Progress towards hepatitis B control in Uganda: epidemiology and public health policy for prevention, care and treatment

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Progress towards hepatitis B control in Uganda: epidemiology and public health policy for prevention, care and treatment

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Abstract

Background. The prevalence of hepatitis B virus (HBV) in Uganda has reduced from 10% in 2005 to 4.1% in 2016 among adults. Prevalence in women (9.1%) was lower than in men (11.8%) in 2005 as well as 2016; 5.4% in men and 3.0% in women. HBV prevalence is mapped by geographical region, and there was a high prevalence in the North (4.6%) and North Eastern (4.4%) compared to the Central and South Western regions at 1.8% and 0.8% respectively. Uganda introduced vaccination against HBV in 2002 to reduce infant infection. The vaccine was combined with other four vaccines give as a pentavalent vaccine. There has been a progressive improvement in immunisation coverage since the start of HBV vaccination in children below five years of age; from 62% in 2005 to 93% in 2018. The government has strengthened health systems in different capacities to enable it to meet the World Health Organisation (WHO) agenda of reducing HBV infection and deaths attributed to it. This thesis aimed to evaluate the progress of Uganda towards meeting the WHO agenda, assessing specifically the prevention and treatment strategies as well as discuss the challenges.

Methodology. A cross-sectional study was done on the data collected from all reporting sites in the DHIS2 between 2015 and 2019. I assessed the epidemiology of HBV and prevention and treatment policies implemented by the government of Uganda. The data was analysed in excel to present the progress of Uganda's performance in the different domains of care provided to HBV at-risk population.

Results. Despite the low HBV testing rates observed the Northern region, a higher HBV positivity rate of 12.1% was found, compared to the rest of the regions in Uganda. There was a noticeable increase in the HBV prevalence rate in the Eastern region; from 23 per 100,000 people in 2015 to 174 per 100,000 in 2019. The admissions of HBV cases in children under 5 years were generally very few with the Eastern region exhibiting the highest number of HBV admission in 2015 at 154 (6.8%); while the HBV case numbers were higher in adults in comparison to children with the Northern region reporting the highest HBV admissions among all regions at 867 (38.4%) in 2015. Western and Central regions showed a gradual increase in the number of unimmunised health Workers; from 16,637 (41.2%) and 12,744 (42.9%) in 2015 to 68,196 (53.1%) and 34,624 (34.1%) in 2019, respectively. The Eastern region in 2016 had the lowest number of HBV vaccinated children; 481,444 (7.5%) of children vaccinated for the first dose of HBV vaccine. The dropout rate increased from the second dose of vaccination to the third dose of vaccination.

Discussion and conclusion. The low HBV testing rate observed is affected by the government's policy that limited point-of-care testing at referral centres. The high yield calls for an active search for the HBV positive cases, like the HIV care strategy that included counselling and referral of lay people and testing in remote places. There was a high admission of HBV cases in patients above five years of age because symptomatic infections are more prevalent in this age group compared to those under five years of age. This may be associated with the innate immunity in children under five compared to

adults. Increased unimmunised health workers with HBV vaccine is attributed to the weak financing of the vaccination program as the government only provided approximately 3 million dollars to finance the HBV vaccination activities in the entire country. In conclusion, the progress towards the HBV elimination has been affected by the country's low testing capacity, which is critical to informing the country on the burden of HBV disease, the effectiveness of test-and-treat strategy, and the immunisation program.

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Abbreviations

AHPR	Annual Health sector Performance Review
ALT	Alanine Transaminase
BD	Birth Dose
CHB	Chronic Hepatitis B
DHIS2	District Health Inforamtion System 2
DNA	Deoxyribonucleic Acid
DPT	Diptheria Pertusis Tetanus
GAVI	Global Alliance for Vaccine Initiative
HAA	Hepatitis Associated Antigen
HAV	Hepatitis A Virus
HBcAg	Hepatitis B core Antigen
HBeAg	Hepatitis B e-Antigen
HBIG	Hepatitis B Immunoglobulin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDV	Hepatistis D Virus
Hep B	Hepatitis B
HEV	Hepatitis E Virus

Hib	Heamophilus influenza type b
HIMS	Health Information Management System
HIV	Human Immune Virus
ICTV	Internation Commitee on Taxonomy of Viruses
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LAM	Lamivudine
LdT	Telbivudine
MOH	Ministry of Health Uganda
MSM	Men who Have sex with Men
SDG	Sustainable Development Goals
TDF	Tenofovir Disopoxil Fumarate
UBOS	Uganda Bureau Of Statistics
UCG	Uganda Clinical Guidelines
UNEPI	Uganda Expanded Program on Immunisation
WHO	World Health Organisation

Chapter 1. Introduction

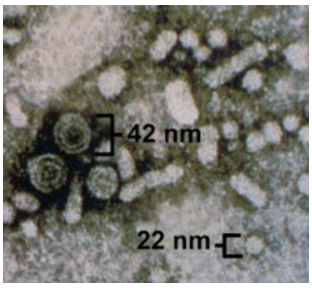
1.1 The genus *Orthohepadnavirus* and Hepatitis B virus (HBV)

Hepatitis B Virus (HBV) is classified under the hepadnaviral family known as *Hepadnaviridae*. It includes *orthohepadnavirus* and *avihepadnaviruses*, which have been commonly isolated in mammals and birds respectively (Schaefer, 2007). The genus *orthohepadnavirus* contains other medically important hepatitis causing viruses in human. These include hepatitis A virus (HAV), hepatitis B (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV) (Lanini *et al.*,2019). Among these five medically important hepatitis viruses, HBV remains endemic in human population in many parts of the world, causing transient and chronic infection of the liver that may result in life threating disease such as liver cancer or cirrhosis if not prevented or treated adequately.

1.1.1 Medical microbiology of HBV

HBV has some distinct features of genome structure, virion structure and polypeptide composition (Gust *et al.*, 1985). HBV is double-stranded DNA viruses covering 42nm diameter (Schaefer, 2007) with lipid envelope containing hepatitis B surface antigen (HBsAg) surrounding the inner nucleocapsid composed of hepatitis B core antigen (HBcAg) (Figure 1) (Liang, 2009). This double-stranded circular DNA genome of 3.2

kilobase(kb) pairs contains four overlapping open reading frames that encode the three hepatitis B surface antigens (HBsAg), hepatitis B e antigen (HBeAg), hepatitis B core antigen (HBcAg), viral polymerase, and a protein X (Zhang and Cao, 2011 and Hong, 2020). The virus contains three particles as visualised under a microscope; two are spherical in shape measuring 20nm in diameter with filamentous structures; and the third particle measures 22nm and does not contain viral nucleic acids (Liang, 2009).



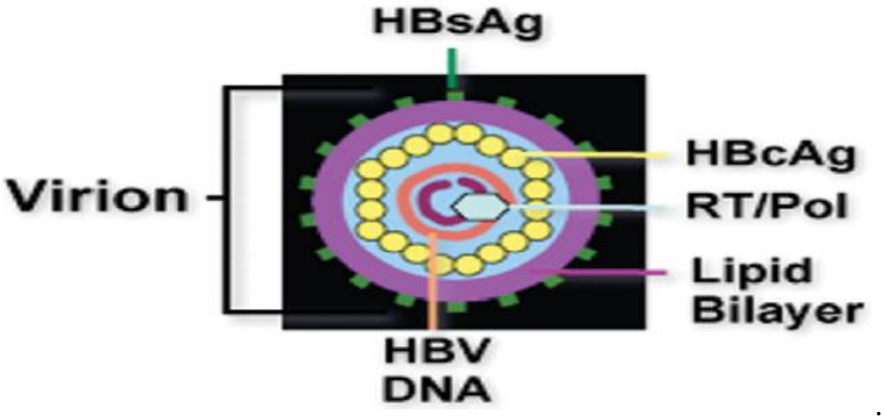


Figure 1. Viral structure of HBV
Reproduced from Liang, 2009.

Original figure legend (Liang, 2009): “Electron micrograph of circulating forms of HBV particles in the blood is shown at the top and a schematic drawing of Dane particle, the infectious HBV particle, is shown at the bottom with various structural features.”

1.1.2 Transmission, pathogenesis, host defence and disease progression

Hepatitis B is a viral infection that causes acute illness with symptoms such as jaundice, abdominal pain, vomiting, as well as chronic disease particularly liver cancer or cirrhosis in human. HBV is transmitted through exposure to body fluids of infected persons. There are several routes of HBV transmission: exposure to infected blood (horizontal transmission) particularly from an infected child to an uninfected child during the first five years of life (WHO, 2020); needlestick injury and exposure to infected blood and body fluids such as saliva, menstrual, vaginal, and seminal fluids (WHO, 2020); mother to child transmission (vertical transmission, perinatal transmission); sexual transmission particularly in men who have sex with men and heterosexual persons with multiple sexual partners and contacts with sex workers (WHO, 2020 and Mihigo *et al.*, 2013).

Once the virus gains entrance to the host, it replicates into a double-stranded DNA which is in a stable form that consciously infects the liver cells (hepatocytes) (Seto *et al.*, 2018). The ability of the virus to stay in the host cell undetected is due to the genetic makeup that plays a role as a weak inducer of the innate immune response, and hence HBV clearance only takes place as a result of mediated adaptive immune response (Khan, Zaman and Ikhlaq Chohan, 2017). The HBV infection has two phases of progression; acute and chronic phases (Khan, Zaman and Ikhlaq Chohan, 2017). The acute phase of HBV infection is characterised with HBV DNA, HBsAg and HBeAg detection in serum

of infected individual, whereby HBsAg can be detected in 1-2 weeks or even at 11-12 weeks after exposure to the virus, and the presence of HBeAg signifies the presence of high level of HBV infectivity and replicability (Liang, 2009). With these viral markers and increased level of serum alanine and aspartate aminotransferase (ALT, AST), infected persons may experience jaundice, and while HBeAg is typically cleared early such as at the height of clinical symptoms, HBsAg and HBV DNA often persist in the serum during clinical manifestations and only cleared when recovered (Liang, 2009). Regarding the antibody responses upon HBV human infection, the antibody to HBcAg (anti-HBc) appears right before the onset of clinical illness, while the antibody to HBsAg arises late during infection such as during recovery or convalescence after clearance of HBsAg, and antibody to HBeAg (anti-HBe) appears shortly after clearance of HBeAg, typically at the peak of illness (Liang, 2009). The chronic phase of HBV exhibits a similar initial serological markers with detection of HBV DNA, HBsAg, HBeAg, and antibody to HBcAg (anti-HBc), but viral replication continues with HBsAg, HBeAg, and HBV DNA persistently detected in serum in high titres, often resulting in HBsAg positivity for many years or for life time (Liang, 2009). Some of these chronic HBV patients further develop chronic liver injury that can lead to cirrhosis and hepatocellular carcinoma (HCC) (Liang, 2009). The inflammation of liver is due to the response of the immune system to the virus (Khan, Zaman and Ikhlaq Chohan, 2017).

The HBV disease is usually insidious with symptoms such as tiredness, anorexia, vague abdominal discomfort, nausea and vomiting, arthralgia, rash and progressive jaundice

(Patel, 2015). Around two-thirds of acute HBV patients are reported with mild, asymptomatic and subclinical illness that may often go undetected, and about one-third of acute HBV adults develop clinical symptoms ranging from mild symptoms such as fatigue and nausea to more notable symptoms such as jaundice and also acute liver failure (Liang, 2009). It is also noted that the incubation period of acute HBV may be around 2-3 months on average and up to around 6 months after exposure (Liang, 2009). The chronic HBV patients typically experience the immune tolerance phase (persistent high levels of HBeAg and HBV DNA) or inactive carrier state (loss of HBeAg and decreased HBV DNA) or HBeAg-negative chronic HBV phase (decreased HBeAg and developed antibody to HBeAg (Liang, 2009). While many chronic HBV patients may be asymptomatic or show nonspecific symptoms, others may show severe symptoms such as constitutional symptoms, jaundice, and end-stage liver disease (Liang, 2009). Chronic HBV patients are often classified as severe cases with around 50% five-year survival rate.

The chronic HBV phase often has five non sequential phases, which can sometimes be reverse (Revill *et al.*, 2019). The first phase is characterised by high serum HBV DNA but normal serum alanine aminotransferase (ALT), and the liver cells almost intact. This stage is known as the HBeAg-positive. The second phase is the immune clearance or HBeAg positive chronic hepatitis. This often follows an acute infection but takes a long time to manifest as it follows a sustained viral replication causing liver necroinflammation, fibrosis, fluctuating serum ALT and anti-bodies appear towards the

end of this phase. Patients whose sero-conversion occurs after 40 years of age usually develop cirrhosis. The third stage also known as the HBeAg-negative chronic infection phase is characterised by suppression of the viral DNA load. There is a low risk of disease progression though minority achieve complete viral clearance (Seto *et al.*, 2018). The fourth phase is when HBeAg-negative chronic hepatitis directly follows an acute hepatitis or start after decades of chronic HBeAg positive infection. This phase is characterized by the absence of HBeAg and persistent viral replication and liver damage (HBV DNA levels of >2000 U/L and increased plasma transaminase levels). Fifth phase, also known as HBsAg-negative phase, is characterized by negative serum HBsAg and positive antibodies to hepatitis B core antigen, with or without detectable antibodies to HBeAg. If HBsAg loss has occurred before the onset of cirrhosis, a minimal risk of liver disease progression occurs. However, this phase can be associated with positive viremia, known as occult HBV infection. HBV DNA can integrate into the hepatocyte genome, and all patients with CHB are at risk of HCC, regardless the level of liver damage (Lanini *et al.*, 2019). There are extrahepatic disease manifestation such as skin changes, glomeruli nephritis, polyarteritis nodosa and mixed cryoglobulinemia (Seto *et al.*, 2018). The disease usually progresses with asymptomatic phase in some patients while others may display signs of easy fatigability, anxiety, anorexia and malaise (Patel, 2015).

