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The burden of severe Hepatitis A disease in South Africa's public sector: A cross sectional study using routine laboratory data from 2016 to 2021.

Dr Mariana Makhanani Khoza (457383)

A research report submitted to the Faculty of Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Medicine (Public Health Medicine).

Supervisors: Dr Ahmad Haeri Mazanderani, Dr Harsha Somaroo

Declaration

I Mariana Makhanani Khoza declare that this Research Report is my own, unaided work. It is being submitted in partial fulfilment of the requirements for the Degree of Master of Medicine (Public Health Medicine) in the School of Public Health, Faculty of Health Sciences, at the University of the Witwatersrand, Johannesburg.

This work has not been submitted before for any degree or examination at any other University.

Signature of candidate

Signed on the 2nd of October 2023 in Johannesburg, South Africa.

Dedication

This work is dedicated to:

My first supervisor Dr Ahmad Haeri Mazanderani, who, through an incredible act of altruism, introduced me to this research topic, then guided me along the journey with immense patience, wisdom and understanding.

My second supervisor Dr Harsha Somaroo, who mentored me with kindness and patience, and taught me how to apply a public health approach when synthesising knowledge.

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Presentations arising from this research

This research was presented at:

1. 2023 Public Health South Africa (PHASA) Conference – Oral presentation
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3. Academic Meeting, Department of Community Health, Wits School of Public Health

Abstract

Background

Hepatitis A virus (HAV) is a common cause of acute viral hepatitis in South Africa, however, there is limited data on the burden of severe HAV disease in the South African population.

Objective

To describe the burden of severe HAV disease in South Africa's public sector by describing the prevalence of laboratory diagnosed acute liver failure (ALF) in patients with HAV infection, during the period January 2016 to December 2021.

Methods

This was a cross-sectional study using retrospective secondary data from the National Health Laboratory Service (NHLS), from January 2016 to December 2021. Laboratory patient records that were positive for HAV IgM were extracted and merged with International Normalised Ratio (INR) test records, using the NHLS Corporate Data Warehouse (CDW) record linking algorithm. All patients with a positive HAV IgM result linked to an INR result ≥1.5 were reported as having laboratory diagnosed ALF. Descriptive statistics and regression analyses were conducted using STATA 17 SE.

Results

A total of 15 261 laboratory patient records were positive for HAV infection. Of the patients with HAV infection a total of 7 824 (51.27%) were linked with an INR test result, and of those a total of 1 420 (18.15%) patients had ALF. The average annual burden of patients with ALF was 237 patients per year (range: 136–333). Children <10 years had the highest number of HAV infections (n= 6 227, 40.80%) and ALF (n=576, 40.56%) for the study period. Patients 50-59 years with HAV infection were most likely to have ALF compared to children <10 years (OR 2.95, 95% CI 2.207 - 3.935, p<0.000).

Conclusion

Whereas adults with acute HAV infection are more likely to develop ALF, severe HAV disease is predominantly a childhood disease in South Africa. This study emphasises the need to strengthen HAV prevention strategies to limit the incidence and burden of severe HAV disease.

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Abbreviations

ALF	Acute liver failure
CDW	Corporate Data Warehouse
EPI	Expanded Program on Immunisation
HAV	Hepatitis A Virus
Anti-HAV IgG	Anti-Hepatitis A Virus Immunoglobulin G
Anti-HAV IgM	Anti-Hepatitis A Virus Immunoglobulin M
HNIG	Human Normal Immunoglobulin
INR	International Normalised Ratio
NHLS	National Health Laboratory Service
WHO	World Health Organisation
UID	Unique Identifier
NPIs	Non-pharmaceutical interventi

1. Chapter 1: Introduction

1.1 Background

Hepatitis A is a vaccine-preventable, notifiable disease of the liver, caused by the hepatitis A Virus (HAV) (1). The virus is commonly transmitted from person to person via the faecal oral-route, and the disease can range from an asymptomatic infection to an acute viral hepatitis (1). In some severe cases the disease can cause acute liver failure (ALF) and other serious complications (1). In countries where HAV is highly endemic, the infection is acquired in early childhood, where it is often asymptomatic or sub-clinical and results in life-long immunity (2).

In the last global seroprevalence study conducted in 2010, the World Health Organisation (WHO) classified Sub-Saharan Africa as highly endemic for HAV (3). This was a consequence of the widespread water and sanitation challenges across the continent, more than 10 years ago (4). However, as standards of hygiene and sanitation have been progressively improving in many low-and middle-income countries, researchers have reported a shift in HAV endemicity in these countries, including those in Sub-Saharan Africa (2,5–8).

In South Africa, the most recent HAV seroprevalence studies suggest that the country has likely transitioned from high to intermediate HAV endemicity (2,7,9,10). Such a transition is related to an increased age of first exposure to HAV, which is a risk factor for severe HAV disease. To protect populations from severe HAV disease, the WHO recommends the routine use of HAV vaccination in countries with intermediate or low HAV endemicity (11). Currently, routine HAV vaccination is only available in South Africa's private health sector and is not included in the public sector's Expanded Program on Immunisation (EPI) schedule (12). Comprehensive evidence on the burden of HAV in South Africa, that could inform population interventions such as the introduction of universal HAV vaccination, is currently limited.

1.2 Problem

Recent HAV seroprevalence studies suggest that South Africa has likely transitioned from high to intermediate HAV endemicity (7,9,13). Such a transition poses a risk for older age of first exposure to HAV, which is associated with increased risk of symptomatic disease and in

some cases, severe HAV disease. In some cases HAV disease can result in the development of severe complications such as ALF (1,14).

The burden of severe HAV disease is not well described in South Africa. This makes it challenging for policymakers to determine the most appropriate response for managing HAV at a population level. Interventions such as the introduction of universal HAV vaccination could be beneficial, however the burden of HAV in the South African population should justify the intervention, especially in the context of competing health needs and limited resources.

1.3 Justification

According to the WHO, if a country has transitioned from high to intermediate HAV endemicity, introduction of universal HAV vaccination should be considered (3,11). However, prior to the introduction of any population-based intervention, various factors would need to be considered. One such factor is the burden of HAV disease. This includes the incidence, prevalence, morbidity, mortality and economic cost of the disease in the population (15). When further considering the burden of HAV as a priority health issue, the burden of other public health issues would need to be considered including other vaccine preventable diseases like congenital rubella, meningococcal meningitis and perinatally acquired hepatitis B virus (16–18). Thus, the introduction of universal HAV vaccination in the South African context, would need to be based on evidence that supports the need for such an intervention in the population and illustrates the intervention's efficiency compared with other alternative interventions or the status quo.

Although recent studies conducted in South Africa have reported on the seroprevalence of HAV in the public sector, very few studies have described the burden of HAV morbidity using population level data (2,7,9). This study will determine the burden of severe HAV disease in South Africa, by describing the prevalence of laboratory-diagnosed ALF in public sector patients that have been diagnosed with HAV infection. The findings from this study will reduce the knowledge gap on HAV morbidity in South Africa's public sector population. Evidence from this study can assist policymakers to determine the need for HAV prevention measures in the public sector.

1.4 Research question

What was the prevalence of laboratory-diagnosed ALF in South African public sector patients who had HAV infection for the period January 2016 to December 2021?

1.5 Aim

The aim of this study was to describe the burden of severe HAV disease in South Africa's public sector, by describing the prevalence of laboratory-diagnosed ALF among patients with HAV infection, for the period 2016 to 2021.

1.6 Objectives

1. To describe the burden of severe HAV disease in patients with HAV infection in the public sector, during the period 2016 to 2021 by describing the prevalence, distribution, and annual trends of:
    a. Acute HAV infections
    b. Acute HAV infections linked to an INR result
    c. Acute HAV infections linked to an INR result $\geq$1.5
2. To describe the factors associated with the prevalence of ALF in patients with HAV infection for the period January 2016 to December 2021

3. Chapter 2: Literature Review

Summary of literature review

A traditional literature review was conducted using google scholar and pubmed to find peer reviewed articles, using the following search terms: Hepatitis A burden OR HAV; hepatitis A AND acute liver failure; HAV outbreak; HAV seroprevalence; HAV vaccinations; HAV in Africa OR developing OR LMIC countries. A snowball approach (citation tracking) was then used to identify other relevant articles. The review was limited to only include publications from the past ten years (2013 – 2023), however, some key publications (such as the last global seroprevalence study from 2010) were also referenced, even though they fell out of the ten-year time-period.

The review begins by describing the burden of HAV globally and locally in South Africa, then compares South Africa's burden to that of other middle-income countries. The characteristics of HAV and its pathogenesis are then outlined as well as how HAV is diagnosed. The review then discusses the clinical presentation of HAV infection, which can range from asymptomatic to severe disease. Severe HAV disease is then expanded on,

primarily describing ALF as a presentation. Having explained the clinical presentation, the review discusses how HAV seroprevalence is determined and the factors that could affect it, and how late age of first HAV exposure can impact HAV clinical presentation and why this is linked to the WHO's recommendation for universal vaccination in populations at risk of late age of first HAV exposure. Hepatitis A virus outbreaks and their potential impact on health systems in populations who are vulnerable to symptomatic infection and severe disease are discussed, as well as the public health measures that are important for HAV control especially in outbreaks. In the final section, the review discusses the management and prevention of HAV.

2.1 The burden of HAV

Hepatitis A is a notifiable communicable disease of the liver and the most common cause of viral hepatitis globally (4). According to the WHO approximately 100 million people are infected with HAV each year, resulting in over 1,4 million clinical cases of HAV disease (4,14) . The case fatality rate of HAV ranges from 0.5% to 1.5%, which translates into a high number of fatalities due to the high number of infections across the globe. In 2016, over 7 000 people died from HAV disease globally (20). It was found that between 1990 to 2019, new cases of HAV increased globally by 13.9%.This increase in cases is discouraging, especially in view of the WHO's global hepatitis strategy, which aims to reduce all new viral hepatitis infections by 90% by 2030 (14,19,20).

In South Africa, understanding the magnitude of the burden of HAV is greatly dependent on the quality and intensity of HAV surveillance in the country. HAV surveillance has mostly been passive and mainly based on patient level data, with the true number of community infections in the population not well identified and recorded (21,22). The notifiable medical conditions surveillance system of the National Institute for Communicable Diseases (NICD) reports that the number of HAV cases that are notified are underestimated and do not reflect the true burden of the disease in the country (23). A study done in 2020 estimated the burden of new HAV infections in South Africa, using laboratory data, and found that the annual HAV incidence rate ranged between 4.23 cases and 4.85 cases per 100 000 population, and the testing rate ranged between 151.46 to 254.03 tests per 100 000 population. The authors, however, cited challenges with missing data (22). The estimated HAV incidence rate in South Africa, is comparable to the rates (5.4 to 21.5 per 100,000) reported from other middle-income countries that have not yet introduced universal HAV vaccination (24).

HAV infections across the globe have been shown to place a considerable burden on health systems, families, and societies (14,25). In Mexico, a study found the total direct costs for HAV related complications was 19 million USD for the year 2019, representing about 0.063% of its healthcare budget (24). The total economic burden of HAV in the country has not yet been reported on in South Africa, however, Patterson et al found that the average cost of hospitalisation for patients admitted with HAV infection in the Western Cape was 1935.41 USD for adult patients and 563.06 USD for paediatric patients(13).

2.2 Characteristics of HAV

Hepatitis A is caused by a single-stranded RNA virus, which is a member of the *Hepatovirus* genus of the *Picornaviridae* (1). The HAV is an enteric virus and can persist in the environment for very long periods due to its ability to remain stable in ambient temperatures and low pH. The virus, however, can be easily deactivated in boiling temperatures and exposure to household bleach (1). It is commonly transmitted through the faecal-oral route and individuals become infected when they ingest contaminated food or water (1). The virus can also be transmitted through direct contact with an infectious person, from contaminated needles in drug-users and, in very rare cases, from blood products (3,26). Once transmission of HAV has occurred, the virus travels via the bloodstream to the liver where it replicates and causes liver cell damage (1). It has a long incubation period which can range between 14 to 50 days (1,22). People at high risk for acquiring HAV infection include those living in crowded areas with poor access to clean water and proper sanitation, such as people living in homeless shelters or refugee camps. People living in a household with a person infected with HAV, men who have sex with men, and people travelling to HAV endemic regions are also at increased risk of being infected with HAV (14).

