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Findings: There is a strong relationship between the prevalence of HBsAg and anti-HBc ($p<0·0001$) across Africa, but the pattern differs between regions. Our data can be interactively visualised at https://hbv-geo.shinyapps.io/oxafricahbv/. In settings with high prevalence of infection, catch-up vaccination may have a transient effect. However, this intervention does not contribute to a sustained decline in prevalence, because a high proportion of adults are either already infected or immune as a result of prior exposure. In contrast, diagnosing and treating infection has a marked impact on reducing prevalence, equivalent to that of neonatal vaccination.

Interpretation: We have developed a high-resolution picture of HBV epidemiology across Africa. In combination with robust neonatal vaccination programmes, testing and treating infection is likely to be of more benefit than catch-up vaccination. This alternative not only

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Application of sero-epidemiology data to inform interventions for HBV in Africa: should diagnosis and treatment replace catch-up vaccination?

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ABSTRACT

Background: International goals for hepatitis B virus (HBV) infection set ambitious targets for elimination by 2030. In populations with a high prevalence of infection, catch-up HBV vaccination of adults is sometimes deployed. An alternative approach of 'test and treat' could be applied as a population intervention for HBV.

Methods: We used a systematic approach to determine the relationship between prevalence of HBV infection (HBsAg) and exposure (anti-HBc) in Africa. We applied a mathematical model to compare the impact of catch-up vaccination with a 'test and treat' strategy in a high prevalence setting.

Findings: There is a strong relationship between the prevalence of HBsAg and anti-HBc ($p<0{\cdot}0001$) across Africa, but the pattern differs between regions. Our data can be interactively visualised at https://hbv-geo.shinyapps.io/oxafricahbv/. In settings with high prevalence of infection, catch-up vaccination may have a transient effect. However, this intervention does not contribute to a sustained decline in prevalence, because a high proportion of adults are either already infected or immune as a result of prior exposure. In contrast, diagnosing and treating infection has a marked impact on reducing prevalence, equivalent to that of neonatal vaccination.

Interpretation: We have developed a high-resolution picture of HBV epidemiology across Africa. In combination with robust neonatal vaccination programmes, testing and treating infection is likely to be of more benefit than catch-up vaccination. This alternative not only benefits the infected individual, but also has impact on transmission, thus contributing to sustained reductions in population prevalence.

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RESEARCH IN CONTEXT

Evidence before this study:

As a starting point for this study, we set out to assimilate evidence for a relationship between the prevalence of HBV infection (typically represented by HBsAg) and exposure (anti-HBc) in Africa, we undertook a systematic review of PubMed and Web of Science for studies published in any language between 01-Jan-1995 and 01-June-2018, according to PRISMA criteria and retrieved data from 89 individual cohorts. We did not identify any previous systematic attempt to address the relationship between infection and exposure. We found published studies that include recommendations for catch-up vaccination in adolescents and adults, but no previous comparison of the impact of catch-up vaccination with the alternative approach of 'test and treat'. We have previously developed a model of HBV transmission and prevention, which can be deployed to investigate a variety of interventions to predict the likely impact on incidence and prevalence of HBV infection.

Added value of this study:

We demonstrated a significant relationship between the seroprevalence of HBsAg and anti-HBc. The strength of this association varies by region, suggesting differences in HBV transmission patterns. In most high prevalence settings, catch-up immunisation is likely to be of benefit to only a small minority of individuals, as a high proportion of the population is either infected or protected by immunity arising as a consequence of previous natural exposure. We use our mathematical model to compare catch-up immunisation with the alternative approach of 'test and treat', and demonstrate that the former intervention offers only transient benefit at population level, while the latter drives sustained progress towards elimination.

Implications of all the available evidence

Although there is some published literature that suggests use of catch-up HBV vaccination in adolescents and adults in high prevalence settings, a progressive body of evidence underlines the need for prioritising diagnosis and treatment. This is particularly true for high prevalence settings. Using a robust, systematic approach, we have shown that seroprevalence of HBsAg and anti-HBc are strongly and positively correlated, but this relationship varies by region. The higher the prevalence of anti-HBc, the less the anticipated impact of catch-up vaccination. Interventions should be based on robust local epidemiology data. Investment in 'test and treat'

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initiatives, modelled on those rolled out for HIV, could be a crucial advance towards HBV elimination goals.

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INTRODUCTION

There is an estimated global burden of 290 million cases of chronic hepatitis B virus (HBV) infection,[1] the majority of which are undiagnosed and untreated.[2] Vaccination to protect against infection is a cornerstone of interventions aiming to curtail this major public health threat, with enhanced efforts arising as a result of United Nations Sustainable Development Goals setting out elimination targets for the year 2030.[3] The vaccine is included in the expanded programme for immunization (EPI), and has been progressively rolled out for infants across southern Africa since 1995. However, despite two decades of implementation, HBV remains endemic in many regions. Optimisation of vaccine deployment, and evidence-based consideration of the impact of parallel interventions, are urgently required if we are to accelerate progress towards elimination targets in neglected, high-prevalence, resource-limited settings.

Prevalence of HBV exposure and infection can be extremely high in some settings; for example, in regions of South Sudan and Northern Uganda, seroprevalence of hepatitis B surface antigen (HBsAg) is estimated at 20-25%.[4,5] High endemicity in such settings can be difficult to tackle, as infection can persist for decades, and a persistent reservoir is maintained by individuals with high viral loads (often corresponding to HBeAg-positive status). Furthermore, robust epidemiology data are lacking, and populations in Africa may have vulnerabilities associated with poverty, stigma, and co-endemic human immunodeficiency virus (HIV) infection.[2] Horizontal transmission within households, particularly affecting young children, is widely described but poorly supported by the literature, and specific routes of acquisition remain uncertain in African populations.