1.1.3 Diagnosis

The HBV infection is diagnosed by detection of the hepatitis B surface antigen (HBsAg) and immunoglobulin M (IgM) antibody to the hepatitis B core antigen (HBcAg) in human blood samples (WHO, 2020; Song and Kim, 2016; and Krajden *et al.*, 2005). Other diagnostic tests include laboratory assessment of the liver function through comparison of the ALT, bilirubin, alkaline phosphates, total proteins, globulin, complete blood count and coagulation with the standard calibrations (Patel, 2015). Tests of viral DNA and DNA polymerase-containing virions are limited to treatment evaluation and research (Patel, 2015).

Chapter 2. Literature review

2.1 Epidemiology of Hepatitis B Virus (HBV)

2.1.1 Global epidemiology of HBV

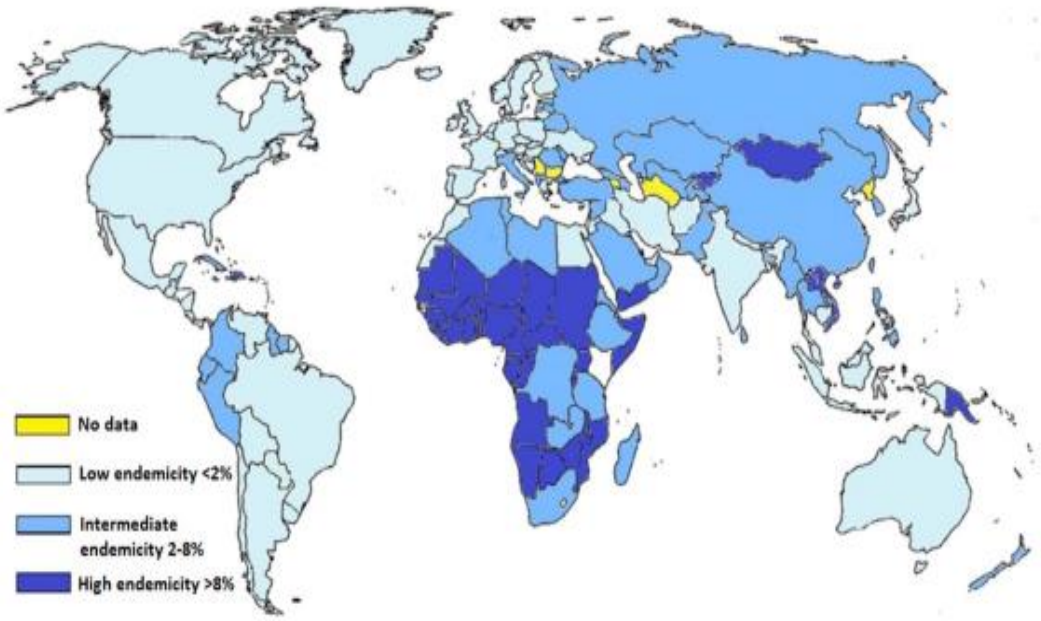
Globally, hepatitis B virus (HBV) remains one of the major public health concerns with more than 240 million chronically infected HBV patients (WHO, 2015) despite a decrease from 350 million in 1990 (Vasilios Papastergiou et al, 2004). The number of chronic HBV infection, defined as hepatitis B surface antigen positive (WH0, 2020), has been on the rise recently from 248 to 257 million people in 2015 and 2018 respectively (Revill *et al.*, 2018). Around 887,000 HBV associated deaths were reported worldwide in 2018 (Revill *et al.*, 2019), mostly due to cirrhosis and hepatocellular carcinoma (WH0, 2020), which was an increase from around 650,000 HBV deaths in 2013 and previous years (WHO, 2015). Chronic HBV has been cited to cause nearly 40% of hepatocellular carcinomas, resulting in the second leading cause of cancer associated deaths in the world (Revill *et al.*, 2019).

The HBV disease is relatively rare in the western countries but endemic in Africa, the Pacific and parts of Asia, accounting for 45% of the HBV infection globally (Lavanchy, 2004). Approximately 6.2% and 6.1% of the adult population in the Western Pacific region and Africa respectively, and around 3.3%, 2.0%, 1.6%, and 0.7% of the general population in Eastern Mediterranean, South-East Asia, Europe, and the Americas

respectively, are estimated to be infected with HBV (WH0, 2020). In HBV endemic areas, HBV transmission often occurs through a perinatal vertical transmission from mother to child at birth or through horizontal transmission due to increased risk of exposure to infected blood or body fluids particularly between children below five years of age **(**WH0, 2020**).** Approximately two million new HBV infections are reported annually in children below the age of five years worldwide (Indolfi *et al.*, 2019). The HBV incidence remains high particularly in women who are not immunised against HBV and are carriers of both hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) (Indolfi *et al.*, 2019). The risk of these women to transmit the hepatitis B virus to their infants is between 70% to 100% in Asia and 40% in Africa, while those with HBsAg and have lost HBeAg are at a lower risk of vertical transmission, ranging between 5-30% in Asia and 5% in Africa (WHO, 2017a).

A recent study by Nannini and Sokal exhibited a worldwide distribution of hepatitis B surface antigen (HBsAg) endemicity during 2011-2016 and HBV genotypes and sub-genotypes (Figure 2) (Nannini and Sokal, 2017). Some sub-Saharan African and Southeast Asian countries showed high endemicity of HBsAg (>8%), followed by the other countries in these regions and some countries in Europe, Middle East, and Latin America with intermediate endemicity (2-8%) (Nannini and Sokal, 2017). The authors also noted ethno-geographic pattern of HBsAg worldwide: genotypes A (A1-A7) and D (D1-D8) prevalent in Europe and Africa, genotypes B and C confined to Asia and

Oceania (Nannini and Sokal, 2017); genotypes E, F, G and H in Asia; genotype I in Laos, Vietnam, India and China; genotype J in Japan (Nannini and Sokal, 2017). The global geographical distribution of HBV genotypes and sub-genotypes are also presented in Figure 3, showing 10 genotypes and over 40 sub-genotypes (Locarnini *et al.*, 2015). A study by Schaefer (2007) states that co-infection of different HBV genotypes can occur, causing superinfection in chronic hepatitis B patients.



Worldwide distribution of hepatitis B surface antigen endemicity 2011–2016.

Figure 2. Global distribution of hepatitis B surface antigen (HBsAg) endemicity

Reproduced from (Nannini and Sokal, 2017).

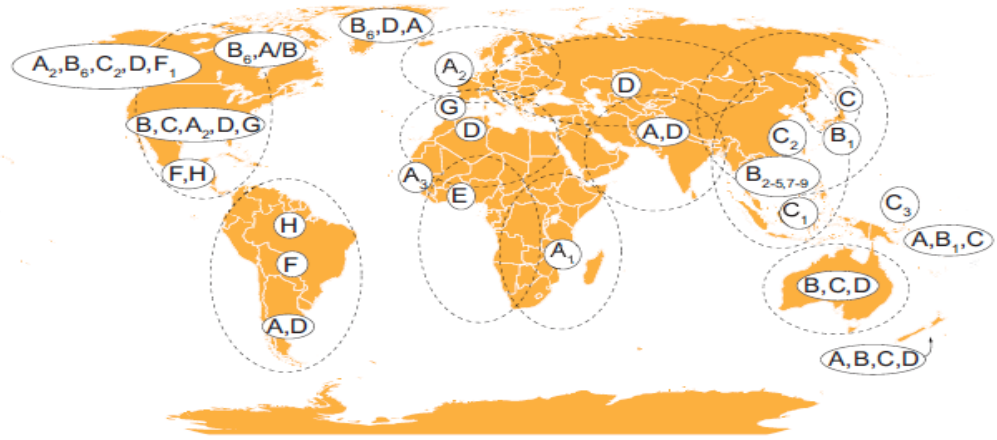


Figure 3. Distribution of HBV genotypes and sub-genotypes worldwide

Reproduced from (Locarnini *et al.*, 2015).

Original figure legend: “Genotype I and J are not shown as they have not been ratified by the ICTV; genotype I is found in Southern China and Vietnam whilst genotype J was identified from a Japanese World War II person who lived in Borneo.”

2.1.2 Epidemiology of HBV in Africa

HBV is endemic in Africa with approximately 100 million people with chronic hepatitis in 2017 (Breakwell *et al.*, 2017). The prevalence of HBsAg is greater than 8% among the general population in Western Africa and around 5-7% in Central, Eastern and Southern Africa (Schweitzer *et al.*, 2015). The prevalence of HBsAg and anti-HBc in Africa by cohort, country, and region exhibited higher burden of HBV infection and exposure to HBV in Western African countries, followed by Central and Southern African countries (Figure 4). Countries in Northern and Eastern Africa regions showed higher susceptibility to HBV (McNaughton *et al.*, 2020).

15%-20% of all persons with chronic hepatitis are estimated to have a risk to hepatocellular carcinoma or cirrhosis depending on the age at infection. The risk of HBV infection is higher in infants below one year of age (70%-90%) compared to children aged between one year and five years (20%-50%), and lower among those above five years of age (5%-10%) (Breakwell *et al.*, 2017). The prevalence varies from rural to urban with the rural areas having the highest prevalence and little or no varying differences between males and females of the same age in Egypt. In Seychelles the ratio was 1.43 to 1 in males and females of age 25-34 years respectively, while in older adults it was 2.26:1 for males and females aged 55-64 years (Kramvis and Kew, 2007). Overall it is estimated that males are 3-5 times more likely at risk of developing hepatocellular

carcinoma than females globally, an observation that has also been witnessed in Africa (Lemoine and Thursz, 2017).

HBV infections have also been found to co-exist in people living with HIV, estimated at 1.96 million (WHO, 2017a). Another vulnerable group of people with high risk of HBV infections in Africa are the health workers, estimated to account for about 66,000 infections annually (Auta *et al.*, 2018). In Africa, like the rest of the world, the main modes of transmission of HBV is through vertical transmission that accounts for 10% of chronic infection, while horizontal infection in children aged 2-10 years is poorly understood (Lemoine and Thursz, 2017).

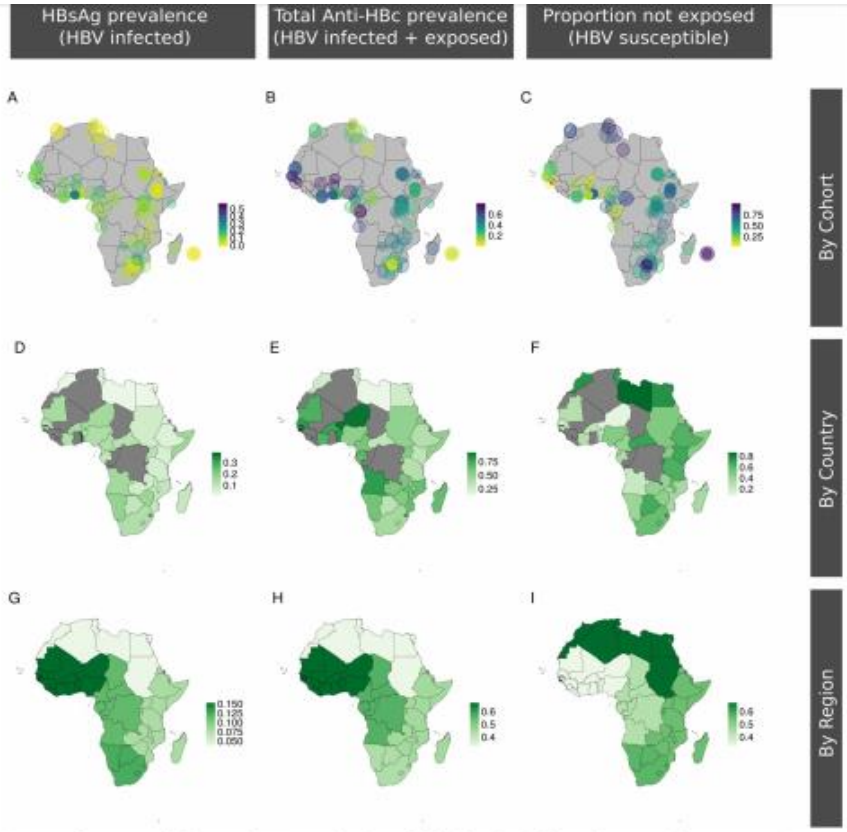


Fig 3. Maps demonstrating the location and HBV seroepidemiology of adult cohorts identified through a systematic literature review. First row shows data by individual cohort, depicting (A) HBsAg prevalence, (B) anti-HBc prevalence (exposed plus infected), and (C) HBV susceptible population (100% of population minus anti-HBc prevalence). Each circle is placed to represent the location of the cohort. 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 online at Figshare: 10.6084/m9.figshare.6154598, and an interactive version of these maps can be accessed online [29]. Outline maps available as open source from http://www.maplibrary.org/library/index.htm. Anti-HBc, antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

https://doi.org/10.1371/journal.pmed.1003068.g003

Figure 4. HBV sero-epidemiology in Africa

Reproduced from (McNaughton *et al.*, 2020).

Original figure legend: “Maps demonstrating the location and HBV sero-epidemiology of adult cohorts identified through a systematic literature review.”

2.1.3 Epidemiology of HBV in Uganda

The HBV prevalence in Uganda prior to the national sero-survey conducted in 2005 was unknown or underestimated due to lack of adequate data and limited research, often conducted at sub-regional level, not representing the national level population data. However, available data provided valuable information to start informing policy making towards HBV control in Uganda. A study conducted by Maynard et al (1970) identified nearly 60% of all patients in the hepatology clinic were positive with Hepatitis Associated Antigen (HAA) and 31% of patients with liver cirrhosis tested positive of the HAA (Maynard *et al.*, 1970). Notably, in 1980, Sobeslavsky (1980) observed the prevalence of HBV in children was lower than that in adults, which was consistent with both national HBV sero-surveys in 2005 and 2016. The estimated HBV prevalence in Uganda showed 3% in 1980 and 0.6% in 2016 in children 0-4 years (Ministry of Health, 2016); and 12.1% in 1980 and 10% in 2005 in adults (Ministry of Health., 2006) and subsequently 2.6% in 2016 (Ministry of Health, 2016). This is contrary to the general findings on the global and regional HBV epidemiology where children, especially infants are estimated to be at higher risk of HBV infections.

