# Evidence-based vaccinology: Supporting evidence-informed considerations to introduce routine hepatitis A immunization in South Africa

by

Jenna Patterson

PTTJEN005

Thesis presented for the degree of

Doctor of Philosophy

In the Division of Epidemiology & Biostatistics

School of Public Health and Family Medicine,

Faculty of Health Sciences, University of Cape Town

July 2022

Supervisors: Associate Professor Benjamin M. Kagina, Professor Rudzani Muloiwa, Professor Gregory D. Hussey, Professor Susan Cleary, and Associate Professor Sheetal P Silal

# Abstract

Hepatitis A is a vaccine preventable disease caused by the Hepatitis A Virus (HAV). Currently, South Africa is classified by the World Health Organization (WHO) as a high hepatitis A endemic region where ≥ 90% of children are assumed to be "naturally immunised" following HAV exposure before the age of 10 years old. In high hepatitis A endemic settings, routine vaccination against HAV is not necessary due to high rates of "natural immunization". Recent data suggest a possible shift from high to intermediate HAV endemicity may be occurring in South Africa. Countries with intermediate HAV endemicity and no routine hepatitis A vaccination program have a high risk of experiencing hepatitis A outbreaks and high costs associated with care. Currently, there is no routine vaccination program against HAV in South Africa.

The aim of this PhD was to generate evidence for decision making on whether a routine vaccination program against HAV should be considered for introduction into the South African Expanded Program on Immunizations (EPI-SA). The objectives included gathering context-specific evidence on the epidemiologic features of hepatitis A, clinical characteristics of the disease, hepatitis A vaccine characteristics and cost of case management. Using this evidence, the PhD estimated the future epidemiology of hepatitis A and impacts of routine hepatitis A vaccination scenarios in the country.

The PhD's overall methods were informed by the principles of Evidence-Based Vaccinology for developing vaccine recommendations. The project included a mixed-methods approach: systematic reviews, a retrospective clinical folder review, mathematical modelling, and economic evaluation. A dynamic transmission model was built to forecast the future epidemiology of hepatitis A and to simulate the impacts of several different childhood hepatitis A vaccination strategies in South Africa.

Selected findings have been published in relevant peer-reviewed journals. In addition, a technical dossier was prepared to submit to the South African National Advisory Group on Immunization (NAGI) on behalf of the Hepatitis A Working Group for considerations of introducing hepatitis A vaccination into the South African EPI.

# Acknowledgements

Over a period of five years, my list of people to thank has grown to be endless. From supervisors to friends and acquaintances in between – each person I met along the way has had an impact in this work.

Thank you to my team of supervisors who tirelessly supported me through this PhD journey. Your contributions to this work and to my learning have been incredibly valuable. I greatly appreciate the effort each one of you has put forward into this work and into my growth.

Thank you to the many co-authors and collaborators. From providing academic insights to real-world experiences, you have enriched each step of the way.

Thank you to the Vaccines for Africa Initiative team assisting me to develop my research skills at both the Masters and PhD levels.

Thank you to the South African Centre for Epidemiological Modelling and Analysis for funding my PhD research and for the amazing support and fun along the way.

Thank you to Cochrane South Africa for providing opportunities to engage at every corner.

Thank you to the National Institute of Communicable Diseases for the ongoing collaboration and providing data insights whenever needed.

Thank you to my parents who have endlessly supported this journey and consistently remind me that hard work always pays off in the end.

Thank you to my husband and Archie for helping me see the light at the end of the tunnel on days when the journey felt like it would never end.

## Plagiarism Declaration

*I know the meaning of plagiarism and declare that all of the work in the dissertation, save for that which is properly acknowledged, is my own.*

Signature: _____

## Note from the National Research Foundation

This material is based upon work supported financially by the National Research Foundation in South Africa. Any opinion, findings and conclusions or recommendations expressed in this material are those of the authors and therefore the NRF does not accept any liability in regard thereto.

# Preface

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the Division of Epidemiology & Biostatistics, School of Public Health & Family Medicine, Faculty of Health Sciences, University of Cape Town. The work included in this thesis is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or, in the case of multi-authored published papers, constitutes work for which the candidate was the lead author.