There is a sound evidence base for interventions to prevent HBV infection early in life, with well-established regimens for prevention of mother to child transmission (PMTCT).[6] PMTCT in combination with routine infant vaccination currently offers the best route to population elimination, albeit with time-scales that are projected to exceed the targets that have been set for 2030.[7,8] Introducing ‘catch-up’ vaccination campaigns in older children and adults can appear an attractive public health response in high prevalence settings.[9] However, there are few data to support such an approach in Africa, and the population impact of this strategy may be negligible,[7] while incurring significant deployment costs. Economic analyses have reported that catch-up HBV vaccine campaigns in young adults are cost-effective only if combined with screening,[10] highlighting the importance of focusing not only on prevention but also on investment in diagnosis and treatment.[11] This concept has been embraced

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for HIV in the roll out of 'Universal Test and Treat', where antiretroviral treatment (ART) is offered at diagnosis,[12] conferring benefits to the individual and also to population health by reducing the risk of transmission.[13-15] Building on this experience from the HIV field, a 'test and treat' strategy for HBV could offer substantial advances. The feasibility, acceptability, and public health consequences of this approach have been positively evaluated through studies in The Gambia.[11,16]

Here, we took a comprehensive approach to investigating the sero-epidemiology of HBV across the African subcontinent, with the specific aim of considering the role for catch-up vaccination with the alternative 'test and treat' approaches at a population level. We applied an existing model to project the likely impact of catch-up vaccination versus alternative interventions in high prevalence settings. Our results have immediate potential for practical influence, aiming to inform the optimum deployment of limited resources for HBV diagnosis, treatment and prevention.

METHODS

HBV seroepidemiology for Africa

In order to improve an understanding of the relationship between the prevalence of active infection (HBsAg) and the prevalence of naturally-acquired immunity (anti-HBc) arising as a result of exposure to infection, we collected serological data from the published literature. We undertook a systematic search of PubMed and Web of Science in June 2018, using PRISMA criteria (Suppl Fig 1). We used the search terms "HBV antibody", "anti-HBc", "HB core antibody", "HBV exposure" or "HBV prevalence" AND "Africa" or [Name of specific country], using the list of countries on the United Nations (UN) geoscheme for Africa (https://unstats.un.org/unsd/methodology/m49/).

Inclusion criteria were as follows:

- Data gathered after the widespread roll-out of infant HBV vaccination in Africa in 1995;
- No reported data collection undertaken pre-1995;
- Reported prevalence of both HBsAg and anti-HBc among cohorts primarily reporting data for adults (age ≥16 years);
- Cohort does not sample a population enriched for HBV infection (see specific exclusions listed in Suppl Fig 1).

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We recorded total anti-HBc prevalence (i.e. proportion of population exposed to HBV, irrespective of chronic infection status, which we have termed 'total exposure') and also calculated the proportion of the population who have cleared infection (i.e. anti-HBc prevalence minus HBsAg prevalence, termed 'exposed and cleared'). For studies reporting prevalence data from ≥2 cohorts (e.g. HIV-positive (HIV+) and HIV-negative populations), we recorded these as a single publication but ≥2 distinct data points. Studies in a language other than English were translated using Google Translate (https://translate.google.com/). We considered Northern Uganda as an exemplar setting where HBsAg seroprevalence in adults may reach >20% in certain communities,[4,17] and where catch-up vaccination has been deployed.

We also sought evidence or recommendations underpinning catch-up vaccination of adolescents and adults in Africa cited in PubMed using the search terms 'hepatitis b virus' or 'HBV', and 'Africa' or [individual country name], with 'vaccin*' and 'catch up' or 'adult'.

Ethics approval was not required for this study, as we only analysed data that are already available in the public domain.

Statistical analysis of metadata

The UN geoscheme classifies Africa into Central, Eastern, Northern, Southern and Western regions; this is a standard approach for sub-dividing macro-geographical areas for statistical analysis. For the regional analysis, each study was assigned equal weighting when analyzing the data, regardless of the study size. We analysed prevalence data for anti-HBc and HBsAg using Graphpad Prism v7.0. For non-parametric data, we sought significant differences between data sets using Mann-Whitney U tests, and for multiple comparisons we used 1-way ANOVA. We used linear regression to derive lines of best fit, 95% confidence intervals and to interpolate HBsAg prevalence from anti-HBc prevalence. We generated maps to illustrate the location of the HBV cohorts and seroprevalence of relevant markers using R (Source code will be made available on acceptance at the following link: https://github.com/ArmandBester/Serology_of_HBV_in_Africa).

Modelling the impact of adult vaccination vs. 'test and treat'

We used a published model that we initially developed to fit the seroepidemiology of Kimberley in South Africa,[7] using Bayesian Markov Chain Monte-carlo to project the impact of various interventions. In this instance, we fitted the model to data from

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Uganda (Suppl Table 1), a setting of high HBsAg prevalence.[4] We modelled PMTCT and vaccine-based interventions as described in the original study,[7] and added a 'test and treat' strategy.

RESULTS

Significant relationship between prevalence of HBsAg (infection) and anti-HBc (exposure)

Through a systematic literature review, we collated prevalence data for HBsAg and total anti-HBc, identifying a total of 89 studies spanning 37 African countries and generating 100 unique data points (complete metadata are available on-line)[18]. The median ages for the cohorts represented was 34·4 years (IQR 29·1-36·2 years) with age data available for 64% of studies. Among the most frequently sampled populations were HIV+ individuals, antenatal women and healthcare workers.

The distribution of these cohorts and the prevalence of HBV serological markers is shown in Fig 1. These data can be interactively explored on-line at https://hbv-geo.shinyapps.io/oxafricahbv/. Pooling data for all regions, the prevalence of HBsAg (infection) is positively correlated with total anti-HBc (exposure), $p<0{\cdot}0001$ by linear regression, Fig 2A. This relationship also holds true for an association between HBsAg prevalence and the 'exposed and cleared' population ($R^2=0{\cdot}07$, $p=0{\cdot}009$, data not shown). We did not find any significant differences in HBsAg or anti-HBc prevalence between HIV+ cohorts (N=26) and other cohorts ($p=0{\cdot}16$ and $p=0{\cdot}42$, respectively; Suppl. Fig 2).