The prevalence of hepatitis B in Uganda is estimated at 4.1% according to the 2016 national sero-survey (Ministry of Health, 2016), a reduction of more than 50% compared to the previous prevalence of 10% in 2005 (Ministry of Health., 2006) (Figure 5). A study by Teshale et al (2015) showed at least 1 out of 6 adults tested positive for HBsAg and 1

out of 20 people among 40-59 year olds HBsAg positive. Nakwagala and Kagimu (2002) study stated that the ratio of male to female with positivity of HBsAg was 3:1, which was exhibited in the sero-survey results from 2005 and 2016 with HBV sero-prevalence in men higher than in women; HBV sero-prevalence in men and women at 11.8% and 9.1% respectively in 2005, and 5.4% and 3.0% in 2016. This may be due to multiple sexual patterners men tend to have compared to women. The level of education may have also played a role in HBV transmission as higher prevalence was found in those with no education compared to people with education. The HBV prevalence did not vary between rural and urban during the sero-survey in 2016 (Ministry of Health, 2016). However, different HBV prevalence was found in various regions of the country such as North (4.6%), Northeastern (4.4%), Central (1.8%), and Southwestern (1.8%). There is paucity of data regarding mortality associated with HBV infections in Uganda. Uganda, like the rest of Africa, shares the similar modes of HBV transmission whereby needle prick injuries in health workers, mother to child transmission, and transmission through sexual behaviour have been main risk factors contributing to the spread of HBV infections.

5a **5b**

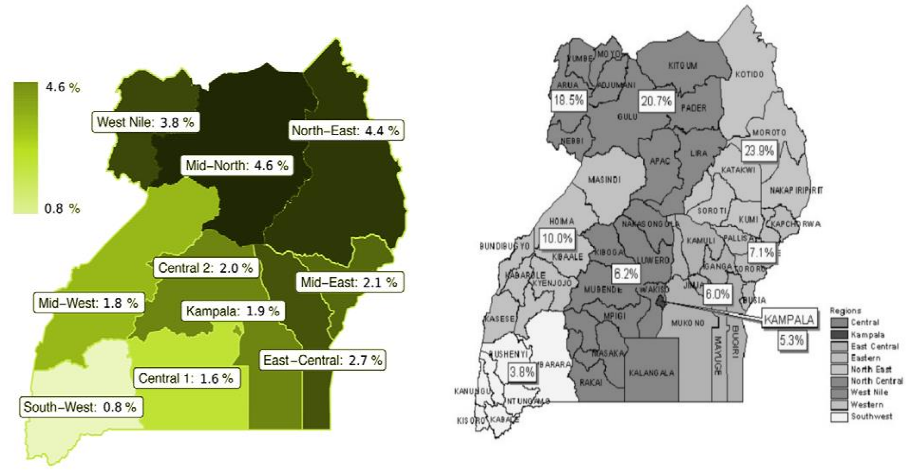


Figure 5. HBV sero-surveys in 2016 and 2005

Reproduced from MOH, 2019 and Bwogi et al, 2009.

Figure legend: Figure 5a is HBV sero-survey in 2016; and 5b is HBV sero-survey result in 2015.

2.2 Global hepatitis elimination strategies

The WHO has adopted the hepatitis elimination goal in 2015 (WHO, 2015). The strategies address all types of hepatitis (A, B, C, D, and E) with particular emphasis on HBV and HCV based on the global hepatitis disease burden (WHO, 2016). The strategies include (WHO, 2016): 1) Elimination of viral hepatitis by reviewing viral epidemics, responses, identifying opportunities and challenges through public health system strengthening; vaccination against hepatitis A, B, and E in early childhood and adults and prevention of mother-to-child transmission; practicing injection safety; effective drug treatment packages for improved management of hepatitis patients; 2) Framing the hepatitis elimination strategy through expanded range of health services, offering quality, available, and affordable essential health services to people; enhanced prevention, diagnosis, and care and treatment to reduce the public hepatitis viral load; 3) Setting global hepatitis elimination targets and adapting them to national targets; global reduction of hepatitis B and C new infections to 30% in 2020 and reduction of all chronic infections by 90%, reduction of mortality associated with hepatitis B and C by 10% in 2020 and 65% by 2030; 4) Strategic direction and prioritized action plans, interventions for impact, delivery of services for equity, financing for sustainability and innovation for acceleration of progress towards meeting the targets; 5) Strategy implementation, partnership building, accountability through monitoring and evaluation, and cost planning for strategy implementation (WHO, 2016).

2.2.1 HBV immunisation strategy

Infant and younger children are at a higher risk of hepatitis infection and diseases due to premature immune system and reduced immune tolerance against HBV antigen (Nannini and Sokal, 2017). The risk of acquiring hepatitis infection from a highly infectious mother by the neonate is at around 90% while that of the pre-school going children is estimated to be around 25%, which is further reduced to lower than 3% in young adults (Yi *et al.*, 2016). Active and passive immunisation was adopted as a strategy to control and prevent HBV infection in infants. Active immunisation is HBV vaccination aimed at provision of a long-term immunity. HBV vaccination at birth has demonstrated to reduce the risk of mother-to-child transmission from 70-90% to 10% among infants of HbsAg-positive or HbeAg positive mothers (Indolfi *et al.*, 2019 and Yi *et al.*, 2016). Passive immunisation refers to hepatitis B immunoglobulin (HBIG) introduction to neonates, who are exposed or at high risk of being infected with HBV by their mothers (Indolfi *et al.*, 2019). A combination of active immunisation and passive immunisation has demonstrated reductions in infection of hepatitis in Taiwan (Yi *et al.*, 2016).

Safe and effective vaccines against hepatitis B have been available since 1982, starting with the plasma-derived vaccines that have been subsequently replaced by recombinant vaccines in 1986 (WHO, 2017). The first universal HBV vaccination program was launched in July 1984 in Taiwan and pregnant women were screened for HBeAg and HBsAg while babies where given vaccines at 0, 1, 2, 12 months of age from plasma

derivatives (Yi *et al.*, 2016). Three different HBV immunisation program strategies have been developed for infants, based on the prevalence of HBV infection; 1) combined passive and active immunisation with maternal screening for HBsAg and HBeAg; 2) combined passive and active immunisation with maternal screening of HBsAg and; 3) active immunisation without screening for the viral makers (Yi *et al.*, 2016). The first two strategies involved giving a birth dose of HBIG 0.5mls within 12-24 hours of birth, followed by the recombinant 3-dose hepatitis B vaccine at 0, 1, 6 months of age. This was considered to have a high cost burden to implement in countries with low financial capability or low prevalence of HBV infection, and such countries opted for the 3-dose vaccination strategy at 0, 1, 6 months of age (Yi *et al.*, 2016).

In 1991, the WHO recommended addition of HBV immunisation to the national immunisation programs of all member countries, which was adopted and implemented starting 1992 (Yi *et al.*, 2016). In 2015, the WHO has made a new recommendation to its member countries to introduce monovalent hepatitis B vaccine birth dose (BD), given within 12-24 hours after birth (WHO, 2017). This birth dose can still be given late as it still has some effect although it reduces in days after birth (WHO, 2017). WHO states that after 7 days the birth dose is effective in preventing horizontal transmission, and it could be given at any time until the next immunisation schedule (Yi *et al.*, 2016). The 2017 WHO position paper on hepatitis B vaccines suggests the primary 3-dose hepatitis B vaccination for infants may consist 1 monovalent birth dose, followed by 2 doses of

monovalent or combination vaccine containing hepatitis B, which can be administered concomitantly when infants visit healthcare facilities to receive the first and third doses of DTP-containing vaccines; or 4-dose hepatitis B vaccination for infants with 1 monovalent birth dose, followed by 3 doses of monovalent or hepatitis B-containing combination vaccines), administered at the time of 3 doses of DTP-containing vaccines (WHO, 2017;World Health Organization, 2019).

The other immunisation schedule is for delayed or interrupted schedule for children, adolescents and adults where 3 doses are recommended at 0, after one month and 6 months after the first dose. A number of people at risk were identified for targeted immunisation, which included; persons with multiple sex partners, men who have sex with men (MSM), people who inject with drugs, diabetic patients, recipients of solid organs, contacts of hepatitis infected person, health care workers, persons interning in prison, people exposed to potential infectious body fluids during work, dialysis patients, persons with chronic liver disease, patients who require blood products and HIV infected persons. Catchup immunisation should be scheduled for all those that missed immunisation in 0, 1, 6 months sequence, while pre- and post-vaccination testing is not recommended (World Health Organization, 2019) (Figure 6).

In Africa, 47 countries have introduced HBV immunisation into their immunisation schedule, accounting for 94% using a combined pentavalent vaccine and 70% of them

following a three-dose schedule of 6, 10, 14 weeks of age. The average coverage is 75% and only 3 countries had achieved a coverage of 90% while birth dose has been introduced in 9 countries with coverage plateauing at 10% since 2010. The performance is due to insufficient financial resources and cold chain storage, high proportion of home births, and lack of tools for monitoring (Breakwell *et al.*, 2017).

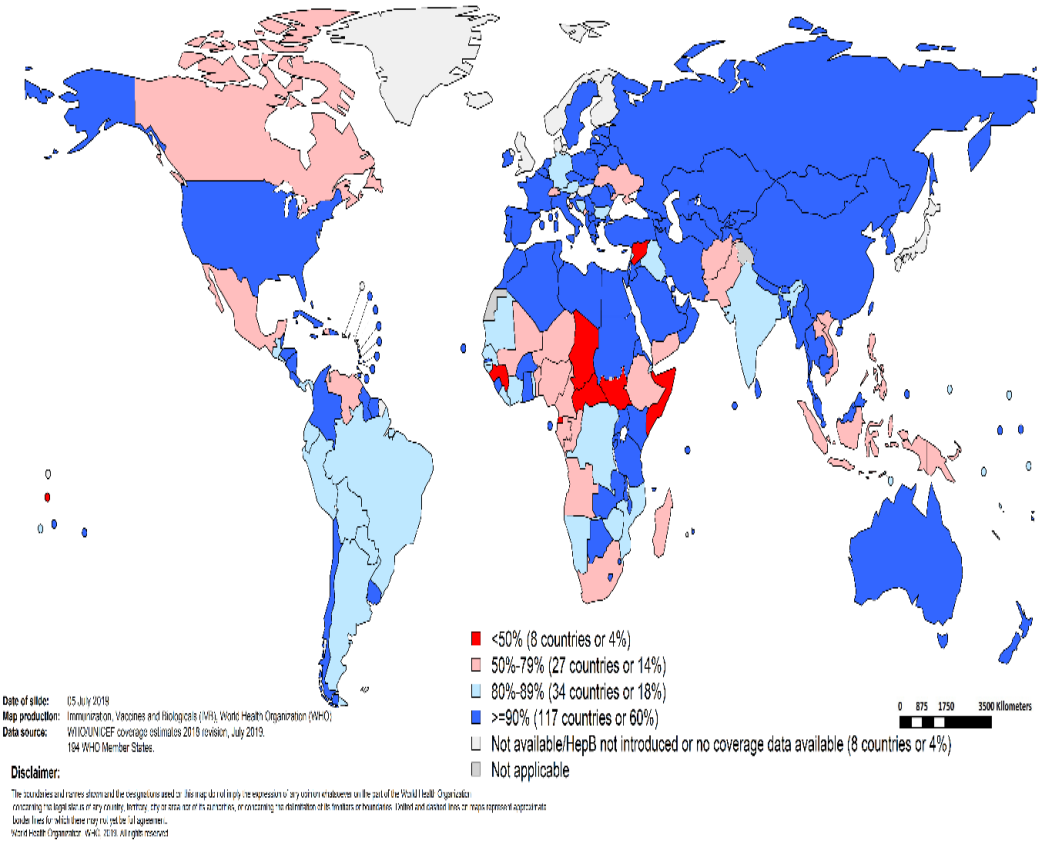


Figure 6. Immunization coverage with HepB3 in infants ('WHO | Hepatitis B', 2019)

Reproduced from WHO, 2019.

2.2.2 Use Prophylaxes in Patients as a Prevention strategy

Mother -to- child transmission has been identified as the common route of infants acquiring HBV infection, accounting for 30-50% of infant HBV infection in 2003 (Nannini and Sokal, 2017 and Yi *et al.*, 2016). Different strategies to prevent the vertical transmissions have been discussed. Mothers who have high viral load of HBV in their pregnancy may infect their babies in three different stages; during pregnancy as HBeAg can cross the placenta barrier in case of immune tolerance from the pregnant woman; during childbirth; and after birth. Neonate vaccination with prophylaxis HBIG has prevent infection in 71% of the infants but has a half-life of 22 days if given a lone (Yi *et al.*, 2016 and WHO, 2017). Other studies have recommended to give HBIG to pregnant women exposed to HBV, however no significant reduction in vertical transmission has been shown (Yi *et al.*, 2016).

WHO recommends using the monovalent vaccine used in catchup vaccination for pregnant women, who are at risk of acquiring the infection (World Health Organization, 2019). Another strategy to prevent includes use of antiviral viral prophylaxis. However, it is not effective in women who are experiencing immune tolerance stage with normal ALT levels compared to those with raised ALT and active replication (Yi *et al.*, 2016). Antivirals that are used in prophylactic treatment include; class B that comprises of Tenofovir (TDF) and Telbivudine (LdT); and class C with lamivudine (LAM) (Pawlowska *et al.*, 2016). TDF has been highly recommended as it has high barrier to

resistance compared to LdT and LAM (Gentile and Borgia, 2014). The treatment is recommended to start in 28-32 weeks of gestation and only stopped 12 weeks after delivery or after meeting the treatment goal (Gentile and Borgia, 2014). Another group that can benefit from the prophylaxis are the health workers as they interact with infectious agents and can act as a vehicle of transmission of HBV infection (WHO, 2015).