2.3 Diagnosis of HAV

Infection with HAV induces an immune response that results in the production of specific HAV antibodies. HAV antibodies include HAV IgM and HAV IgG (1). Diagnosis of acute HAV infection is done by measuring HAV IgM titre in the serum (1). Following an acute infection, there is an increase in HAV IgM, which is detectable from five to ten days before the appearance of symptoms and usually declines after three months post infection (1). HAV IgM is undetectable after one year post infection, however, there are rare instances where it has been detected after more than one-year post-acute infection (4,27). Some false positives of HAV IgM have been reported in people who have no evidence of recent infection (27). This has been ascribed to specificity issues with the antibody tests and in some cases the

HAV vaccine (28). To improve diagnostic certainty, it is often recommended that HAV testing is only conducted when there is clinical suspicion (28). HAV IgG antibodies appear two to three months after an acute infection and once produced, provide life-long immunity (4). HAV IgG is often used to determine population seroprevalence.

Diagnosis of HAV can also be done using nucleic acid tests, a method used to detect HAV RNA in stool, plasma, water, and food samples. This method is rarely used for routine diagnosis as it is not available in a number of countries (14,27,28). In South Africa, nucleic acid tests are more commonly used to monitor and detect HAV in the environment such as in water samples as part of HAV environmental surveillance to ensure water safety (29).

2.4 HAV clinical presentation

Any person who has not had prior infection or been vaccinated can become infected with HAV (14). However, infection with HAV does not always lead to disease (1). The appearance of symptomatic disease varies depending on age of first exposure (1). Most children who are six years or younger and are exposed to HAV in early childhood, have asymptomatic or very mild infection (1,4,14). Once the age of first exposure is above six years, most HAV infections are associated with symptomatic clinical disease (1,4,14). In regions which are highly endemic for HAV, majority of early childhood infections are asymptomatic (2,4).

Common symptoms of HAV disease include fever, malaise, jaundice, dark urine, joint, muscle and abdominal pain (1). An infected individual is most infectious two weeks before jaundice appears or the liver enzymes become elevated, which is also the period when the viral load in the stool is the highest (4). Once jaundice appears, the viral load in the stool starts to decline and the infected individual is less infectious (4). The jaundice can last for a couple of weeks before full recovery (1). Most individuals are no longer infectious one week post the appearance of jaundice; however, in some instances, children have been reported to shed the virus in their stool for periods as high as six months post the appearance of jaundice (4). Hepatitis A virus in some patients can cause relapsing disease, characterised by relapse of symptoms four to fifteen weeks after the initial symptoms had resolved (1). Furthermore, it has been found that if patients return too soon to work or school before full recovery, HAV symptoms may reappear (1,12). Therefore, HAV infection can result in significant loss of productivity in many households and the economy, as infected persons await long periods of recovery before returning to their normal work or school activities.

In some cases, HAV infection can result in severe HAV disease, sometimes referred to as complicated HAV disease, which may vary in presentation (30,31). An estimated 7% of patients with HAV infection will develop complicated HAV disease (32). Complications of HAV include ALF, aplastic anaemia, Guillain-Barre syndrome and transverse myelitis (30).

2.4.1 HAV infection complicated by acute liver failure

Between 0.5 to 1% of patients with HAV infection develop ALF (1). These patients develop rapid deterioration of their liver function (also referred to as fulminant hepatic failure) which results from massive liver cell necrosis and inflammatory infiltrate caused by the virus as it replicates (1,14). Acute liver failure is characterised by coagulopathy, signalling deterioration of liver function, indicated by an international normalised ratio (INR) of $\geq$1,5 and development of hepatic encephalopathy, in the absence of pre-existing liver cirrhosis (1,14,33–35). Patients with pre-existing liver cirrhosis are more susceptible to developing an acute on chronic liver failure and have poorer prognosis than patients with no pre-existing liver failure (1,31,35). Of the patients with HAV infection who develop ALF, 70% will have spontaneous resolution however 30% of patients will require liver transplantation and in the absence of receiving this, these patients are reported to have fatality rates between 80% to 100% (1,14,36–38).

Hepatitis A virus infection is the leading cause of ALF requiring liver transplantation in paediatric patients, which is commonly seen in several other countries (24,33,39). Improving the prognosis of patients infected with HAV infection who have developed ALF requires early recognition and urgent referral to a transplant unit. Currently South Africa has limited capacity for liver transplantation, with only two liver transplant units in the country, one in Johannesburg and one in Cape Town (40).

The reasons why some patients with HAV infection progress to develop ALF are not well understood (38). Some authors have cited various factors such as age and minor pre-existing liver disease while others have reported evidence of specific viral genetic factors (36–38). Some studies have previously cited low HAV viral load to be related to why some patients progress to have ALF, however Lee et al (31) found that low HAV viraemia was not the most important factor associated with ALF. Regardless of the disease process, HAV induced ALF remains a serious event when it does occur, requiring the mobilisation of highly specialised resources, placing a considerable burden on the health system.

Figure 1 below provides a simple illustration of the disease pathway for persons infected with HAV.

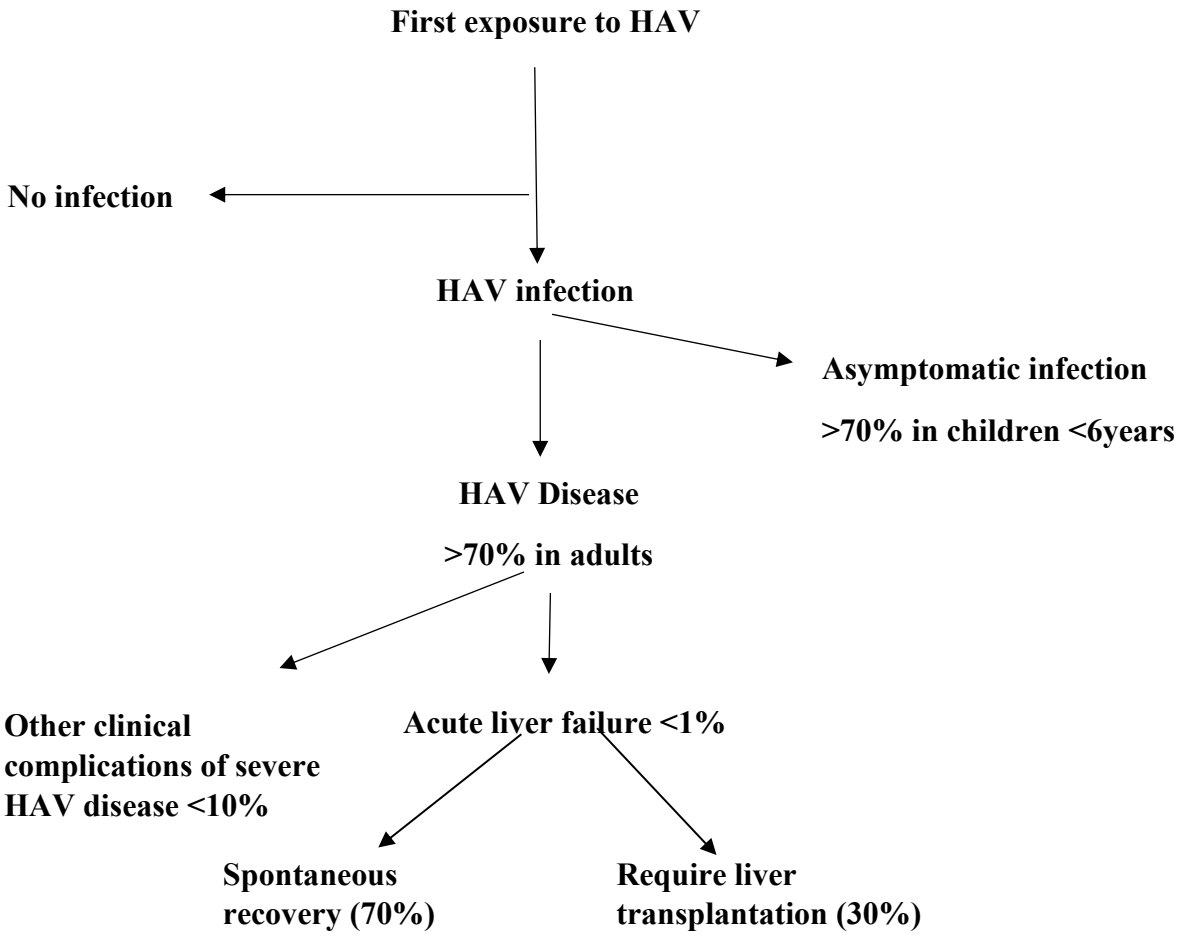


Figure 1: Hepatitis A virus disease pathway

Adapted by author from literature (1,33,36,39)

2.5 HAV seroprevalence

HAV seroprevalence can be determined using the presence of HAV IgG or total antibodies, in the population (7). The WHO classifies HAV endemicity according to HAV IgG seroprevalence in the population. Table 1 below describes how the three levels of HAV endemicity are categorised (11).

Table 1: WHO classification of HAV endemicity

Endemicity	IgG seroprevalence
Low	<50% IgG seroprevalence by age 15 but ≥ 50% by 30 years
Intermediate	< 90% IgG seroprevalence by age 10 but ≥ 50% by 15 years
High	> 90% IgG seroprevalence by age 10

Source: WHO position paper on hepatitis A vaccines: June 2012

HAV seroprevalence differs significantly between countries (25,41). High-income countries which commonly have adequate access to clean water and sanitation, typically have low HAV incidence rates, resulting in most older children and adults escaping early childhood infection and remaining susceptible to HAV (14,25,41). Highly HAV endemic regions are commonly found in low-and middle-income countries which usually have poorer access to clean water and sanitation compared to developed countries (14,25,41). Seroprevalence studies done in low-income countries indicate that almost 100% of older children and adults have detectable serum HAV IgG (4,41). Meanwhile, middle-income countries such as South Africa, have more complex HAV seroprevalence (4). The small differences in economic status within subpopulations in middle-income countries have been linked to varying HAV seroprevalence profiles within these countries (41). Overall, however, most middle-income countries have been shown to have transitioning HAV endemicity, from being highly endemic regions to intermediate or low endemic regions (14,25,41).

In the last global HAV seroprevalence study, published in 2010, Sub-Saharan Africa was categorised as highly endemic for HAV (4,41). Thus, majority of the population in Sub-Saharan Africa had early first exposure to HAV and subsequent lifelong HAV immunity by late childhood and early adolescence (4). However, the latest evidence on HAV endemicity in South Africa indicates that the country is in a transitional phase with features of both low-and middle-income countries and high-income countries evident (2,9). Some authors have even suggested that South Africa has likely already transitioned to intermediate HAV endemicity (2,7). Mazanderani et al (7) found that South Africa's anti-HAV seroprevalence only reaches >90% in adults who are >25 years of age, indicating intermediate endemicity according to the

WHO classification. Enoch et al (9) showed similar findings in their study from the Western Cape province, finding a seroprevalence of 44,1% in the one to seven year age group, also indicating intermediate HAV endemicity (9).

2.6 Factors affecting HAV seroprevalence

HAV seroprevalence is affected by multiple factors, most notably, access to clean water and sanitation (41). Improvement in the water and sanitation of a region has been associated with decreased incidence of HAV and decreased exposure to the virus in early childhood (41). This results in a growing population of seronegative individuals, who are vulnerable to symptomatic HAV disease should they get HAV infection (41,42).

As the incidence of HAV decreases in early childhood, a higher proportion of older children, adolescents and adults become vulnerable to symptomatic HAV disease should they get HAV infection (41,42). This phenomenon has been seen globally where incidence rates have decreased, the average age of infection has increased and so has the incidence of severe HAV disease (4,14,41). Mohd et al explain this as the paradoxical nature of HAV: the better the living conditions, the lower the infection rate in early childhood but the greater the risk for severe HAV disease with first exposure at a later age (42).

