Invited article

South African Gastroenterology Review

Sustainable Development Goals for HBV elimination in South Africa: challenges, progress, and the road ahead

Tongai G Maponga[1], Chikezie Nwankwo[2], Philippa C Matthews[3,4*]

[1] Division of Medical Virology, Stellenbosch University, Francie van Zijl Avenue, Cape Town, 7505, South Africa

[2] Division of Gastroenterology, Tygerberg Hospital, Cape Town, 7505, South Africa

[3] Department of Infectious Diseases and Microbiology, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK

[4] Medawar Building for Pathogen Research, Nuffield Department of Medicine, University of Oxford, South Parks Road, Oxford OX1 3SY, UK

* Corresponding author: philippa.matthews@ndm.ox.ac.uk

ABSTRACT

International Sustainable Development Goals set ambitious elimination targets for hepatitis B virus (HBV) infection by 2030. We here set out to review barriers, challenges and opportunities for progress towards these goals, with a particular focus on South Africa. Although many African populations still have a high prevalence of HBV infection (defined as ≥8%), interventions and planning have been hampered by limited data. The majority of HBV infections (>90%) currently remain undiagnosed, and - even when a diagnosis is made - cases are not well stratified to determine prognosis, risk of transmission, and treatment eligibility. Nucleos(t)ide analogues can be successful in suppressing the virus but must generally be taken life-long, and there are concerns around the possible emergence of drug and vaccine resistance. Poor funding, advocacy and education, and the stigma associated with infection represent further barriers. Despite these diverse challenges, we are in an era of opportunity to advance South Africa's progress towards elimination goals. Widespread deployment of the HBV vaccine in infancy has already markedly reduced paediatric infection, and birth dose vaccinations will further reduce the risk of vertical transmission. South Africa can capitalise on the laboratory and clinical infrastructure that already supports HIV diagnosis and treatment, by expansion of services to include HBV. HBV treatment and diagnostics are now on WHO lists of essential drugs and equipment. In the decade ahead, South Africa can make significant advances, but this will require sustained attention and investment from stakeholders in policy, public health, clinical care, and basic science.

KEY WORDS: HBV, hepatitis B virus, South Africa, Africa, elimination, Sustainable Development Goals, vaccination, PMTCT, treatment, cost

ABBREVIATIONS

- 3TC Lamivudine
- ALT Alanine aminotransferase
- APRI Aspartate aminotransferase to platelet ratio index
- ART Antiretroviral therapy
- BD Birth dose
- cccDNA covalently closed circular DNA
- CHB Chronic Hepatitis B virus infection
- DBS Dried blood spot
- ETV Entecavir
- GAVI Global Alliance for Vaccines and Immunization (now known as the Vaccine Alliance)
- GHSS Global Health Sector Strategy
- GLOBOCAN Global Cancer Observatory
- GPR Gamma-glutamyl transpeptidase to platelet ratio
- HBeAg Hepatitis B virus e-antigen
- HBIg Hepatitis B Immunoglobulin
- HBsAg Hepatitis B virus surface antigen
- HBV Hepatitis B virus
- HCC Hepatocellular carcinoma
- HCV Hepatitis C virus
- HCW Healthcare worker
- HDV Hepatitis Delta virus
- HIV Human Immunodeficiency virus
- IFN Interferon
- LFTs Liver function tests
- MSM Men who have sex with men
- MTCT Mother to child transmission
- NA Nucleos(t)ide analogue
- PCR Polymerase Chain Reaction
- PEPFAR President's Emergency Plan for Aids Relief
- PMTCT Prevention of mother to child transmission
- POCT Point of care test
- PWID People who inject drugs
- RT Reverse transcriptase
- TAF Tenofovir alafenamide
- TDF Tenofovir Disoproxil Fumarate
- SA South Africa
- sSA sub-Saharan Africa
- SDG Sustainable Development Goals
- UN United Nations
- VL Viral load
- WHO World Health Organisation
- YLL Years of Life Lost

1. EPIDEMIOLOGY OF HBV INFECTION

1.1 Global HBV Epidemiology

Hepatitis B virus (HBV) is currently responsible for an estimated global burden of 260-290 million chronic infections,[1,2] of which 60-80 million are in Africa.[2,3] Global Burden of Disease studies have highlighted an increase in the number of deaths attributable to viral hepatitis over time, with a disproportionate burden of disease occurring in low and middle income countries,[2,4–6] such that by 2015, viral hepatitis was the 7th leading cause of mortality worldwide, above tuberculosis, malaria and HIV.[7] In keeping with the rise in HBV cases, a substantial proportion of the global burden of hepatocellular cancer (HCC) is attributable to chronic HBV infection (CHB),[8,9] such that HCC now ranks the second biggest cancer killer in sub-Saharan Africa.[10] Unlike most other cancers, HCC incidence and mortality is increasing over time.[4,11]

1.2 South African HBV epidemiology

The current estimated burden of CHB in South Africa is 3.5 million cases,[12] representing a population prevalence of 6-9% in different population groups.[13,14] This estimated epidemiology may be skewed by gaps in data, and selective sampling of particular groups. The distribution of infection varies substantially by region, risk factors, sex and age, and certain groups (pregnant women, healthcare workers (HCW), HIV-infected cohorts and blood donors) are over-represented by the current literature.[3] The variability in HBsAg prevalence across South Africa is exemplified by studies reporting rates of 2-16% in HIV-negative adults,[15,16] 10% in a cohort of HCW,[17] and as high as 35% reported in a cohort of HIV positive adults.[16] In many HBV cohorts, men outnumber women (typically by a factor of 1.5-2:1),[3,18] and men are also more likely to meet eligibility criteria for treatment,[18] and to develop hepatocellular carcinoma,[9] suggesting biological differences between the sexes in response to infection.