2.2.3 Treatment to reduce mortality

There is no treatment for HBV disease currently available that can completely eliminate the viral DNA from the nucleus of the infected hepatocyte (Fanning *et al.*, 2019). However, efforts to treat HBV patients have been made, which include: 1) effective inhibition of viral replication; 2) reduction of liver inflammation and injuries; 3) HBeAg seroconversion and; 4) prevention of liver complications such as cirrhosis and HCC (Yi *et al.*, 2016). The WHO aims to reduce HBV associated mortality through the test and treat program, reducing the infection rate and enhancing proper adherence to anti-viral drugs that have been recommended (WHO, 2017). There is no indication for treatment of patients, who are in inactive status with negative HBeAg and normal serum ALT (Access, 2013). The drugs have been used in combination to increase the efficaciousness of treatment; entecavir with TDF may be useful as half of the patients develop resistance on using entecavir monotherapy (Access, 2013).

2.3 HBV prevention and control in Uganda

2.3.1 Immunisation as a strategy to prevent hepatitis B infection in Uganda

In 1992, the WHO recommended countries to introduce hepatitis vaccine in their routine immunisation schedule (WHO, 2015). Uganda introduced hepatitis vaccination in 2002 with a particular focus on reducing HBV infections in infants, using a pentavalent vaccine targeting diphtheria, pertussis, tetanus and haemophilus influenza (DPT, Hib, Hepatitis B) (Teshale *et al.*, 2015). It was to be given at 6 weeks of age for the first dose, 10 weeks of age for the second dose, and the third dose at 14 weeks of age (UBOS, 2017). Uganda as a country has improved immunisation coverage since the start of hepatitis B vaccination in children with a progressive performance from 62% in 2005 to 93% in 2018 (World Bank report, 2018). The HBV immunization coverage in infants with three doses and birth dose during 1990 and 2015 has increased significantly from around 41% in 2002 to nearly 90% in 2015 (Figure 7) (WHO, 2019). This contribution has been visible as there is a reduction in the HBV prevalence as evidenced in a study by Teshale *et al* (2015) and the HBV sero-survey in 2016. There was no set national agenda in Uganda regarding the hepatitis elimination despite the sero-surveys and studies, until the WHO adoption of global hepatitis elimination strategy in 2015.

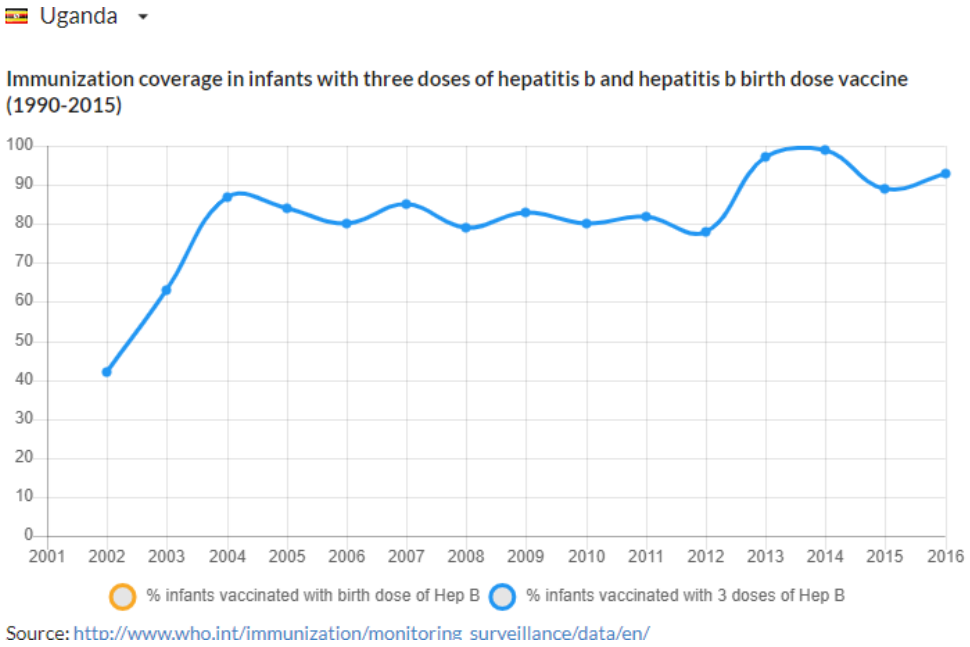


Figure 7. Immunisation coverage of three doses of HBV and birth dose vaccine

Reproduced from WHO, 2019.

2.3.2 Testing and treatment of hepatitis B patients in Uganda

The WHO recommended that 90 percent of population should know their HBV sero-status, and among those who need treatment, 90 percent should be initiated with efficacious treatment and monitored to achieve a viral suppression (WHO, 2016). The government of Uganda developed a target agenda of mass HBV testing in all highly endemic areas in-country, according to the HBV sero-survey conducted in 2005, particularly targeting adolescents aged 14 years and above (Uganda gazette, 2018). More than 200 Selexon HBV screen machines were procured and distributed in high endemic areas (Katamba *et al.*, 2019).

Improvements in HBV clinical management have also been made as new clinical guidelines were published in 2016 for the management of both acute and chronic HBV infection (UCG, 2016). The guideline recommended screening of all HBsAg positive patients for HIV co-infection and if found positive for HIV, he or she should be recommended with a viable antiviral therapy irrespective of their viral status. The guidelines further outlined periodic monitoring of HBsAg patients for Hepatocellular Carcinoma (HCC) and liver cirrhosis. As for the pregnant women and the rest of the population who are not HIV positive, evaluation is recommended for start of antivirals according to the set HBV viral load cut offs and HBV disease status. The government has further expanded treatment centres to include regional referral levels, and incorporated antiviral commands such as Tenofovir disoproxil fumarate (TDF) for adults and entecavir for children in the patient management guidelines (UCG, 2016).

2.3.3 Uganda HBV national health system strengthening

Uganda first introduced HBV immunisation in 2002 among children below the age of 5 years as part of the Uganda National Expanded Program on Immunisation (UNEPI) (Bwogi *et al.*, 2009). Adult immunisation was not introduced in Uganda until 2014, when two statutory instruments were established: the Public Health Order (Declaration of Hepatitis B as a Formidable Epidemic Disease), 2014 (SI No 104); and the Public Health Rules (Vaccination of Health Workers against Hepatitis B Virus), 2014 (SI No.105) (Law society report, 2015). The massive HBV vaccination was introduced targeting older children and adults aged 14 years and above, starting with health workers, followed by students, armed forces, and the general public. Uganda has targeted to cover 17 million people at risk of HBV infection and HBV endemic regions, starting with the Northern region in the first round of HBV vaccination. In 2016, a national HBV sero-survey was conducted to analyse the prevalence of hepatitis B (Ministry of Health, 2016). The government has committed USD3 million in the annual government health budget to improve the hepatitis service delivery (Uganda gazette, 2018). The country has set a target of putting on treatment all identified HBV patients through mass screening. Clinical guidelines of HBV treatment were published, and medicines included in the essential medicines tool kit (AHPR 2018/2019, 2019). The national and regional hospitals in Uganda have rolled out trainings on the management of HBV patients, though the training programs remained at a slow pace (AHPR 2018/2019, 2019). The reporting of viral hepatitis cases has been enhanced by development of the health information system

(HIMS) tools, which have been incorporated into the online national reporting platform. Uganda has improved on its testing capacity through innovating a laboratory hub system for sample referral testing in the newly commissioned hepatitis laboratory with 200 staffs, trained in operating the viral load testing equipment for treatment management and point of care testing for screening of population at risk.

2.4 Aim of the study

Hepatitis B is one of the major public health concerns in Uganda with high disease burden and associated disability. The national HBV sero-survey conducted in 2016 showed the estimated HBV prevalence of around 4.1%. Patients infected with HBV may transmit the infectious virus to others through contact with body fluids. Once infected, some patients progress to acute disease while others progress to chronic hepatitis, a life-threatening debility that manifests as chronic liver diseases. Around 80% of the liver hepatic disease admissions are due to cirrhosis and hepatocellular carcinoma. Both liver cirrhosis and HCC have contributed to nearly 73% mortality on the hepatology ward of the national referral hospital in Uganda. The introduction of HBV control strategies by the government of Uganda aimed to reduce HBV incidences and meet the global HBV elimination goal and targets set by the WHO. These targets are aimed at reducing new infections caused by hepatitis B by 90% as well as reducing mortality related to hepatitis by 60% by 2030.

In this thesis, I have focused my research on evaluating the progress of the HBV control strategies that have been put forward by the government of Uganda on the HBV prevalence and associated disease severity and mortality, and HBV immunisation coverage over the period of 2015 and 2019 across all provinces. In **Chapter 1**, I introduced the background of HBV, covering the medical microbiological aspect of HBV and its pathogenesis, host defence, disease progression, and diagnosis. In **Chapter 2**, I conducted a literature review on the epidemiology of HBV worldwide and in Africa and Uganda, followed by the global efforts towards HBV elimination and the HBV prevention and control measures that have been put in place by the government of Uganda, primarily the HBV immunisation strategy, testing and treatment of HBV patients, and HBV national health system strengthening. In **Chapter 3**, research methodology including the data collected and analysis conducted is elaborated, followed by results of these analyses presented in Chapters 4 and 5. In **Chapter 4**, I presented my analysis results on the prevalence of HBV across all provinces in Uganda, followed by HBV hospitalisation and case fatality rates during 2015 and 2019. In **Chapter 5**, I analysed the HBV immunisation status across Uganda during the investigated period from 2015 until 2019, focusing on HBV vaccination coverage among children and in health workers, the at-risk sub-population group targeted by the government of Uganda for prioritized HBV immunisation. In **Chapter 6**, I summarised the key findings and general discussion points on the public health measures taken by the government of Uganda to control HBV and reduce the disease burden, severity and case fatality

associated with HBV in the country, as well as some of the challenges to control HBV in Uganda.

Chapter 3. Research Methodology

3.1 Study Setting and population

Uganda is a landlocked country and shares borders with Kenya in the east, South Sudan in the north, Democratic republic of Congo to the west, Rwanda to the south west and Tanzania to the south. According to service delivery, it is divided in to four regions; Central, Eastern, Northern, and Western regions. The country's health system is arranged from the village level (village health team), parish level (health centre II), sub-county level (health centre III), constituency level (health centre IV, district level (general hospital, district health office), regional level (regional referral hospital), national level (ministry of health, national referral hospital and governmental Agencies), which are administrative and referral units (MOH, 2018). The totally population of Uganda is approximately 40,308,000 with 19,780,500 males and 20,527,500 females. The population includes children under 5 years, including around 3,538,000 boys and 3,449,500 girls (Uganda Bureau of Statistics, 2020). The population of health workers during the review period 2015 and 2019 was 412,249 people (Uganda Bureau of Statistics, 2020).

3.2 Study Design

A cross-sectional study was done on a study population comprising of all patients reported in the District Health Information System 2 (DHIS2) between 2015 and 2019 by

all reporting facilities. The population included patients that presented at outpatient department and in-patient department. This is a true representation of Uganda's population as the database captures all population nationwide seeking healthcare (MOH, 2010). The study included all patients reported in the years from 2015 to 2019 in DHIS 2 that accessed services for hepatitis B such as immunisation against hepatitis B, patients tested positive for hepatitis B and enrolled for care at healthcare facilities, and those tested for hepatitis B. The study considered all patients in the outpatient and in-patients in the last 5 years from 2015 to 2019, who were screened for hepatitis B using HBsAg test (MOH, 2019).

The formula used for calculation of percentage of tests conducted, positivity rate and prevalence rate were:

Number of people tested in the region in the year X 100 = percentage of people tested/year
Estimated population in the region in the year

Number of people tested positive for HBV in the region in the year X 100 = positivity rate
Total number of people tested for HBV for in the region in the year

Number of people tested positive for HBV in the region in the year X 1000 = prevalence rate
Estimated population in the region in the year

The study assessed the care provided in terms of admission and fatality rates after admission of the HBsAg positive patients, and immunisation strategic outcomes of the

patients who tested negative on HBsAg test. The formulae used to calculate fatality rate were:

$$\frac{\text{Total number of deaths after admission due to HBV in the region in the year}}{\text{Total number of admitted cases in the region in the year}} \times 100$$

The study reviewed data on children and health workers' compliance to the immunisation schedule of hepatitis B: first dose at first contact in adults or at six weeks in children under five years; second dose after a month in adults while in children at ten weeks of age; and third dose after six month from the receipt of first dose in adults while in children under five years at fourteen weeks of age (MOH, 2019). The study followed the guidelines of Uganda Ministry of Health to qualify children and adults receiving second and third doses, whereby they must demonstrate evidence that they received the last dose prior to the present dose. This helped the researcher to categorise them as fully immunised (received all three doses), partially immunised (received one or two doses) and unimmunised (did not receive or could not demonstrate that he received any vaccination) (MOH, 2019). The quality of care given to the HBsAg positive clients, who were admitted into care was also assessed by reviewing the number of client admitted into the inpatients care and HBV associated deaths reported (MOH, 2019).

3.3 Data analysis and presentation

The statistical analysis of data, using the variables of immunisation (coverage and completion) and initiation on treatment (admission to a treatment centre), was conducted

to assess the prevalence of HBV infection and quality of care provided to patients identified positive with HBV. Microsoft excel was used to calculate the proportion and prevalence rate of HBV positive patients, HBV confirmed patients hospitalised, HBV associated deaths and vaccination status per region per year.