Improved access to clean water and sanitation has contributed to the transition in HAV endemicity seen in several African countries over the last decade (5,13). In South Africa, access to safe clean water has increased from 84.4% to 88.2% from 2002 to 2019, whilst access to improved sanitation in the rural population, increased from 52% to 77% from 1990 to 2015 (43,44). Some authors argue that access to water and sanitation does not adequately explain the differences seen in HAV endemicity across regions (25,41). Their argument is that although environmental improvements are a crucial factor, economic indicators such as the gross national income per capita or human development index are also predictors of HAV endemicity (25,41). Higher household income, higher levels of education, less household crowding are all associated with decreased HAV exposure (25,41). The decreased HAV exposure is also likely a result of environments that facilitate improved infection prevention behaviours such as frequent hand and food washing. In addition to the described socioeconomic factors, Jacobsen (41) further adds that t globalisation, increased human mobility and international food trade are also increasingly affecting the risk of HAV risk in populations.

2.7 HAV outbreaks

Hepatitis A virus poses a risk for increased transmission and spread in settings where there is low immunity to the virus, which can lead to potential outbreaks (22,41). Outbreaks can occur in vulnerable high-risk groups, such as injecting drug users, men who have sex with men, people living in homeless shelters or refugee camps, nursing homes, prisons and psychiatric facilities (14,22,41). Outbreak investigators can find it challenging to identify the primary source of a HAV outbreak, as HAV outbreaks can occur from a variety of sources and the virus has a long incubation period. Foodborne outbreaks are more commonly seen in high-income countries, and these have been linked to imported frozen food products from HAV endemic regions (41). Some outbreaks have occurred from childcare facilities where caregivers contract the virus from asymptomatic infected children (41). Waterborne outbreaks occur in low-and middle-income countries, often due to sewage-contaminated water (14,22). This is a risk for South Africa, where HAV has been isolated from sewage, treated wastewater and other various water sources. Despite the virus being easily eliminated by household bleach and boiling temperatures, it has been shown that it can be resistant to wastewater treatment processes and can remain infectious for days in both treated and untreated wastewater (29). The risk for HAV is thus increased in communities that make use of rivers which receive treated wastewater discharge (29). Three publications have reported on the risk of HAV exposure from contamination of rivers that receive wastewater from treatment plants in the Eastern Cape Province. Two authors concluded that HAV detected in their samples posed a significant risk for potential HAV exposure to communities whilst one author did not detect any HAV in the samples they collected (29,45,46). Worryingly, in 2020 a HAV outbreak occurred in the Overberg district, Western Cape province and the source of the outbreak was suspected to be contaminated water from burst water pipes and blocked drains (22). This illustrates the risk of HAV infections from environmental sources, especially in the likelihood of an increasing vulnerable population and justifies the importance of adequate environmental surveillance of HAV.

HAV outbreaks can place considerable pressures on the health system, especially if they occur in vulnerable populations who may acquire symptomatic or severe disease. The sudden increase that could occur in the number of patients needing in-patient management during a HAV outbreak is a potential threat to health systems such as South Africa’s, which already have stretched health resources under non-outbreak conditions.

The major differences in socioeconomic conditions in South Africa and the transition to intermediate endemicity will mean the country will find itself in a transition window where there is decreasing HAV incidence in some groups, whilst there is ongoing presence of the virus in other groups and the environment (41). This increases the risk of introduction of the virus to non-immune individuals and, if they are outside of early childhood, the potential of severe complications like ALF. Therefore, the country should be ensuring that public health control measures are in place to mitigate and contain any outbreaks when they occur. These measures include population health protection from HAV infections through continuous clinical and environmental surveillance and immediate action, such as implementing contact tracing when cases are detected (47). Ensuring preparedness for potential outbreaks by having national protocols and guidelines outlining the actions that should be taken in facilities and at the community level is an example of another important preparedness step. In addition, identifying high-risk groups that need interventions such as people in homeless shelters requiring proper sanitation, injecting-drug users requiring clean needles, healthcare workers and people working in childcare centres requiring vaccination can also prevent HAV outbreaks from occurring. Strengthening health promotion activities such as education about proper hygiene practices can also improve the infection risks in many communities (47). The introduction of universal HAV vaccinations is a pharmaceutical public health measure that would also decrease the number of people susceptible to HAV during outbreaks, as vaccinated people would have immunity despite not being exposed to the virus. It is however important to mention that the success of HAV vaccination as measure to prevent outbreaks would be highly dependent on good vaccine coverage once implemented.

2.8 HAV prevention and treatment

There is no specific treatment or drug that can be used to treat HAV (1). The South African national guidelines for hepatitis management advise that patients with severe disease should be hospitalised and managed using supportive methods, such as intravenous fluids (12). In cases where patients have complications, additional management of those complications would be required. In addition to supportive measures, it has been found that patients should not return to work or school too early, or at least for up to two weeks after the onset of jaundice, due to the risk of developing relapsing hepatitis (12). In people with high risk of infection or severe disease, passive immunity can be provided by administering human normal immunoglobulin (HNIG), which is effective for both pre-exposure and post-exposure prophylaxis (1,27). In South Africa, HNIG is recommended for travellers and

immunocompromised patients who have been exposed to HAV. HNIG should ideally be given within 72 hours of HAV exposure.

To protect populations from severe HAV disease, the WHO recommends the routine use of HAV vaccination in countries with intermediate or low HAV endemicity (14). The HAV vaccine has been shown to be effective for both pre-exposure and post-exposure prophylaxis. It is highly immunogenic and well tolerated but is only licensed for use in individuals older than one year (12,27,41). For pre-exposure prophylaxis a single dose of the vaccine is given, with a booster at 6 months and this provides 95% efficacy and protection for a minimum of 20 years (12,27). The HAV vaccine is routinely administered in South Africa's private sector at 1 year followed by a booster dose at 18 months. However, it is not routinely available as part of the national immunisation schedule (7). In the South African public sector, only individuals who are at risk of exposure (such as in instances of an outbreak) and are identified to be at high risk of severe HAV can be considered for pre-exposure prophylaxis (12). This could include people sharing a household with an infected individual, healthcare workers, travellers visiting South Africa, immunocompromised individuals and pregnant women (12). Vaccine post-exposure prophylaxis has also been shown to be effective if given within 14 days of exposure and in the public sector it is indicated for individuals who are identified as high-risk for developing severe HAV disease although the vaccine is not documented in the South African essential drug list and access to it in the public sector is unclear (12,27).

In 2019 it was reported that HAV vaccine was used routinely in only 34 countries (14,41). Jacobsen (41) suggests that middle-income countries are the regions where universal childhood vaccination should be introduced as they have significant risk of HAV infection in people old enough to have severe disease, that can progress to serious complications such as ALF. Some middle-income countries which have experienced similar changes as South Africa in HAV endemicity, have already introduced routine childhood HAV vaccination and have reported favourable outcomes (5,6,41). In South Africa, a study was conducted to model the potential impact of a HAV vaccination program. The authors found that administering the single dose vaccine in children younger than two years would result in the prevention of over 136 000 HAV cases and over 31 000 HAV related deaths for the period 2023 to 2030 (48). The authors noted however that although the single dose vaccine would provide health benefits, it was not cost-effective against the cost effectiveness threshold for one averted disability-adjusted life year (DALYs) used in the country (48).

Finally, some authors caution that even with the introduction of universal vaccination as recommended by the WHO, it would not be able to eliminate the risk of HAV as long as other regions remain endemic. Thus non-pharmaceutical public health measures should regarded as the first intervention for HAV control in South Africa (41).

4. Chapter 3: Methods

3.1 Study design

This is a cross-sectional study using secondary data.

3.2 Study setting

South Africa is an upper-middle income country situated at the most southern point of the African continent. The country has a population of 60 million people, of which 51.1% are females and 48.9% are male (44). The life expectancy in 2021 was 59.3 years for males and 64.6 years for females. Almost 28.3% of the population is younger than 15 years (44). The country is made up of nine provinces, of which Gauteng is the most populated with 15.8 million people, followed by KwaZulu-Natal with 11.5 million people (44). The Northern Cape is the province with the least population of 1.3 million people (44).

South Africa has a two-tiered health system, made up of a private and public sector. Majority of South Africans make use of the public sector whilst approximately 16.1% of the population use private health care services (44).

The NHLS is the sole provider of diagnostic pathology services for the public health sector. It includes two other entities, the National Institute of Communicable Diseases and the National Institute of Occupational Health (45). The NHLS has over 230 laboratories across the nine South African provinces (50).

3.3 Study population

All patients in South Africa's public health sector who tested positive for HAV infection during the period January 2016 to December 2021 were included in this study.

3.4 Study sample

All public healthcare facilities in South Africa making use of the NHLS which conducted a HAV IgM test which was captured into the NHLS CDW database for the period January

2016 to December 2021, were automatically included in this study. No additional sampling was done.

3.5 Definitions used in this study

Hepatitis A virus associated Acute liver failure

Acute liver failure (ALF) is defined as the occurrence of liver dysfunction, identified by coagulopathy (INR ≥1.5) and associated clinical encephalopathy, in a patient with no reported underlying liver disease (25,26).

For the purposes of this study, ALF is defined as any positive HAV IgM result matched with a corresponding INR test result of >1,5 reported 1 week prior to or up to 1 month after the HAV IgM result.

HAV infection

The term HAV infection in this study is used to describe the acute period in an individual who has been infected with HAV irrespective of any clinical symptoms. This acute period is identified by the presence of HAV IgM antibodies in the individual's serum.

HAV disease

The term HAV disease in this study describes HAV infection that results in the presence of clinical symptoms.

Severe HAV disease

The term severe HAV disease in this study refers to HAV disease that is associated with complications, which for the purposes of this study has been limited to HAV associated ALF.

3.6 Inclusion criteria

Table 2: Inclusion criteria

Variable	Inclusion Criteria
CDW Unique Identifier (UID)	Only patients with an NHLS CDW UID were included in this study
Age	All patients older than 1 month and younger than 99 years were included in this study

Sex	All patients with male, female and unknown sex were included in this study
Facility	All healthcare facilities that were in the NHLS database with a recorded HAV IgM result during the study period were included in this study. All Hospital facilities included in the database were coded as 'hospital' and all primary healthcare facilities included in the database were coded as 'clinic'.
Province	Only HAV IgM results in the NHLS database from the nine South African provinces were included in this study
IgM result	This study only included patient who had a positive HAV IgM result during the study period
INR result	All linked INR values that were greater than 0 were included in this study. The included INR results were limited to results one week prior and one month after the positive HAV IgM result

3.7 Data Extraction

A total of 1 125 health facilities reported positive HAV IgM results during the period January 2016 to December 2021. An anonymised dataset of all positive HAV IgM results was extracted from the NHLS Corporate Data Warehouse (CDW).

HAV IgM and INR result record linkage was achieved by using the CDW Unique identifier (UID) record-linking algorithm (described below). All positive HAV IgM results were linked with INR results associated with the same CDW UID. INR results were limited to results one week prior and one month after the positive HAV IgM result. In the case where there were multiple HAV IgM and INR results within the given period for one UID, the first reported HAV IgM result and the highest INR result were used for analysis.

<u>Explanation of the NHLS CDW algorithm</u>

The NHLS CDW algorithm, is a record-linking algorithm used to de-duplicate test-level data that assigns the same unique patient identifier to all episode numbers (unique number assigned to every submitted test request form) likely belonging to the same patient. The linkage is based on the patient's ID number (when available) or other identifying

demographic variables, including first name, surname date of birth, sex, and facility folder number. The methodology of the algorithm has been previously reported on by Radebe et al (51), whilst the accuracy has been assessed and reported by Bassett et al (52). Basset et al found that the NHLS CDW algorithm had a low false linking (matching) rate of 0.3% (52).

3.8 Data cleaning and analysis

The data were de-duplicated and cleaned in STATA 17 SE.

There were no extracted IgM results that were missing. However, there were HAV IgM results that were linked to missing INR values or INR values that were less than 0, these IgM results were removed before analysis for ALF. All irrelevant variables were dropped before data analysis.

