

1                   **HBV seroepidemiology data for Africa provides**  
2                   **insights into transmission and prevention**

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29

30 **FOOTNOTE PAGE:**

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36 **Abbreviations:**

- 37 • Anti-HBc – antibody to hepatitis B core antigen
- 38 • ART – antiretroviral therapy
- 39 • EPI – Expanded Programme for Immunization
- 40 • HBeAg – Hepatitis B e-antigen
- 41 • HBIG – Hepatitis B immunoglobulin
- 42 • HBsAg – Hepatitis B surface antigen
- 43 • HBV – Hepatitis B virus
- 44 • HIV – Human immunodeficiency virus
- 45 • IQR – Interquartile range
- 46 • PMTCT – prevention of mother to child transmission
- 47 • SDGs – Sustainable Development Goals
- 48 • UN – United Nations

49

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52 **ABSTRACT**

53 International goals for elimination of hepatitis B virus (HBV) infection set ambitious  
54 targets for 2030. In many African populations, HBV prevalence remains high ( $\geq 8\%$ )  
55 despite the roll-out of infant HBV immunisation from the mid-1990's onwards.  
56 Enhanced efforts are now urgently required to improve an understanding of population  
57 epidemiology, in order to determine which interventions are most likely to be effective  
58 in advancing populations towards elimination goals. In populations with a high  
59 prevalence of infection, catch-up HBV vaccination of adults has sometimes been  
60 deployed as a preventive strategy. An alternative approach of 'test and treat' could be  
61 applied as a tool to interrupt transmission. We used a systematic approach to  
62 investigate the relationship between prevalence of HBV infection (HBsAg) and  
63 exposure (anti-HBc) in Africa, and then applied a mathematical model to investigate  
64 the impact of catch-up vaccination and a 'test and treat' strategy in Uganda,  
65 representing a high prevalence setting. We demonstrate a strong relationship between  
66 the prevalence of HBsAg and anti-HBc ( $p < 0.0001$ ), but with region-specific differences  
67 that may reflect different patterns of transmission. In high prevalence settings, catch-  
68 up vaccination may have a transient effect but this intervention does not contribute to  
69 a sustained decline in prevalence. In contrast, diagnosing and treating infection has a  
70 marked impact on reducing prevalence, equivalent to that of infant immunisation.  
71 Conclusion: We have developed a high-resolution picture of HBV epidemiology across  
72 Africa. Developing insights into regional differences provides an evidence base for the  
73 most effective interventions. In combination with robust neonatal immunisation  
74 programmes, testing and treating infection is likely to be of most impact in making  
75 advances towards elimination targets.

## 76 INTRODUCTION

77 There is an estimated global burden of 290 million cases of chronic hepatitis B virus  
78 (HBV) infection (1), the majority of which are undiagnosed and untreated (2).  
79 Prevalence of HBV exposure and infection can be extremely high in some settings in  
80 Africa. For example, in regions of South Sudan and Northern Uganda, seroprevalence  
81 of hepatitis B surface antigen (HBsAg) is estimated at 20-25% (3, 4). High endemicity  
82 in such settings can be difficult to tackle, as infection can persist for decades, and a  
83 persistent population reservoir includes individuals with high viral loads (often  
84 corresponding to those with positive HBV e-antigen (HBeAg) status). Furthermore,  
85 robust epidemiology data are lacking, and populations in Africa may have  
86 vulnerabilities associated with poverty, stigma, and co-endemic human  
87 immunodeficiency virus (HIV) infection (2). Horizontal transmission within households,  
88 particularly affecting young children, is reported as a significant acquisition route (5-7),  
89 but the specific routes and timing of transmission remain uncertain for many African  
90 populations.

91  
92 Vaccination to protect against HBV infection is a cornerstone of interventions aiming  
93 to curtail this major public health threat, with enhanced efforts arising as a result of  
94 United Nations Sustainable Development Goals (SDGs) setting out elimination targets  
95 for the year 2030 (8). HBV vaccination is included in the Expanded Programme for  
96 Immunization (EPI), and has been progressively rolled out for infants across southern  
97 Africa since 1995. Interventions to prevent mother to child transmission (PMTCT) of  
98 HBV infection include accelerated infant vaccination (including a birth dose), combined  
99 with antiviral treatment of high risk mothers, and HBV immune globulin (HBIG), if  
100 available (9). Routine infant vaccination and enhanced PMTCT regimens currently  
101 offer the most likely route to population elimination. However, despite two decades of

102 vaccine implementation, HBV remains endemic in many regions, with time-scales for  
103 success that are substantially beyond the SDG targets for 2030 (10, 11).

104

105 Tackling the large population reservoir of infection in adults is important, and various  
106 strategies are employed to reduce new incident infections in adults, working alongside  
107 the established vaccination and PMTCT interventions aimed at children. Introducing  
108 'catch-up' vaccination campaigns in older children and adults can appear an attractive  
109 public health response in high prevalence settings (12), and this has been undertaken  
110 in some settings, despite evidence to suggest a limited population benefit (10) and lack  
111 of endorsement by routine recommendations (9). Economic analyses have reported  
112 that catch-up HBV vaccine campaigns in young adults are cost-effective only if  
113 combined with screening (13), highlighting the importance of focusing not only on  
114 prevention but also on investment in diagnosis and treatment (14). The latter concept  
115 has been embraced for HIV under the banners of 'Treatment for Prevention' (originally  
116 coined 'T4P') and more recently 'Universal Test and Treat' (15), where antiretroviral  
117 treatment (ART) is recognised for its role in conferring benefits both to the individual  
118 being treated, and also to population health by reducing the risk of transmission (16-  
119 18).

120

121 Building on this experience from HIV, a 'test and treat' HBV strategy could offer  
122 substantial advantages. The feasibility, acceptability, and public health consequences  
123 of this approach have been positively evaluated through studies in The Gambia (14,  
124 19). Optimisation of vaccine deployment, and evidence-based consideration of the  
125 impact of parallel interventions, are urgently required if we are to accelerate progress  
126 towards elimination targets in neglected, high-prevalence, resource-limited settings.

127

128 Here, we used a systematic approach to investigate the sero-epidemiology of HBV  
129 across the African subcontinent, based on the principle that understanding the  
130 distribution of both active HBV infection and exposure to infection could be of  
131 substantial influence in highlighting regional differences and informing the best choice  
132 of interventions, especially in situations where resources are limited. Recognising that  
133 catch-up vaccine campaigns are being deployed in some locations, we considered the  
134 evidence for any benefit, and also assessed the potential impact of a ‘test and treat’  
135 approach. We used an existing model to project the influence of each of these public  
136 health interventions in high prevalence settings. Our results have immediate potential  
137 for clinical and public health practice, aiming to inform the optimum deployment of  
138 limited resources for HBV diagnosis, treatment and prevention.

139

## 140 **METHODS**

### 141 ***HBV seroepidemiology for Africa***

142 We set out to determine the relationship between the prevalence of active HBV  
143 infection (HBsAg) and the prevalence of exposure to infection (anti-HBc), through a  
144 systematic review of serological data from the published literature. We undertook a  
145 systematic search of PubMed and Web of Science in June 2018, using PRISMA  
146 criteria (Suppl Fig 1). We used the search terms “HBV antibody”, “anti-HBc”, “HB core  
147 antibody”, “HBV exposure” or “HBV prevalence” AND “Africa” or [Name of specific  
148 country], using the list of countries on the United Nations (UN) geoscheme for Africa  
149 (<https://unstats.un.org/unsd/methodology/m49/>).