This thesis includes published manuscripts, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications. The following manuscripts (three published and one being prepared for submission) are included in the thesis and are presented as self-contained chapters in the following order:

1. Patterson, J., Abdullahi, L., Hussey, G. D., Muloiwa, R., & Kagina, B. M. (2019). A systematic review of the epidemiology of hepatitis A in Africa. *BMC infectious diseases*, *19*(1), 651. https://doi.org/10.1186/s12879-019-4235-5.
2. Patterson, J., Hussey, H. S., Silal, S., Goddard, L., Setshedi, M., Spearman, W., Hussey, G. D., Kagina, B. M., & Muloiwa, R. (2020). Systematic review of the global epidemiology of viral-induced acute liver failure. *BMJ open*, *10*(7), e037473. https://doi.org/10.1136/bmjopen-2020-037473.
3. Patterson, J., Cleary, S., Silal, S. P., Hussey, G. D., Enoch, A., Korsman, S., Goddard, E., Setshedi, M., Spearman, W. C., Kagina, B. M., & Muloiwa, R. (2022). A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa. *BMC infectious diseases*, *22*(1), 45. https://doi.org/10.1186/s12879-021-06993-w.
4. Patterson, J., Cleary, S., van Zyl H., Awine T., Mayet S., Norman, J., Kagina, B. M., Muloiwa, R., Hussey, G. D., Silal, S. P., Modelling the cost-effectiveness of hepatitis A vaccination in South Africa. *Being prepared for submission.*

The contribution of the candidate to each manuscript is outlined at the start of each chapter. The candidate was the lead and corresponding author on all manuscripts. All co-authors reviewed and approved the submitted manuscripts and the candidate reviewed co- author comments and integrated them into the manuscripts prior to submission. The candidate's primary supervisor has confirmed to the University of Cape Town Doctoral Degrees Board that the included papers all overwhelmingly reflect the candidates own scientific work.

# List of Abbreviations

| | |
|---|---|
| ALF | Acute Liver Failure |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| CA16 | Coxsackievirus |
| CDC | Centres for Disease Control and Prevention |
| CET | Cost-effectiveness Threshold |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CMV | Cytomegalovirus |
| DALYs | Disability-Adjusted Life Years |
| DW | Disability Weight |
| EBV | Epstein Barr Virus |
| EIA | Competitive Enzyme Immunoassay |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EPI | Expanded Program on Immunization |
| EPI-SA | Expanded Program on Immunization in South Africa |
| ES | Estimate |
| EtR | Evidence to Recommendation |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| GSH | Groote Schuur Hospital |
| HAdVs | Adenovirus |
| HAV | Hepatitis A Virus |
| HBs-Ag | Hepatitis B Surface Antigen |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HDV | Hepatitis D Virus |
| HEV | Hepatitis E Virus |
| HHV-6 | Human Herpesvirus 6 |
| HPIVs | Human Parainfluenza Viruses |
| HPV | Human Papillomavirus Virus |
| HSV1 | Herpes Simplex Virus-1 |
| HSV2 | Herpes Simplex Virus-2 |
| HTA | Health Technology Assessment |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| INR | International Normalized Ratio |
| LMICs | Low- and Middle-Income Countries |
| LOS | Length of Stay |

| | |
|---|---|
| MASHA | Modelling and Simulation Hub Africa |
| MESH | Medical Subject Headings |
| MoH | Ministries of Health |
| NAGI | National Advisory Group on Immunization |
| NESI | Network for Education and Support in Immunization |
| NICD | National Institute for Communicable Diseases |
| NIP | National Immunization Program |
| NITAGs | National Immunization Technical Advisory Groups |
| nRCTs | Non-Randomized Control Trials |
| NRF | Department of Science and Innovation and the National Research Foundation |
| PDE | Patient Day Equivalent |
| PHC | Public Health Clinic |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-analyses |
| R0 | Basic reproductive rate |
| RCH | Red Cross War Memorial Children's Hospital |
| RCTs | Randomized Control Trials |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |
| SIR | Susceptible-Infected-Recovered |
| U/L | Units per Litre |
| UFPS | Uniform Patient Fee Schedule |
| UNICEF | United Nations Children's Fund |
| USD | United States Dollars |
| VACFA | Vaccines for Africa Initiative |
| VPDs | Vaccine Preventable Diseases |
| VZV | Varicella-Zoster Virus |
| WASH | Water, Hygiene, and Sanitation Standards |
| WHO | World Health Organization |
| YFV | Yellow Fever Virus |
| YLD | Years Lived with Disability |
| ZAR | South African Rands |

# Table of Contents

# List of Figures

# List of Tables

# List of Supplementary Figures



# List of Supplementary Tables

# 1 Chapter 1: Introduction

## 1.1 Overview and structure of the thesis

This thesis consists of an introductory chapter, two systematic reviews, two primary results chapters, and a discussion chapter synthesizing the findings of the overall thesis in the form of a policy dossier and supporting appendices.