Chapter 4. Epidemiology of Hepatitis B in Uganda

4.1 Prevalence of HBV in the different regions of Uganda

Generally, the proportion of people tested was low, but there was a noticeable increase in the absolute number tested from 2015 to 2016 (Table 1). The Northern region had a higher percentage of people tested for HBV (11.2%) in 2016 compared to the rest of the regions. Both Figure 8 and Table 1 show a general decrease in the positivity rate in the four regions of Uganda. The highest reduction was observed in the Eastern region from 9.8% in 2015 to 3.5% in 2019, while the lowest observed in the Northern region from 14.2% in 2015 to 12.1% in 2019. The Northern region initially had a decrease from 14.2% in 2015 to 7.6% in 2016, however it started increasing steadily to 12.1% in 2019. There was a gradual reduction in the HBV positivity rate in the Eastern region from 9.8% (2015) to 7.1% (2017), and then a sharp drop to 3.8% (2018) and 3.5% (2019) (Table 1).

Despite the low proportion of testing, the rate of positivity is high across all regions. The Northern region had the highest positivity rate of 12.1% in 2019 (last year of the review period) and Eastern had 3.5% in 2019 (Table 1). The Western region is the third most populated region after the Eastern, however it had the lowest number of HBV tests done: 10,064 (2015), 2,205 (2016), 3,081 (2017), 4,303 (2018), and 3,912 (2019); but had the second highest positivity rate: 10% (2015), 10.6% (2016), 8.1% (2017), 5.8% (2018), and 6.3% (2019) (Table 1). Generally, the HBV prevalence increased in all regions with the

Western region registering the lowest prevalence; from 11 per 100,000 people in 2015 to 38 per 100,000 people in 2019, while the Eastern region showed the highest prevalence, with an increase from 23 per 100,000 in 2015 to 174 per 100,000 in 2019. The Northern region, unlike the other regions, initially recorded a sharp increase in the HBV prevalence from 56 per 100,000 people in 2015 to 856 per 100,000 people in 2016 but reduced gradually to 89 per 100,000 people in 2019. There was a relatively constant HBV prevalence observed in the Central region after a rise to 92 per 100,000 people in 2019 (Table 1).

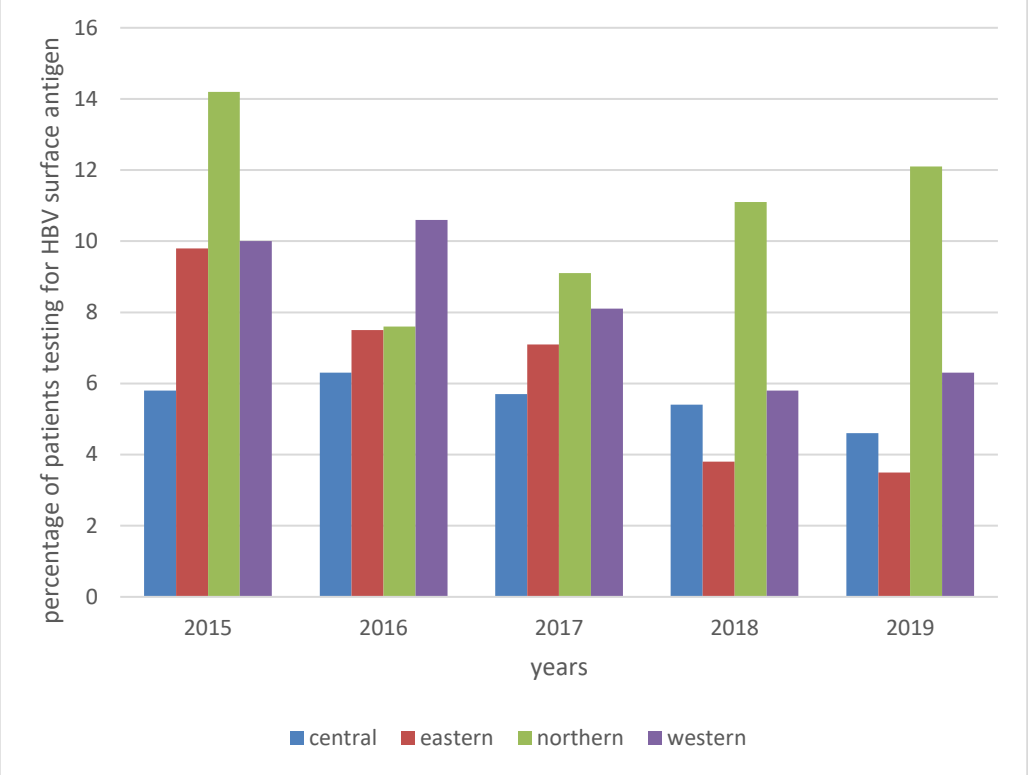


Figure 8. Proportion of patients positive for HBsAg

Figure legend: This figure shows the percentage of HBV test positives using HBsAg testing kits in populations screened for HBV in all regions of Uganda during 2015-2019. The Central, Eastern, Northern, and Western regions are represented by coloured lines of blue, red, green, and purple respectively. The x-axis shows the years from 2015 to 2019. The y-axis shows percentage of HBV test positive patients.

Table 1. HBV positivity rate and prevalence in all regions of Uganda

Region	Variables	Year				
		2015	2016	2017	2018	2019
Central	No. of population	9,657,400	10,113,100	10,459,200	10,816,100	11,816,100
	No. of people tested	43,769	92,661	123,624	182,767	242,375
	% of people tested[1]	0.5	0.9	1.2	1.7	2.1
	No. of test positive	2,525	5,809	7,068	9,914	11,129
	% of test positive[2]	5.8	6.3	5.7	5.4	4.6
	Prevalence per 100,000[3]	26	57	68	92	94
Eastern	No. of population	9,269,800	9,570,300	9,877,000	10,192,100	10,512,200
	No. of people tested	22,160	361,472	304,228	613,680	528,798
	% of people tested	0.2	3.8	3.1	6.0	5.0
	No. of test positive	2,161	27,038	21,585	23,409	18,329
	% of test positive	9.8	7.5	7.1	3.8	3.5
	Prevalence per 100,000	23	283	219	230	174
Northern	No. of population	7,365,200	7,601,400	7,843,700	8,092,600	8,346,600
	No. of people tested	29,246	855,020	565,219	127,211	61,789
	%people tested	0.4	11.2	7.2	1.6	0.7
	No. of test positive	4,161	65,030	51,255	14,062	7,449
	% of test positive	14.2	7.6	9.1	11.1	12.1
	Prevalence per 100,000	56	856	653	174	89
Western	No. of population	9,086,200	9,367,900	9,659,000	9,958,200	10,264,700
	No. of people tested	10,064	20,730	38,152	74,310	61,825
	%people tested	0.1	0.2	0.4	0.7	0.6
	No. of test positive	1,006	2,205	3,081	4,303	3,912
	% of test positive	10	10.6	8.1	5.8	6.3
	Prevalence per 100,000	11	24	31	43	38

[1] % of people tested = $\frac{\text{Number of people tested}}{\text{Number of population}} X\ 100$ [2] % of test positive = $\frac{\text{Number of test positive}}{\text{Nnumber of people tested}}$ X 100 [3] Prevalence per 100000 = $\frac{\text{Number of test positive}}{\text{Number of population}}$ X 100000

4.2 Inpatient admissions by age for Hep B confirmed patients

The total number of HBV admitted cases throughout the review period in 2015-2019 was observed to be low compared to the HBV positive cases registered. Table 2 and Figure 9 generally show a high HBV admission percentage of children above five years of age and adults compared to those less than five years of age in all the regions between 2015and 2019. The admissions of HBV cases in children under 5 years were generally very few with the Eastern region registering the highest number of HBV admission in 2015 at 154 (6.8%) and 53 (2.2%) in 2019, while the Northern region registered the lowest admission rate of HBV cases between 33 (1.1%) in 2017 and 45 (1.8%) in 2018. Figure 9 and Table 2 show that there was no consistent trend in the pattern of HBV admissions, however there was an observed increase in admission of HBV case in three regions (Central, Eastern and Western) in 2019: with the highest increase seen in the Eastern region, from 23 (0.2%) in 2018 to 53(2.2%) in 2019; and the lowest in the Western region, from 5 (0.2%) admission in 2018 to 24 (1.0%) in 2019.

The hospital admissions of HBV patients aged five years and above were higher than those of under-fives of age (Figure 9). The Northern region reported the highest HBV case admissions amongst all regions: 867 (38.4%) in 2015, 1,626 (54.1%) in 2016, 1,827 (59.2%) in 2017, 863 (33.9%) in 2018, and 877 (35.9%) in 2019. The lowest HBV cases hospitalised were in Western region those aged five years and above: 305 (13.5%) in 2015, 388 (12.9%) in 2016, 313 (10.1%) in 2017, 259 (10.2%) in 2018, and 329 (13.5%)

in 2019. The HBV case admissions in the Northern region increased more than two-folds: from 867 (38.4%) in 2015 to 1,826 (59.2%) in 2017; then dropped to 877 (35.9%) in 2019 compared to the rest of regions that recorded an increase in the HBV admissions during 2018 and 2019.

Table 2. Age-group stratified hospital admission of Hep B confirmed patients

Region	Age	Year				
		2015	**2016**	**2017**	**2018**	**2019**
		N[1]=2256	**N=3010**	**N=3084**	**N=2546**	**N=2445**
		n[2] (n/N=%)	n (n/N=%)	n (n/N=%)	n (n/N=%)	n (n/N=%)
Central	**<5yr**	10(0.4)	8(0.3)	10(0.3)	18(0.7)	39(1.6)
	≥5yr	457(20.3)	461(15.3)	476(15.4)	539(21.2)	541(22.1)
Eastern	**<5yr**	154(6.8)	53(1.8)	5(0.2)	23(0.9)	53(2.2)
	≥5yr	408(18.1)	422(14.1)	398(12.9)	794(31.2)	548(22.4)
Northern	**<5yr**	37(1.6)	21(0.7)	33(1.1)	45(1.8)	34(1.4)
	≥5yr	867(38.4)	1,626(54.1)	1,826(59.2)	863(33.9)	877(35.9)
Western	**<5yr**	18(0.8)	31(1.0)	23(0.7)	5(0.2)	24(1.0)
	≥5yr	305(13.5)	388(12.9)	313(10.1)	259(10.2)	329(13.5)

[1] Total number of Hep B confirmed patients from all regions admitted to hospitals per year
[2] Number of Hep B confirmed patients admitted to hospitals per region per year

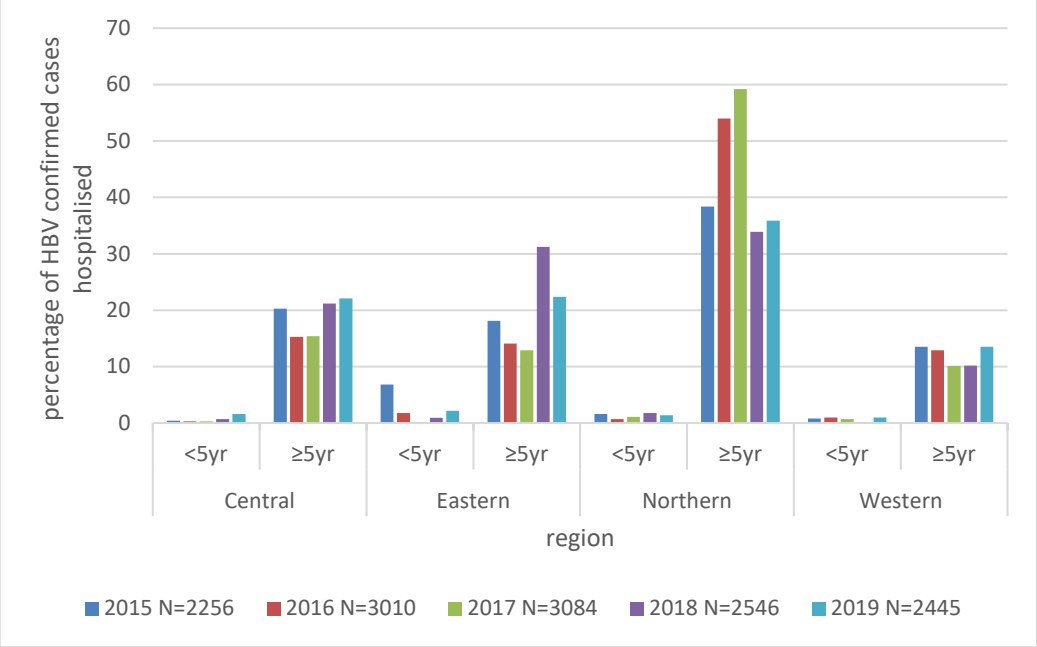


Figure 9. Percentage of HBV confirmed cases hospitalised by age stratification

Figure legend: This figure shows HBV admissions per age-group across all regions of Uganda. The x-axis shows the age groups and regions while the y-axis shows percentage of admitted HBV cases. The blue, red, green, purple and light blue colours represent the years 2015, 2016, 2017, 2018 and 2019 respectively across all regions.