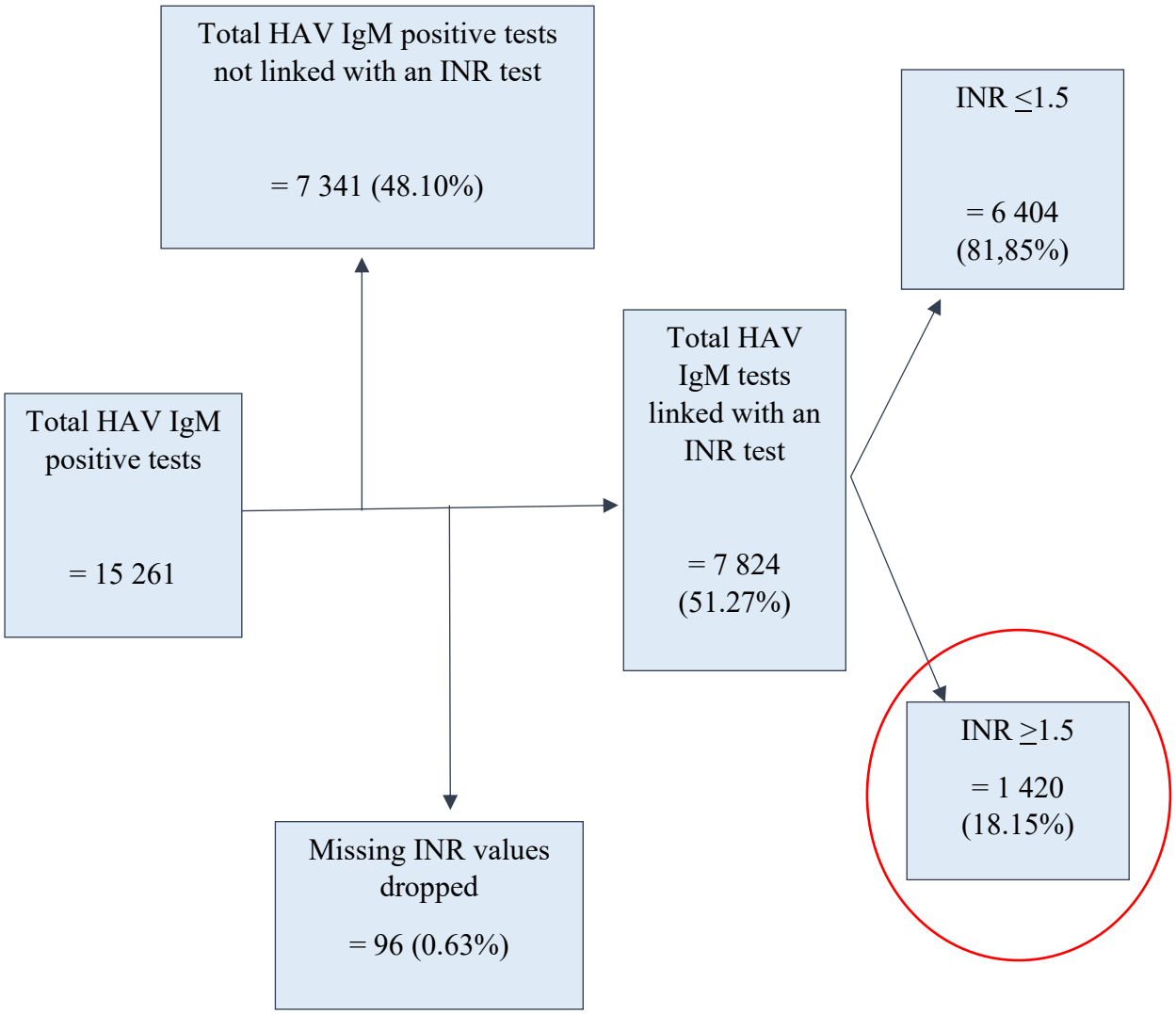
To assess the presence of ALF, a new binary variable for liver failure was created. All INR values equal to or above 1.5 were coded as ALF and all values less than 1.5 were coded as no liver failure.

Summary statistics were calculated in STATA 17 SE using frequency summaries and proportions for the variables age, sex, province, and facility. Univariate and multiple logistic regression models were conducted to analyse the relationship between age, sex, province, facility (independent variables) and ALF (dependent variable). All variables from the univariate logistic regression with a p-value less than 0.2 ($p < 0.2$) were included for analysis in the multiple logistic regression. The cut-off of a p-value of 0.2 was decided from reviewing literature (47). The output of the regression analysis was reported using odds ratios, p-values and 95% confidence intervals.

3.9 Ethics

The research proposal for this study was submitted for ethics approval to the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and approval was granted. The study reference number is M220325 MED22-03-036. Permission to use the dataset was obtained from the NHLS Academic Affairs and Research Management System (AARMS), reference number PR2227138.

Figure 2 below illustrates the data analysis pathway.



HAV – Hepatitis A virus; INR – International Normalised Ratio

Figure 2: Data analysis pathway

5. Chapter 4: Results

The distribution of the demographic and geographic characteristics for HAV infections, HAV infections linked to an INR result and those with an INR≥1.5 (laboratory diagnosed ALF) is summarised in Table 3 below.

4.1 Prevalence distribution and annual trend of HAV infections

A total of 15 261 patients had acute HAV infection whilst the average number of annual HAV infections was 2 764 infections per year (range 1 440 - 2 975). The most number HAV infections was reported in 2016 and the least number of infections was reported in 2021.

Of the total 15 261 patients that had acute HAV infection, children aged less than 10 years (n=6 227, 40.80%) had the highest number of overall HAV infections whilst adults older than 60 years (n=354, 2.32%) had the least.

Of the total acute HAV infections (N=15 261) that were reported, the Western Cape province had the highest number (n=3 708, 24.30%), followed by Kwazulu-Natal (n=3 541, 23.20%) and Gauteng (n=3 053, 20.01%). The province with the lowest number of infections was the Northern Cape (n=429, 2.81%).

The number of acute HAV infections in 2021 were 52.10% lower than the average number of infections reported in the preceding 5 years. However, the distribution of the proportion of HAV infections across the age groups was similar to the preceding years.

Table 3: Summary statistics of all HAV infections, HAV infections linked to an INR result and those with an INR>1.5 (laboratory diagnosed acute liver failure)

Variable	Category	HAV N=15 261 (Column %)	Linked HAV and INR N=7 824 (Column %)	ALF N=1 420 (Column %)
Age (years)	<10	6 227 (40.80)	3 087 (39.45)	576 (40.56)
	10 – 19	3 297 (21.60)	1 587 (20.28)	193 (13.59)
	20 – 29	2 662 (17.44)	1 488 (19.02)	241 (16.97)
	30 – 39	1 106 (7.25)	726 (9.28)	128 (9.01)
	40 – 49	517 (3.39)	336 (4.29)	84 (5.92)
	50 – 59	345 (2.26)	221 (2.82)	87 (6.13)
	>60	354 (2.32)	211 (2.70)	71 (5.00)
	Unspecified	753 (4.93)	168 (2.15)	40 (2.82)
Sex	Female	7 061 (46.27)	3 585 (45.82)	677 (47.68)
	Male	7 648 (50.11)	4 162 (53.20)	733 (51.62)
	Unspecified	552 (3.62)	77 (0.98)	10 (0.70)
Province	Western Cape	3 708 (24.30)	2 446 (31.26)	356 (25.07)
	KwaZulu-Natal	3 541 (23.20)	2 291 (29.28)	443 (31.20)
	Gauteng	3 053 (20.01)	1 717 (21.95)	296 (20.85)
	Limpopo	1 451 (9.51)	272 (3.48)	62 (4.37)
	Eastern Cape	952 (6.24)	434 (5.55)	81 (5.70)
	Mpumalanga	878 (5.75)	200 (2.56)	46 (3.24)
	North West	535 (3.51)	145 (1.85)	32 (2.25)
	Free State	446 (2.92)	191 (2.44)	73 (5.14)
	Northern Cape	429 (2.81)	128 (1.64)	31 (2.18)
	Unknown	268 (1.76)		
Facility	Primary health facility (Clinic)	2 836 (18.58)	499 (6.38)	24 (1.69)
	Hospital	12 425 (81.42)	7 325 (93.62)	1 396 (98.31)

HAV – Hepatitis A virus; INR – International Normalised Ratio; ALF- acute liver failure

Figure 3 below illustrates the annual trend distribution of HAV infections by age-group.

There was a decreasing trend in the number of HAV infections between the period 2017 to 2020 for adolescents 10-19 and all adults older than 30 years. Children aged less than 10 years and young adults aged 20-29 years, showed an increasing trend in HAV infections between 2018 to 2019 and 2018 to 2020 respectively.

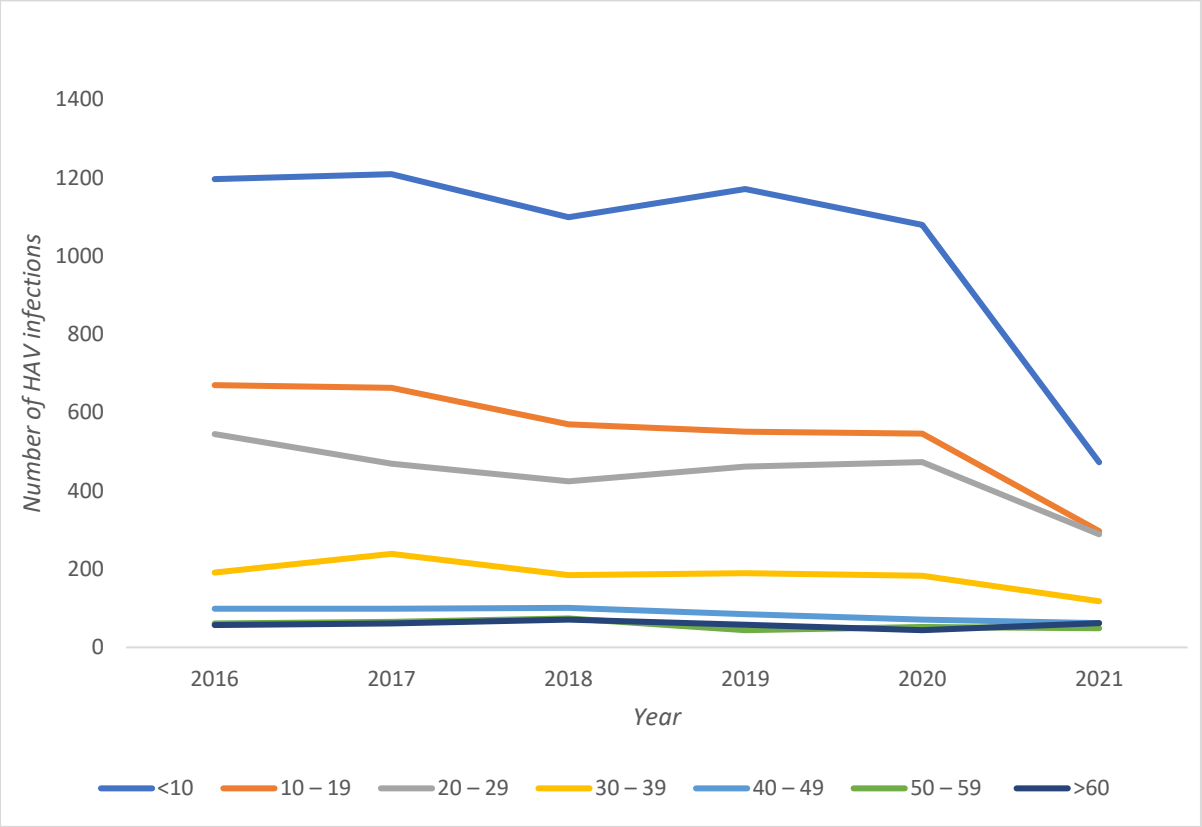


Figure 3: Annual distribution of HAV infections by age-group

4.2 Prevalence distribution and annual trend of HAV infections linked to an INR result (i.e., INR tested)

The total number of HAV IgM results linked with an INR was 7 824 (51.27% of 15 261). The average annual number of linked results was 1 416 from 2016 to 2020 (range 745 - 1 609). The highest annual number of HAV infections linked to and INR result was reported in 2017, and the lowest in 2021. In 2021, the number of HAV infections linked to an INR result was 47% below the average for the previous 5 years.

