAg-positive prevalence to 1 in 1000 (0.1%) in the whole population, relative to the pre-intervention era.

Fitting of cohort data on HIV serostatus and HBV vaccine-induced protection
We started with the assumptions that (i) protection is either constant or decays with age, (ii) vaccine efficacy reported elsewhere for infants is representative of protection levels in the
population cohort of 1 year olds (infants), and (iii) HIV status may alter protection levels and
decay of vaccine-mediated protection over time (75).

First, using a response threshold of $\geq 100$ mIU/ml as a correlate of protection (75), we
calculated the percentage of protected individuals in age 1, 2, 3, 4 and 5 years old, as available
in the cohort data. Following assumption (i), we normalized the percentage of protected
individuals in age by the percentage found for 1 year olds. Following assumption (ii) we
multiplied this scaled variable ([0,1]) by an informed, literature-based baseline vaccine-
induced protection (to infection) of 95% for HIV-negative infants and 75% for HIV-positive
infants (see (75) for a recent literature review). The transformed protection cohort series are
shown in red on Figure Supplement 1AB. The obtained efficacy in the age group of 1 year
olds is seen to be ~95% for HIV- and ~75% for HIV+, as expected.

We then used nonlinear weighted least-squares to fit the transformed protection cohort series
(Figure Supplement 1AB) and projected protection in ages, with weights equal to the inverse
of the (empirical) standard error for each age class (Figure Supplement 1C). The nonlinear
model ($Y=a^*X^b$) fitted the data closely (Figure Supplement 1AB) for both HIV-positive and
HIV-negative individuals (with resulting coefficients $a=0.7842$ $b=-1.0477$ for HIV-positive and
$a=0.95246$ $b=-0.05265$ for HIV-negative). As reported elsewhere (75), projection of protection
by age showed a significant difference depending on HIV serostatus, both in level of vaccine-
mediated antibodies, and in decay of protection with age (Figure Supplement 1C).

**Modelled HBV vaccine-induced protection in the context of HIV status**

Given that the age classes in the dynamic model are discrete (<1, 1-6, 6+ years of age) and
for simplicity, we parameterized protection according to the predicted (Gaussian) distributions
at the mean age of each age class in the model (Figure Supplement 1D). That is, we used the
predicted mean (M) and standard deviation (SD) at ages 0.5, 3.5, 32.5 years as proxies for
protection at model age classes <1, 1-6, 6+ years of age, respectively. The resulting
distributions (shown in Figure Supplement 1D-F) were: HIV-negative aged <1y with $M=0.952$
and SD=0.024, aged 1-6y with $M=0.892$ and SD=0.023, aged 6+y with $M=0.796$ and
SD=0.074; HIV-positive aged <1y with $M=0.784$ and SD=0.148, aged 1-6y with $M=0.217$ and
SD=0.070, aged 6+y with $M=0.031$ and SD=0.039. These estimations were in accordance
with previous studies and pooled ranges reported (75). Note that these values equate to
protection at the individual level of each age class, such that, for example, HIV-negative aged
<1y with $M=0.952$ equates to a mean of 95.2% vaccine-induced protection in that age class.
Vaccine-induced protection is modelled in the dynamic system using the term \((1-\Delta x)\) in equations 4 and 7-10, where \(x\) relates to a specific age class. The term \((1-\Delta x)\) therefore models a reduction in risk of infection, with \(\Delta x\) being the protection offered by the vaccine. Given that vaccine-induced protection is dependent on HIV status, \(\Delta x\) takes the following forms:

\[
\begin{align*}
\Delta_i & = P_{x^+}^+ \times v_x^+ + (1.0 - P_{x^+}^+) \times v_x^- \\
\Delta_x & = P_{x^+}^+ \times v_x^+ + (1.0 - P_{x^+}^+) \times v_x^- \\
\Delta_a & = P_{x^-}^+ \times v_x^+ + (1.0 - P_{x^-}^+) \times v_x^-
\end{align*}
\]