Variations by region and by country

For most regions, we observed the same association between HBV exposure (total anti-HBc) and prevalence of infection (HBsAg), Fig 2B-E. The highest population exposure and correspondingly highest rates of HBsAg positivity are in Western Africa (Fig 2E, 3B). In contrast, Northern Africa has significantly lower prevalence rates of infection than other regions (red bars, Fig 2A). This variation in HBsAg prevalence is significantly different between regions, (for Northern Africa compared to Western and Southern Africa, $p=0{\cdot}0002$ and $p=0{\cdot}04$ respectively, Fig 3B); and cannot be explained only by lower population exposure rates: although anti-HBc prevalence is somewhat lower in Northern than Western Africa ($p=0{\cdot}001$), there is no difference in anti-HBc prevalence between Southern and Northern Africa ($p=0{\cdot}99$). Indeed, the predicted HBsAg prevalence was approximately 50% lower in Northern than

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Southern Africa for any given anti-HBc prevalence (Fig 2B, D; Suppl. Table 2; Suppl Fig 3).

Central African regions display a different relationship, whereby a high population exposure to HBV is not consistently associated with a correspondingly high prevalence of infection (Fig 2F). This is likely to be a robust representation of the region, as the data cover a 15-year period, and represent multiple countries from where a median of 455 subjects were analysed (IQR 225-782 subjects).

Focusing specifically on Uganda, in Eastern Africa, we also found a significant relationship between HBsAg and anti-HBc prevalence; p=0·01, Fig 2G, 3A. However, even within this single country, considerable differences are seen in prevalence of HBsAg and anti-HBc as determined by different studies (see metadata on-line).[18]

Impact of catch-up vaccination of adolescents and adults

We did not identify any published evidence for catch-up vaccination of adolescents and adults either in the form of intervention studies or based on reviews of the existing literature. However, a number of authors do suggest catch-up vaccine programmes as a way of tackling high population HBV prevalence (data from literature review summarised in Suppl Table 3; for examples, see the following citations).[4,9,19,20]

Based on the mean prevalence values from the combined Uganda cohorts represented by our literature review, 54·3% of adults across this country have been exposed (among these, a total of 11·1% of the adult population is actively HBV-infected and the remainder have been infected and cleared). This leaves 45·7% of the total adult population potentially susceptible (orange bars, Fig 2A). Only a small proportion of this susceptible pool of adults would be exposed to infection each year (there are few data to estimate this exposure rate, but one study from another region of East Africa estimates this at 3-4%).[21] The natural history of HBV infection in adults suggests that <5% of exposure events lead on to chronic infection. Thus, the predicted proportion of the total adult population predicted to avoid chronic infection through catch-up vaccination each year is, roughly, 50% (vulnerable) x 4% (exposed) x 5% (develop chronicity) = 0·1%.

Using an established model of HBV transmission and prevention,[7] we investigated the impact of catch-up vaccination among adults, within a high HBV prevalence

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setting, exemplified by Uganda[4] (Suppl Table 1). Fig 4 presents selected results from simulations, in which a catch-up immunization programme in adults is projected to have only a transient impact on reducing new cases of HBV infection. In the long-term, this strategy offers no sustained overall benefit in progress towards elimination targets, even when deployed at 100% population coverage (Fig 4A, orange band). The poor impact of catch-up vaccination is due to a limited pool of susceptible adults and the lack of impact on the actively infected population. In contrast, enhanced coverage of other interventions, including PMTCT and neonatal vaccination will lead to shorter time-frames for reducing HBsAg prevalence, given their direct impact on the rate of new chronic infections, the main reservoir of HBV infection.

Impact of 'test and treat' in highly endemic settings

We also modelled the impact of 'test and treat', projecting that this strategy has the fastest reduction in HBV population prevalence of all interventions (Fig 4A, purple band). Recognising the significant barriers to identifying all cases of infection, (including silent infection, lack of education, poor access to laboratory facilities for testing, and stigma)[2], we also modelled the outcome for 'test and treat' strategies that reach <100% of the HBV-infected population. Diagnosis and treatment for 80% of infected adults (Fig 4B, green band) or 50% of the whole infected population (Fig 4B, red band) delivers a reduction in HBsAg prevalence over time that is comparable to neonatal vaccination (Fig 4A, blue band). Even reducing the population tested and treated to only 50% of adults (Fig 4B, orange band) is still substantially more effective than 100% catch-up vaccination (Fig 4A, orange band).

DISCUSSION

United Nations Sustainable Development goals have set an ambitious time-frame in which to make significant reductions in both prevalence and incidence of HBsAg carriage by the year 2030.[3] Careful, evidence-based deployment of interventions is essential if sustained and collective progress is to be made towards these targets, and existing epidemiology data can provide important insights into patterns of infection and susceptibility. Although it can seem intuitive to deploy catch-up vaccination for adolescents and adults in high prevalence HBV settings, we here demonstrate that only a limited proportion of the population remains susceptible, representing a minority who will potentially benefit from catch-up vaccination, illustrated by Fig 5. For this reason, catch-up vaccination will frequently not be a prudent use of resources as a public health intervention, although in some settings, there may be cost benefits in targeting young populations with catch-up

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vaccination.[22] The distinct regional patterns of HBV epidemiology, and the lack of overlap between the epicentres of HCV infection in North Africa, HIV in Southern Africa and endemic HBV, suggest different patterns of transmission of HBV between regions, and different transmission routes for different blood-borne viruses across the continent. Notably, even with a single country – exemplified here by Uganda – there is evidence of region-specific patterns of exposure and transmission.