Figure 4 shows the annual percentage of HAV infections linked to an INR result. The average percentage of HAV infections linked to and INR result across the period was 52%, with an increasing trend noted between 2018 to 2020.

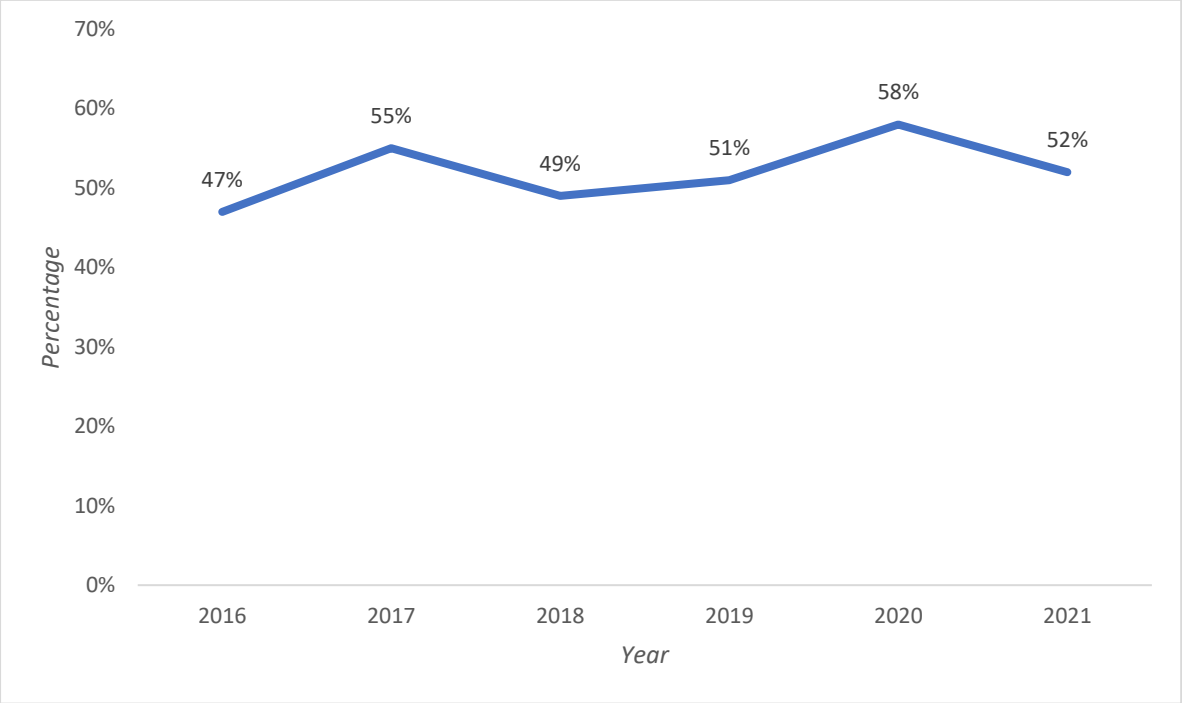


Figure 4: Annual percentage of patients with linked HAV and INR results

Of the total linked HAV IgM and INR results (N=7 824), children less than 10 years was the age-group with the highest number of linked results (n=3 087, 39.46%), whilst the age-group adults older than 60 years had the least linked results (n=211, 2.67%).

Figure 5 below shows the proportion of IgM results linked to an INR result (%INR tested) within each age-group.

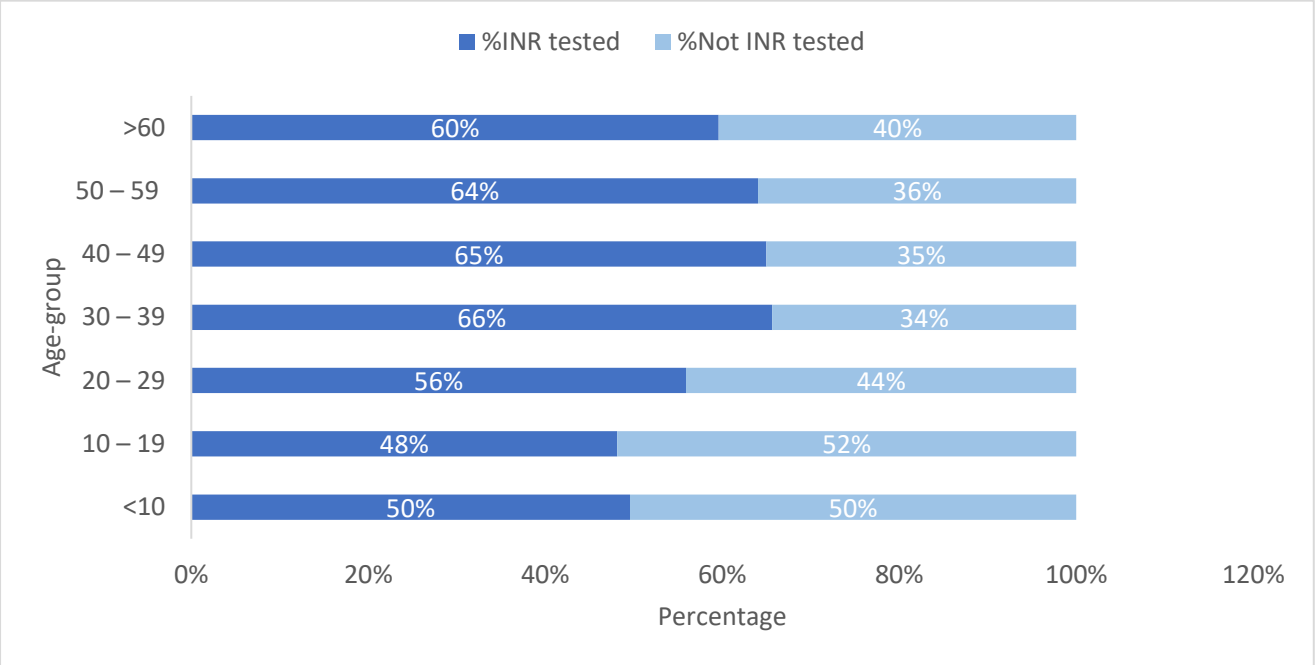


Figure 5: Proportion of HAV infections linked to an INR result (INR tested) by age-group

Figure 6 shows the annual distribution of HAV infections linked to an INR result by age-group. An increasing trend was noted for children less than 10 years, adolescents 10-19 years and young adults 20-29 years between 2018 to 2020, whilst a decreasing trend was noted for all adults older than 30 years for the same period.

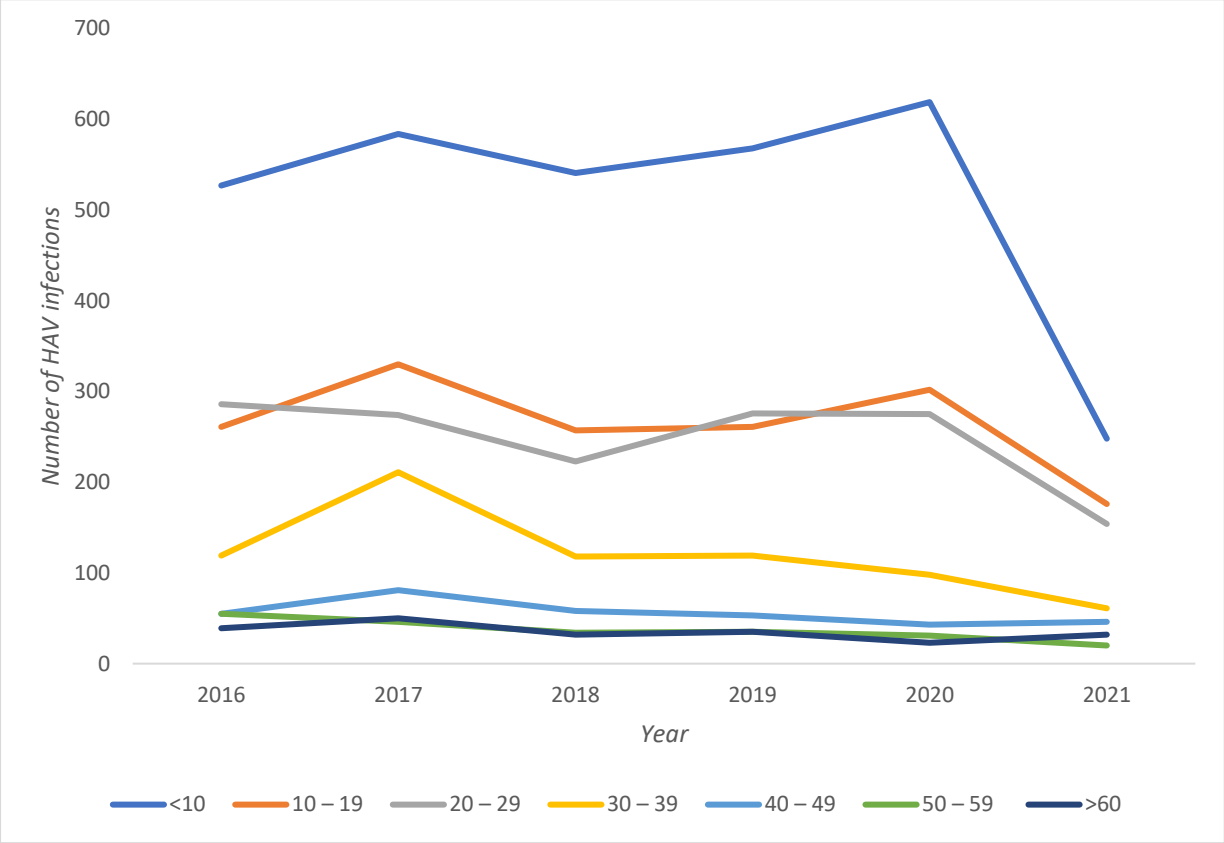


Figure 6: Annual distribution of HAV infections linked to an INR result by age group

Of the total linked HAV IgM and INR results (N=7 824), most were from the Western Cape (n=2 446, 31.26%), KwaZulu-Natal (2 291, 29.28%) and Gauteng (1 717, 22.15%). The provinces that accounted for the least number of linked results were the Northern Cape (n=128, 1.64%), the North-West (n=145, 1.85%) and the Free State (n=191, 2.44%).

Figure 7 shows the total number of linked IgM and INR results by province and the proportion of linked results within each province. The province which had the highest proportion of linked results was the Western Cape (n=2 446, 66%) and the province with the lowest proportion was Limpopo (n=272, 19%).