Where \(P_{x^+}\) is the HIV prevalence at a certain age \(x\), \(v_x^+\) the vaccine-induced protection at a certain age \(x\) for HIV-positive individuals, and \(v_x^-\) the vaccine-induced protection at a certain age \(x\) for HIV-negative individuals (as determined in the approach detailed above). HIV prevalence levels used in the context of Kimberley were 1% for <1 years of age, 5% for 1-6 years of age, and 15% for >6 years of age (based on communications with clinicians in South Africa, (76)).
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Li W, Urban S. Entry of hepatitis B and hepatitis D virus into hepatocytes: Basic insights and clinical implications. Journal of Hepatology. 2016;64(1):S32–40.
Figure 1: Hepatitis B surface antibody (anti-HBs) titres mediated by vaccination in HIV-positive (HIV+) and HIV-negative (HIV-) children aged 6-60 months in Kimberley, South Africa. A: Scatter plot representing vaccine-mediated antibody titres, indicating median and interquartile ranges (p-value by Mann Whitney U test). B: Proportion of children with anti-HBs ≥10 mIU/ml or ≥100 mIU/ml (p-values by Fisher’s Exact Test).
Figure 2: Relationship between age and vaccine-mediated Hepatitis B surface antibody (anti-HBs) titres in HIV-positive and HIV-negative children in Kimberley, South Africa.

A: Ages of children attaining anti-HBs titres $\geq 100 \text{ mIU/ml}$ for HIV-positive and HIV-negative children age 6-60 months. Median ages, interquartile ranges and p-values by Mann-Whitney U test are indicated. B: Relationship between age and vaccine-mediated Ab titre among HIV-positive children including those age 6-60 months and an older cohort age >60 months (range 64-193 months). P-value by Mann Whitney U test. C: Anti-HBs titre and proportion of subjects with a detectable titre for HIV-positive and HIV-negative children according to age. On the solid lines, each point represents the mean titre (with 95% confidence intervals) for the group of children aged $\leq$ 12 months (1 yr), 13-24 months (2 yrs), 25-36 months (3 yrs), 37-48 months (4 yrs), 49-60 months (5 years). For the same groups of children, the dotted lines represent the proportion of subjects with a detectable titre and the 95% confidence intervals. Trends within the data were assessed using linear regression analysis D: Odds ratios for protective response to HBV vaccination in children age 6-60 months in Kimberley, South Africa are shown for anti-HBs titre $<10\text{ mIU/ml}$ and $<100\text{ mIU/ml}$ in the whole cohort (green) and in HIV-positive children (black). Statistically significant OR are denoted * and significant p-values are indicated in bold.
surface antibody (anti-HBs) titres in HIV-positive and HIV-negative children in Kimberley, South Africa.

Figure 3: Diagram showing model of HBV dynamics in a population, fitted solutions and parameter posteriors. (A) Diagram of the ODE model. Susceptibles ($S_x$) and vaccinated ($V_x$) are divided into 3 classes representing infants ($x=i$, <1 years of age), children ($x=c$, 1-6 years of age) and older individuals ($x=a$, >6 years of age). Further details in the Methods section.

(B1-B2) Distributions of pre-intervention ODE model output at equilibrium for the fitted classes: (B1) carriers ($I+C+C^*$, HBsAg+, salmon) and recovered ($R$, HBcAg+, green); (B2) relative proportions of HBeAg+ ($C^*$, purple) and HBeAg- ($C^*$, red) among chronic carriers ($C^*+C^-+C^*$). Distributions of target variables (fitted, B1, B2) are obtained by running the deterministic model with 10,000 samples of the posteriors shown in subplots C-E. Dashed vertical lines present...
the target fitted proportions based on the SA cohort and literature reports (see Methods Section). (C-E) Posterior distributions for the fitted parameters (1.5 million samples), with informative priors drawn with dashed red lines (1000 samples from distributions). Support results for the cohort data-driven approach related to HIV status and HBV vaccine-induced protection are in Figure 3 - Supplement Figure 1.