Exposure to HBV infection early in childhood is associated with the highest risk of chronic infection (estimated as >90%).[19] The changing age structure of populations, a process referred to as 'demographic transition', may contribute to reductions over time in the population burden of HBV infection in Africa,[20] although this effect has not been specifically evaluated for South Africa.

1.3 HBV transmission in South Africa

Mother to child transmission (MTCT) of HBV is typically associated with high maternal viral loads and HBeAg-positivity. Although these features are most consistently seen in association with genotypes B and C infection (predominant in Asia), and somewhat less characteristically associated with genotypes A, D and E (prevalent in Africa), MTCT nevertheless represents an important transmission route across the African subcontinent.[21,22] In Africa, horizontal HBV transmission within households is also reported as important in contributing to infections acquired early in life;[23] however, evidence for the specific nature and timing of these transmission events remains lacking.[24] Enhanced transmission is also recognised within other high risk groups, including men who have sex with men (MSM), HCWs, and sex workers,[14,25] but the extent to which these groups contribute to overall transmission at a population level has not been robustly assessed.

South Africa benefits from a high rate of blood donations compared to other African countries (estimated 18 donations per 1000 population per year), but ongoing efforts are required to assure a supply of voluntary, non-renumerated donors.[26] The risk of transmission of blood-borne viruses through blood transfusion has fallen sharply, in parallel with improvements in consistency and sensitivity of screening donations since the early 1980's, funded by the WHO, the Global Fund and the US President's Emergency Plan for Aids Relief (PEPFAR).[25] However, due to the long window period for the detection of anti-HBc antibody and HBsAg after acute

infection (up to 50 days), and the potentially reduced sensitivity of nucleic acid testing arising as a result of low viral loads in HBV infection, the overall sensitivity of screening donated blood for HBV remains substantially lower than for either HIV or HCV.[27] Furthermore, robust screening is dependent on widely available, quality assured laboratories.[28] An alternative approach, explored and shown to be cost-effective by a European study, is to mandate vaccination of blood donors against HBV infection following confirmation of negative antiHBc and HBsAg status.[27]

1.4 Rates of HBV diagnosis and treatment

The success of diagnosis and treatment is often represented as a 'cascade of care', starting with the total pool of infected individuals, and then considering serial reductions in those who are diagnosed, accessing care, on treatment, and virally suppressed.[29,30] Based on current data from the Global Burden of Disease study for the WHO African region, <0.3% of HBV has been diagnosed and among those eligible for treatment, fewer than <1% are accessing it.[14]

1.5 Gaps in epidemiological data

At present, there are wide confidence intervals around estimates of vaccine coverage, prevalence of infection in different geographical settings and population groups, incidence of HCC, and mortality attributable to HBV infection.[14] Given the regional differences, lack of reliable data, and poor ascertainment of new cases, careful study of local epidemiology is crucial to identify regions of high prevalence, and to determine where and when transmission events are occuring. Detailed country- and region-specific data are important to inform interventions that are targeted specifically to the needs of different populations.[31,32]

2. HBV ELIMINATION TARGETS

In recognition of the substantial burden of morbidity and mortality caused by viral hepatitis, United Nations Sustainable Development Goals have set ambitious challenges for the

elimination of these infections as a threat to public health by the year 2030.[33] The Global Health Sector Strategy (GHSS) for viral hepatitis was established in 2016,[34] leading to the establishment of specific targets for HBV, including a 90% reduction in new infections, a 65% reduction in deaths attributable to viral hepatitis by 2030, and a reduction in prevalence in children aged under 5 years to 0.1%. Progress in vaccination and prevention of mother to child transmission (PMTCT) can be specifically assessed by monitoring this paediatric target.[35] Incidence is more challenging to monitor, as the majority of acute infections are asymptomatic, particularly in children.[21]

Compared to other infectious diseases that cause a comparable burden of morbidity and mortality, HBV has been neglected by funders, advocacy, research and clinical care.[29] Large strides are now needed if meaningful progress is to be made towards elimination targets. In order to promote progress, high profile international assessment and recommendations have recently been published for both HBV and HCV infection.[14] These set out proposed indicators for tracking the progress in interventions, with metrics that include the proportion of the population receiving timely birth dose HBV vaccine and third dose vaccine, proportion of all blood donations screened, proportion of those with CHB who have been diagnosed, coverage of treatment among eligible individuals, and coverage of needle/syringe distribution for people who inject drugs (PWID).[14]