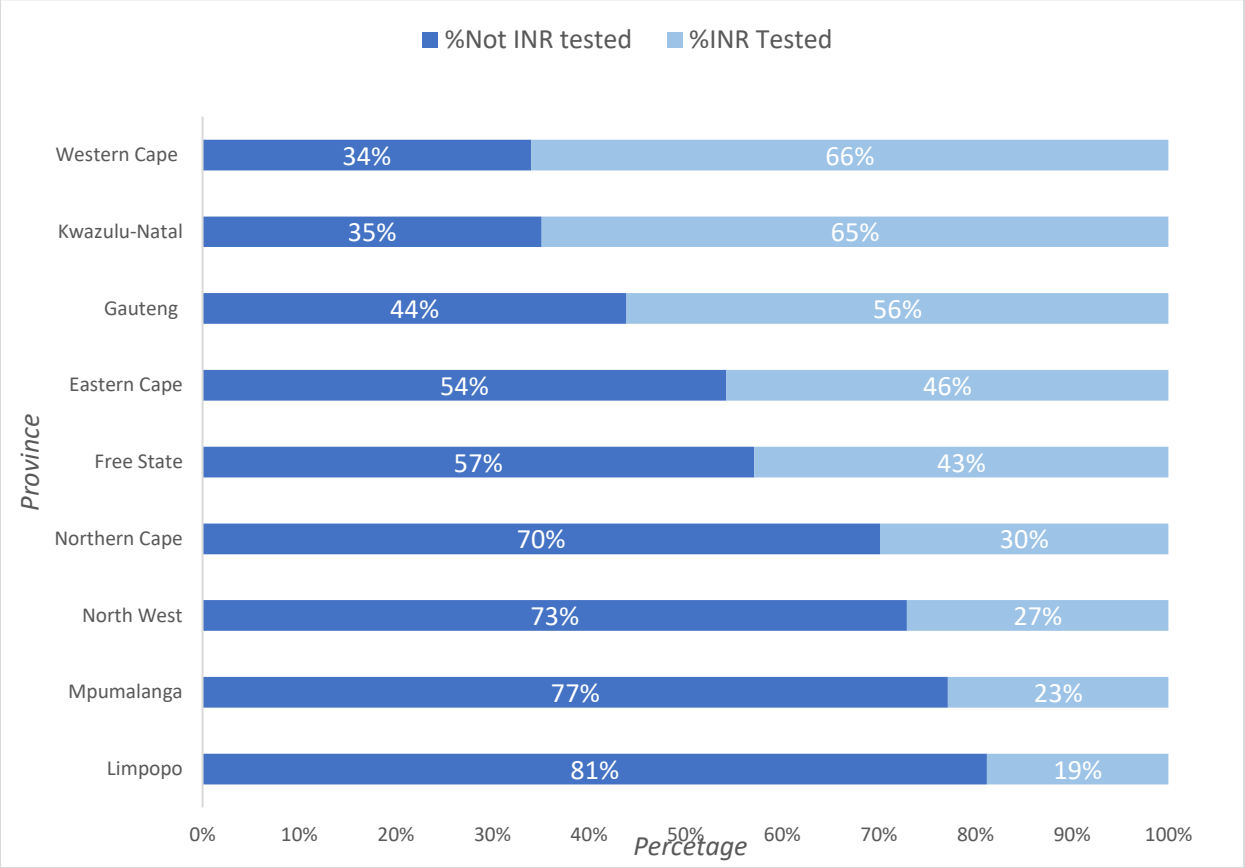


Figure 7: Proportion of HAV infections linked to an INR result (INR tested) within each province

4.3. Prevalence distribution and annual trend of INR tested HAV infections with laboratory diagnosed acute liver failure (INR ≥1.5)

A total of 1 420 (18.15%) patients with laboratory confirmed HAV infection had laboratory diagnosed ALF (INR≥1.5). The average number of patients with laboratory diagnosed ALF was 237 (range 136 - 333).

Figure 8 below shows the trend of HAV infections, HAV infections linked to an INR result (INR tested), HAV infections with laboratory diagnosed ALF (total ALF) and the percentage of laboratory diagnosed ALF in all INR linked results for the study period (%ALF in INR tested). The highest and lowest number of patients with laboratory diagnosed ALF were reported in 2017 and 2021, respectively.

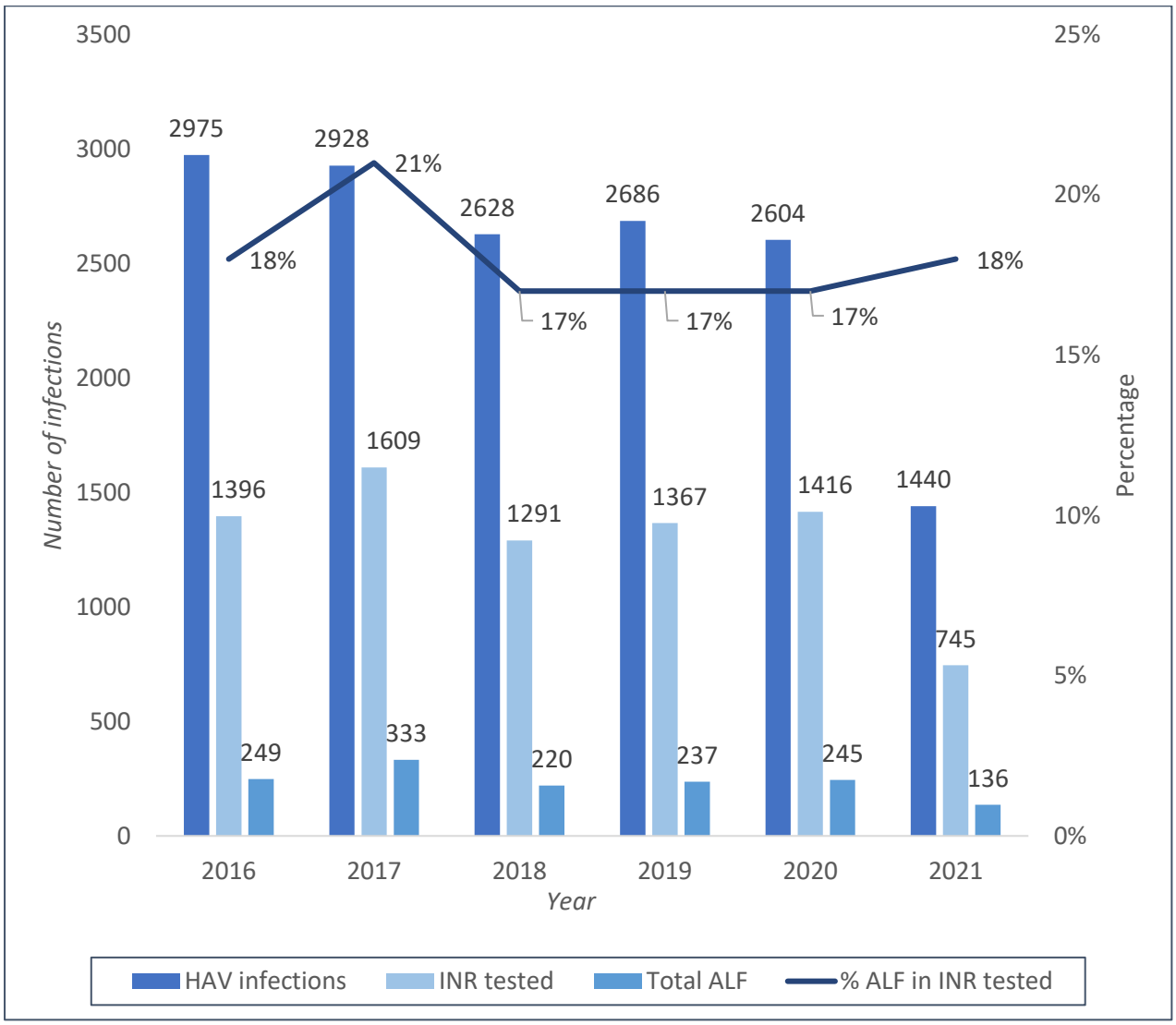


Figure 8: Annual trend of HAV infections, HAV infections that were INR tested and HAV infections with laboratory diagnosed acute liver failure from 2016 to 2021

Of the total HAV infected patients with an INR result of ≥1.5 (N=1 420), children less than 10 years had the highest total number of patients with ALF (n=576, 40.56%), and adults older than 60 years had the lowest total number (n=71, 5.00%).

Figure 9 shows the proportion of cases with ALF within each age-group. Within each age-group, adults older than 60 years had the largest proportion of ALF (n=71; 34%).

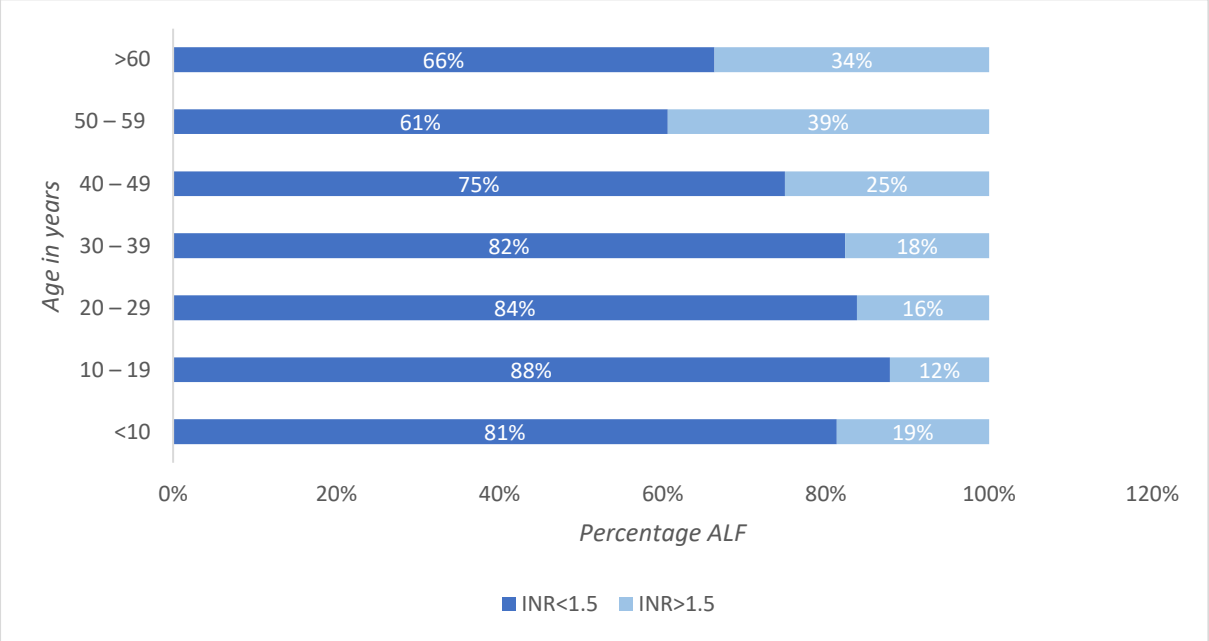


Figure 9: Proportion of acute liver failure within each age-group

Figure 10 shows the trend of ALF cases by age group for the study period. There was an increasing trend for children less than 10 years and adolescents 10-19 years between 2018 to 2019 and 2018 to 2020 respectively.

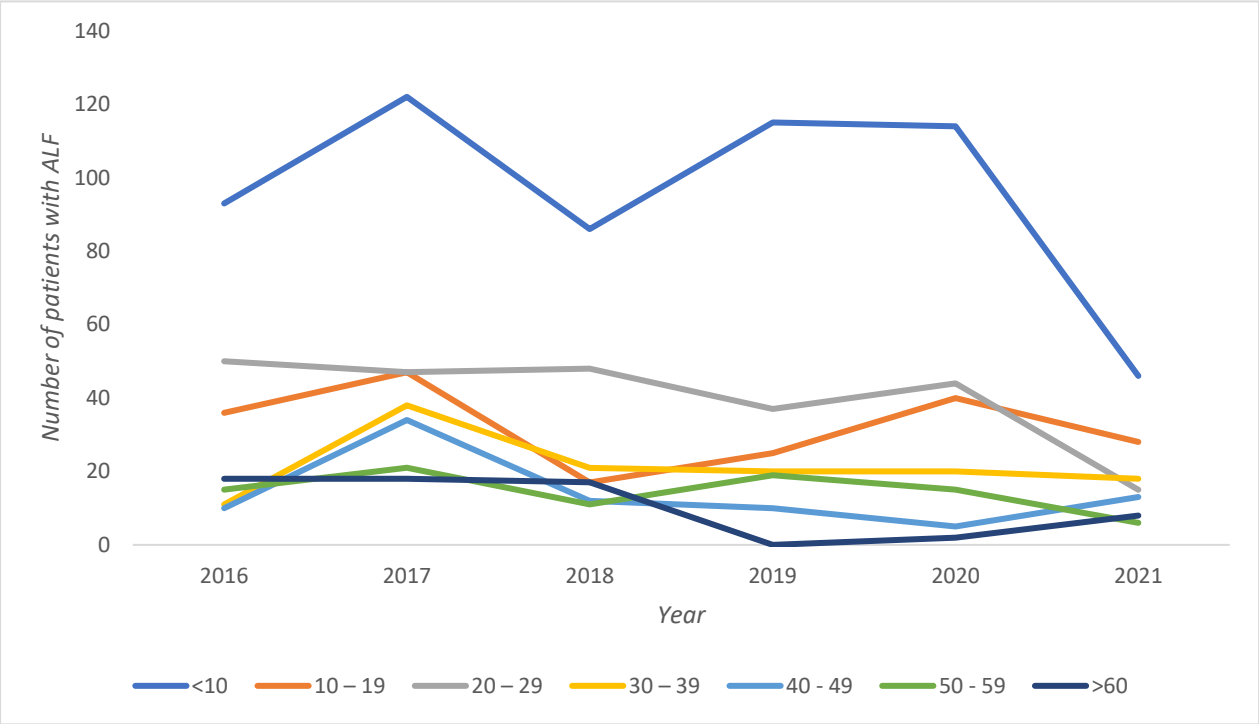


Figure 10 Annual trend of ALF by age-group

Figure 11 shows the total number of cases with ALF in each province. The provinces that accounted for the highest number of total patients with ALF were KwaZulu-Natal (n=443, 31.20%) and the Western Cape (n=356, 25.07%), whilst the provinces with the lowest number were the Northern Cape (n=31, 2.18%) and North-West Province (n=32, 2.25%).