150

151 Inclusion criteria were as follows:

- 152 • Data gathered after the widespread roll-out of infant HBV vaccination in Africa  
153 in 1995, in order to provide insights that are relevant in the post-vaccine era;
- 154 • No reported data collection undertaken pre-1995;

- 155       • Reported prevalence of both HBsAg and anti-HBc among cohorts primarily  
156           reporting data for adults (age  $\geq 16$  years);
- 157       • Cohort does not sample a population enriched for HBV infection (specific  
158           exclusions are listed in Suppl Fig 1).

159

160 We recorded total anti-HBc prevalence (i.e. proportion of population exposed to HBV,  
161 irrespective of chronic infection status, termed 'total exposure') and also calculated the  
162 proportion of the population with cleared infection (i.e. anti-HBc prevalence minus  
163 HBsAg prevalence, termed 'exposed and cleared'). For studies reporting prevalence  
164 data from  $\geq 2$  cohorts (e.g. HIV-positive and HIV-negative populations), we recorded  
165 these as a single publication but  $\geq 2$  distinct data points. Studies in a language other  
166 than English were translated using Google Translate (<https://translate.google.com/>).

167 We considered Uganda as an exemplar setting where HBsAg seroprevalence in adults  
168 may reach  $>20\%$  in Northern regions (3, 20), and where catch-up vaccination has been  
169 deployed. We also sought evidence for recommendations underpinning catch-up  
170 vaccination of adolescents and adults in Africa cited in PubMed using the search terms  
171 'hepatitis b virus' or 'HBV', and 'Africa' or [individual country name], with 'vaccin\*' and  
172 'catch up' or 'adult'.

173

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

176

### 177 ***Statistical analysis of metadata***

178 The UN geoscheme classifies Africa into Central, Eastern, Northern, Southern and  
179 Western regions; this is a standard approach for sub-dividing macro-geographical  
180 areas for statistical analysis. For the regional analysis, each study was assigned equal  
181 weighting when analyzing the data, regardless of the study size. We analysed

182 prevalence data for anti-HBc and HBsAg using Graphpad Prism v7.0. For non-  
183 parametric data, we sought significant differences between data sets using Mann-  
184 Whitney U tests, and for multiple comparisons we used 1-way ANOVA. We used linear  
185 regression to derive lines of best fit, 95% confidence intervals and to interpolate HBsAg  
186 prevalence from anti-HBc prevalence. We generated maps to illustrate the location of  
187 the HBV cohorts and seroprevalence of relevant markers using R (Source code will be  
188 made available on acceptance at the following link:  
189 [https://github.com/ArmandBester/Serology\\_of\\_HBV\\_in\\_Africa](https://github.com/ArmandBester/Serology_of_HBV_in_Africa)).

190

### 191 ***Modelling the impact of adult vaccination vs. ‘test and treat’***

192 In this study we adapted a published dynamic model and Bayesian Markov Chain  
193 Monte Carlo approach that we previously developed to fit the seroepidemiology of a  
194 population in South Africa, projecting the impact of interventions in that transmission  
195 setting (10). As these methods are already published, we have not replicated them in  
196 this paper. For ease of reference, we have provided a summary overview of the model  
197 population classes and parameters in Suppl Table 1. In this instance, we fitted the  
198 model to data from Uganda (Suppl Table 1), in order to represent a setting of high  
199 HBsAg prevalence (3).

200

201 We used published seroepidemiology variables, as follows: HBsAg prevalence 10.3%,  
202 anti-HBc prevalence 42% and HBeAg-positive (HBeAg+) relative prevalence at 27%  
203 (Suppl Table 1), which the model robustly recovered at 10% (95% CI 7.92-11.7%),  
204 42.1% (95% CI 40.2-44.0%), and 26.9% (95% CI 24.8-29.0%), respectively. We left  
205 four parameters free to be fitted (vertical transmission rate for HBeAg+ and HBeAg-  
206 negative (HBeAg-), rate of conversion from HBeAg+ to HBeAg-, and spontaneous  
207 clearance of chronic HBV), for which the posteriors matched literature expectations  
208 (Suppl Table 1). PMTCT (combining accelerated neonatal immunisation with HBIg and



209 antiviral therapy in pregnant mothers) and vaccine-based interventions were modelled  
210 as previously described (10), and we added a ‘test and treat’ strategy. The latter was  
211 simplified to reducing the transmission potential of the HBV infected proportionally to  
212 the control effort (e.g. 20% coverage of test and treat in a particular age-group equated  
213 to a 20% reduction in that group’s force of infection).

214

## 215 **RESULTS**

### 216 ***Significant relationship between prevalence of HBsAg (infection) and anti-HBc*** 217 ***(exposure)***

218 Through a systematic literature review, we collated prevalence data for HBsAg and  
219 total anti-HBc, identifying a total of 88 studies spanning 37 African countries and  
220 generating 100 unique data points (complete metadata are available on-line) (21).  
221 Information on studies reporting prevalence data from  $\geq 2$  cohorts (n=12) is recorded  
222 in Suppl Table 2. The median ages for the cohorts represented was 34.4 years (IQR  
223 29.1-36.2 years) based on age data available for 64% of studies.

224

225 The distribution of these cohorts and the prevalence of HBV serological markers is  
226 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  
227 (infection) was positively correlated with total anti-HBc (exposure),  $R^2=0.35$ ,  $p<0.0001$   
228 by linear regression, Fig 2A. Median HBsAg prevalence across Africa was 9.3% (IQR  
229 5.5-15.1%) with an anti-HBc prevalence of 53.0% (IQR 34.4-69.2%). We did not find  
230 any significant differences in HBsAg or anti-HBc prevalence between HIV+ cohorts  
231 (N=26) and all other cohorts (N=74;  $p=0.16$  and  $p=0.42$ , respectively; Suppl. Fig 2).

232

### 233 234 ***Variations by region and by country***

235 For most regions, we observed the same overall association between total anti-HBc  
236 and HBsAg, Fig 2B-E, but with some interesting variations. Northern Africa has lower  
237 prevalence rates of infection than other regions (Fig 2B and Fig 3A,B). In contrast,  
238 Western Africa has the highest population exposure and correspondingly highest rates  
239 of HBsAg positivity (Fig 2E, Fig 3). HBsAg prevalence differs significantly between  
240 regions (for Northern Africa compared to Western and Southern Africa,  $p=0.0002$  and  
241  $p=0.04$  respectively, Fig 3B); and cannot be explained only by lower population  
242 exposure rates: although anti-HBc prevalence is somewhat lower in Northern than  
243 Western Africa ( $p=0.001$ ), there is no difference in anti-HBc prevalence between  
244 Southern and Northern Africa ( $p=0.99$ ). Indeed, the predicted HBsAg prevalence was  
245 approximately 50% lower in Northern than Southern Africa for any given anti-HBc  
246 prevalence (Fig 2B, 2D; Suppl Table 3).