3. BURDEN OF DISEASE

3.1 Assessment of liver disease

One approach to making progress towards elimination targets is to improve management of the established burden of HBV disease, thereby reducing transmission and lowering mortality.[14,25,32] Assessment for the presence and severity of HBV-associated liver disease in the form of fibrosis, cirrhosis or liver cancer is recommended using liver function tests (LFTs), HBV viral

load, detection of HBeAg, fibrosis scores derived from laboratory blood tests, imaging, and/or liver biopsy.[36] WHO guidelines suggest at least one annual measurement of HBsAg, HBeAg, HBV viral load, ALT, and either elastography or APRI (aspartate aminotransferase to platelet ratio index), with more frequent monitoring suggested for individuals at elevated risk of disease progression.[37]

LFTs are cheap and widely available, but are non-specific, can be insensitive for liver disease,[36] are poorly calibrated for application to African populations,[38,39] and serial monitoring is required to determine whether persistent liver inflammation is present. Fibrosis scores are intended to provide an assessment of liver fibrosis, but have varying degrees of sensitivity and specificity in different settings. The gamma-glutamyl transpeptidase to platelet ratio (GPR) is suggested by one West African study as being more accurate than other scores to predict liver fibrosis in CHB infection,[40] and a new score has recently been proposed to assess eligibility for HBV treatment, combining ALT and HBeAg status.[41] Further research is needed to optimise scoring systems that are sensitive for liver disease in the setting of HBV infection.

Transient elastography (an ultrasound-based approach to measurement of liver stiffness) is well established as part of the assessment criteria for treatment, but is not universally available. Other imaging such as ultrasound and cross-sectional imaging is more expensive and less commonly available. Liver biopsy is not available in all settings, as it requires skilled practitioners and supporting infrastructure, but South African guidelines represent the potential importance of collecting biopsy data, as ALT may be relatively normal even in the setting of high HBV DNA viral loads.[36] An interesting recent development is the demonstration that fine needle aspiration of the liver is safe and well-tolerated; although this approach does not allow evaluation of liver architecture, with additional experience it may become a strategy that permits assessment of cellular populations and immuno-phenotyping of liver tissue.[42]

To date, viral genotyping is not usually done as part of routine clinical assessment, but it is recognised to have bearing on prognosis, response to treatment, and transmission potential.[43] Current South African guidelines do endorse viral genotyping,[36] and this practice may have an increasing role in patient stratification for treatment.

3.2 Hepatocellular Carcinoma (HCC)

The incidence of HCC in South Africa is likely to be under-estimated due to poor registration of cases,[11] as many individuals with HCC present late and die without the formal tissue diagnosis that is required for the pathology-based National Cancer Registry of South Africa.[25,44] In South Africa, the majority of HCC cases are accounted for by CHB and incidence is highest in males of black ethnicity, between the age of 30-40 years, with genotype A or D infection.[9,45] Global Cancer Observatory (GLOBOCAN) estimates that the age standardized incidence rates (SIR) for primary liver cancer in South Africa (75%-85% of which is HCC) are 7.6/100,000 persons/year among males and 3.3/100,000 persons/year among females.[46] These incidence rates are closely mirrored by age-standardized mortality rates (7.2/100,000 and 3.1/100,000 persons/year among males and females respectively), as a result of low rates of diagnosis and treatment of chronic hepatitis infections and late presentation of malignancy.[47]

3.3 Co-Infection with other blood borne viruses

The overlap of the epicentre of the global HIV pandemic with regions of high HBV endemicity in South Africa make HIV/HBV co-infection common.[48] The precise nature of the interplay between these viruses in chronic infection is difficult to establish, as reports differ between contexts and populations.[48] However, if untreated, HIV infection is likely to be a risk factor for higher HBV viral load, increased risk of vertical transmission, and increased risk of death from liver disease, while HBV may also accelerate HIV disease.[25,48]

The overall burden of HCV infection in South Africa is low, making co-infection relatively uncommon.[48,49] However, in specific high-risk groups, such as MSM and PWID, HCV exposure and infection is more common,[50] leading to a higher chance of HBV/HCV co-infection. In HCC cohorts, there is an enrichment of both HBV and HCV infection,[51] so clinicians should be vigilant to the potential for co-infection. In South Africa, HDV co-infection is rare in the setting of CHB.[52,53] From a clinical perspective, scrutiny for the presence of HDV coinfection should remain important for individuals who originate from elsewhere in the continent, particularly central and West Africa,[53] as HDV infection is typically associated with accelerated liver disease.

3.4 HBV mortality

The Global Burden of Disease data for 2016 suggests that the years-of-life-lost (YLL) from cirrhosis and and chronic liver diseases due to hepatitis B were 43,260. In contrast to the greater health burden of CHB in South Africa, YLL due to HCV were 17,960.[54] The YLL from HBV infection in South Africa between 1990-2016, are compared to regional data in Figure 1.