In order to make progress towards achieving HBV elimination goals, we therefore suggest that the public health agenda should focus primarily on active 'test and treat' programmes aimed at older children and adults. Success of this strategy depends on education, resource and infrastructure. Our results are congruent with the findings of a recent review of HBV vaccination in South Africa highlighting the need to prioritise infant immunization above catch-up campaigns in adolescents,[20] and with previous economic evaluations of the 'test and treat' approach.[23,24] In practice, achieving success through 'test and treat' requires multi-pronged investment including education, laboratory infrastructure to provide assessment and monitoring of infection, and provision of effective, sustained drug therapy for both HBV monoinfection and HIV/HBV coinfection. In order for treatment to be successfully rolled out, focus on diagnosis is pre-requisite,[11,25] parallel investment in infra-structure is paramount to triage cases for treatment (based on including laboratory and radiological criteria), and additional scrutiny will be required for drug resistance.[26]

The epidemiology and dynamics of infection are different in certain high-risk subgroups (health care workers, sex workers and their clients, MSM, partners and household contacts of infected individuals), and continuing to target these individuals with preventive vaccination remains very important. Likewise, we continue to emphasise the importance of routine neonatal immunization campaigns which are a cornerstone of elimination strategies.[7]

Relationship between exposure and active HBV infection in Africa

Our seroepidemiology review highlighted considerable regional differences in the relationship between HBV exposure and active infection. A diverse range of factors influence the risk of developing chronic HBV infection after acute infection (Suppl Table 4), with age at exposure among the most robustly recognised. Our data suggest that in regions with low HBsAg prevalence in the setting of high anti-HBc (epitomised by countries in central Africa), most exposure events may be occurring in adults. In contrast, in Western Africa, where HBsAg prevalence is highest, the

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majority of exposure events may be in early life. Our data illustrate the marked variation in epidemiology even within individual countries, as shown for Uganda (Fig 2G); for this reason, careful data collection and review is required to underpin the most effective interventions for specific locations.

Genotype of infection and transmission routes may also be relevant. HBV genotypes A, D and E are most prevalent in Africa, with a substantial proportion of infections accounted for by horizontal transmission during early childhood.[27] Data remain scarce but, an increased HBV e-antigen (HBeAg) prevalence amongst genotype E infected individuals has been reported,[28] which typically correlates with higher viral loads and an increased risk of mother to child transmission.[29] Genotype E is geographically restricted to Western Africa, where we describe the highest HBsAg prevalence, suggesting infection in this region may be occurring at an earlier age than elsewhere. Likewise, traditional cultural practices that confer exposure to HBV at specific ages may be common in some regions but not others. Scarification has been correlated with increased HBV risk in Nigeria,[30] and the use of traditional healers, unsafe medical practices and a lack of awareness of risk factors for HBV are all likely to contribute towards transmission.

Relationship between HBV and HIV

There was no evidence from our dataset that HIV+ individuals were more likely to be either HBV infected or exposed, in keeping with previous reports.[29] This observation reflects different transmission patterns of the two viruses: HIV is less infectious than HBV when transmitted by blood and is largely sexually transmitted in Africa. In contrast, the risk of developing chronic HBV infection is high in early life and declines with age. However, robust analysis of the influence of HIV is made difficult by limited data. While we were able to identify a large number of HIV+ cohorts, only three of these had directly comparable HIV-negative cohorts (data from South Africa and Uganda).[18] Among all other published cohorts, which we have assumed to be HIV-negative, a background prevalence of HIV infection is likely but not clearly reported.

Caveats and limitations

Given Africa's population of >1·2 billion people and the substantial public health problem that HBV represents for this continent, there are very limited epidemiological data to inform the most appropriate interventions. Our maps highlight geographical gaps in the data (Fig 1), while existing cohorts are often relatively small and biased by the recruitment of specific groups who may not represent the general population.

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The published literature does not account for the prevalence of occult HBV, which is rarely detected due to lack of availability of HBV DNA testing. However, individuals with occult HBV would still generate anti-HBc; thus while we may be underestimating the prevalence of active infection, these subjects are still included within our exposed population. We included papers published after the EPI introduction in 1995, although not every country in the study adopted recommended vaccine schedules immediately. Based on the age of adults represented in most of our cohorts, we can assume the majority of subjects in the study were unlikely to have been vaccinated at birth. Future sero-surveys will provide more insights into the impact of routine infant HBV vaccination. An assessment of vaccine-mediated immunity (anti-HBs) would also be useful in estimating the impact of infant HBV vaccination in Africa.

Implications for practice

An improved understanding of HBV epidemiology at local and regional levels will be highly informative for the design of public health initiatives, allowing relevant, targeted interventions to be deployed in individual settings. Our data show the substantial potential impact of 'test and treat' approaches for HBV. Such strategy has gained traction in a population health approach to HIV, but has not been widely adopted for HBV to date. We advocate significant investment in capacity building for improving HBV diagnosis and treatment, including point-of-care testing, antenatal screening, availability of TDF as monotherapy. A sustained and systematic commitment to diagnosis and treatment represents a key component of the journey towards HBV elimination.

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LEGENDS

Fig 1: Maps demonstrating the location of adult HBV cohorts identified through a systematic literature review.
First row shows data by individual cohort, depicting (A) HBsAg prevalence, (B) total anti-HBc prevalence, and (C) HBV susceptible population (100% of population minus anti-HBc prevalence). Each circle is placed to represent the location of the cohort, and the colour represents the prevalence of the attribute (scale bar as shown on each panel). Second row shows data by country (D-F), and third row by region (G-I). Each area is coloured to reflect high to low prevalence of the attribute in question (scale bar as shown on each panel). Countries shown in grey have no data. The cohort metadata are available on-line,[18] and an interactive version of these maps can be accessed on line using the following link: https://hbv-geo.shinyapps.io/oxafricahbv/. The source code can be accessed here: https://github.com/ArmandBester/Serology_of_HBV_in_Africa.