247

248 Central African regions display a different relationship, whereby high population HBV  
249 exposure is not associated with a correspondingly high prevalence of infection (Fig  
250 2F). This is likely to be a robust representation of the region, as the data cover a 15-  
251 year period, and represent multiple countries from where a median of 455 subjects  
252 were analysed (IQR 225-782 subjects). Focusing specifically on Uganda, in Eastern  
253 Africa, we also found a significant relationship between HBsAg and anti-HBc  
254 prevalence;  $p=0.01$ , Fig 2G, 3A. However, even within this single country, considerable  
255 differences are seen in the ratio of HBsAg:anti-HBc between different studies (see  
256 metadata on-line (21)).

257

258 In three studies that assessed both HIV-positive and HIV-negative cohorts, HBsAg  
259 prevalence was higher among HIV-positive subjects (mean 2.23-fold) (22-24). Anti-  
260 HBc prevalence was also higher in HIV-positive cohorts than in HIV-negative cohorts  
261 for 2/3 studies (22, 24). In a third study of highly exposed cohorts in South Africa, anti-

262 HBc prevalence was similar irrespective of HIV status, suggesting the increased  
263 HBsAg prevalence in the HIV-positive cohort was the result of reduced clearance rates  
264 relative to the HIV-negative cohort (23).

265

### 266 ***Impact of catch-up vaccination of adolescents and adults***

267 We did not identify any published evidence or specific recommendations for catch-up  
268 vaccination of adolescents and adults, either in the form of intervention studies or  
269 literature reviews. However, a number of authors do suggest catch-up vaccine  
270 programmes as a way of tackling high population HBV prevalence (3, 12, 25, 26) (data  
271 from literature review summarised in Suppl Table 4).

272

273 Based on combining the mean prevalence values from Uganda cohorts to provide a  
274 broad overview, 54% of adults across this country have been exposed (among these,  
275 a total of 11% of adults are actively HBV-infected, and the remainder have been  
276 infected and cleared). This leaves 46% of the total adult population potentially  
277 susceptible (orange bars, Fig 3A). Only a small proportion of this susceptible pool of  
278 adults would be exposed to infection each year (there are few data to estimate this  
279 exposure rate, but one study from another region of East Africa estimates this at 3-  
280 4%) (27). The natural history of HBV infection in adults suggests that <5% of exposure  
281 events lead on to chronic infection. Thus, the predicted proportion of the total adult  
282 population predicted to avoid chronic infection through catch-up vaccination each year  
283 is, roughly, 50% (vulnerable) x 4% (exposed) x 5% (develop chronicity) = 0.1%.

284

285 Using our established model of HBV transmission and prevention (10), we investigated  
286 the impact of catch-up vaccination among adults within a high HBV prevalence setting,  
287 exemplified by Uganda (3) (Suppl Table 1). Selected results from simulations are  
288 presented in Fig 4, in which a catch-up immunization programme in adults is projected

289 to have only a transient impact on reducing new cases of HBV infection. In the long-  
290 term, this strategy offers no sustained overall benefit in progress towards elimination  
291 targets, even when deployed at 100% population coverage (Fig 4A, orange band). The  
292 poor impact of catch-up vaccination, estimated at only an 8% reduction over 200 years  
293 (Fig 4A), is due to a limited pool of susceptible adults and the lack of impact on the  
294 actively infected population. In contrast, enhanced coverage of other interventions,  
295 including PMTCT and infant immunisation will lead to shorter time-frames for reducing  
296 HBsAg prevalence, given their direct impact on the rate of new chronic infections, the  
297 main reservoir of HBV infection.

298

### 299 ***Impact of ‘test and treat’ in highly endemic settings***

300 We also modelled the impact of ‘test and treat’, based on the premise that the whole  
301 population is screened, projecting that this strategy has the fastest reduction in HBV  
302 population prevalence of all interventions with 62% reduction in prevalence by 50  
303 years, and 98% at 200 years (Fig 4A, purple band). Recognising the significant barriers  
304 to identifying all cases of infection, (including silent infection, lack of education, poor  
305 access to laboratory facilities, and stigma) (2), we also modelled the outcome for ‘test  
306 and treat’ strategies that reach <100% of the HBV-infected population. Diagnosis and  
307 treatment for 80% of infected adults (Fig 4B, green band) or 50% of the whole infected  
308 population (Fig 4B, red band) delivers a reduction in HBsAg prevalence over time that  
309 is comparable to infant immunisation (Fig 4A, blue band). Even reducing the population  
310 tested and treated to only 50% of adults (Fig 4B, orange band) is still substantially  
311 more effective than 100% catch-up vaccination (Fig 4A, orange band).

312

## 313 **DISCUSSION**

314 United Nations Sustainable Development goals have set an ambitious time-frame in  
315 which to make significant reductions in both prevalence and incidence of HBsAg

316 carriage by the year 2030 (8). Careful, evidence-based deployment of interventions is  
317 essential if sustained and collective progress is to be made towards these targets. We  
318 have here shown how existing epidemiology data can provide important insights into  
319 patterns of infection and susceptibility. Other systematic reviews and global estimates  
320 of HBsAg prevalence have been published over the last few years (1, 4, 28); our  
321 approach differs in also accounting for the prevalence of exposure, and in considering  
322 the relationship between infection and exposure in different settings.

323

324 Although it can seem intuitive to deploy catch-up vaccination for adolescents and  
325 adults in high prevalence HBV settings, we here demonstrate that only a limited  
326 proportion of individuals remain susceptible in these populations, representing a  
327 minority who will potentially benefit from catch-up vaccination. The effectiveness of  
328 catch-up vaccination is strongly linked to the size of the susceptible population, as  
329 illustrated by Fig 5B, with a greater impact seen in low-prevalence populations. For  
330 this reason, catch-up vaccination will frequently not be a prudent use of resources,  
331 although in some settings, there may be cost benefits in targeting young populations  
332 with catch-up vaccination (29). The distinct regional patterns of HBV epidemiology,  
333 and the lack of overlap between the epicentres of HCV infection in North Africa, HIV in  
334 Southern Africa and endemic HBV, suggest different patterns of transmission of HBV  
335 between regions, and different transmission routes for different blood-borne viruses  
336 across the continent. Notably, even with a single country – exemplified here by Uganda  
337 – there is evidence of region-specific differences in exposure and transmission.

338

339 In order to make progress towards HBV elimination goals, we therefore suggest that  
340 the public health agenda should prioritise active ‘test and treat’ programmes aimed at  
341 older children and adults. Success of this strategy depends on education, resource  
342 and infrastructure. Our results are congruent with the findings of a recent review of

343 HBV vaccination in South Africa highlighting the need to prioritise infant immunization  
344 above catch-up campaigns in adolescents (26), and with previous economic  
345 evaluations of the 'test and treat' approach (30, 31). In practice, achieving success  
346 through 'test and treat' requires multi-pronged investment including education,  
347 laboratory infrastructure to provide assessment and monitoring of infection, and  
348 provision of effective, sustained drug therapy for both HBV mono-infection and  
349 HIV/HBV coinfection. In order for treatment to be successfully rolled out, focus on  
350 diagnosis is pre-requisite (14, 32), parallel investment in infra-structure is paramount  
351 to triage cases for treatment (based on including laboratory and radiological criteria),  
352 and additional scrutiny will be required for drug resistance (33).

353

354 The epidemiology and dynamics of infection are different in certain high-risk subgroups  
355 (health care workers, partners and household contacts of infected individuals, sex  
356 workers and their clients, men who have sex with men), and continuing to target these  
357 individuals with preventive vaccination remains very important. Likewise, we continue  
358 to emphasise the importance of routine infant immunization campaigns which are a  
359 cornerstone of elimination strategies (10).