4.3 In-patient admission by Sex of the Hep B confirmed cases

Table 3 and Figure 10 show that the HBV cases admitted are more in males than females in all the regions across the review period from 2015 and 2019. The Northern region had the highest HBV case admissions of both sexes with an increase in the total HBV admissions from 904 (40.1%) in 2015 to 1,859 (60.3%) in 2017, then declined to 911 (37.3%) in 2019. However, this region showed the highest proportion of HBV admissions among all regions. The females in the Northern region had higher HBV admission percentages, especially in 2016 at 785 (26.1%) and in 2017 at 902 (29.2%), compared to all other regions (Eastern, Central and Western). Both Table 3 and Figure 10 showed a decline in the percentage of patients admitted in both sexes from 2015 to 2016 in three regions; Central, Eastern and Western. The lowest decline in percentage of HBV case admission in both sexes was in the Western region, from 14.3% in 2015 to 13.9% in 2016; while the Eastern region had the highest decline, from 24.9% in 2015 to 15.8% in 2016. There was an observed rise in total HBV cases in 2019 compared to the previous year in three regions; Central, Northern and Western. The highest rise in HBV admissions in both sexes was recorded in the Western region, from 264 (10.4%) in 2018 to 345 (14.1%) in 2019; and the lowest increase in the Central region, from 557(21.9%) in 2018 to 580 (23.7%) in 2019 (Table 3)

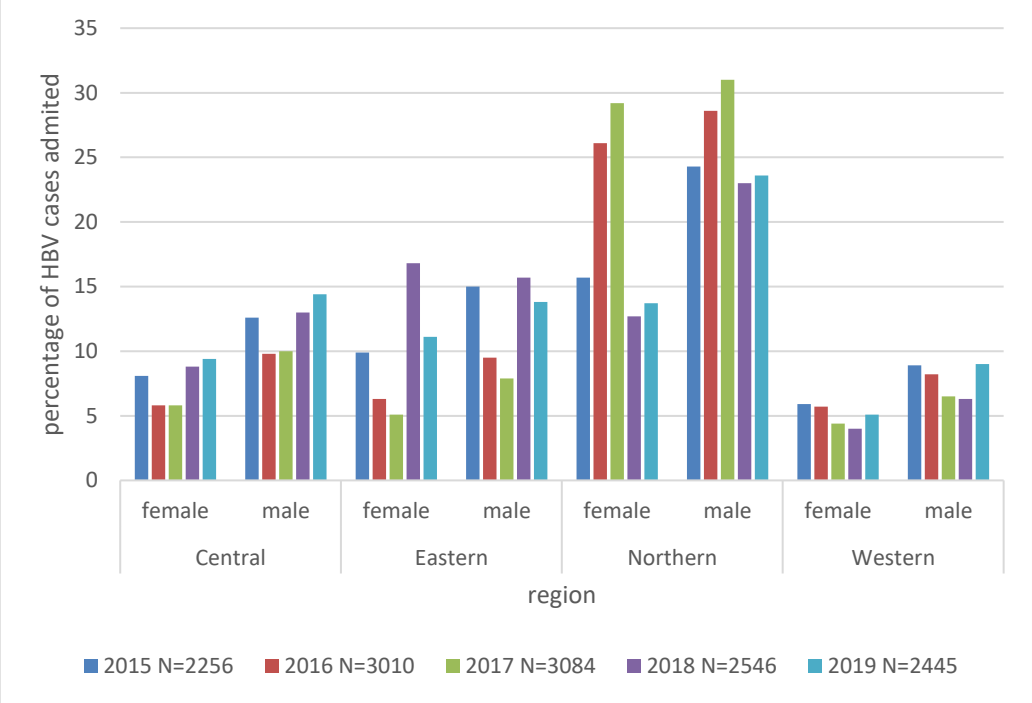


Figure 10. Hep B confirmed patients stratified by sex admitted to hospital

Figure legend: Percentage of hospital admission of HBV patients for men and women across the regions with the x- axis showing the different sex per region and the y- axis showing the percentage of HBV patients admitted.

Table 3. Distribution of hospital-admitted Hep B confirmed patients by sex from 2015-2019

Region	sex	Year (2015-2019), (N=13,341)				
		2015	**2016**	**2017**	**2018**	**2019**
		N[1]=2,256	**N[1]=3,010**	**N[1]=3,084**	**N[1]=2,546**	**N[1]=2,445**
		n[2] (n/N=%)	n[2] (n/N=%)	n[2] (n/N=%)	n[2] (n/N=%)	n[2] (n/N=%)
Central	**female**	182(8.1)	174(5.8)	179(5.8)	225(8.8)	229(9.4)
	male	285(12.6)	295(9.8)	307(10.0)	332(13.0)	351(14.4)
	Total	467(20.7)	469(15.5)	486(15.8)	557(21.9)	580(23.7)
Eastern	**female**	224(9.9)	190(6.3)	158(5.1)	429(16.8)	272(11.1)
	male	338(15.0)	285(9.5)	245(7.9)	388(15.2)	337(13.8)
	Total	562(24.9)	475(15.8)	403(13.1)	817(32.1)	609(24.9)
Northern	**female**	355(15.7)	785(26.1)	902(29.2)	323(12.7)	334(13.7)
	male	549(24.3)	862(28.6)	957(31.0)	585(23.0)	577(23.6)
	Total	904(40.1)	1647(54.7)	1859(60.3)	908(35.7)	911(37.3)
Western	**female**	134(5.9)	171(5.7)	135(4.4)	104(4.0)	125(5.1)
	male	189(8.4)	248(8.2)	201(6.5)	160(6.3)	220(9.0)
	Total	323(14.3)	419(13.9)	336(10.9)	264(10.4)	345(14.1)

[1] Total number of Hep B confirmed patients from all regions admitted to hospitals per year
[2] Number of Hep B confirmed patients admitted to hospitals per region per year

4.4 Fatality rate of HBV confirmed patients admitted during 2015-2019

There was a general reduction in the case fatality rate of HBV confirmed patients in all regions during 2015-2019, except in the Eastern region (Figure 11 and Table 4). The highest HBV case fatality rate was observed in the Northern and Western regions: 18.1% (Northern) and 14% (Western) in 2015 and 13.8%(Northern) and 14.8% (Western) in 2019. Three regions recorded a reduction in HBV fatality rates: from 18.1% (Northern), 13.3% (Western), and 9.4% (Central) in 2015 to 8.6% (Western), 6.6% (Northern) and 6% (Central) in 2017. However, there was an increase in HBV fatality rates in all three regions, Central (10.4%), Northern (13.8%) and Western (14.8%) in 2018. The Eastern region reported an increase in the HBV related deaths: from 4.8% in 2015 to 12.7% in 2017, which dropped gradually to 6.5% in 2018 and was maintained at 7.2% in 2019 (Figure 11 and Table 4).

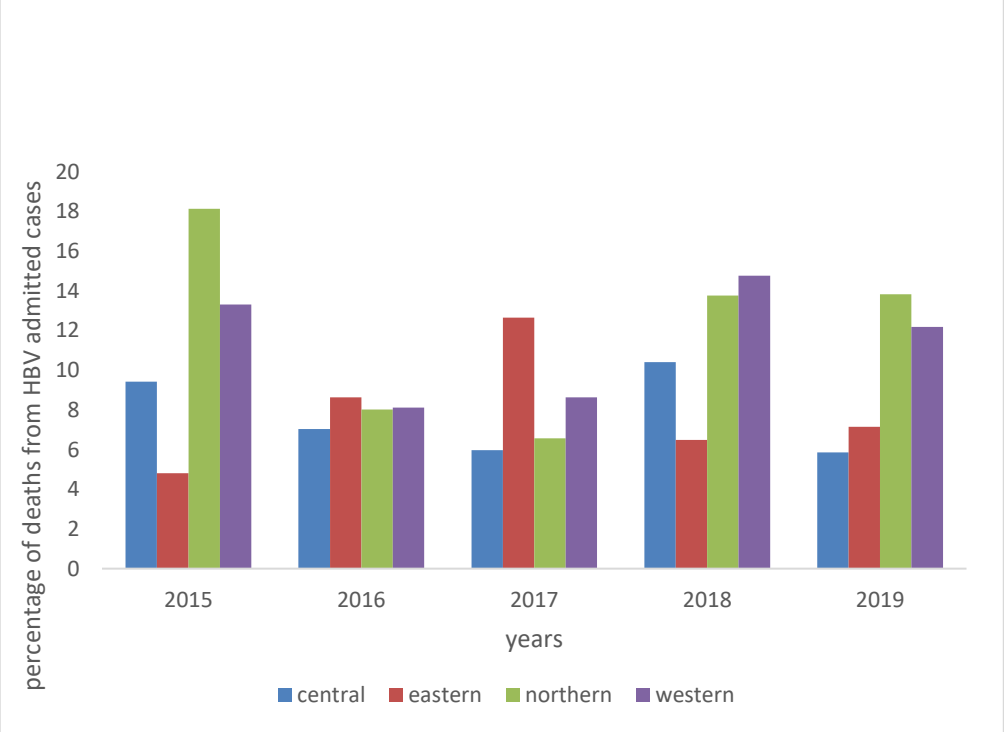


Figure 11. Case fatality rate among HBV patients admitted to hospital per region

Figure legend: The figure shows fatality rates of Hep B patients admitted in different health facilities of Uganda per region per year. The blue, red, green, purple colour represent the fatality rate per region in Central, Eastern, Northern and Western regions, respectively. The x-axis represents time in years while the y-axis represents HBV case fatality rate in percentage.

Table 4. Case fatality rate among HBV confirmed patients admitted to hospital region from 2015-2019

Region	Variables	Years					total
		2015	2016	2017	2018	2019	
Central	No. of people positive case admitted	467	469	486	557	580	2,073
	No. of death after admission due to HBV	44	33	29	58	34	198
	Case fatality rate (%)[1]	9.4	7	6	10.4	5.9	9.6
Eastern	No. of people positive case admitted	562	475	403	817	601	2,858
	No. of death due to HBV after admission	27	41	51	53	43	215
	Case fatality rate (%)	4.8	8.6	12.7	6.5	7.2	7.5
Northern	No. of people positive case admitted	904	1,647	1,859	908	911	6,229
	No. of death due to HBV after admission	164	132	122	125	126	669
	Case fatality rate (%)	18.1	8	6.6	13.8	13.8	10.7
Western	No. of people positive case admitted	323	419	336	264	353	1,695
	No. of death due to HBV after admission	43	34	29	39	43	188
	Case fatality rate (%)	13.3	8.1	8.6	14.8	12.2	11.1

[1] case fatality rate $= \frac{\text{number deaths after admission due to HBV}}{\text{number of HBV positive case admitted}} \text{ X } 100$

Chapter 5. Immunisation status

5.1 Immunisation performance of health workers against HBV across the four regions of Uganda

There was an increase in the proportion of health workers completing immunisation (receiving 3-dose HBV vaccine on Three different time intervals based on the immunisation schedule) in 2019 across all regions, with the Northern region having the highest completion (fully immunised) at 110,206 (133.4%) and the Central region showing the lowest completion rate of full doses at 16,169 (15.9%). The Northern region registered an increase in the proportion of health workers completing the vaccination schedule (receiving all 3 doses) across the 5-year period of review starting from 12,998 (41.9%) in 2015 to 110,206 (133.4%) in 2019, while the other regions had a relatively levelled completion (Table 5).

There was a relative increase in health workers partially immunised across all regions between 2015 and 2017. A gradual increase in partial immunisation of HBV among health workers in the Western region was shown at 21,137 (16.5%) in 2019 (Table 5). A complete reduction of partial immunisation was shown in health workers in the Northern region at 0 (0%) in 2019. The Eastern region continued to register an increase in the proportion of health workers with partial immunisation: from 12,603 (49.3%) in 2015 to 58,950 (59.0%) in 2019. Throughout 2015 and 2019, the Western and Central regions

showed a gradual increase in the number of unimmunised health workers: from 16,637 (41.2%) and 12,744 (42.9%) in 2015 to 68,196 (53.1%) and 34,624 (34.1%) in 2019 respectively. The Northern and Eastern regions showed a constant reduction in the number of unimmunised health workers from 12,759 (41%) and 13,392 (37.5%) in 2015 to 5,169 (6.3%) and 7,168 (7.2%) in 2019, respectively (Table 5)

Table 5. HBV immunisation status of health workers by region per year

Region	Immunisation status	2015	2016	2017	2018	2019
		N[1]=29,705	**N=76,392**	**N=84,464**	**N=94,172**	**N=101,435**
		n[2] (%=n/N)	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**
Central	**fully immunised[3]**	3,494(11.8)	7,201(9.4)	10,139(12.0)	12,496(13.3)	16,169(15.9)
	partially immunised[4]	13,467(45.3)	40,268(52.7)	41,029(48.6)	39,482(41.9)	50,642(49.9)
	Unimmunised[5]	12,744(42.9)	28,923(37.9)	33,296(39.4)	42,194(44.8)	34,624(34.1)
		N=35,696	**N=83,277**	**N=86,877**	**N=103,165**	**N=99,893**
		n (%=n/N)	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**
Eastern	**fully immunised**	4,701(13.2)	10,177(12.2)	14,683(17.0)	16,373(15.9)	33,775(33.8)
	partially immunised	17,603(49.3)	43,281(52.0)	41,205(47.4)	60,663(58.8)	58,950(59.0)
	unimmunised	13,392(37.5)	29,819(35.8)	30,989(35.7)	26,129(25.3)	7,168(7.2)
		N=31,118	**N=78,922**	**N=81,175**	**N=86,241**	**N=82,585**
		n (%=n/N)	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**
Northern	**fully immunised**	5,361(17.2)	13,584(17.2)	32,634(40.2)	40,292(46.8)	110,206(133.4)
	partially immunised	12,998(41.8)	44,346(56.2)	43,360(53.4)	41781(48.4)	0(0)
	unimmunised	12,759(41.0)	20,992(26.6)	5,181(6.3)	4,168(4.8)	5,169(6.3)
		N=40,230	**N=9,1357**	**N=10,9830**	**N=12,9640**	**N=128,336**
		n (%=n/N)	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**	**n (%=n/N)**
Western	**fully immunised**	8,247(20.5)	12,004(13.1)	12,071(11.0)	18,019(13.9)	39,003(30.4)
	partially immunised	15,346(38.1)	38,356(42.0)	49,157(44.8)	44,555(34.4)	21,137(16.5)
	unimmunised	16,637(41.2)	40,997(44.9)	48,602(44.2)	67,066(51.7)	68,196(53.1)

[1] The total number of health workers in all regions per year

[2] Number of health workers per immunisation status per region per year

[3] Fully immunised: Received 3 full doses of HBV vaccination (with 2nd and 3rd doses received one month and six months after the 1st dose of vaccination)

[4] Partially immunised: Received at least one or two doses of HBV vaccine, but not completed the 3 full doses of HBV vaccination (or has no evidence of completion as per the immunisation card)

[5] Unimmunised: Received any doses of HBV vaccines (or has no evidence of HBV vaccination per immunisation card)

5.2 Compliance of health workers to the hepatitis B immunisation schedule

There was a reduction in the proportion of health workers who received the first dose of HBV vaccine and followed-up to complete the third dose in 2015. The Central region had the highest number of health workers not completing the second and third doses of HBV vaccine: 15,043 (50.6%) health workers received the first dose, of whom 3,384 (11%) followed-up to receive the second dose and 2,088 (7.0%) for the third dose, subsequently (Figure 12 and Table 6). The Western region showed a relatively low level of lost to follow-up: 6,022 (15.0%) received the first dose, followed-up by 5,005 (12.4%) for the second dose and 2,984 (7.4%) for the third dose (Figure 12 and Table 6). However, there was a reduction in the number of health workers who received the first, second, and third doses in 2019 in the Central, Eastern and Northern regions (Figure 12 and Table 6).