Fig 2: Relationship between population prevalence of anti-HBc (exposure) and HBsAg (active infection) for (A) the entire African sub-continent, (B) Northern (C) Eastern (D) Southern (E) Western (F) Central, (G) Uganda. UN geoschemes used to classify the regions can be found at https://unstats.un.org/unsd/methodology/m49/). Data derived from a review of the published literature (full metadata available on-line)[18]. R^2 and p values by linear regression (solid line). Outer dashed lines show 95% confidence intervals. Linear regression plots and 95% confidence intervals (shaded regions) are shown for the whole of Africa in grey and for each region in red, and for a single country in blue. Plots B-G have been shown with the whole of Africa for comparison.

Fig 3: Estimated proportion of the population with active HBV infection, previous exposure and susceptibility to HBV infection, divided by (A) country and (B) region of Africa. Countries have been grouped according to the UN geoscheme for Africa. The number of studies per country is given in brackets next to the country name. Two studies were counted twice as they contained cohorts from two different countries. In (B), boxplots show the mean, inter-quartile ranges and range of the data sets, with all significant differences indicated. All studies are listed in on-line metadata.[18] See methods for definitions of infection, previous exposure and susceptibility.

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Fig 4: Simulation of change in HBsAg prevalence over time in response to population interventions. The pre-intervention prevalence is set close to 10%, based on population prevalence of HBV infection in Uganda (Suppl Table 1). Decline in prevalence is shown over time; bands are 95% CI for each intervention based on 5000 stochastic simulations using parameter samples form the posteriors obtained by fitting the model. (A) Comparison of interventions applied to 100% of the population: catch-up vaccination of all ages as a one-off event at time=0 (orange), routine immunisation of children aged >6 years (green), PMTCT all births (red), routine neonatal immunisation (blue) and diagnosis and treatment 'Dx + Tx' (purple); (B) Comparison of Dx + Tx applied to different proportions of the population: 50% of adults (orange), 80% of adults (green); 50% of whole population (red); 80% of whole population (blue); 100% of whole population (purple). Fitted baseline prevalence is indicated by the dashed line. All interventions modelled as previously described,[7] and the new 'Dx + Tx' is based on reducing the force of infection of each population group directly by the specified amount.

Fig 5: Cartoons to illustrate seroepidemiology of HBV infection in Africa. (A) Using data from Uganda (Supp Data Table 1), we illustrate the small proportion of adults who would potentially be protected through catch-up immunization. Immunization would prevent chronic infections in only 1-2% of the susceptible adult population who are exposed to HBV at an estimated rate of 3-4% per year,[21] among whom >95% would be predicted to clear spontaneously. Regions of Northern Uganda have a markedly higher prevalence of both active infection and population exposure than other regions with only 27-35% of the population susceptible to infection (see Fig 2G). (B) After exposure to HBV, the risk of developing chronic infection is highest amongst young infants and this risk gradually declines with age until adulthood, where there is low risk of developing of chronic infection. Figure informed by parameters in Suppl Data Table 1.

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SUPPLEMENTARY DATA

Full metadata for our systematic literature review are available on-line.[18]

Suppl. Table 1: Population data and HBV seroepidemiology for Uganda used to inform a model to determine impact of interventions. Further details of the model have been previously described.[7]

Suppl. Table 2: Predicted HBsAg prevalence for Northern, Eastern, Southern, Western and Central Africa with a given anti-HBc prevalence. Data to inform the analysis were derived from a systematic literature review (full metadata on-line)[18]. Linear regression analysis data for the African regions was simulated to predict HBsAg prevalence with a given anti-HBc prevalence ranging from 5-60% and increasing in increments of 5%. Values plotted in Suppl. Fig 3.

Suppl. Table 3: Results of a systematic literature review to identify evidence or recommendations for use of catch up HBV vaccination in adolescents and adults in Africa.

Suppl. Table 4: Factors that may contribute to regional differences in prevalence of anti-HBc and HBsAg across Africa.

Suppl. Fig 1: PRISMA chart to show the search criteria and relevant literature identified through a systematic literature review to describe the relationship between the prevalence of HBsAg and anti-HBc in subSaharan Africa. The resulting metadata set is available on-line.[18]

Suppl. Fig 2: Average prevalence of anti-HBc and HbsAg in confirmed HIV-positive cohorts and all other cohorts based on data for Africa collected through a systematic literature review. Boxplots show the mean, inter-quartile ranges and range of the data sets. No significant differences were identified for either anti-HBc or HBsAg prevalence (p=0·42 and 0·16 respectively).

Suppl. Fig 3: Predicted HBsAg prevalence for Northern, Eastern, Southern, Western and Central regions of Africa with a given total anti-HBc prevalence.

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AUTHORS' CONTRIBUTIONS

The article was conceived and designed by ALM, JS, RN, PO and PCM. The paper was written by ALM, JL and PCM with editorial contributions from all authors. ALM, SFL, JM and DF undertook the systematic literature review. JL and SG provided the mathematical model and simulations, with input from NG. PAB analysed epidemiology data and generated interactive maps. KRK provided expertise in health economics. TGM, KRK, JS, RN and PO provided expertise on local HBV interventions in South Africa and Uganda. All authors approved the final manuscript.

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CONFLICTS OF INTEREST

We have no conflicts of interest to declare.