4. HBV VACCINATION AND PMTCT

4.1 Routine infant HBV vaccination

Major gains in reducing the childhood prevalence of HBV infection have been made through the inclusion of the vaccine in the WHO Expanded Programme on Immunization (EPI),[55] introduced in South Africa in 1995.[24] To date, in South Africa (and many other countries in sSA), this vaccine has been delivered as a component of heptavalent or hexavalent immunisation routinely administered at six weeks of age. At present, total vaccine coverage with three doses is estimated at 75%, with birth dose vaccine coverage in Africa estimated at only 10%,[56] so major efforts will be required to bring total coverage up to the target of 90%.[28]

In recent studies of children in the Northern Cape and in KwaZulu Natal, <1% were infected, demonstrating the success of this vaccine campaign in preventing infections early in life.[57–59] In these studies, HIV-infected children were highlighted as being at additional risk, with lower vaccine-mediated antibody titres,[58] and higher rates of HBV infection,[59] compared to their HIV-negative counterparts. However, this relationship may change over time, as anti-retroviral therapy (ART) is now routinely started for all HIV-infected children, improving population-level immunity.[58]

4.2 Prevention of mother to child transmission (PMTCT)

PMTCT can be considered in four domains, comprising antenatal screening, treatment of HBV-infected pregnant women with tenofovir, Hepatitis B Immunoglobulin (HBIg) for high risk infants, and accelerated infant HBV vaccination (starting with a birth dose, BD). While antenatal HBV screening is actively advocated by WHO guidelines, it has not been incorporated into South African guidelines for routine practice, and coverage is therefore patchy.[60] Improved, consistent antenatal screening would be a positive aspiration for maternal and child health in South Africa, but must be followed up with linkage to care for HBsAg-positive mothers. A recent literature review of PMTCT interventions for Africa concluded that the most cost-effective strategy is universal three dose infant vaccination, including BD immunisation.[61] Delivery of BD vaccine also presents a valuable opportunity for education, screening and data collection.[61]

Recognition of the risks of delaying the first vaccine dose have prompted a move towards a universal monovalent BD vaccine in South Africa.[22] This process is complicated by the need for procuring monovalent HBV vaccine, and will require enhanced efforts to ensure high coverage, particularly for infants born outside healthcare settings.[62] A 2018 report states that fewer than 50% of all births in South Africa were registered at healthcare facilities,[63] suggesting many births

still take place at home or in the community, while another report suggests that 10% of births occur outside health facilities.[64] Recognition that existing vaccines have a period of stability outside the cold chain is important,[62] while longer-term availability of HBV BD vaccines that are less dependent on the cold chain will improve coverage for babies born outside health facilities.[65,66] In order to be a success, this needs to be coupled with the training of community-based or traditional midwives. GAVI's vaccine plan for 2021-2025 includes consideration of funding for widespread HBV BD vaccination.[62,67]

HBIg administration to high risk infants at birth is expensive, requires a robust cold-chain, and is not available in most settings across sSA.[21] There is some evidence suggesting that consistent three-dose vaccination, starting at birth, may be as effective as HBIG in PMTCT,[68] so it is reasonable for the priority for South Africa to be to focus primarily on optimisation of vaccine schedules,[22] rather than on attempts to procure and fund HBIg.

4.3 Barriers to success of immunisation campaigns

Although infant vaccination is a cornerstone of population-level interventions, there are nonetheless barriers to the deployment, cost-effectiveness and impact of immunisation campaigns. In some settings, high prevalence of HBV infection has prompted extended use of vaccinations, including deployment of 'catch up' campaigns for adolescents and adults. This intervention should be undertaken with caution, as high rates of exposure and infection in adults correspond with a proportionately small population of susceptible individuals, and resources in this situation may be better allocated to diagnosis and treatment.[58] Beliefs and behaviour are strong determinants of the acceptability of vaccine campaigns, and it is important to consider not only the logistical and financial aspects of immunisation campaigns but also cultural and societal factors that may influence uptake.[69,70]

4.4 Evidence from modelling studies

Modelling studies provide projections of HBV interventions over time.[58,71] Although vaccination and PMTCT are powerful strategies, projections suggest that in the setting of the large population reservoir of undiagnosed and untreated infection, continuation of these programmes in isolation will not be sufficient to achieve elimination goals.[71,72] These predictions are supported by epidemiological data that actually suggest a slight rise in HBV prevalence in South Africa over time.[13] Together, this evidence points to the need for enhanced use of existing strategies, together with additional efforts in diagnosis and treatment, and investment in cure strategies for long-term success.