Figure 4: Stochastic impact of neonatal vaccination and PMTCT on HBV incidence (HBsAg) and HBeAg+ prevalence, showing time to reach sustainable development goals when using interventions independently. (A1-A2) Impact on HBV incidence (HBsAg) (A1) and time to reach sustainable development goal (SDG) (A2) for varying routine immunization coverage of neonates. (B1-B2) Impact on HBeAg+ prevalence (B1) and time to reach SDG (B2) for varying routine immunization coverage of neonates. (C1-C2) Impact on HBV incidence (HBsAg) (C1) and time to SDG (C2) for varying PMTCT coverage. (D1-D2) Impact on HBeAg+ prevalence (D1) and time to reach SDG (D2) for varying PMTCT coverage. (A1, B1, C1, D1) Lines are the mean and shaded areas the standard deviation of model output when running 50 stochastic simulations per intervention (sampling the parameter posteriors shown in Figure 1). (A2, B2, C2, D2) HBV incidence
HBsAg) SDG is set to a reduction of 90%. HBeAg+ prevalence SDG is set to 1/1000 individuals. Beige areas mark interventions reaching SDGs after 500 years on average. Boxplots show the variation of the 50 stochastic simulations. Numbers above and below boxplots show the 2.5% lower and 97.5% upper limits of the solutions. (All subplots) Intervention coverage varies from 0.25 to 1 (as coloured and named in subplot A1). Support results: deterministic solutions of neonatal vaccination and PMTCT are in Figure 4; for stochastic solutions of neonatal vaccination and PMTCT with impact on total prevalence (acute and chronic) are in Figure 4 – Figure supplement 1; for stochastic solutions of neonatal vaccination and PMTCT with impact on total prevalence (acute and chronic) are in Figure 4 – Figure supplement 2.

Figure 5: Sensitivity of mean intervention impact on HBV incidence (HBsAg) and HBeAg+ prevalence based on combinations of routine neonatal vaccination and PMTCT. (A1-A2) Mean impact of interventions on HBV incidence (HBsAg) (A1) and mean time to reach sustainable development goals (SDGs) (A2). (B1-B2) Mean impact of interventions on HBeAg+ prevalence (B2) and mean time to reach SDG (B2). (All subplots) Impact is shown as percent reduction in incidence or prevalence compared to pre-intervention levels (e.g. 50 indicates a 50% reduction compared to before the start of the intervention). HBV incidence (HBsAg) SDG is set to a reduction of 90%. HBeAg+ prevalence SDG is set
to 1/1000 individuals. Mean results are obtained from 50 stochastic simulations per intervention combination (vaccination, PMTCT) with parameters sampled from the posteriors shown in Figure 1. Start of interventions in the stochastic simulations is in year 1995 to simulate an appropriate time scale to address impact by 2030. Support results: impact and time to reach SDGs when considering combinations of PMTCT and routine vaccination of individuals at the age of 6 are in Figure 5 – Figure supplement 1; impact and time to reach SDGs when considering combinations of PMTCT and neonate routine vaccination plus a complete catch-up campaign are in Figure 5 – Figure supplement 2.

**Figure 6:** Yearly estimated probabilities of achieving sustainable development goals for HBV incidence (HBsAg) and HBeAg+ prevalence based on particular combinations of interventions and local HIV prevalence levels. A total of 1000 stochastic simulations are run independently for each set of particular interventions (coloured legend, subplot A2), with each using a random parameter sample from the posteriors shown in Figure 1. Interventions start in year 1995. For every year post-intervention start, the proportion of simulations that have achieved the sustainable development goals (SDGs) is recorded and taken to be the probability. **(A1)** Probability of reaching HBV incidence (HBsAg) SDG in time (goal is set to a reduction of 90%). **(A2)** Probability of reaching HBeAg+ prevalence SDG in time (goal is set to...
to 1/1000 individuals). (B1, B2) Same as subplots A1-A2 but addressing sensitivity to HIV prevalence levels in the population for a particular intervention (green, $\omega n=0.9$, $\zeta=0.9$, catch-up 0% (WHO)). Solid line is the same as in subplots A1-A2 (named HIV prevalence at baseline). Other lines present results assuming zero HIV prevalence (full line with points) or higher prevalences (dotted, dashed, line with squares). (All subplots) The dashed horizontal lines mark 0.5 and 0.975 probability of achieving SDGs. The grey shaded area marks the time period before 2030. In the interventions, $\omega n$ is routine vaccination of neonates, $\zeta$ the PMTCT effort, $\omega a$ routine vaccination of +6 years of age, and catch-up a one-off event of vaccination in some age groups or general population.