The introduction chapter places the issue of informing considerations of introducing routine hepatitis immunization into the Expanded Program on Immunization South Africa (EPI-SA) into context and describes the objectives of the thesis, which were conceptualized in 2017.

**Chapters 2 and 3**, the systematic reviews, present an overview of the epidemiology of hepatitis A and viral-induced liver failure at the continental and global levels, respectively. These levels were chosen for each systematic review based on the data availability for meta-analyses included in the reviews. Special interest was paid to South African data in each of these studies as to relate directly to the evidence generation aims.

**Chapter 4** presents the results from a retrospective folder review of hepatitis A cases at two tertiary healthcare facilities in Cape Town, South Africa. This chapter reports the outcomes and costs associated with paediatric and adult hepatitis A cases. While the authors note that Cape Town is not representative of the entire South Africa population, the Western Cape has a strong healthcare system and is the ideal setting for the potential initiation of an immunization program.

**Chapter 5** presents the results of a modelling study that explores the health outcomes, cost-effectiveness associated with several potential hepatitis A vaccination strategies to be included in the EPI-SA.

The findings of this combined work are synthesized in **Chapter 6** in the form of a policy dossier to be submitted to the National Advisory Group on Immunization (NAGI) on behalf of the Hepatitis A Working Group.

As all relevant discussions are contained in each manuscript chapter, **Chapter 7** reflects on the findings and conclusions of the thesis. The chapter discusses the significance of findings from the results and discusses the need for more hepatitis A data related in South Africa.

A summary of Chapters 2-4 of this thesis is reflected in **Table 1.2**. Chapters 2-4 are either published manuscripts or being prepared for submission.

## 1.2 Evidence-Informed decision-making for Vaccines and Immunization

Evidence-Informed Decision Making (EIDM) is the practice of including the best available evidence into the decision-making process for public health policies, including immunization practices. As additional vaccines become available for public health use, countries are faced with an increasingly complex decision-making landscape regarding which vaccines to include in National Immunization Program (NIP) schedules (1). With the number of vaccines available constantly growing, NIPs routinely experience budget and programmatic constraints that adds complexity to EIDM for vaccines and immunization policies. Emergence of infectious diseases such as COVID-19 and concerns around optimal vaccine confidence are other factors that EIDM specialists must grapple with when making evidence-based immunization recommendations for considerations by the Ministries of Health (MoH). Vaccine introduction is rarely based just on the epidemiology of a disease. Consequently, countries must balance the evidence of epidemiological need and vaccine cost-effectiveness with the realities of equity and supply.