5. HBV DIAGNOSIS

5.1 Clinical laboratory diagnostics and monitoring for HBV infection

The WHO 'Essential Diagnostics List', published for the first time in May 2018,[73] includes consumables for HBV testing, recognising the crucial role that diagnostics play in managing the existing burden of infection and supporting progress towards elimination targets.[14] In most settings, conventional diagnostic testing for HBV infection relies on HBsAg detection, undertaken either from serum samples in a clinical laboratory, or as a point of care test (POCT).[74] Diagnosis can also be made from dried blood spot testing (DBS), although this may not be as sensitive as testing serum.[75,76] HBeAg antigen testing is typically employed as a surrogate marker for high viral loads, but may perform less well for this purpose in populations where there is a high prevalence of HBV genotypes A1 and D which are more frequently associated with HBeAg negativity, particularly in patients under age 30 years.[77] In this setting, the absence of HBeAg does not necessarily mean reduced infectivity, and does not correlate well with clinical end-points such as HCC incidence.[78]

POCT for HBV has been specifically evaluated in both community[18] and antenatal settings; it is well accepted, and can be implemented alongside routine screening for HIV and syphilis.[79] The caveat of reliance on HBsAg for screening is that cases of occult infection are missed (HBV DNA+ / HBsAg-). Assessment of eligibility for treatment, and identification of antenatal women who are at the highest risk of vertical transmission, conventionally depend on further evaluation with either HBV DNA quantification (viral load) and/or HBeAg testing, both of which require centralised clinical laboratory facilities. The additional cost of infrastructure, manpower and resources means that access to these additional tests are often limited.[80] For this reason, an alternative approach that has been considered is to screen only for HBsAg and to treat all pregnant women who test positive (without further stratification) with TDF during trimester three, in addition to immunising their infants with accelerated birth dose vaccination.[81] Further evaluation of the costs, risks, benefits and acceptability of this simplified approach is required in real world studies.

5.2 New approaches to HBV diagnosis and monitoring

A welcome development is the availability of the Xpert HBV Viral Load test,[82] which can be easily integrated on the GeneXpert platform that is being widely-used for the diagnosis of TB and determining HIV viral loads.[83,84] However, the GeneXpert platform has high costs.[80] A cheaper alternative for viral load testing are quantitative real-time PCR tests that have been positively evaluated in West Africa.[85]

New ‘third generation’ sequencing platforms offer longer-term options for diagnostic testing that also provides other valuable data for individual patients and public health purposes. Nanopore sequencing (Oxford Nanopore Technologies, https://nanoporetech.com/) can be used to generate full length HBV viral sequence, providing not only a portable diagnostic test but also information about drug and vaccine resistance mutations, genotype of HBV infection, detection

of viral polymorphisms that may influence disease outcomes, and the potential for phylogenetic reconstruction to provide new insights into transmission networks.[43,86] While further optimisation and field testing will be necessary before such approaches can be deployed in practice for HBV, the approach has already yielded rapid changes in practice in other fields, as epitomised by TB diagnostics.[87]

6. TREATMENT OF CHRONIC HBV INFECTION

6.1 Eligibility for therapy

The requirement for HBV treatment is conventionally assessed as described in section 3.1. Viral load testing and Fibroscan require infrastructure, hardware and trained staff, and are frequently not available, so the proportion of individuals meeting the threshold for treatment is currently not known in many settings.[28] For this reason, there may be pragmatic grounds for simplified assessment, and in the case of PMTCT, provision of antiviral treatment to all antenatal women who test HBsAg-positive could be a cost-effective strategy.[81] Outside the specific setting of PMTCT, there has been debate about more inclusive criteria for treatment, and conversely some interest in the idea that in some situations treatment could be safely stopped.[88–90] Based on the different epidemiology and disease outcomes in different populations, and taking account of local infrastructure, resources, facilities, and constraints, these are questions that still need careful evaluation in different settings.

6.2 Choice and availability of therapy

Antiviral therapy comprises either pegylated interferon-α (IFN-α) or nucleos(t)ide analogues (NA's),[36] namely Tenofovir Disoproxil Fumarate (TDF), lamivudine (3TC), or entecavir (ETV). IFN-α can induce clearance of HBsAg, which is most likely to be successful in patients with hepatic necroinflammation.[36] Unfortunately, the rate of IFN-α-mediated clearance is typically low, and treatment is often not well tolerated.

TDF is typically now the first-line NA therapy, being affordable, accessible, well tolerated, safe in pregnancy, and with a high genetic barrier to drug resistance.[91,92] TDF is also part of the backbone of first-line ART for HIV,[93] so no change is required to the ART regimen in individuals with HBV/HIV co-infection. Reflecting its essential place in treatment of both viruses, TDF is now included in the WHO essential medicines list.[94] While this overlap of drug regimens can make selection of therapy - and compliance with long-term treatment - easier in the setting of co-infection, the widespread use of ART in southern Africa also raises possible concerns for the selection and persistence of drug resistant viral variants.[95] Despite being widely used for HIV treatment across sSA, TDF is not always easily available as monotherapy, being more readily accessed as a component of combined ART.[32,80] Indeed, a study conducted in the Western Cape suggested that patients with HBV/HIV co-infection had better liver disease status compared to those with HBV alone, as the co-infected group are more likely to be both on antiviral therapy and under clinical scrutiny.[96]

Despite its widespread use, TDF is not always an appropriate choice. Tenofovir alafenamide (TAF) is an alternative formulation that is less nephrotoxic, and has less impact on bone mineral density, making it an appealing option particularly for more elderly patients or those with pre-existing renal disease.[97] Monotherapy with 3TC is no longer advocated, due to the high rate of selection of drug resistance. Currently, ETV is too expensive for both the public and private health sectors in South Africa. In practice, neither TAF nor ETV are widely available, and to manage toxicity a reduced dose of TDF may be the best option. In some patients, TDF fails to suppress HBV viraemia, even when the patient is fully compliant with therapy. There are some animal data,[98] and *in vitro* evidence [99] for a synergistic effect on HBV suppression when TDF is combined with other NA's, and combination therapy with two agents may be employed,[100] although this is not underpinned by guidelines or robust evidence.[101] In the long-term, access to

second-line treatment options and improved evidence for drug combinations will improve success, safety and tolerability of antiviral therapy.