There was a gradual increase in the uptake of the third dose in the Central, Eastern, and Northern regions. The Northern region recorded the highest gradual increase in the uptake of the third dose among health workers from 3,583 (11.5%) in 2015 to 13,932 (16.9%) in 2019 (Table 6). The Western region recorded a gradual decrease in the dose 3 uptake: from 2,984 (7.4%) in 2015 to 7,290 (5.7%) in 2019. The Eastern and Northern regions recorded a higher proportion of health workers being vaccinated across all the 3 vaccination schedules compared to the Central and Western regions. Only the Eastern region had an increase in the proportion of health workers receiving the second and third

dose from 5,131 (14.4%) in 2015 to 31,815 (31.9%) in 2019 for the second dose, and from 3,582 (10.0%) in 2015 to 27,172 (27.2%) in 2019 for the third dose (Table 6).

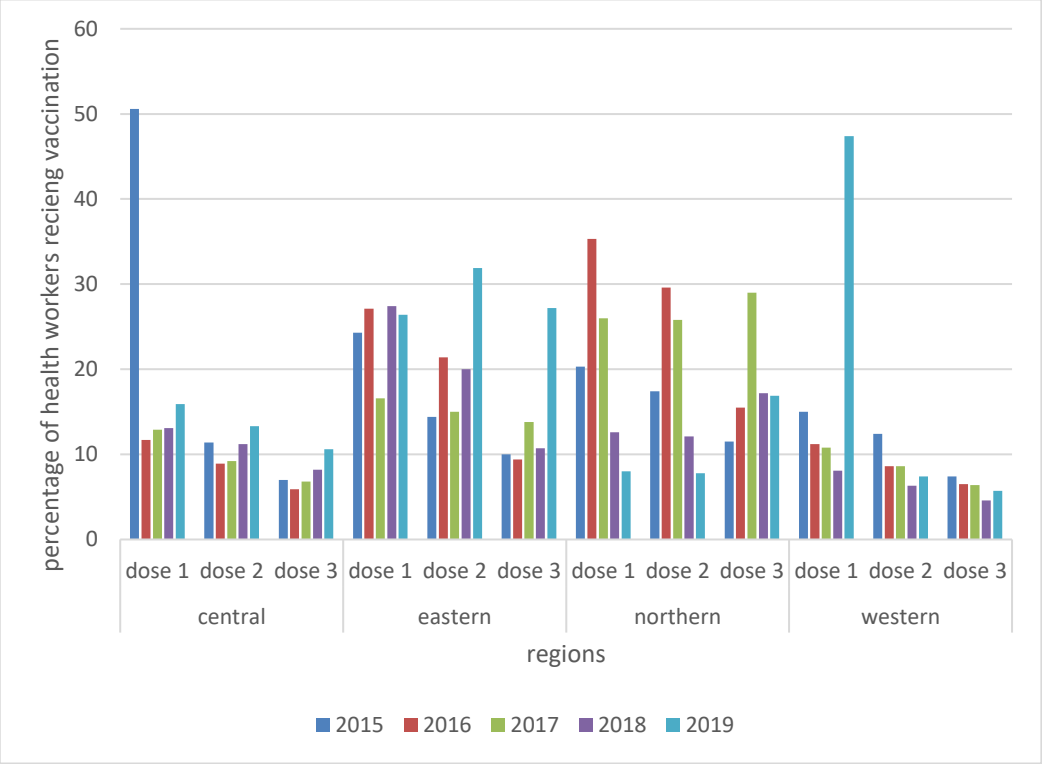


Figure 12. Hep B vaccination among health workers per region during 2015-2019

Figure legend: This graph shows HBV vaccination and completion among health workers. The blue, red, green and light blue represent health workers vaccinated per year for the first, second and third doses. The x-axis represents the regions and the doses, while the y-axis represents the percentage of health workers vaccinated.

Table 6. Proportion of health workers who received scheduled doses of HBV vaccine during 2015-2019

Region	Dose	2015	2016	2017	2018	2019
		N[1]=29,705 n[2] (%=n/N)	**N=76,392 n (%=n/N)**	**N=84,464 n (%=n/N)**	**N=94,172 n (%=n/N)**	**N=101,435 n (%=n/N)**
Central	**Dose 1[3]**	15,043(50.6)	8,959(11.7)	10,935(12.9)	12,370(13.9)	16,154(15.9)
	Dose 2[4]	3,384(11.4)	6,795(8.9)	7,770(9.2)	10,564(11.2)	13,475(13.3)
	Dose 3[5]	2,088(7.0)	4,496(5.9)	5,728(6.8)	7,768(8.2)	10,775(10.6)
		N=35,696 n (%=n/N)	**N=83,277 n (%=n/N)**	**N=86,877 n (%=n/N)**	**N=103,165 n (%=n/N)**	**N=99,893 n (%=n/N)**
Eastern	**Dose 1**	8,662(24.3)	22,528(27.1)	14,402(16.6)	28,231(27.4)	26,351(26.4)
	Dose 2	5,131(14.4)	17,846(21.4)	13,067(15.0)	20,603(20.0)	31,815(31.9)
	Dose 3	3,582(10.0)	7,869(9.4)	11,973(13.8)	10,993(10.7)	27,172(27.2)
		N=31,118 n (%=n/N)	**N=78,922 n (%=n/N)**	**N=8,1175 n (%=n/N)**	**N=86,241 n (%=n/N)**	**N=82,585 n (%=n/N)**
Northern	**Dose 1**	6,304(20.3)	27,895(35.3)	21,128(26)	10,845(12.6)	6,572(8.0)
	Dose 2	5,428(17.5)	23,326(29.6)	20,959(25.8)	10,407(12.1)	6,429(7.8)
	Dose 3	3,583(11.5)	12,203(15.5)	23,536(29.0)	14,826(17.2)	13,932(16.9)
		N=40,230 n (%=n/N)	**N=91,357 n (%=n/N)**	**N=109,830 n (%=n/N)**	**N=129,640 n (%=n/N)**	**N=128,336 n (%=n/N)**
Western	**Dose 1**	6,022(15.0)	10,224(11.2)	11,818(10.8)	10,501(8.1)	60,844(47.4)
	Dose 2	5,005(12.40)	7,819(8.6)	9,431(8.6)	8,130(6.3)	9,476(7.4)
	Dose 3	2,984(7.4)	5,980(6.5)	7,052(6.4)	5,991(4.6)	7,290(5.7)

[1] Total number of health workers in all regions per year

[2] Number of health workers per HBV immunisation status per region per year

[3] Dose 1: Received HBV vaccine for the first time (for a person who has not been vaccinated before with HBV vaccine or who does not have any evidence of prior HBV vaccination based on immunisation card)

[4] Dose 2: Received HBV vaccine for the second time following the first vaccination received a month prior to the current vaccination (documented in the immunisation card).

[5] Dose 3: Received HBV vaccine for the third time following the second vaccination received six months after first vaccination prior to the current vaccination (documented in the immunisation card).

5.3 Hep B immunisation program performance among children under 5 years of age from 2015-2019

Overall, a low uptake of HBV immunisation services in children under five years was shown in 2015 in all regions, which increased in the following years (Figure 13). The highest number of children immunised with HBV vaccine in the review period of 2015-2019 was in the Eastern region in 2016 with 481,444 (7.5%) of the children vaccinated for the first dose of HBV vaccine (Figure 13 and Table 7). There was an increase in the proportion of children immunised with HBV vaccines out of the total number of children under five years starting 2016 onwards across all regions. The Northern region recorded the lowest proportion of children under five years vaccinated according to the HBV vaccination program. The lowest level of HBV immunisation was exhibited in 2015 with a record of 176,396 (2.8%) children vaccinated with the first dose, 162,421 (2.6%) vaccinated with the second dose, and 163,636 (2.6%) vaccinated with the third dose. The Central region had the highest proportion of children completing the full doses of HBV immunisation; from 4.1% to 7.1% of the first dose and from 3.6% to 6.4% of the third dose in 2015 and 2019, respectively (Table 7). The Northern region had the lowest rage of children completing the full doses of HBV immunisation: from 2.8% to 5.3% of the first dose and from 2.6% to 5.0% of the third dose in 2015 and 2019, respectively (Table 7).

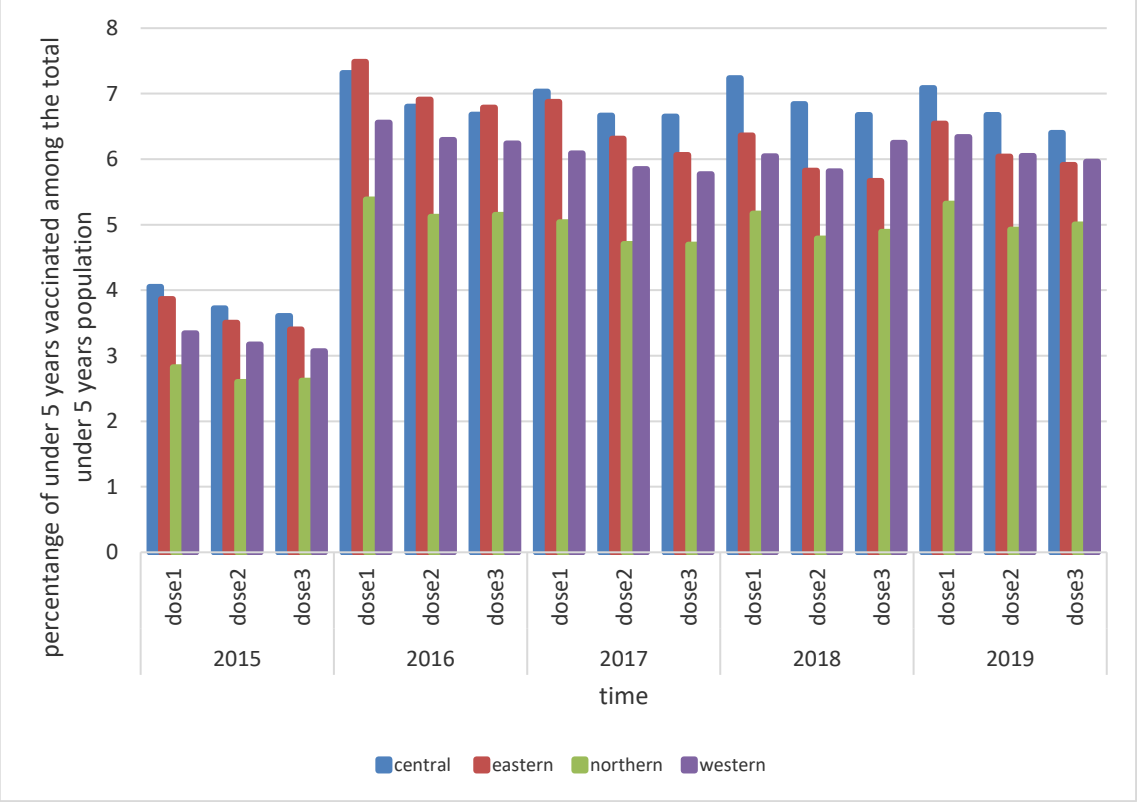


Figure 13. Trend of HBV vaccination uptake in the different regions of Uganda

Figure legend: This graph shows immunisation status of children under five-years according to the HBV vaccination schedule represented on the x-axis per year as dose 1, dose 2, dose 3. The y-axis represents the proportion of children immunised per dose (appointment/schedule) and the regions of Central, Eastern, Northern and Western, represented by the colours blue, red, green, purple, respectively. There is an increase in the vaccination uptake in all region from 2015 to 2016 and then levels off until 2019. The Northern region has the lowest uptake across all scheduled doses and the Central region has the highest uptake.