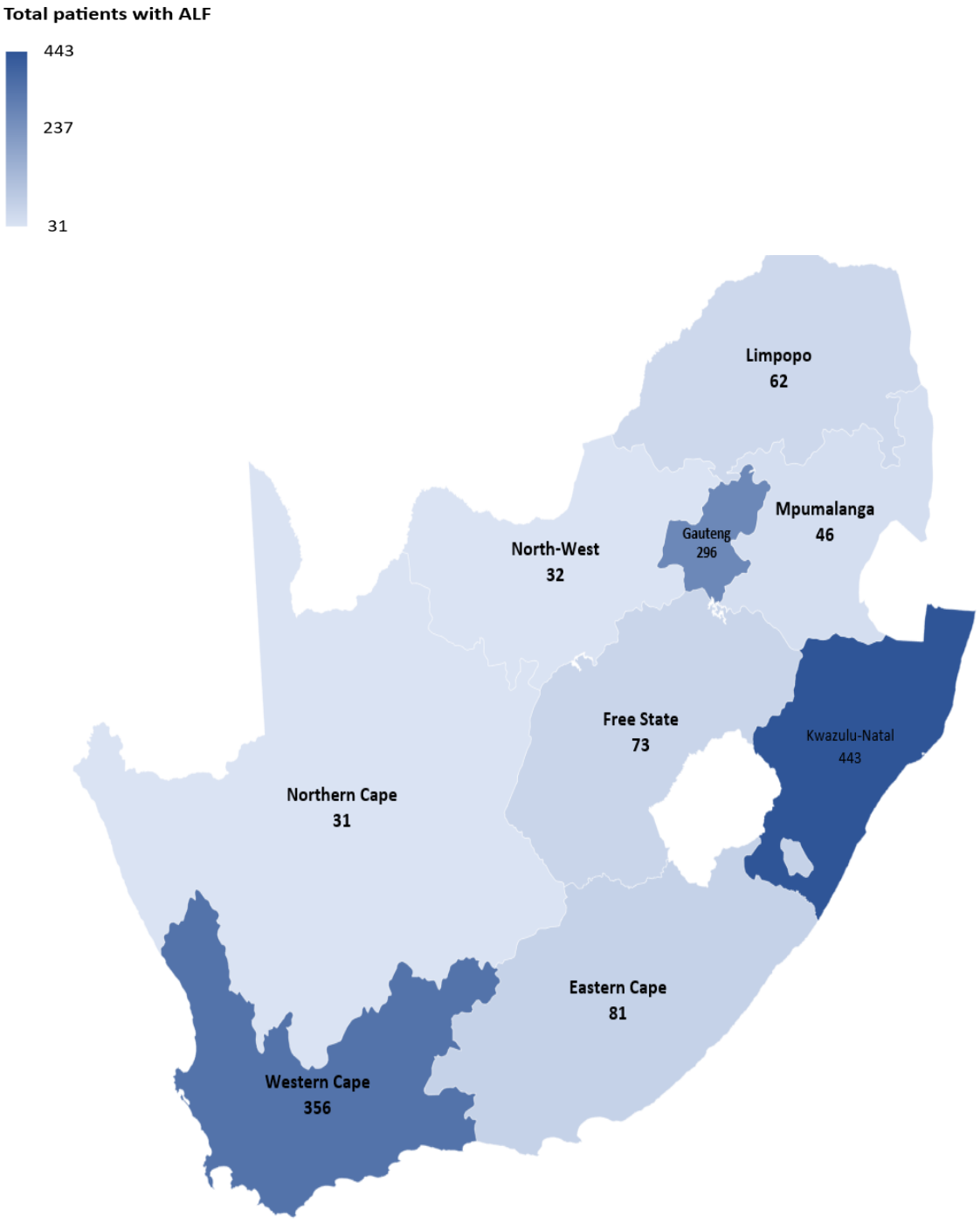


Figure 11: Total number of patients with acute liver failure by Province

Figure 12 shows the proportion of people with HAV infection who had ALF within each province. The Free State had the highest proportion of diagnosed HAV cases with ALF within the province (n=73, 38.22%).

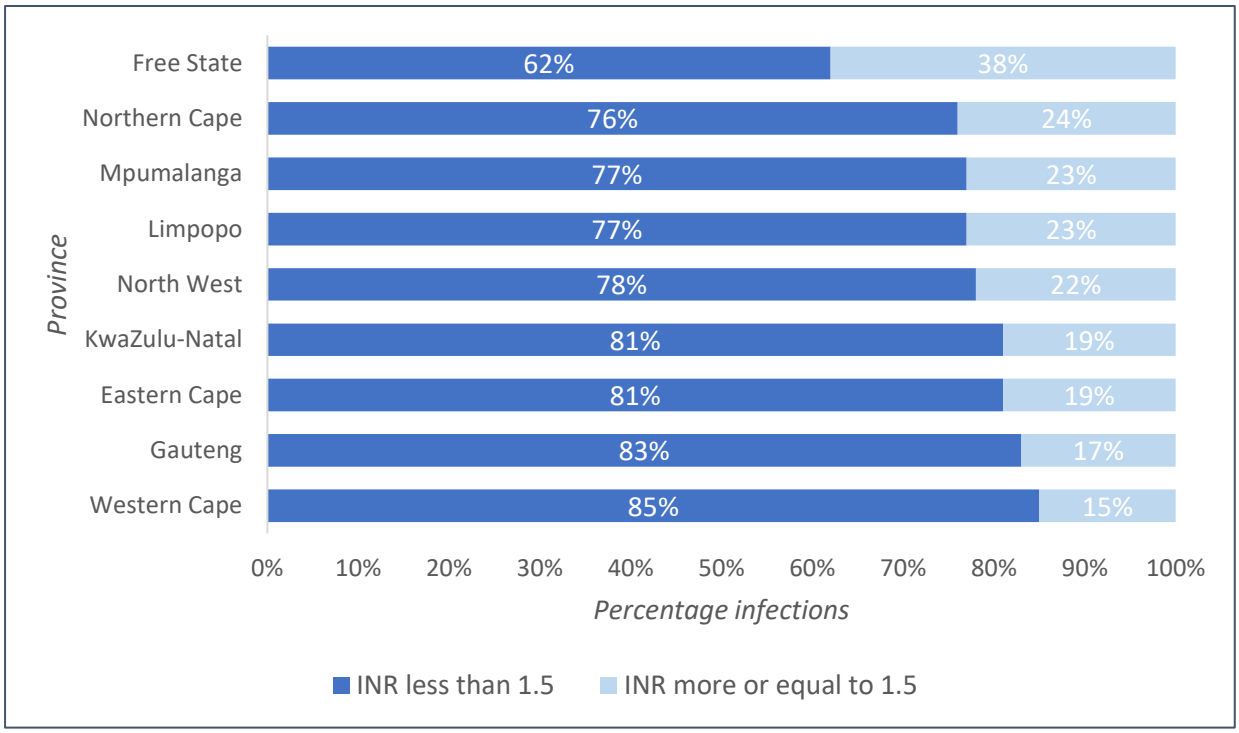


Figure 12: Proportion of acute liver failure within each province

4.4. Association between predictor variables and acute liver failure (ALF)

Table 5 describes the factors associated with the presence of ALF in patients with HAV infection.

Compared to children less than 10 years, all adults older than 40 years had greater odds of having ALF, however, adults 50-59 years had the highest odds of having HAV associated acute liver failure (OR 2.95, 95% CI 2.207 - 3.935). Adolescents 10-19 had a lower odds of ALF compared with children <10 (OR 0.64, 95% CI 0.536 - 0.765).

Compared to the Western Cape, patients with an INR test from the Free State (OR 3.01, 95% CI 2.188 - 4.152), Northern Cape (OR 1.74, 95% CI 1.139 - 2.670) and Mpumalanga (OR 1.69, 1.187 - 2.408) had greater odds of having HAV associated ALF.

Compared to patients from hospitals, patients from clinics were less likely to have associated ALF (OR 0.40, 95% CI 0.261 - 0.613).

Table 4: Univariate and multivariate analysis for predictive factors associated with acute liver failure (INR >1.5)

Variable	Level	Univariate			Multivariate		
		Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	<10 (Ref)	1	Ref	Ref	1	Ref	Ref
	10-19	0.60	0.506 - 0.720	<0.001	0.64	0.536 - 0.765	<0.001
	20-29	0.84	0.714 - 0.993	0.042	0.92	0.779 - 1.093	0.353
	30-39	0.93	0.755 - 1.153	0.521	1.02	0.819 - 1.260	0.885
	40-49	1.45	1.117 – 1.890	0.005	1.51	1.158 -1.975	0.002
	50-59	2.83	2.129 – 3.762	<0.001	2.95	2.207 - 3.935	<0.001
	>60	2.21	1.638 - 2.983	<0.001	2.06	1.518 - 2.800	<0.001
	Missing	1.36	0.944 - 1.965	0.098	1.45	0.997 - 2.121	0.052
Sex	Male (Ref)	1			1		
	Female	0.06	0.967 - 1.219	1.219			
	Unspecified	0.24	0.357 - 1.361	1.361			
Province							
	Western Cape (Ref)	1	Ref	Ref	1	Ref	Ref
	Eastern Cape	1.35	1.030 - 1.756	0.029	1.34	1.024 - 1.759	0.033
	Free State	3.63	2.653 - 4.958	0.000	3.01	2.188 - 4.152	<0.001
	Gauteng	1.22	1.033 - 1.446	0.020	1.09	0.915 - 1.298	0.336
	Kwazulu-Natal	1.40	1.205 - 1.636	0.000	1.33	1.137 - 1.562	<0.001
	Limpopo	1.73	1.276 - 2.347	0.000	1.54	1.131 - 2.105	0.006
	Mpumalanga	1.75	1.236 - 2.480	0.002	1.69	1.187 - 2.408	0.004
	North West	1.65	1.094 - 2.474	0.017	1.59	1.050 - 2.400	0.029
	Northern Cape	1.85	1.219 - 2.820	0.004	1.74	1.139 - 2.670	0.011
Facility	Hospital (Ref)	1	Ref	Ref	1	Ref	Ref
	Clinic	0.32	0.209-.482	0.000	0.40	0.261 - 0.613	<0.001

6. Chapter 5: Discussion

5.1 Prevalence of ALF in patients with HAV infection

This study aimed to describe the burden of severe HAV disease by describing the prevalence of laboratory diagnosed ALF in patients with HAV infection. The major finding from this study indicated that ALF was prevalent in 9.31% of all patients with laboratory confirmed HAV infection, and 18.15% of patients with laboratory confirmed HAV infection who were INR tested. The average annual burden of patients with ALF was 237 per year (range 136-330).