6.3 Drug Resistance

HBV resistance associated mutations (RAMs) are best reported from patients on 3TC treatment, where >90% of viruses have been reported to contain mutation(s) at 5 years, most commonly the M204I/V substitution in RT.[95,102] The genetic barrier to TDF resistance is high, but there are emerging data to support the possibility of drug resistance,[95,100] and further scrutiny is needed to establish the extent to which this may be of clinical significance. There are few data describing the rate of viral suppression following commencement of TDF therapy, but a meta-analysis of studies of HIV/HBV coinfection describe HBV viraemic suppression in only 57%, 79% and 86% at one, two and three years, respectively.[103]

The distribution of HBV drug resistance across sub-Saharan Africa has been described,[95] but the data are patchy and the literature is strongly biased by most studies focusing on HIV/HBV co-infected populations. Prospective studies, including a clear focus on HBV mono-infection, will be important in determining the epidemiology and clinical significance of drug resistance, supported by scale-up of diagnostic infrastructure that supports viral sequencing.

6.4 Strategies for HBV cure

Although NA therapy is successful in bringing about viraemic suppression in the majority of patients, it does not typically result in clearance of HBsAg, due to the hepatic reservoir of covalently closed circular DNA (cccDNA) that becomes established in the nuclei of infected cells.[43] While ‘functional’ cure (disappearance of HBsAg) is a desirable end-point, it is still associated with the potential risk of future relapse due to cccDNA reactivation. The ultimate aspiration for cure strategies is therefore to deliver ‘sterilising’ cure (complete removal of

cccDNA from the liver). At present these terms are theoretical, as there is no clinical test that can differentiate between the two endpoints.

Due to the long time-frames projected for current interventions to deliver population-level elimination of HBV infection, and the low rates of HBsAg clearance even in treated populations, there has been an enhanced focus on cure strategies. In recent years, direct-acting antiviral therapy has been a high profile success for HCV infection,[104] but curative therapy for HBV currently remains elusive. There is active investigation in a range of approaches targeting different aspects of the HBV replication cycle (summarised in the 2017 Conference on Viral Hepatitis report)[30], including entry inhibitors (Myrcludex), immunotherapeutic advances,[105,106] and/or drugs that aim to reduce or eliminate the cccDNA reservoir.[106]

6.5 HBV treatment as prevention

The public health benefits of treatment to prevent transmission have been widely applied to HIV.[107] The concept has not been so widely pursued for HBV, although the fundamental importance of diagnosis and treatment is enshrined in many recommendations and policy documents.[14,25,30,60] At present, there are few real world data to support this approach for HBV,[80] but an economic evaluation in The Gambia reports that screening and treatment are cost-effective,[108] and modelling projections suggest population-level benefits in reducing HBV prevalence through widespread treatment.[58] Another study that evaluated all the published evidence in order to produce an economic evaluation of testing and treatment did not reach firm conclusions, due to the limitations of too few data.[109]

One approach to improving deployment of treatment is to focus on high risk groups who are likely to contribute the most to generating new infections, either as a result of behaviour, child-bearing, and/or high viral loads. The latter group is often identified through expression of

Hepatitis B e-antigen (HBeAg), and it may be prudent to divert increased resources to this group, normally representing approximately 25% of the population with CHB.[48]

7. STRUCTURE OF SERVICES

South Africa has the largest HIV management program in the world due to the high number of HIV infections. The success of the program and the infrastructure that has been set up can be leveraged for other health challenges, including viral hepatitis.[14,110] HBV interventions can also be successfully deployed alongside other services, such as maternal health and cancer prevention programmes.[62] Efforts will be needed to link HBV-infected individuals into structured care, supported by appropriately educated and trained staff.

8. EDUCATION AND ADVOCACY

Lack of education among the public, patients and HCW has been highlighted as a barrier to HBV diagnosis and treatment.[111] Stigma and discrimination (or the fear of these responses) can have a powerful influence in deterring diagnosis, care-seeking, and adherence to treatment.[111,112] To date, there are very few robust assessments of the nature and impact of stigma for HBV, and more data are needed to identify the extent of this problem and determine the best ways to tackle it. In contrast to HIV, the social and political profile of HBV is very low. This could be improved by public role models with HBV infection, and mass media campaigns that capitalise on radio, television and social media.[111]