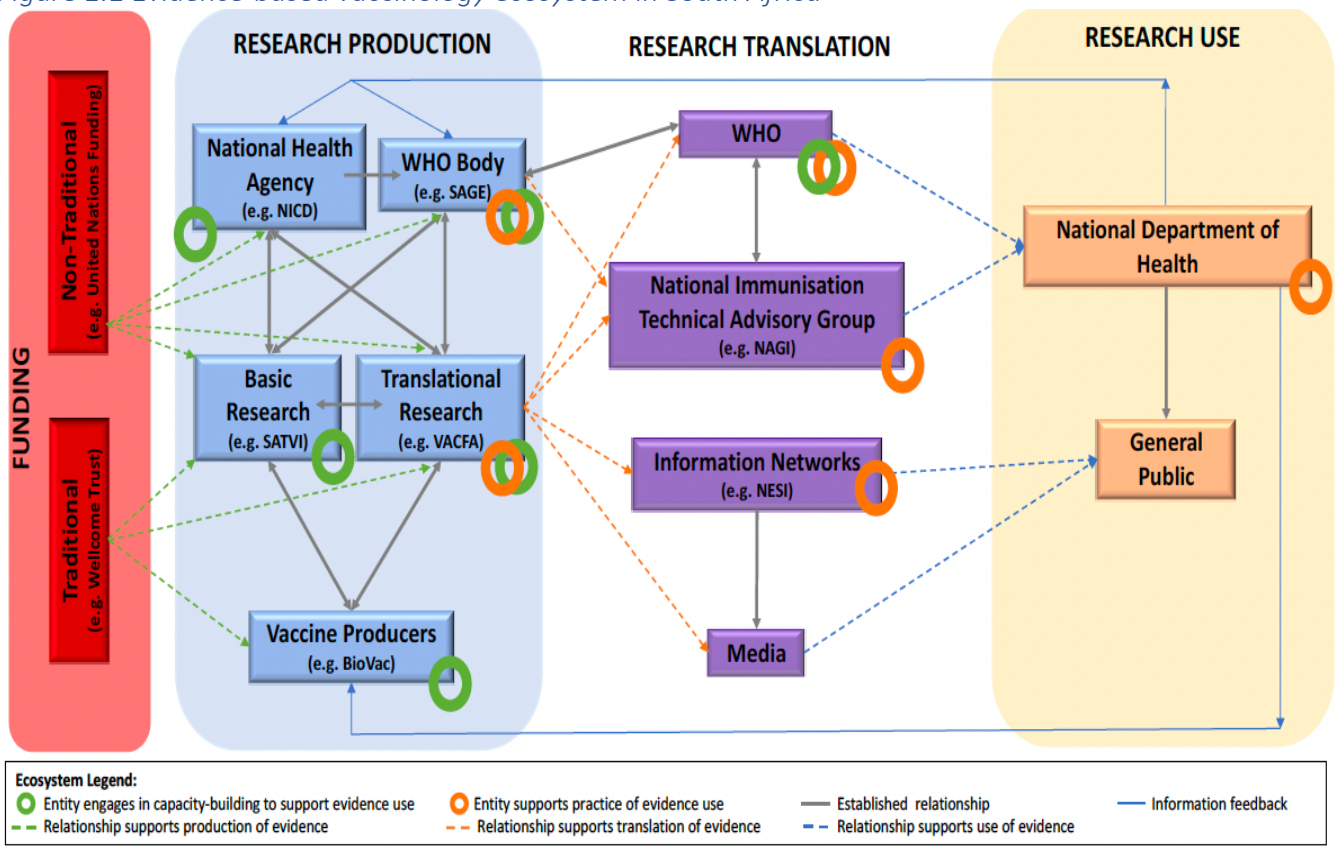
### 1.2.1 Key players in the vaccine ecosystem

In the context used in this PhD project, the term "vaccine ecosystem" refers to the space that begins with vaccine development and ends with vaccine implementation at a public health level. The key players in the vaccine ecosystem include vaccine manufacturers, technical partners (e.g. WHO, UNICEF, GAVI), academics (e.g. researchers), Non-Governmental Organizations (NGOs), the public, the governments (MoH) and National Immunization Technical Advisory Groups (NITAGs).

Players in the vaccine ecosystem (**Figure 1.1**) should work together to generate, synthesize, and translate relevant evidence to advance NIPs. While MoH are ultimately responsible for issuing policies regarding immunization practices, NITAGs are independent, expert advisory groups that advise the ministry on these policies (2). NITAGs represent one of the many efforts aimed to increase the use of

EIDM processes in the formation of public policy, globally (2). To support the work of NITAGs, technical partners such as the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) work to strengthen the capacity of these groups to utilize often complex evidence to develop recommendations. NITAGs are often faced with the "twin-challenge" of information overload (especially at global level) for some decision-making elements as well as a lack of contextually relevant data for others (1). The pharmaceutical industry and academic researchers within the vaccine ecosystem work to generate and synthesize existing data with the goal of advancing immunization programs.

*Figure 1.1 Evidence-based vaccinology ecosystem in South Africa*




## 1.2.2 Role of research

Multi-sectoral partnerships underpinned by independent and rigorous research often produce the high-quality evidence needed to inform NITAG recommendations on immunization practices. Just as it is important for NITAGs to remain independent with a clear separation from national governments, it is essential that the academic research published is non-partial and contextually relevant to support NITAG deliberations. Research plays a critical role within the vaccine ecosystem. Research assists in evidence

production, such as the epidemiology of vaccine preventable diseases (VPDs) and key issues arising from the burden of disease. Additionally, research is useful to identify the immunization policy options through the modelling of various scenarios before implementation, cost-effectiveness analyses and support the advancement of recommendations by NITAGs through MoH and Ministries of Finance.