SUPPORTING FIGURES

Figure 3 – Figure supplement 1: Fitting HBV vaccine response according to HIV serostatus. (A, B) Data on HBV vaccine response (see sections Waning of vaccine response with age, and Odds of developing an anti-HBs response) dependent on HIV serostatus. Data (points) and standard error (dashed) are shown in black for HIV+ (A) and purple for HIV- (B). Fit and 95% CI is shown in red. (C) Predicted HBV vaccine response dependent on HIV serostatus (HIV+ black, HIV- purple) across all ages. Dashed lines are the fitted 95% CI; dotted lines are the fitted standard deviation; solid bold lines are the fitted mean. (D, E) Boxplots in red show distributions obtained with 10,000 samples from a gaussian distribution with mean and standard deviation equal to the point prediction at mean ages of each age class in the dynamic model (0.5 years for class <1 years old, 3.5
years for class 1-6 years old, 32.5 years for age class 6+ years old). Distributions in subplot D are for HIV-
individuals and in subplot E are for HIV+ individuals. Red dots show the gaussian sampled standard deviation
(which is seen approximating the fitted standard deviation). (F) Summary of the distributions found in subplots
D and E according to HIV serostatus and later used in the dynamic model (HIV- in purple with <1y mean=0.952
std=0.024, 1-6y mean=0.892 std=0.023, 6+y mean=0.796 std=0.074; HIV+ in black with <1y mean=0.784
std=0.148, 1-6y mean=0.217 std=0.070, 6+y mean=0.031 std=0.039). (A-C) For fit details refer to methods
section.