360

### 361 ***Relationship between exposure and active HBV infection in Africa***

362 Our seroepidemiology review highlighted considerable regional differences in the  
363 relationship between HBV exposure and active infection. A diverse range of factors  
364 influence the risk of developing chronic HBV infection after acute infection (Table 1),  
365 with age at exposure among the most robustly recognised. Our data suggest that in  
366 regions with low HBsAg prevalence in the setting of high anti-HBc (epitomised by  
367 countries in central Africa), most exposure events may be occurring in adults. In  
368 contrast, in Western Africa, where HBsAg prevalence is highest, the majority of

369 exposure events may be in early life. Careful data collection and review is required to  
370 underpin the most effective interventions for specific locations.

371

372 Genotype of infection and transmission routes should also be considered as factors  
373 influencing sero-epidemiology. HBV genotypes A, D and E are most prevalent in  
374 Africa, with a substantial proportion of infections accounted for by horizontal  
375 transmission during early childhood (34). Data remain scarce but, an increased HBV  
376 HBeAg prevalence amongst genotype E infected individuals has been reported (35),  
377 typically correlating with higher viral loads and increased risk of vertical transmission  
378 (36). Genotype E is geographically restricted to Western Africa, where we describe the  
379 highest HBsAg prevalence, suggesting infection in this region may be occurring at an  
380 earlier age than elsewhere. Likewise, traditional cultural practices that confer exposure  
381 to HBV at specific ages may be common in some regions but not others. Scarification  
382 has been correlated with increased HBV risk in Nigeria (37), and unsafe medical  
383 practices and a lack of awareness of risk factors for HBV may contribute towards  
384 transmission in some populations.

385

### 386 ***Relationship between HBV and HIV***

387 There was no evidence from our dataset that HIV+ individuals were more likely to be  
388 either HBV infected or exposed, in keeping with previous reports (36). This observation  
389 reflects different transmission patterns: HIV is less infectious than HBV when  
390 transmitted by blood and is largely sexually transmitted in Africa. In contrast, the risk  
391 of developing chronic HBV infection is high in early life and declines with age. However,  
392 robust analysis of the influence of HIV on HBV exposure and acquisition is made  
393 difficult by limited data. While we were able to identify a large number of HIV+ cohorts,  
394 only three of these had directly comparable HIV-negative cohorts (data from South  
395 Africa and Uganda) (21). Among all other published cohorts, which we have assumed

396 to be HIV-negative, a background prevalence of HIV infection is likely but not clearly  
397 reported.

398

### 399 ***Caveats and limitations***

400 Given Africa's population of >1.2 billion people and the substantial public health  
401 problem that HBV represents for this continent, there are very limited epidemiological  
402 data to inform the most appropriate interventions. Our maps highlight geographical  
403 gaps in the data (Fig 1), while existing cohorts are often relatively small and biased by  
404 the recruitment of specific groups who may not be representative of the general  
405 population. The published literature does not account for the prevalence of occult HBV,  
406 which is rarely detected due to lack of availability and high cost of HBV DNA testing.  
407 However, individuals with occult HBV would still generate anti-HBc; thus while we may  
408 be underestimating the prevalence of active infection, these subjects are still included  
409 within our exposed population.

410

411 We did not include data for anti-HBs prevalence (immunised population) as a limited  
412 number of papers report the prevalence of anti-HBs together with anti-HBc and HBsAg  
413 data. The most common reason for study exclusion from the literature review was no  
414 anti-HBc prevalence reported (Suppl Fig 1). Making the inclusion criteria more  
415 stringent would have limited the findings from the study.

416

417 We included papers published after the EPI introduction of HBV vaccine in 1995, in  
418 order to make our study applicable to current-day vaccinated populations, although in  
419 practice, roll-out of the vaccine was patchy and adopted at a variable rate over the  
420 decade that followed. There are limited data for many regions describing the  
421 prevalence of three-dose vaccine coverage. Based on the age of adults represented  
422 in most of our cohorts, we can assume the majority of subjects in the study were



423 unlikely to have been vaccinated at birth. Future sero-surveys will provide more  
424 insights into the impact of routine infant HBV vaccination. An assessment of vaccine-  
425 mediated immunity (anti-HBs) would also be useful in estimating the impact of infant  
426 HBV vaccination in Africa.

427

428 For this study, we focused on adult populations only, as the age-associated risk of  
429 developing chronic HBV is a confounding factor in younger cohorts, making inference  
430 about the anti-HBc prevalence challenging across multiple age groups. It would be of  
431 interest to determine age-specific prevalence of HBsAg and anti-HBc because age is  
432 likely to be an important source of heterogeneity. However, metadata are poorly  
433 reported by existing literature and we were unable to disaggregate serological data by  
434 age.

435

436 Our dynamic model includes a series of simplifying assumptions. For instance, our  
437 'test and treat' intervention does not stratify individuals for therapy, but works on the  
438 basis of treating anyone who is HBsAg-positive. In current clinical practice, guidelines  
439 recommend treatment in the context of high viral load and/or evidence of inflammatory  
440 liver disease (38). However, explicitly stratifying population subgroups for 'test and  
441 treat' within our framework would have required the inclusion of epidemiological  
442 classes (e.g. clinical progression or population classes stratified by viral load or liver  
443 transaminases), which would have added significant uncertainty to our projections. Our  
444 model framework does not include explicit age-specific or risk-group assumptions  
445 regarding force of transmission, and again we argue that little data exists to inform this  
446 parameterization and adds extra classes with added uncertainty. Keeping  
447 parameterisation simple was an intended approach, as is general practice in dynamic  
448 modelling. Our projections are not intended to be exact quantifications of impact over

449 time, but serve as means of comparing the dynamic and non-linear outcomes of  
450 different strategies.

451

452 ***Implications for practice***

453 An improved understanding of HBV epidemiology at local and regional levels will be  
454 informative for the design of public health initiatives, allowing relevant, targeted  
455 interventions to be deployed in individual settings. Catch-up vaccination is not routinely  
456 endorsed by guidelines, but is nevertheless being deployed by some public health  
457 initiatives devised in response to high prevalence settings. Our data show the added  
458 value of 'test and treat' approaches for HBV, building on experience gained from HIV.  
459 We advocate significant investment in capacity building for improving HBV diagnosis  
460 and treatment, including point-of-care testing, antenatal screening, and provision of  
461 TDF. A sustained and systematic commitment to diagnosis and treatment represents  
462 a key component of the journey towards HBV elimination.