### 1.2.3 Evidence to inform immunization policies

An Evidence to Recommendation (EtR) process is utilized by NITAGs when developing immunization recommendations that are subsequently submitted to the MoH for policy considerations. The EtR process makes use of pre-specified information such as the disease epidemiology, clinical features of the disease, vaccine characteristics, economic considerations and impact on existing immunization programs as well as social, legal and ethical considerations (3). The evidence used in the EtR process is routinely ranked into three different levels: critical, important, and not critical. Critical evidence refers to high-quality and up-to date information that must be accessed or generated before a recommendation is issued by NITAGs. Critical evidence commonly includes factors such as disease epidemiology, clinical characteristics, vaccine characteristics, and cost-effectiveness of the proposed immunization policy question (4). To address critical factors and where data already exists, systematic reviews are regarded as the best approach to provide evidence as the study design is based on synthesizing multiple studies identified through systematic literature searches (5). Where contextually relevant data on critical factors is missing, operational research such as modelling is commonly chosen to support the EIDM process. Modelling can assist in understanding the dynamics of a disease in a population as well as the cost-effectiveness of proposed immunization scenarios (6). Important and not critical factors included in the EtR process include health systems opportunities and existence of or interaction with other intervention, strategies social impacts, legal and ethical considerations (3).

### 1.2.4 Epidemiological-economic modelling

The epidemiological-economic modelling refers to a combination of mathematical disease models and cost-effectiveness analyses to aid in EIDM. This approach is particularly useful when considering the introduction of a new vaccine into a NIP schedule. Economic-epidemiological models are useful to assess whether a proposed immunization recommendation is affordable in relation to the estimated impact of the vaccine on the burden of disease (6). Dynamic compartmental models are classically used to simulate infectious disease transmission and progression in a population. Standard compartmental models such as the susceptible-infected-recovered (SIR) model are extended to include relevant disease

states such as exposed, asymptomatic, hospitalized, etc. (7). Transitions between these disease states are characterized by parameter values such as the basic reproductive rate ($R_0$), rate of disease recovery, and mortality rates – which under best practice are values extracted from systematic reviews. Each disease state in the compartmental model also carries a cost component which allows researchers to not only estimate the impact of the proposed immunization policy on the disease burden, but also on the cost of care, and cost-effectiveness of the intervention. The extended usefulness of epidemiological-economic models is that more than one immunization policy question can be explored with ease and robust sensitivity analyses on both model parameter values, and cost inputs can be conducted.

### 1.2.5 Translating evidence-based recommendations to practice

The availability of high-quality evidence on critical elements such as disease epidemiology, vaccine characteristics, and cost-effectiveness does not automatically mean the uptake of this evidence into NITAG considerations. Knowledge translation must occur between knowledge producers (researchers) and knowledge users (NITAGs) for the application of evidence in the EIDM processes (8). Evidence producers must work closely with evidence users as early in the process as framing of the policy question. Early and ongoing collaborations between evidence researchers and NITAGs ensures that the right pieces of evidence are being generated and synthesized to support contextually relevant decision-making. The evidence to support immunization practices often contains technical and challenging information such as epidemiological transitions and incremental-cost effectiveness ratios, thus the key findings of research must be adapted in a stakeholder-relevant and understandable way. Clear, concise policy dossiers and the development of toolkits such as user-friendly interfaces for modelling should be included as a part of research infrastructure. These tools increase the uptake of evidence in policy considerations as they allow decision-makers to further interrogate and understand key evidence.

Once evidence is translated to NITAGs, these bodies must work to integrate recommendations into the national decision-making frameworks. Recommendations must be financially feasible and political will must exist to support the adoption into policy. As implementation of new vaccines requires large upfront investments and the success of vaccination programs is often uncertain in LMICs, the political will to drive adoption must be fostered along the EIDM process as early as development of the policy question.