The prevalence of laboratory diagnosed ALF from this study is higher than what has been reported from previous studies. A recent South African study looked at hospitalised patients with HAV infection and found that 13% of the patients developed complicated HAV disease and all of them had features of acute liver injury (13). A similar study in Somalia reported the prevalence of ALF in children hospitalised with HAV infection was 11% (8). Both the above quoted studies, however, do not describe the population prevalence of ALF in HAV cases, unlike this study. Although this study reports on the population prevalence of ALF in patients with HAV infection, it represents the prevalence in the population of patients with HAV infection who had symptomatic disease, accessed healthcare services, and had an INR test (as a marker of ALF). The National guidelines for the management of viral hepatitis state that that the assessment of clinical severity should include liver profile and an INR test at all levels of care, whether or not a patient with HAV infection is INR tested, however, is most likely influenced by clinician index of suspicion and the availability of resources to conduct the testing. Patients with acute HAV infection, who present with more severe symptoms are more likely to be suspected of having ALF and therefore have an INR test conducted if the facilities are available. Thus, in the absence of this, HAV infected patients with ALF may be not appear in the NHLS CDW database, resulting in an underestimation of the prevalence of ALF reported in this study.

The 9.31% prevalence of severe HAV disease reported in this study reflects the burden of patients with HAV infection that could need liver transplantation. Currently there are only two liver transplant centres in South Africa limiting the capacity available to give definitive treatment to patients with ALF requiring liver transplants, thus the most practical intervention maybe to prevent severe HAV cases from occurring (40).

5.2 Age distribution of ALF in patients with HAV infection

The study findings were in line with what has been reported in literature that HAV infection at an older age is associated with increased likelihood of ALF (1,5,27,41). However, the study found that children less than 10 years carried the highest burden of patients with HAV infection alone and those with associated laboratory diagnosed ALF. This indicates that although a lower proportion of children with HAV infection develop ALF, they comprised most of the laboratory diagnosed ALF cases on account of high incidence of HAV infections. Thus, the study findings show that severe HAV disease is predominantly a paediatric condition in South Africa, and further suggest that the burden of HAV associated ALF is carried by the paediatric population. These findings are in keeping with a study that reported that HAV infection was the most common cause of children undergoing liver transplantation in South Africa (39). Furthermore, the number of children less than 10 years with severe HAV disease supports the theory that children are likely contracting the virus after early childhood where they are more at risk of developing serious complications like ALF. This is further in keeping with the findings that South Africa has likely transitioned to intermediate HAV endemicity(7). The burden of severe HAV disease observed in this study may likely increase in the context of intermediate HAV endemicity, as more children escape early HAV exposure, and become vulnerable to HAV infection as older children or adults later in life. This will potentially affect the number of HAV infected people presenting with severe disease and requiring hospital care, and in some cases, highly specialised services.

5.3 Geographic distribution of ALF in patients with HAV infection

There was some variation in the distribution of ALF across the provinces. The highest prevalence of acute HAV infections and laboratory diagnosed ALF cases was in the most populated provinces in South Africa. The Western Cape, KwaZulu-Natal and Gauteng were the provinces accounting for majority of patients with ALF, however the likelihood of patients with HAV infection having associated ALF was highest in the Free State province. This province conducted a lower proportion of INR tests in patients with HAV infection, suggestive of either low index of clinical suspicion or limited capacity to do INR testing in the province. This will need further investigation as it may be that many patients infected with HAV who developed ALF were missed. Overall, the geographical and facility distribution of ALF from this study findings, likely reflects testing behaviour, access to healthcare services and referral pathways.

5.4 Facility distribution of in patients with HAV infection

Almost all HAV cases with evidence of ALF from this study were detected in hospitals. There is potential for under-reporting patients in the NHLS CDW database who present with severe HAV disease if they are not properly worked-up (both in primary facilities and hospitals) or if they are not referred appropriately from the primary healthcare level.

5.5 Annual trend distribution of ALF in patients with HAV infection

The data showed relatively stable trends for HAV infections, INR testing and HAV infections with ALF between 2016 and 2020. A major decrease in HAV infections, INR testing and HAV infections with ALF was seen in the year 2021. There are three hypotheses that can be considered to explain this drop. The first is that this may be reflective of an error in the NHLS data collection or extraction processes which resulted in missing data. Missing HAV laboratory data has been previously cited by other authors (22). The second and third hypotheses are related to the potential effect of the COVID-19 pandemic on HAV infections. The second hypothesis is that less patients with symptomatic HAV disease presented to health facilities due to the lockdown restrictions, and thus were not attended to and captured on the laboratory database. The third hypothesis is that the number of HAV infections in 2021 could reflect a true decrease due to the strict and intensely applied non-pharmaceutical interventions (NPI) that were introduced to combat COVID-19. The NPIs which may have specifically impacted the incidence of HAV infections include the promotion of regular hand washing and physical distancing. Zhang et al (54) support the latter hypothesis by suggesting that the NPIs during COVID-19 resulted in the significant reduction of other infectious diseases. This is an important consideration in the South African context, as some NPIs for controlling HAV can be more widely and easily implemented compared to pharmaceutical interventions such as vaccinations. Targeted NPIs aimed at highly vulnerable groups could be explored (54). It is worthwhile noting however that a counter to the COVID-19 hypotheses is that a decrease in HAV infections should have also been reflected in 2020.

7. Chapter 6: Limitations

The following limitations should be considered when interpreting the study findings:

- The NHLS dataset reflects patients who presented to public facilities, and whose samples were sent to the laboratory for testing. Thus, the findings from this study are vulnerable to patient health-seeking behaviour, access to laboratory services and clinician management.
- There are potential confounders that could impact the distribution and trends of ALF in patients with HAV infections that could not be controlled for, due to limitations of the laboratory data. These factors include other causes of hepatitis and ALF (such as Hepatitis B and E), comorbidities, drug related liver injury, pre-existing liver disease, access to NHLS laboratory services, socioeconomic status, and access to clean water.
- There is potential risk (albeit low) that some positive HAV IgM results may have been false positive from specificity issues with the serum tests and in some cases the HAV vaccine.
- The true burden of severe HAV disease in all patient's infected with HAV is likely to be underreported in this study, as patients that were not tested for both HAV IgM and INR were not reported on in our study.
- The location of the data results is restricted to the facility where the test was requested and may not reflect the true geographical location of where patients reside.
- The CDW algorithm has been noted to under-link patient data and thus there is a risk of under-reporting ALF in our study, as some patients with acute HAV may not have been successfully linked to their INR results.

8. Chapter 7: Conclusion and Recommendations

7.1 Conclusion

This is the first study that has described the burden of severe HAV disease in South Africa's public sector, using a national database.

Despite the study's limitations, which potentially resulted in underreporting of ALF, the findings show that whereas adults with HAV are more likely to develop ALF, the burden of severe HAV disease is predominantly in the paediatric population in South Africa.

Given that there are other manifestations of severe HAV disease and that not all patients with HAV-disease are likely to access health services, the prevalence of ALF found in this study likely represents the minimum burden of severe HAV disease within the public sector population. Considering that HAV infection is vaccine preventable, fatal cases of ALF due to HAV infection are essentially avoidable. Strategies such as universal HAV vaccination may have benefits, but these will need to be assessed and compared with the burden of other vaccine-preventable diseases to inform the introduction of new vaccines in South Africa's EPI.

This study showed that HAV infection is not an inconsequential early childhood infection in South Africa and emphasises the need to strengthen HAV prevention strategies to limit the incidence and burden of severe HAV disease in the South African population.

7.2 Recommendations

Following the findings from this study on the prevalence of severe HAV disease, the following recommendations are made:

- The key recommendation is for further research to be conducted using patient file records to:

  1) Link the laboratory findings from this study to the clinical course of illness and to assess final health outcomes, for patients with severe hepatitis A disease.

  2) Quantify the associated cost of illness of severe HAV disease from the payers (national department of health) and the patient's perspective.

- The next recommendation from this study is that targeted public health measures to prevent acute HAV infections in the paediatric population should be strengthened. The public health measures include ensuring that there is safe clean drinking water and proper sanitation provided to communities.

- It is further recommended that health workers (both in hospitals and primary healthcare) are trained to have high level of suspicion for ALF in paediatric and adult patients presenting with HAV infection, and not delay INR testing or delay referral in low-resource settings, to aid early intervention such as early referral for transplantation where needed.
- Finally, further research quantifying the economic burden of HAV on the health system, on patients, households and society is recommended. This will complement these findings on HAV morbidity and can also be followed by a cost-effectiveness analysis to determine if introducing universal HAV vaccination in the South African context is both medically and economically justifiable.

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10.Appendices

Appendix A – Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Mariana Makhanani Khoza (Student number: 457383) am a student registered for the degree of Master of Medicine (Public Health Medicine) in the academic year 2023.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 02.10.2023

Appendix B – Turnitin Report

turnitin

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Page count:	46
Word count:	11,866
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I **Dr Ahmad Haeri Mazanderani** confirm that I have checked and approved the originality report for this MMed Research Report.

Signature: Date: 13/10/2023

I **Dr Harsha Somaroo** hereby confirm that I have checked and approved the originality report for this MMed Research Report.

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Appendix C – Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Dr M Khoza
Wits School of Public Health
Department of Community Health
Medical School
University

E-mail: Mariana.Khoza@wits.ac.za

CC: Supervisor: Drs A Haeri Mazanderani and H Somaroo
<ahmadh@nicd.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/11/09

REF: R14/49

PROTOCOL NO: **M220325** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *The burden of hepatitis A disease in South Africa's public sector: a descriptive study using routine laboratory data from 2016 to 2021*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Dr M Khoza

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220325

NAME: (Principal Investigator)	Dr M Khoza
DEPARTMENT:	Wits School of Public Health Department of Community Health Medical School University
PROJECT TITLE:	*The burden of hepatitis A disease in South Africa's public sector: a descriptive study using routine laboratory data from 2016 to 2021*
DATE CONSIDERED:	2022/03/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs A Haeri Mazanderani and H Somaroo
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/11/09

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6155
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

18 July 2022

Applicant: Mariana Khoza
Institution: NHLS / NICD
E-mail Address: marianak@nicd.ac.za
Cell: 073 646 9976

CC: Ahmad Haeri Mazanderani, Harsha Somaroo

Project Title: The burden of hepatitis A disease in South Africa's public sector: A descriptive study using routine laboratory data from 2016 to 2021
Reference Number: PR2227138

Research Application Type(s):
1. Request for Data

RE: APPROVAL LETTER: REQUEST TO ACCESS NHLS RESOURCES FOR RESEARCH PURPOSES

This letter serves to advise that the application requesting permission to conduct the above-mentioned research using the listed NHLS resources has been reviewed and **"Approved"**. Please note that the approval is granted on the condition that you comply with the NHLS Research Material and Data Access Policy and requirements stated below.

1. All material and data requested shall be used as per the research protocol submitted to the NHLS and as approved by the relevant Health Research Ethics Committee (HREC) in South Africa.
2. Access to the NHLS material and/or data shall be limited to the minimum required for successful completion of the approved study and shall be made available ***without patient names***.
3. Confidentiality shall be maintained at the participant and institutional level and there shall be no disclosure of personal information or confidential information.
4. The material and/or data obtained from the NHLS shall be anonymised and not, for any reason, be used to track or recruit patients as no pre-approval/consent is obtained from patients.
5. Processes shall be discussed with the relevant NHLS departments (i.e. Corporate Data Warehouse (CDW), NHLS Laboratory Management, Operations Office, etc.) and agreed upon.
6. Any amendments to the study requirements, including the use of the material and/or data for purposes not initially disclosed to the NHLS) shall be cleared by an approved HREC and submitted to the NHLS for approval via the AARMS system – https://aarms.nhls.ac.za.
7. The NHLS shall be acknowledged as a source of material and/or data in any output, such as abstracts and journal articles, emanating from the project.
8. A final report of the research study and any published output resulting from this study shall be submitted to the NHLS via AARMS

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. The NHLS entities tasked with providing the material and/data may have additional requirements for access. Data related queries may be directed to NHLS CDW, email: zarina.sabat@nhls.ac.za; contact number: 011 386 6074 and sample related queries (if applicable) shall be directed to the relevant business manager.

pp. Dr. Babatyi Malope-Kgokong

20/07/2022

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research