463

464 **Table 1: Factors that may contribute to regional differences in prevalence of anti-**  
 465 **HBc and HBsAg across Africa**

<b>Factor</b>	<b>Rationale for contribution to regional differences in HBV seroepidemiology</b>
<b>Circulating HBV viral genotype</b>	Predominant genotype varies by region with genotype-A common in Southern Africa, genotype-D in the North and genotype-E in the West (39).
<b>Host ethnicity and genetics</b>	HLA-type and T-cell repertoire have been linked to the ability to control the infection (40-42).
<b>Transmission differences</b>	Subtle differences in the transmission patterns (vertical vs horizontal) of the HBV genotypes have been documented. Transmission route is fundamentally linked to age at exposure (43).
<b>Age at exposure</b>	The probability of developing chronic HBV after exposure is strongly associated with age (44). Populations with a younger age at exposure are therefore likely to have a higher HBsAg prevalence relative to the anti-HBc prevalence (Fig 5A).
<b>Co-infection within population</b>	Risk factors for acquisition of blood-borne viruses overlap between HIV, HBV and HCV. Egypt and the Nile Delta have some of the highest reported prevalences of HCV globally. Co-infection of HBV and HCV has been linked to spontaneous clearance of HCV although evidence of the impact on HBV remains scarce (45, 46).
<b>Political instability</b>	Central Africa includes several regions disrupted by recent conflict and resulting population migration, with powerful influence on increases in interpersonal violence and sexual assault, reduced access to barrier contraception, inadequate screening of blood products, and reduced access to healthcare, all of which can increase exposure rates in the adult population.
<b>Traditional cultural practices</b>	Exposure to blood-borne viruses is influenced by traditional healing practices, scarification, piercing, tattooing and non-sterile surgical practice (e.g. circumcision).
<b>Uptake of HBV vaccination in the region</b>	Countries with earlier uptake of the HBV vaccine are likely to have lower anti-HBc and HBsAg prevalence than countries that implemented the vaccine later. Prevalence of vaccine escape mutants may contribute, although data for Africa are scarce (33).
<b>Potential role of insect vector</b>	Biting insects capable of mechanical transmission of HBV may be prevalent in some regions, although there is a lack of firm evidence base for HBV transmission (47).

466

467

468 **LEGENDS**

469

470 **Fig 1: Maps demonstrating the location and HBV seroepidemiology of adult**  
471 **cohorts identified through a systematic literature review.**

472 First row shows data by individual cohort, depicting (A) HBsAg prevalence, (B) total  
473 anti-HBc prevalence, and (C) HBV susceptible population (100% of population minus  
474 anti-HBc prevalence). Each circle is placed to represent the location of the cohort.  
475 Second row shows data by country (D-F), and third row by region (G-I). Each area is  
476 coloured to reflect high to low prevalence of the attribute in question (scale bar as  
477 shown on each panel). Countries shown in grey have no data. The cohort metadata  
478 are available on-line, (21) and an interactive version of these maps can be accessed  
479 on line using the following link: <https://hbv-geo.shinyapps.io/oxafricahbv/>. The source  
480 code can be accessed here:  
481 [https://github.com/ArmandBester/Serology\\_of\\_HBV\\_in\\_Africa](https://github.com/ArmandBester/Serology_of_HBV_in_Africa).

482

483 **Fig 2: Relationship between population prevalence of anti-HBc (exposure) and**  
484 **HBsAg (active infection) for different regions of Africa.** Data are shown for (A) the  
485 entire African sub-continent, (B) Northern (C) Eastern (D) Southern (E) Western (F)  
486 Central, (G) Uganda. These data are derived from a review of the published literature  
487 (full metadata available on-line)(21). The UN geoscheme used to classify the  
488 geographic regions can be found at <https://unstats.un.org/unsd/methodology/m49/>.  $R^2$   
489 and p values by linear regression (solid line). Outer dashed lines show 95% confidence  
490 intervals. Linear regression plots and 95% confidence intervals (shaded regions) are  
491 shown for the whole of Africa in grey, for each region in red, and for a single country  
492 in blue. Data in plots B-G have been shown together with data for the whole continent  
493 for comparison.

494

495 **Fig 3: Estimated proportion of the population with active HBV infection, previous**  
496 **exposure and susceptibility to HBV infection, divided by (A) country and (B)**  
497 **region of Africa.** Countries have been grouped by region according to the UN  
498 geoscheme for Africa. The number of studies per country is given in brackets next to  
499 the country name. Two studies were counted twice as they contained cohorts from two  
500 different countries. In (B), boxplots show the mean, inter-quartile ranges and range of  
501 the data sets, with all significant differences indicated. All studies are listed in on-line  
502 metadata.(21) See methods for definitions of infection, previous exposure and  
503 susceptibility.

504

505 **Fig 4: Simulation of change in HBsAg prevalence over time in response to**  
506 **population interventions.** The pre-intervention prevalence is set close to 10%, based  
507 on population prevalence of HBV infection in Uganda (Suppl Table 1). Decline in  
508 prevalence is shown over time; bands are 95% CI for each intervention based on 5000  
509 stochastic simulations using parameter samples from the posteriors obtained by fitting  
510 the model. (A) Comparison of interventions applied to 100% of the population: catch-  
511 up vaccination of all ages as a one-off event at time=0 (orange), routine immunisation  
512 of children aged >6 years as an alternative catch-up strategy (green), PMTCT all births  
513 (combining accelerated neonatal immunisation with HBIg and antiviral therapy in  
514 pregnant mothers, red), routine neonatal immunisation (blue) and diagnosis and  
515 treatment 'Dx + Tx' (purple); (B) Comparison of Dx + Tx applied to different proportions  
516 of the population: 50% of adults (orange), 80% of adults (green); 50% of whole  
517 population (red); 80% of whole population (blue); 100% of whole population (purple).  
518 Fitted baseline prevalence is indicated by the dashed line. All interventions modelled  
519 as previously described (10), and the new 'Dx + Tx' is simplified to a reducing the  
520 force of infection of each population group by the specified amount (see main text).

521 The numbers at time points  $t=50$  and  $t=200$  years are the mean reduction in HBsAg  
522 prevalence achieved for each of the interventions.

523

524 **Fig 5: Cartoons to illustrate seroepidemiology of HBV infection in Africa and the**  
525 **differential impact of HBV interventions according to population targeted. (A)**

526 After exposure to HBV, the risk of developing chronic infection is highest amongst  
527 young infants and this risk gradually declines with age until adulthood, where there is  
528 low risk of developing of chronic infection. Figure informed by parameters in Suppl  
529 Table 1. (B) Populations from Sudan (48) Uganda (3) and Burkina Faso (49) represent  
530 the 25th, 50th and 75th percentiles in the data set collected from our literature review.

531 In adults, assuming that different populations are exposed at the same rate and the  
532 risk of chronic infection is constant (estimated to be 5% in healthy adults as shown in  
533 Fig 5A), the incidence of new chronic HBV infection in the population is related to the  
534 susceptible proportion ( $S$ ). Without intervention, 100% of predicted new cases will  
535 occur. If 50% of the adult population is vaccinated in a catch-up campaign, chronic  
536 infection will be prevented only among the population  $S$ . The impact of catch-up  
537 vaccination on incidence is therefore related to  $S$ , with reduced impact in highly  
538 exposed populations. In a test and treat scenario, with 50% of cases identified and  
539 treated, incidence is consistently reduced, regardless of  $S$ .

540

541 **SUPPLEMENTARY DATA**

542

543 Full metadata for our systematic literature review are available on-line (21).

544

545 **Suppl. Table 1: Population data and HBV seroepidemiology for Uganda used to**  
546 **inform a model to determine impact of interventions.** Further details of the model  
547 have been previously described (10).

548

549 **Suppl. Table 2: Details of studies from Africa reporting HBV prevalence data**  
550 **from  $\geq 2$  cohorts.** These studies (n=12) were recorded as a single study but  $\geq 2$  data  
551 points (as appropriate). Differences in the cohorts are highlighted in city/location,  
552 cohort characteristics and cohort size. Complete metadata for the manuscript are  
553 available at <https://figshare.com/s/4414fce1d474bc8a6198>.