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Figure

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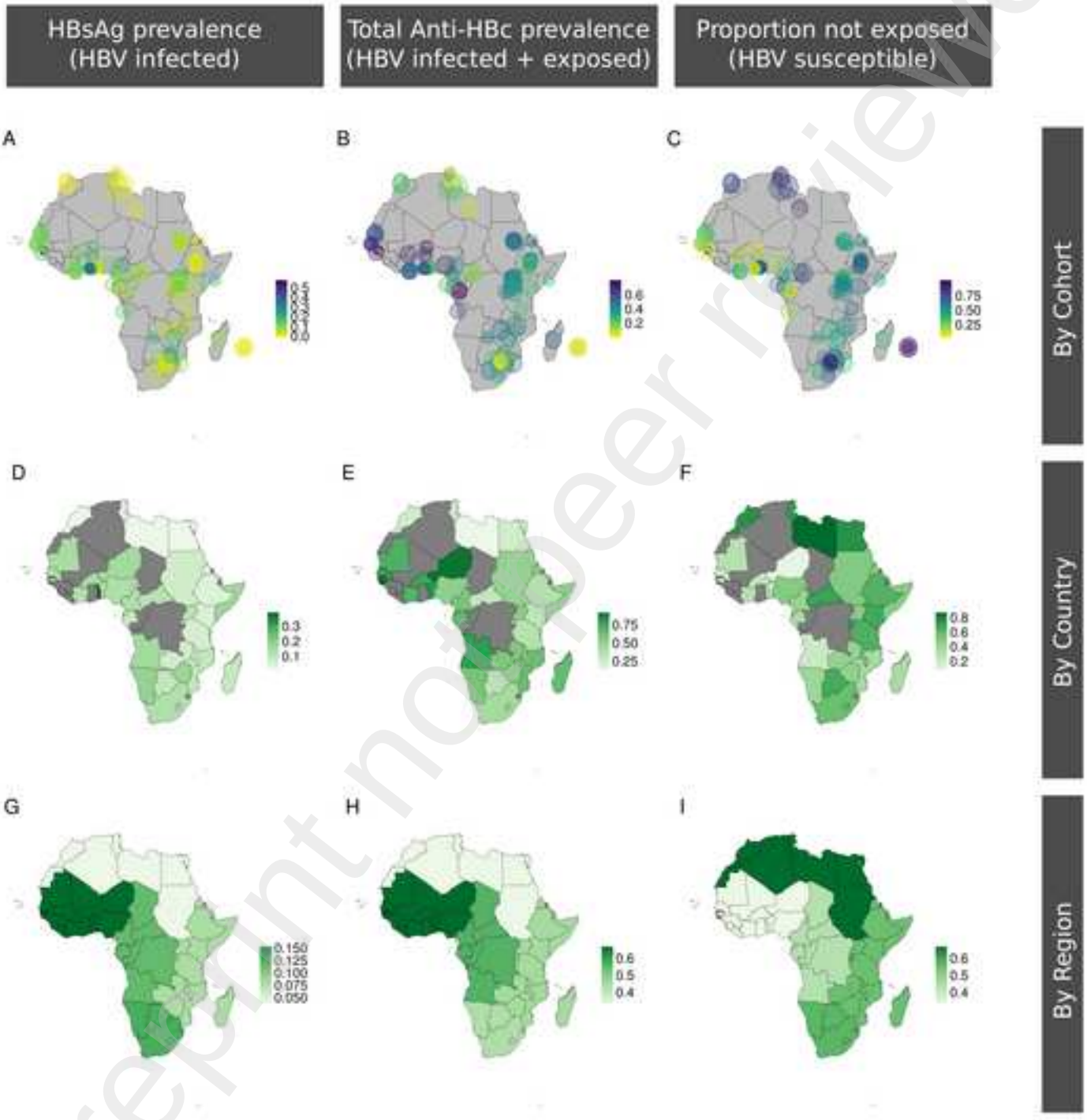

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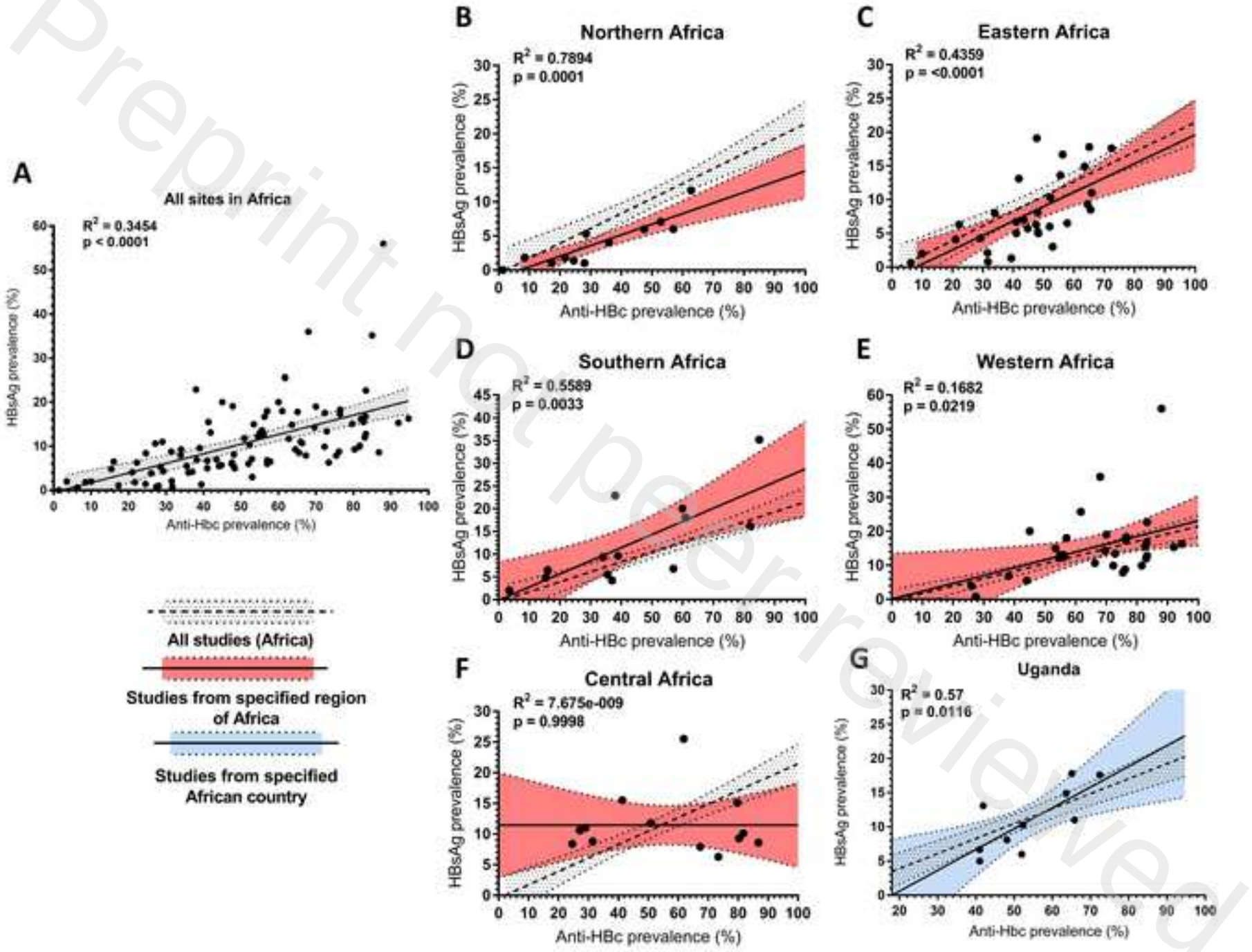