9. POLICY AND INVESTMENT

9.1 National and International Strategy for Viral Hepatitis

A large international review highlights the need for country-specific approaches to viral hepatitis planning.[14] For South Africa, this is emerging in the form of an evaluation estimating the impact of a five-year National Investment Plan,[60] focusing on HBV birth dose vaccination, HBV PMTCT,

and HBV treatment, as well as incorporating new direct acting antiviral (DAA) treatment for HCV as part of an integrated overall approach to chronic viral hepatitis infections. The results of the analysis, comprising multi-disciplinary analysis of cost, impact, cost-effectiveness and financing were presented at the World Hepatitis Summit in Brazil in 2017.[113] Interim assessments will be required ahead of the 2030 deadline, with a previous suggestion for a progress review in 2020.[25]

On the international stage, there have been calls for sustainable financing,[56] and for the development of a global coalition for viral hepatitis that could unify recommendations and strategy, improve data management, provide technical advice and assistance, and advocate for resources, thereby adding efficiency and reducing duplication of efforts.[62] The requirement for both focused, national strategies and a co-ordinated international effort was summarised by the strapline of 'thinking globally, acting locally' at the 2017 International Conference on Viral Hepatitis.[30]

9.2 Cost of South Africa's national plan

Implementing these national recommendations is estimated to require ZAR3.8 billion (US$294 million) over five years. Overall, this represents less than 1% of total government health expenditure. Based on the anticipated health benefits, the impact of this expenditure has been been formally evaluated and is deemed cost effective at US$ 5021/DALY for HBV (based on reference to benchmark GDP = US$7620/capita), a prudent use of limited resources, and feasible within the national health budget.[60] This finding is mirrored by other large analyses that consider the cost effectiveness of elimination strategies.[62]

10. CONCLUSIONS AND NEXT STEPS

This review highlights the diverse challenges and opportunities that face the HBV elimination campaign in South Africa (summarised in Table I). Although we have a safe, effective vaccine, and oral antiviral drugs that are cheap and well tolerated, these strategies are predicted to take many decades to bring about elimination - and only then if high population coverage is maintained. Ultimately, a cure strategy may be needed to achieve elimination targets. However, there are many opportunities to be embraced in the decade ahead, with gains to be made through implementation of BD vaccine, enhanced diagnostic testing and linkage to treatment, ongoing education and advocacy, and investment in clinical and basic science research.

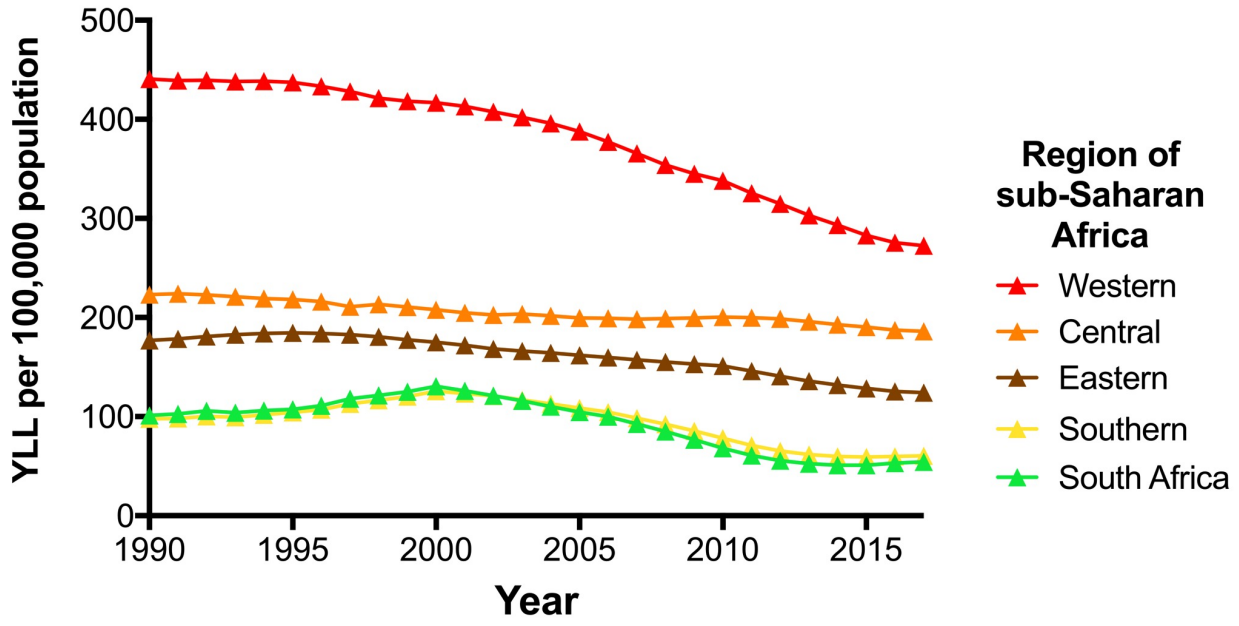
Table I: Challenges and opportunities for tackling HBV in South Africa