**Figure 4 – Figure supplement 1: Sensitivity of interventions with deterministic output.** Impact of (A) neonate
vaccination (ωn), (B) vaccination at 6 years of age (ωa), and (C) PMTCT (ζ), on HBV prevalence (HBsAg) in
time. The coverage / effort of simulated interventions quantified on the color scale to the right from 0 (no
coverage / effort) to 1 (full coverage / effort). Impact is quantified by post-intervention reductions in HBV
prevalence (HBsAg). Impact is highest for neonate vaccination, followed by PMTCT and lastly vaccination at 6
years of age for the same intervention effort. Simulations use the median parameter values of the posteriors
shown in Figure 1. Results with stochastic simulations are presented in Figures 4-6 of the main text (and
corresponding Support Figures).
Figure 4 – Figure supplement 2: Post-intervention stochastic impact on HBV prevalence (HBsAg), with time to reach sustainable development goals when using routine neonatal vaccination and PMTCT independently. (A, B) Impact (reduction) on HBV prevalence (HBsAg) (A) and time to reach sustainable development goal (SDG) goal (B) for varying coverage of neonates. (C, D) Impact (reduction) on HBV prevalence (HBsAg) (C) and time to reach SDG (D) for varying PMTCT. (All subplots) Intervention coverage / effort varies from 0.25 to 1 (as colored and named in subplot A). (A, C) Lines are the mean and shaded areas are the standard deviation of model output when running 50 stochastic simulations per intervention (sampling the posteriors shown in Figure 1). (B, D) Beige areas mark interventions reaching SDGs after 500 years on average. Boxplots show the variation of the 50 stochastic simulations. Numbers above and below boxplots show the 2.5% lower and 97.5% upper limits of the solutions. The SDG is 1 in a 1000 individuals. Compared to Figure 4 in the main text: measuring impact with SDG on HBV incidence (HBsAg) (as opposed to HBV prevalence) results in more optimistic projections, i.e. shorter times to SDG (compare Figure 4 A2, C2 with this figure subplots B, D). PMTCT is unable to present solutions reaching the SDG for HBV prevalence (HBsAg) in 500 years (D).
Figure 5 – Figure supplement 1: Sensitivity of mean intervention impact on HBV incidence (HBsAg) and HBeAg+ prevalence, with estimated mean year to reach sustainable development goals for combinations of routine +6 years vaccination and PMTCT. (A1-A2) Mean impact of interventions on HBV incidence (HBsAg) (A1) and mean time to reach sustainable development goals (SDGs) (A2). (B1-B2) Mean impact of interventions on HBeAg+ prevalence (B2) and mean time to reach SDG (B2). (All subplots) Impact is shown as percent reduction in incidence or prevalence compared to pre-intervention levels (e.g. 50 indicates a 50% reduction compared to last time step before intervention start). HBV incidence (HBsAg) SDG is set to a reduction of 90%. HBeAg+ prevalence SDG is set to 1 in a 1000 individuals. Mean results are obtained from 50 stochastic simulations per intervention combination (vaccination, PMTCT) with parameters sampled from the posteriors shown in Figure 1. Start of interventions in the stochastic simulations is in year 1995 to simulate an appropriate time scale to address impact by 2030. Compared to Figure 5 main text: the combination of PMTCT and routine vaccination of +6 years is highly suboptimal, with perfect routine coverage and PMTCT (top right cell, subplots A1, B1) achieving reductions of HBV incidence (HBsAg) and HBeAg+ prevalence by 2030 similar to half the vaccination coverage for neonates and half the PMTCT effort seen in Figure 5 (top right cell, subplots A1, B1), for example.
Figure 5 – Figure supplement 2: Sensitivity of mean intervention impact on HBV incidence (HBsAg) and HBeAg+ prevalence, with estimated mean year to reach sustainable development goals for combinations of routine neonatal vaccination and PMTCT plus a complete catch-up campaign. (A1-A2) Mean impact of interventions on HBV incidence (HBsAg) (A1) and mean time to reach sustainable development goals (SDGs) (A2). (B1-B2) Mean impact of interventions on HBeAg+ prevalence (B2) and mean time to reach SDG (B2). (All subplots) Impact is shown as percent reduction in incidence or prevalence compared to pre-intervention levels (e.g. 50 indicates a 50% reduction compared to last time step before intervention start). HBV incidence (HBsAg) SDG is set to a reduction of 90%. HBeAg+ prevalence SDG is set to 1 in a 1000 individuals. Mean results are obtained from 50 stochastic simulations per intervention combination (vaccination, PMTCT) with parameters sampled from the posteriors shown in Figure 1. Start of interventions in the stochastic simulations is in year 1995 to simulate an appropriate time scale to address impact by 2030. Complete catch-up campaign stands for a one-off event with 100% coverage of all susceptible individuals in the population at the start of interventions. Compared to Figure 5 main text: adding one 100% catch-up campaign to the interventions in Figure 5 is beneficial, for which the highest reductions of HBV incidence (HBsAg) and HBeAg+ prevalence by 2030 are achieved, as well as the shorter times to SDG. However, 100% catch-up is logistically and economically not feasible and the added benefits are small. For example, with complete neonatal coverage and PMTCT (top right cell, subplots A1, B1), the catch-up campaign would only add <5% in the mean reduction of HBV incidence (HBsAg) and HBeAg+ prevalence up to year 2030 (compare to top-right cells of subplots A1 and B1 in Figure 5).
SUPPLEMENTARY DATA

Suppl data 1. Metadata for three paediatric cohorts recruited in Kimberley, South Africa, including longitudinal CD4+ T cell and viral load data for paediatric HIV cohort age ≤60 months in Kimberley, South Africa. This file is available on-line via the following link: https://figshare.com/s/cd1e4f324606949d1680

FIGURE SUPPLEMENTS

Figure 3 – Figure supplement 1: Fitting HBV vaccine response according to HIV serostatus.

Figure 4 – Figure supplement 1: Sensitivity of interventions with deterministic output.

Figure 4 – Figure supplement 2: Post-intervention stochastic impact on HBV prevalence (HBsAg), with time to reach sustainable development goals when using routine neonatal vaccination and PMTCT independently.

Figure 5 – Figure supplement 1: Sensitivity of mean intervention impact on HBV incidence (HBsAg) and HBeAg+ prevalence, with estimated mean year to reach sustainable development goals for combinations of routine +6 years vaccination and PMTCT.

Figure 5 – Figure supplement 2: Sensitivity of mean intervention impact on HBV incidence (HBsAg) and HBeAg+ prevalence, with estimated mean year to reach sustainable development goals for combinations of routine neonatal vaccination and PMTCT plus a complete catch-up campaign.
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Nil

CONFLICTS OF INTEREST

None to declare

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