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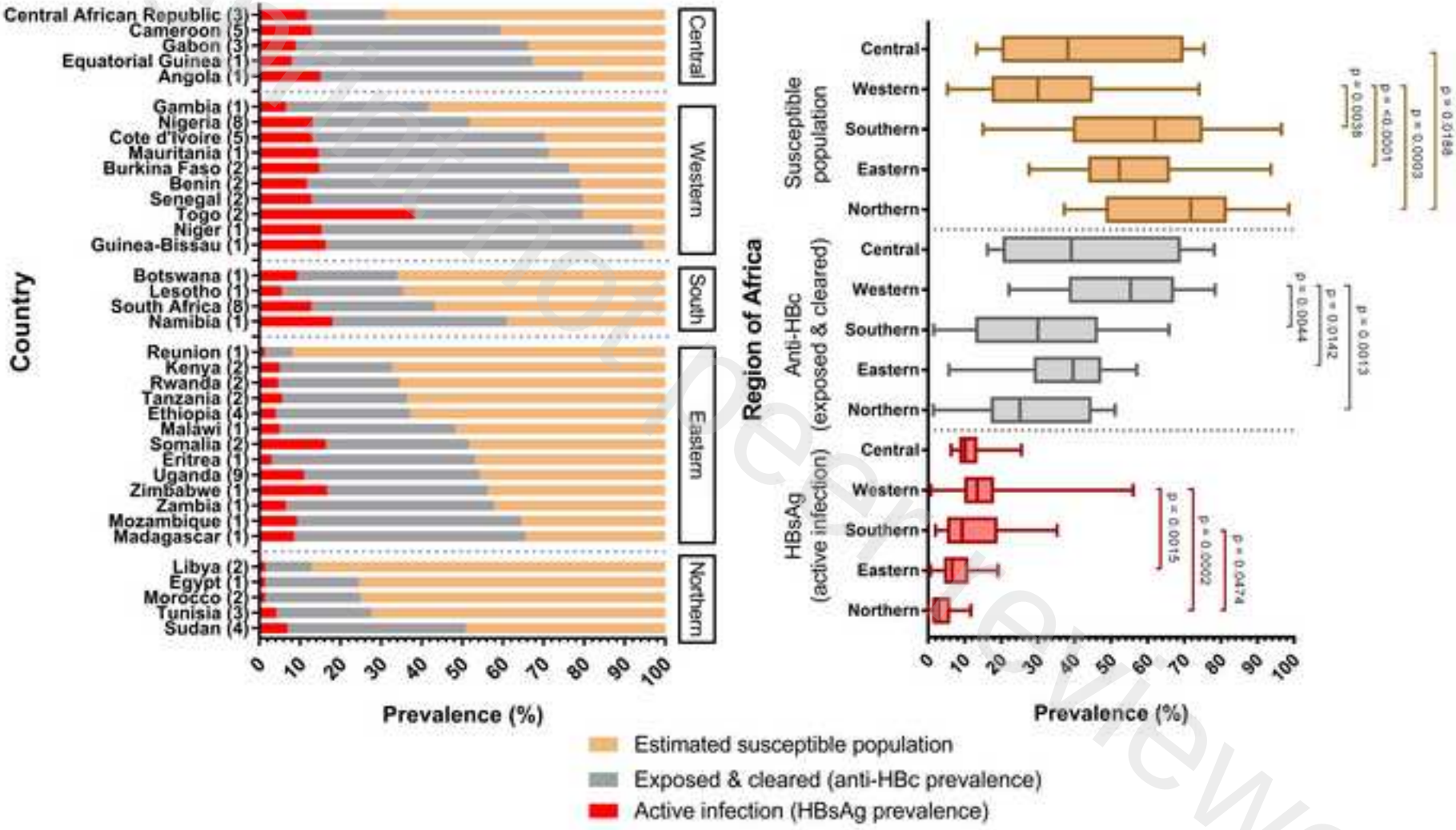