Table 7. HBV immunisation uptake in children under 5years during 2015-2019 in Uganda

Year	Dose received	Region			
		Central n[1] (%=n/N[2])	Eastern n (%=n/N)	Northern n (%=n/N)	Western n (%=n/N)
2015(N=6,249,100)	**1 dose**[3]	253,097(4.1)	241,465(3.9)	176,396(2.8)	208,774(3.3)
	2 doses[4]	232,611(3.7)	218,895(3.5)	162,421(2.6)	198,312(3.2)
	3 doses[5]	225,418(3.6)	212,638(3.4)	163,626(2.6)	191,607(3.1)
2016(N=6.430,500)	**1 dose**	470,515(7.3)	481,444(7.5)	346,338(5.4)	421,820(6.6)
	2 doses	437,524(6.8)	444,367(6.9)	329,272(5.1)	404,665(6.3)
	3 doses	429,477(6.7)	436,460(6.8)	331,227(5.2)	401,143(6.2)
2017(N=6,627,800)	**1 dose**	465,870(7.0)	455,713(6.9)	333,879(5.0)	403,455(6.1)
	2 doses	441,760(6.7)	418,423(6.3)	312,003(4.7)	387,508(5.8)
	3 doses	427,590(6.6)	401,934(6.1)	311,081(4.7)	382,380(5.8)
2018(N=6,627,800)	**1 dose**	494,044(7.2)	434,353(6.4)	352,953(5.2)	412,605(6.1)
	2 doses	466,875(6.8)	397,593(5.8)	326,824(4.8)	396,759(5.8)
	3 doses	455,552(6.7)	386,710(5.7)	333,851(4.9)	426,557(6.3)
2019(N=6,988,300)	**1 dose**	495,122(7.1)	457,204(6.5)	371,938(5.3)	442,972(6.3)
	2 doses	466,543(6.7)	421,910(6.0)	344,194(4.9)	422,795(6.1)
	3 doses	447,333(6.4)	413,017(6.4)	349,557(5.0)	416,636(6.0)

[1] Number of children under 5 years of age immunised per dose per region per year

[2] Total number of children under 5 years of age in all regions per year

[3] HBV vaccination for the first time for a child who has not been vaccinated (or does not have evidence of receiving a Hep B vaccine based on immunisation card).

[4] HBV vaccination for the second time following the first vaccination received a month prior to the current vaccination (based on immunisation card).

[5] HBV vaccination for the third time following the second vaccination received six weeks after the first vaccination prior to the current vaccination. The first and second vaccination doses should have been documented in the immunisation card.

5.4 Trend of missed opportunities in the immunisation program for children under 5 years against Hep B in Uganda from 2015-2019

Overall, there was a decrease in the dropout rate of children who received the first dose of HBV vaccine and due for the subsequent doses, as per the HBV immunisation schedule during 2015-2019 (Table 8 and Figure 14). The Western region exhibited lower dropout rates of the second dose at 10,462 (5.0%) in 2015 and 15,846 (3.8%) in 2018 compared to the other regions (Table 8). The dropout rates in the Western region for the third dose was 17,167 (8.2%) in 2015 and -13,952 (-3.4%) in 2019. The Eastern region had the highest dropout rate for the second dose at 22,570 (9.3%) in 2015 and 25,294 (7.7%) in 2019 while the third dose was recorded at 28,827 (13.2%) in 2015 and 44,187(9.7%) in 2019 (Table 8). The Northern region initially recorded a reduction in the dropout rate from 13,975 (7.9%) in 2015 to 17,066 (4.9%) in 2016 but increased to 27,744 (5.4%) in 2019. Similarly, the Central region recorded a reduction in the dropout rate of dose 3 from 27,679 (10.9%) in 2015 to 38,492 (7.8%) in 2018, and then increased to 47,789 (10.2%) in 2019 (Table 8).

Table 8. Missed opportunity for vaccination (MOV) or dropout rate per dose for HBV immunisation in under 5 years of age

		Central		Eastern		Northern		Western	
Year	**Dose**	**# children vaccinated (n)**	**MOV[1] (or drop-out) * n (%)**	**# children vaccinated (n)**	**MOV (or drop-out) * n (%)**	**# children vaccinated (n)**	**MOV (or drop-out) * n (%)**	**# children vaccinated (n)**	**MOV (or drop-out) * n (%)**
2015	dose 1	253,097		241,465		176,396		208,774	
	dose 2	232,611	20,486(8.1)	218,895	22,570(9.3)	162,421	13,975(7.9)	198,312	10,462(5.0)
	dose 3	225,418	27,679(10.9)	212,638	28,827(13.2)	163,626	12,770(7.2)	191,607	17,167(8.2)
2016	dose 1	470,515		481,444		346,338		421,820	
	dose 2	437,524	32,991(7.0)	444,367	37,077(7.7)	329,272	17,066(4.9)	404,665	17,155(4.1)
	dose 3	429,477	41,038(8.7)	436,460	44,984(10.1)	331,227	15,111(4.4)	401,143	20,677(4.9)
2017	dose 1	465,870		455,713		333,879		403,455	
	dose 2	44,1760	24,110(5.2)	418,423	37,290(8.2)	312,003	21,876(6.6)	387,508	15,947(4.0)
	dose 3	427,590	38,280(8.2)	401934	53,779(11.8)	311,081	227,98(6.8)	382,380	21075(5.2)
2018	dose 1	494,044		434,353		352,953		412,605	
	dose 2	466,875	27,169(5.5)	397,593	36,760(8.5)	326,824	26,129(7.4)	396,759	15846(3.8)
	dose 3	455,552	384,92(7.8)	38,6710	10,883(11.0)	333,851	19,102(5.4)	426,557	-13952(-3.4)
2019	dose 1	495,122		457,204		371,938		442,972	
	dose 2	466,543	28,579(5.8)	421,910	35,294(7.7)	344,194	27,744(7.5)	422,795	20177(4.6)
	dose 3	447,333	47,789(10.2)	413,017	44,187(9.7)	349,557	22,381(6.0)	416,636	26336(5.9)

[1] MOV (or drop-out) % formula: patients who started HBV immunisation but did not complete the second or/and third doses of immunisation.

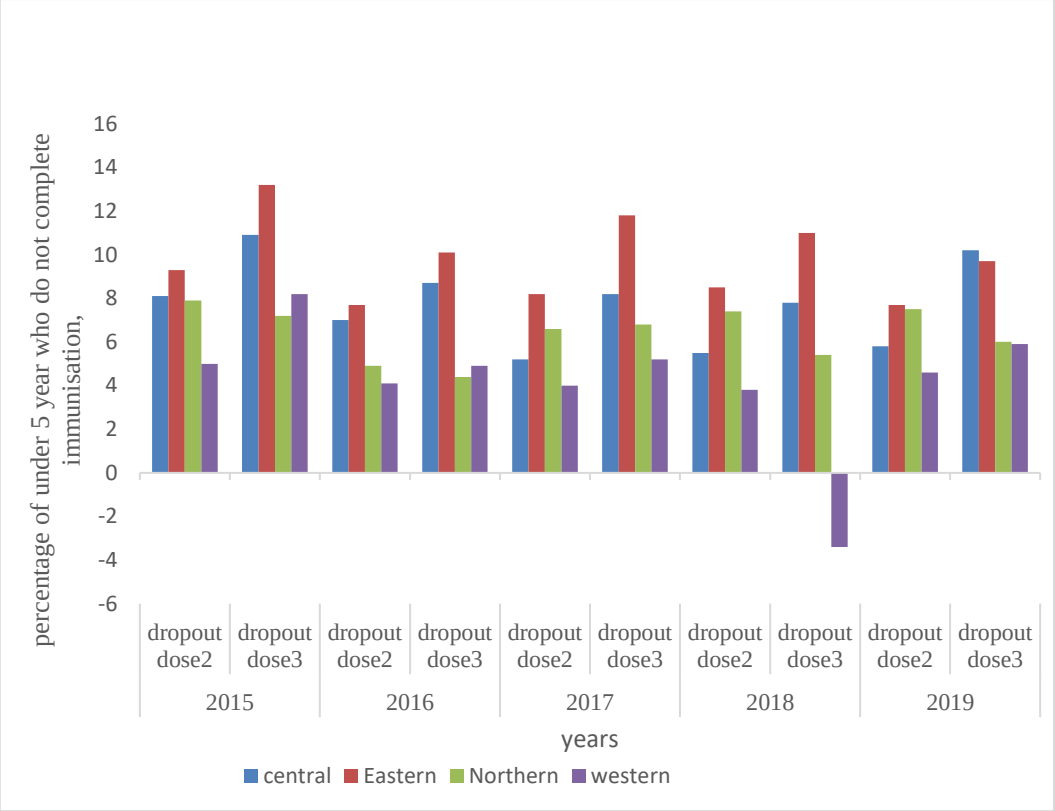


Figure 14. Dropout rate of children under 5 years in different regions of Uganda

Figure legend: This graph exhibits different regions of Uganda; Central, Eastern, Northern and Western regions represented in colour-coded bars in blue, red, green, and purple respectively. The x- axis shows time in years per dropout of either dose 2 or dose 3. The y-axis represents the proportion of dropout rates of HBV vaccination.

Chapter 6. General discussion

Testing for HBV plays a critical role in the access to the continuum of care for Hepatitis. The higher the proportion of individuals tested for hepatitis B, the higher the self-awareness of individuals and the ability of the health system to keep track of all HBV patients who need hepatitis care services (WHO, 2015). The proportion of the population tested for HBV was far smaller than the estimated population suspected to be at risk of hepatis B in Uganda by the government records (Ministry of Health, 2016). The low testing rate observed is affected by the government policy that limited the point-of-care testing to referral centres (UCG, 2016 and MOH, 2019). The HBV transmissions through contact with infected body fluids, mostly sexual fluids and its association with Human Immune Virus (HIV), has led to stigma of the individuals affected. Stigma is one of the biggest contributors to the under-utilisation of health care services such as testing, as observed in other studies on HIV service delivery (Ministry of Health, 2016).

There was an observed high yield in the HBV positivity rates among the individuals tested for HBV during the review period from 2015 to 2019 in Uganda. The HBV positivity in 2019 exhibited the high rates in the Western (6.3%), Northern (12.1%), Central (4.6%), and Eastern (3.5%) regions. The high yield calls for an active search for the HBV positive cases similar to the HIV care strategies adapted, which included

counselling and referral by lay people or/and testing in remote places (UCG, 2016)(World Health Organization, 2019).

The prevalence of Hep B has been declining since the start of the immunisation against Hepatitis B in 2002. The serological survey of 2005 indicated that hepatitis B in Uganda was prevalent, and has reduced for over a decade according to the hepatitis B serological survey conducted in 2016, with HBV immunization as the primarily adapted public health intervention during this period (Ministry of Health, 2016). However, this reduced HBV prevalence may not reflect the possibility of under-screenings as observed in the study.

The WHO and the Global Hepatitis Assembly recommended an early treatment of hepatitis cases to reduce the viral load circulation in the community and prolong the life of those infected (WHO, 2016). The Ministry of Health of the Ugandan government has put in place a policy that required all hepatitis B symptomatic patients to be enrolled in healthcare and eligible ones initiated on treatment in 2015. There was an observed low number of HBV admissions for proper treatment in the review period 2015-2019. This is in agreement with the WHO report (WHO, 2017) that documented that around 8% of the HBV diagnosed patients are put on treatment. This may be due to the lack of awareness in general population, limited knowledge on HBV disease management by the health personnel, as well as challenges at primary healthcare facilities in testing and providing

adequate treatment for hepatitis B infected patients (Mugisha *et al.*, 2019). Low admissions are also attributed to weak health systems that lack adequate human resource to manage hepatitis B cases (MOH, 2019 and AHPR 2018/2019, 2019).

The low funding and lack of equipment have contributed to the slow reduction of mortality rates of all admitted HBV patients during the review period. The high admission of cases in those aged five years and above based on the national hepatitis B sero-survey in 2016 showed there were more symptomatic infections in older children and adults than infants in Uganda (Ministry of health, 2016 and Bwogi et al, 2009). This seems contradictory to the general HBV epidemiology exhibited globally and in the region. This may be associated with the innate immunity in younger children aged under five years (Yi *et al.*, 2016), but further research is warranted to better understand the age-specific risk factors, host immunity, and transmission routes in infants and younger children in Uganda context.. The higher percentage of HBV hospital admissions in males than females in Uganda is similar to the existing publications, which may be associated with sexual behaviours with multiple partners. Another contributing factor may be the poor health sicking behaviours of males as they visit healthcare facilities at an advanced stage of HBV infection (Rights *et al.*, 2019). The observed high admissions in the Northern region and Eastern regions during the review period may be associated with the higher number of people who missed HBV vaccination since the HBV immunisation program started in Uganda in 2002 (MOH, 2019). The areas that time where still

experiencing insecurity due to civil war and some were just coming out of the civil war, which made access to healthcare facilities difficult.

The WHO guidelines on the prevention and management of viral hepatitis (WHO, 2015) was adopted by Uganda (MOH, 2019), and immunisation has been identified as one of the cornerstones in HBV prevention in both children and adults. Health workers were identified as the people most at risk of HBV infections and transmissions (Law society report,2015). The WHO strategy is aimed at achieving 90% HBV immunisation coverage or completion of the 3 full doses of HBV vaccination (WHO, 2017a and Waheed *et al.*, 2018). However, there was an observed high number of unimmunised health workers in all the regions in Uganda during the study period. This is due to the weak financing of the HBV immunization programs in Uganda as the government only provided 3 million dollars to finance the entire program in nation-wide (Uganda gazette, 2018). The weak immunization record system in low-income countries (Gavi, 2020) including Uganda also contributes to the failure to track vaccination program as some of the data is lost or poorly filled in. Failure to immunise a critical mass including women increases the risk of mother-to-child transmission of hepatitis B in the event a mother who may have an HBV infection with a high viral load (WHO, 2017). The performance of immunisation has equally been similar in children under five years of age as the coverage has been low. Reducing the dropout rates of HBV immunisations for the full 3 doses is important in ensuring full protection of the immunised against HBV infection, however there were

observations of unimmunised children which is attributed to poor accessibility to vaccines in context of general inequities in the society (Gavi, 2020).

In conclusion, the process towards the HBV elimination has been affected by the country's inability to immunise a critical mass of the high risk population as identified by the government, low testing capacity, and the limited impact of the test and treat strategy due to the lack of knowledge on HBV screening and inadequate resources to provide adequate treatments. This thesis has few limitations due to the limited variables in the available datasets obtained from the government of Uganda and analysed. This research was unable to assess more comprehensive and detailed driving factors in the Uganda public health system that may have further contributed to the positive or negative performance of the proposed strategies by the country.

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