554

555 **Suppl. Table 3: Predicted HBsAg prevalence for Northern, Eastern, Southern,**  
556 **Western and Central Africa with a given anti-HBc prevalence.** Data to inform the  
557 analysis were derived from a systematic literature review (full metadata on-line)(21).  
558 Linear regression analysis data for the African regions was simulated to predict HBsAg  
559 prevalence with a given anti-HBc prevalence ranging from 5-60% and increasing in  
560 increments of 5%. Values plotted in Suppl. Fig 3.

561

562 **Suppl. Table 4: Results of a systematic literature review to identify evidence or**  
563 **recommendations for use of catch up HBV vaccination in adolescents and**  
564 **adults in Africa.**

565

566 **Suppl. Fig 1: PRISMA chart to show the search criteria and relevant literature**  
567 **identified through a systematic literature review to describe the relationship**

568 **between the prevalence of HBsAg and anti-HBc in subSaharan Africa.** The  
569 resulting metadata set is available on-line (21).

570

571 **Suppl. Fig 2: Average prevalence of anti-HBc and HbsAg in confirmed HIV-**  
572 **positive cohorts and all other cohorts based on data for Africa collected through**  
573 **a systematic literature review.** Boxplots show the mean, inter-quartile ranges and  
574 range of the data sets. No significant differences were identified for either anti-HBc or  
575 HBsAg prevalence ( $p=0.42$  and  $0.16$  respectively).

576

577 **Suppl. Fig 3: Predicted HBsAg prevalence for Northern, Eastern, Southern,**  
578 **Western and Central regions of Africa with a given total anti-HBc prevalence**  
579 **(reflecting exposure).** Linear regression analysis data for each region was simulated  
580 to predict HBsAg prevalence with a given anti-HBc prevalence ranging from 5-60%  
581 and increasing in increments of 5%. Plotted from values given in Suppl. Table 2.

582



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729

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730 **AUTHORS' CONTRIBUTIONS**

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

738

739 **CONFLICTS OF INTEREST**

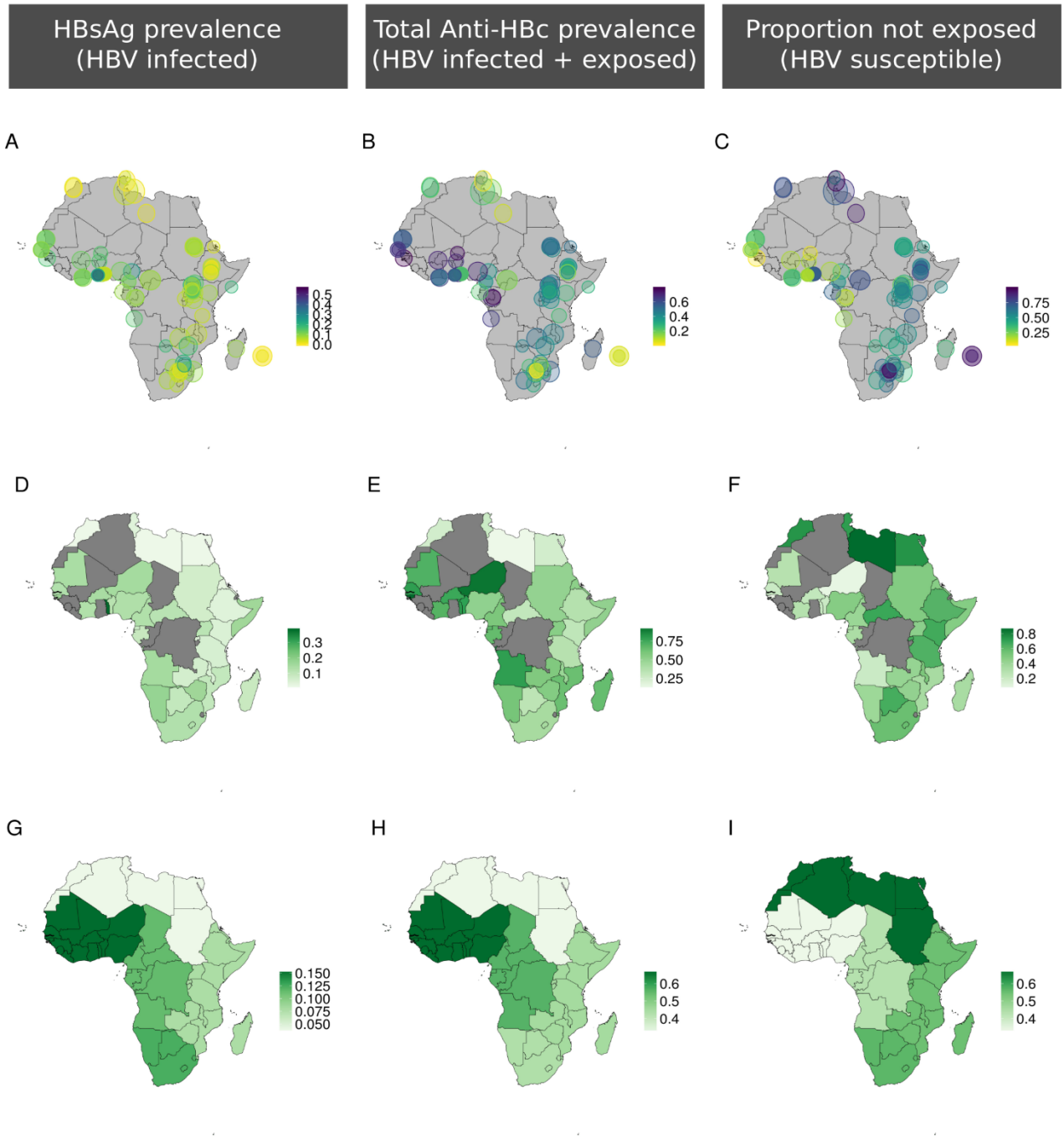
740 We have no conflicts of interest to declare.