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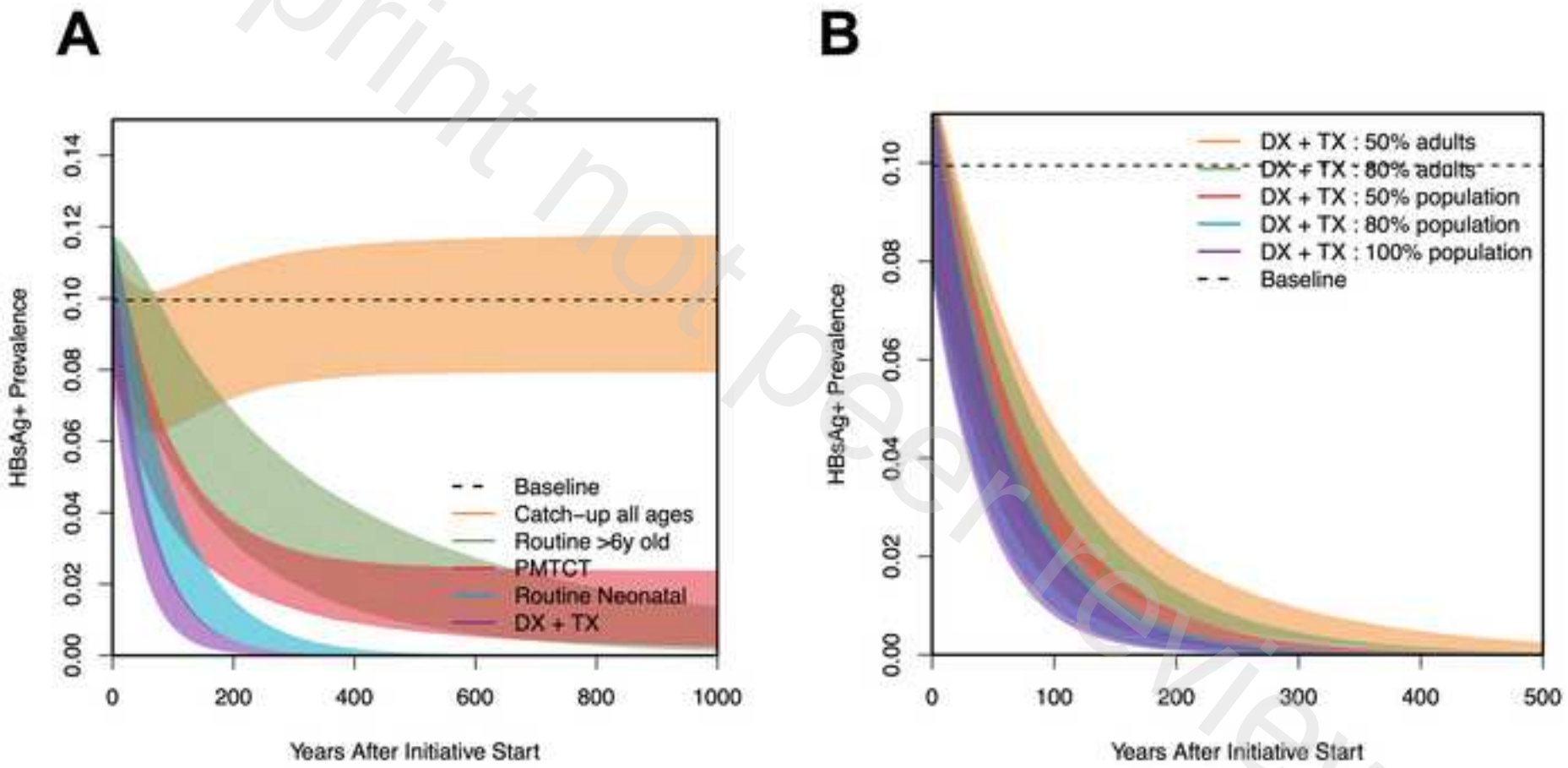

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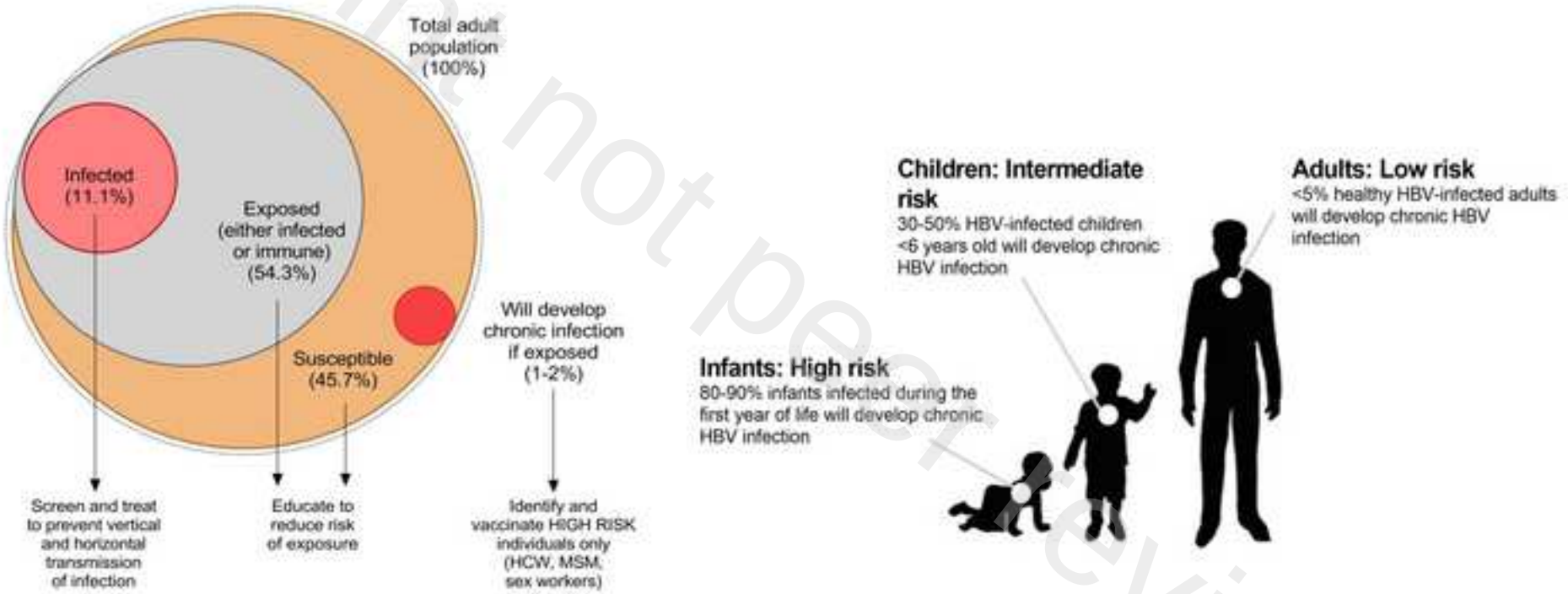

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