Domain	Challenges	Opportunities
Epidemiology	● There is a current lack of reliable, up-to-date data for many parts of sub-Saharan Africa, including limited information about sub-groups that are underpin most transmission.[14] ● Elimination targets variably focus on prevalence, incidence and mortality, which may be achieved at different rates using different approaches.[72] ● Determination of incidence is difficult as acute infection is frequently asymptomatic. ● It is difficult to measure deaths attributable to HBV, as infection is frequently undiagnosed. ● There is poor registration of HCC, as cancer frequently presents late and treatment is palliative.[44]	● Improved data can be collected through serosurveys and diagnostics, including identification of high risk groups.[32] ● Basic serology is widely available, and other tests including POCT and dried blood spot testing can be applied.[75,79] ● More studies will arise as a result of the South African Action Plan, including an analysis of antenatal HBV prevalence.[60] ● Increasing application of mathematical models,[58,71] founded on real-world data, will underpin projections that inform prevention strategies.
Prevention	● There is currently a lack of widespread screening, including gaps in specific groups (e.g. need to enhance efforts in antenatal screening) ● Multivalent paediatric vaccines, with the first dose delayed until age 6 weeks, leave a window of opportunity for perinatal transmission.[22] ● Catch up vaccine campaigns may not be effectively deployed to target the right groups, and may have little impact at a population level.[25]	● Introduction of a monovalent birth-dose vaccine is planned. ● Significant efforts are required to reach babies born outside healthcare settings,[62] and to maintain three-dose coverage. ● 'Treatment as prevention' can be deployed as a powerful population level intervention,[14,60,108] reducing transmission as well as benefiting individual patients. ● Better vaccination coverage is needed for high risk groups (MSM, HCW, sex workers, household contacts of HBsAg-positive individuals).[17] ● Screening of blood products has improved significantly, reducing transmission through transfusion, but further improvements are required to ensure consistency of screening and supply of appropriate donors.[26]
Diagnosis	● >90% of adults with the infection are currently unaware of their status. ● Lack of education, costs, and	● Existing diagnostic tests are on the WHO essential diagnostics list.[73] ● New affordable approaches to diagnosis and patient stratification

	stigma may be barriers to testing.[25,111] ● Over-reliance on HBsAg as a screening test will lead to a proportion of cases being missed (occult infection).	are evolving. ● Longer term, molecular tests can provide information about genotype, drug resistance, viral diversity and transmission networks.[43] ● Awareness is improving, with healthcare services increasingly offering screening and linkage to treatment, supported by data from feasibility studies.[109,114] ● WHO recommendations for antenatal HBV testing should be incorporated into national guidelines, supported by linkage to care.
Treatment	● TDF monotherapy can be difficult to access. ● Alternatives to TDF (TAF and ETV)[97] are usually not available. ● There are few good data to inform prescribing in situations where TDF is contra-indicated or fails to suppress viraemia. ● Long-term treatment for chronic HBV infection has implications for cost, supply and distribution. ● TDF drug resistance may be an emerging problem, but insights are currently limited.[95,100]	● TDF is safe, effective, cheap, can be used in pregnancy and is on the WHO essential medicines list.[92,94] ● Advocacy is required to promote the availability of alternative treatments (e.g. TAF and ETV). ● Increasing clinical data, viral sequencing data, and in vitro viral assays are required to determine the prevalence and clinical significance of drug resistance.[95] ● Improved prognostication (e.g. through viral sequencing, or new biomarkers) will inform better patient-stratified management.[43] ● Long term investment is required to drive the search for new cure strategies.
Service structure	● There is a lack of formal, structured services for HBV care provision. ● Individuals with a diagnosis of HBV infection are frequently not linked to care.[18]	● There is promising potential for HBV diagnosis and treatment to be incorporated into existing infrastructure (e.g. HIV and antenatal programmes).[14,110]
Education and advocacy	● HBV is associated with poverty, and the resulting liver disease is a result of inequities in access to care.[115] ● A lack of understanding and awareness puts populations at risk, and may underpin stigma and discrimination.[111] ● HBV is not widely viewed as a public health priority. ● There is a lack of high profile role models. [111]	● There is a need to develop education, advocacy, and media coverage. ● The representation of HBV in health-sciences curricula should be strengthened.[115] ● Expansion of population health initiatives can provide education, and reduce co-factors in liver disease (e.g. alcohol, aflatoxin).[9,32]

Policy and Investment	● Country-specific data, policy, and investment are required.[32] ● High risk groups are criminalised or stigmatised (eg PWID, sex workers, MSM).[116] ● To date, there has been lack of high level political awareness and engagement.[29,111]	● There are currently no significant sources of external international funding. Therefore careful allocation of domestic budgets will be crucial,[14] informed by cost-effectiveness studies. ● Interim progress reviews are required ahead of the 2030 deadline.[25] ● Public-private partnerships can be used to support interventions.[32]

Figure 1. Years of life lost (YLL) as a result of chronic liver disease due to hepatitis B virus infection. Data for both sexes and all ages, shown by region. Data from the Global Burden of Disease Study, downloaded from the Global Health Data Exchange.[117]



FUNDING STATEMENT

Philippa Matthews is funded by Wellcome (Grant Ref. 110110).

AUTHOR CONTRIBUTIONS

PM conceived the idea for the article. The text and figures were prepared by PM and TG. CN provided references and insights based on local practice. All authors have seen and approved the final manuscript.

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