741

742

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**Figure 1**



By Cohort

By Country

By Region



Figure 2

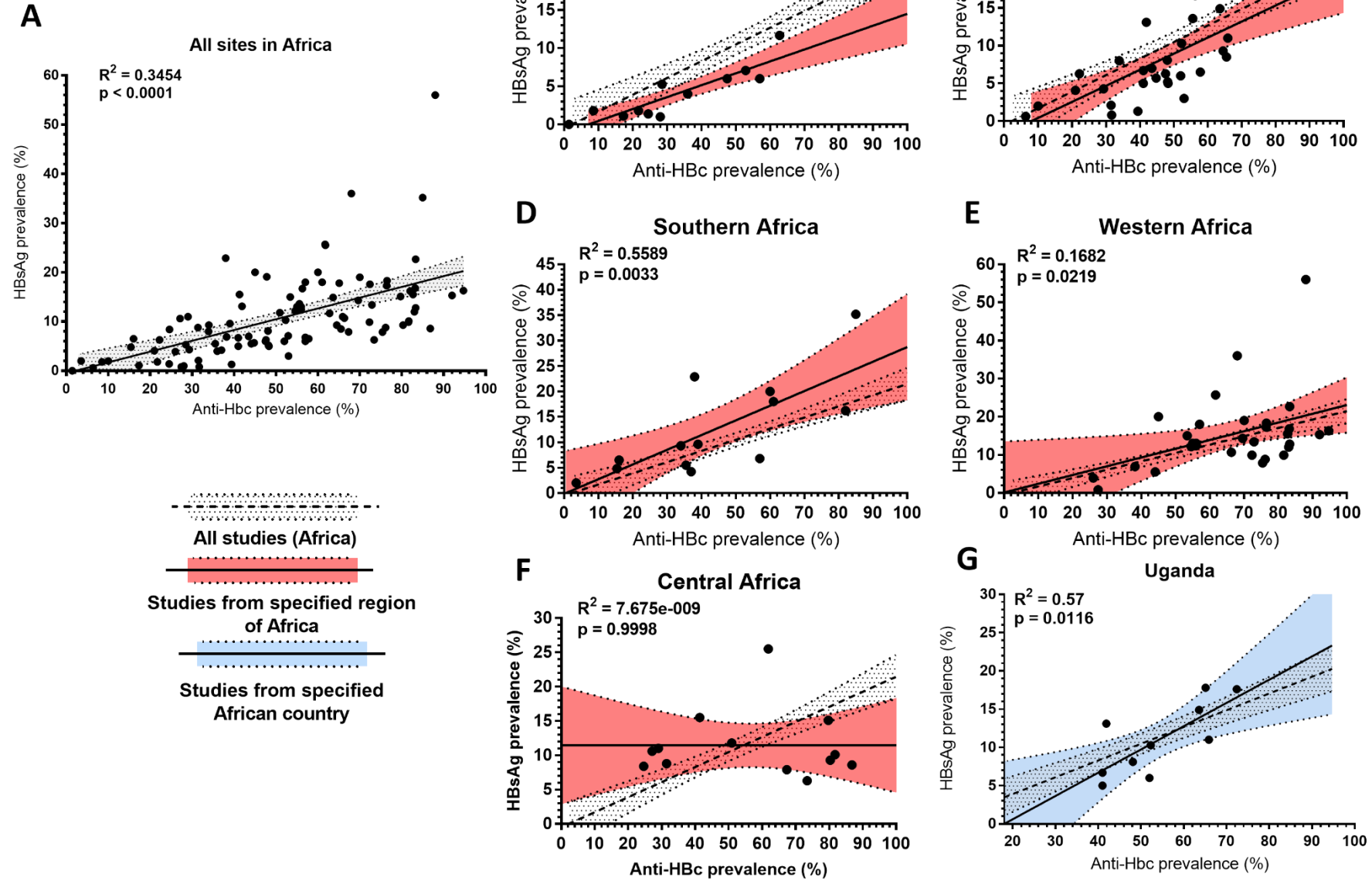
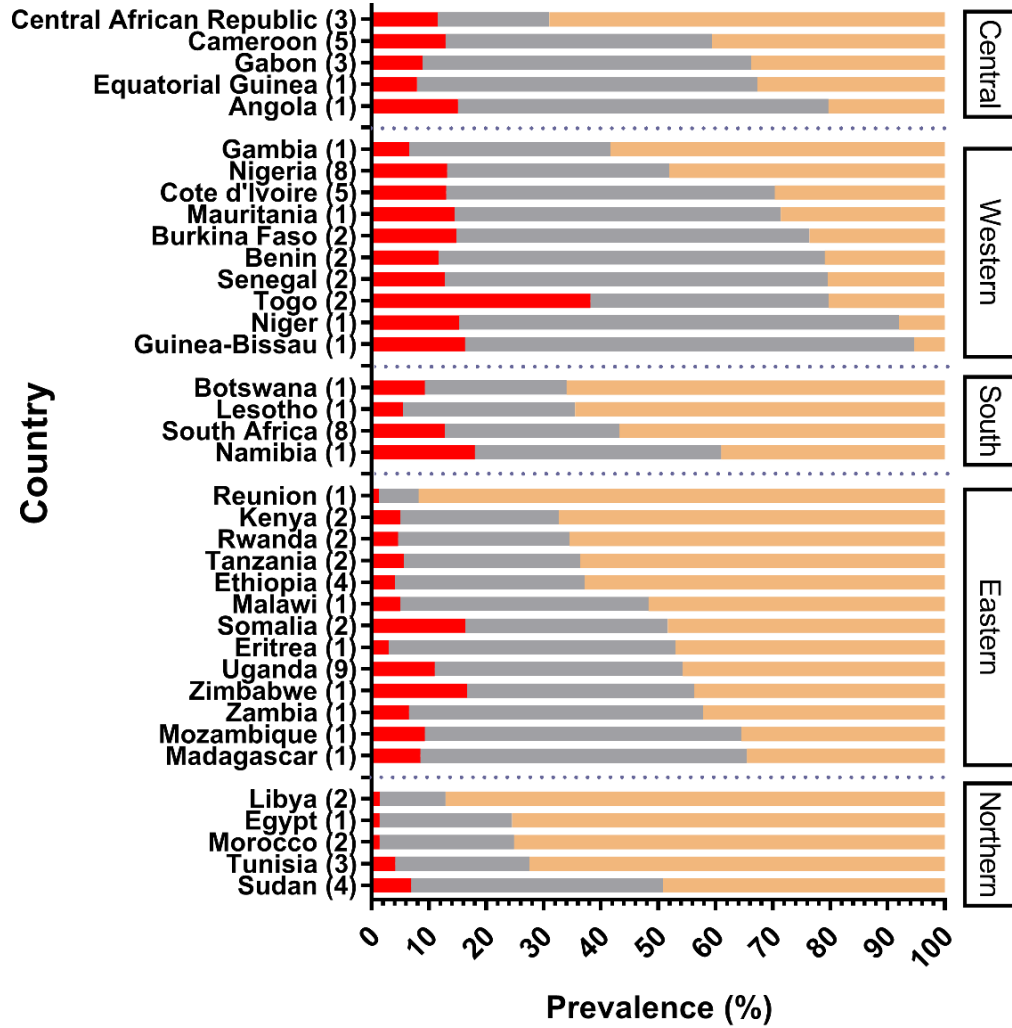




Figure 3

**A**



**B**

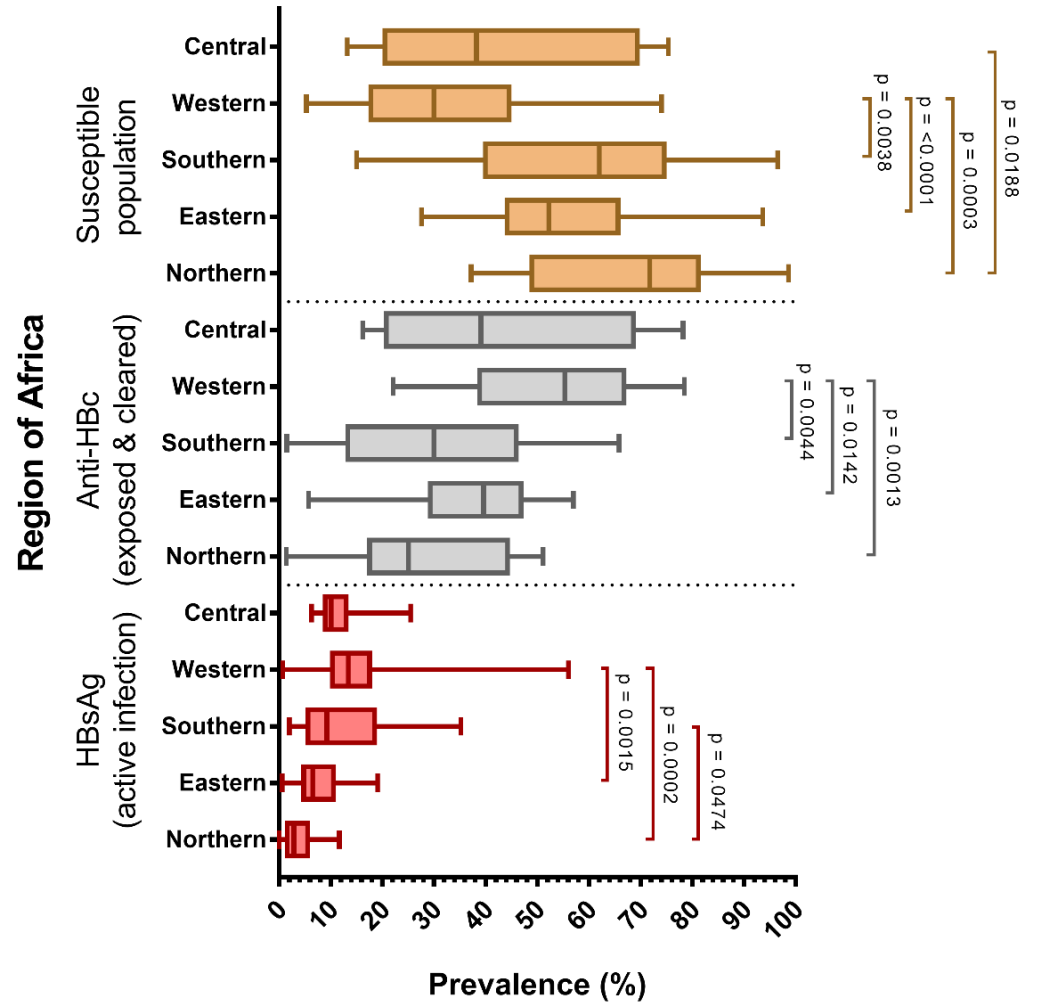
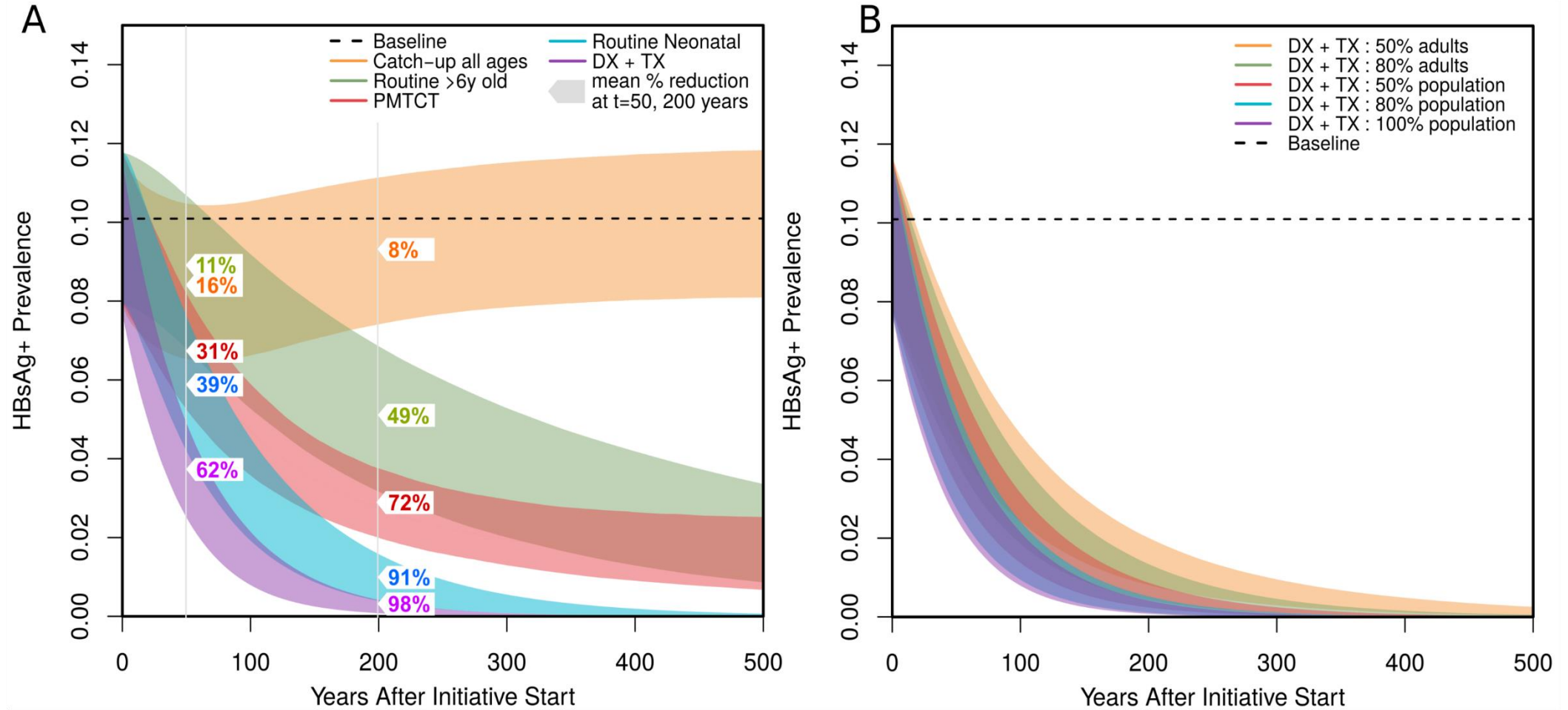
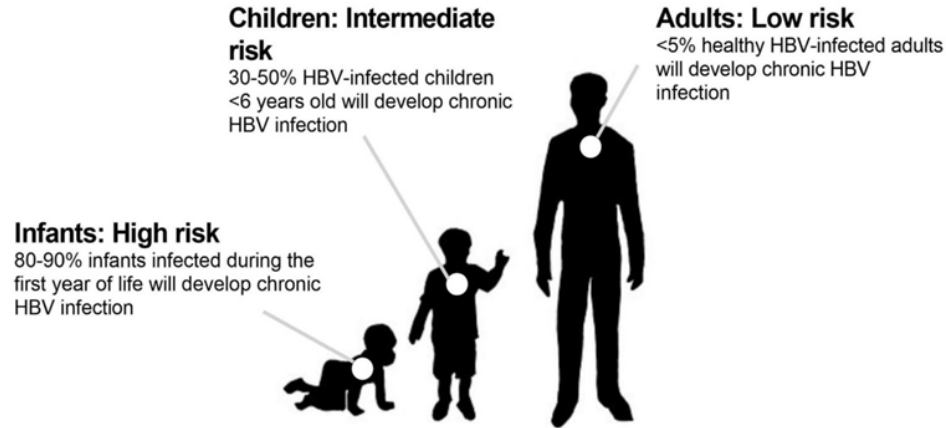


Figure 4



**Figure 5**

**A**



**B**