## 1.3 Evidence to Support Considerations of Introducing Hepatitis A Vaccines into the South African Expanded Program on Immunization

The Expanded Program on Immunization (EPI) was introduced in South Africa in 1995, after initial conception by the WHO in 1974 (9). Since the initiation of the Expanded Program on Immunization in South Africa (EPI-SA), the schedule has grown from six to twelve antigens (9). The most recent addition to the EPI-SA was the human papillomavirus (HPV) vaccine in 2014 (10). The EPI-SA is among the most advanced in Africa. South Africa was the first country on the continent to introduce the hepatitis B, Haemophilus influenzae type b, pneumococcal and rotavirus vaccines with full government funding. The South African NITAG, named the National Advisory Group on Immunization (NAGI), was instrumental in the introduction of pneumococcal and rotavirus vaccines in the country (11).

### 1.3.1 Hepatitis A immunization

In addition to the original EPI vaccines that included antigens against diphtheria, pertussis, tetanus, measles, poliomyelitis, and tuberculosis, several other vaccines have been introduced in a wide range of Low- and Middle-Income Countries (LMICs). These vaccines have either been recently approved or are recommended for use in specific endemic regions (12). In these instances, countries must monitor the epidemiology of the disease. For example, the WHO suggests that countries routinely collect and review information needed to estimate their national burden of hepatitis A as routine vaccination is recommended in countries with intermediate or low hepatitis A endemicity as a part of a comprehensive viral hepatitis strategy. Hepatitis A endemicity is measured by the proportion of people in the population with hepatitis A antibodies. High hepatitis A virus (HAV) endemicity is defined as ≥ 90% of population having been previously infected with hepatitis A and developing Immunoglobulin G (IgG) anti-HAV antibodies by 10 years of age. Intermediate HAV endemicity is defined as ≥ 50% of population having been previously infected with hepatitis A and developing Immunoglobulin G (IgG) anti-HAV antibodies by 15 years of age. Low HAV endemicity is defined as ≥ 50% of population having been previously infected with hepatitis A and developing Immunoglobulin G (IgG) anti-HAV antibodies by 30 years of age (13). As the transmission of hepatitis A occurs through the faecal-oral route, early infection and recovery from hepatitis A infection with the development of IgG anti-HAV antibodies has consistently been observed in settings with poor water, hygiene, and sanitation standards (WASH). With the ongoing socio-economic developments in many LMICs, these settings are beginning to experience a shift from early exposure when infection is often asymptomatic to HAV infection in later years of life

when it is more likely to be symptomatic. The increasing mean age of infection in countries transitioning from high to intermediate or low endemicity is marked by an increase in the incidence of symptomatic hepatitis A infection, including the increased risk of liver failure (13).

Several hepatitis A vaccines are licensed for use in children and adolescents in South Africa including Avaxim®, Havrix®, and Twinrix®. Avaxim® and Havrix® are inactivated vaccines indicated for active immunization against infection caused by the hepatitis A virus. Twinrix® is a combined vaccine for active immunization against hepatitis A and hepatitis B. Within two to four weeks of the first dose of inactivated hepatitis A, up to 100% of children and young adults achieve seroconversion (13). Some studies further indicate that inactivated hepatitis A vaccines are protective after a single dose (13). Published vaccine efficacy estimates for dose 1 and subsequent doses of inactivated hepatitis A vaccines range from 95-98% (13).

### 1.3.2 Hepatitis A in Africa

The epidemiology of hepatitis A has historically been considered on regional or sub-regional levels. The WHO conducted a review of the global prevalence of hepatitis A and combined Botswana, Lesotho, Namibia, South Africa, Eswatini (Swaziland), and Zimbabwe into the South Sub-Saharan African region (14). The hepatitis A epidemiological data included in this review were published between 1986-2002 and indicated high endemicity. The combination of these countries into a sub-region for classification of hepatitis A endemicity is problematic as it includes a variety of country income levels and different hepatitis A transmission risk levels mainly indicated by WASH standard.

### 1.3.3 Hepatitis A in South Africa

Recent primary studies conducted between 2004 and 2014 have identified a rise in symptomatic hepatitis A cases in South Africa. *Solomons et al.* conducted a record review of clinically ill paediatric hepatitis A cases over a 3-year period and suggested a significant risk to young children, including on morbidity and mortality (15). *Enoch et al.* conducted a cross-sectional seroprevalence study and noted a very low proportion of hepatitis A antibodies in young populations (16). These results have called for evidence-based considerations to introduce hepatitis A vaccines into the EPI-SA. Though these data indicate a possible transition from high to intermediate or low hepatitis A endemicity in South Africa, there is a paucity of data regarding the true burden of hepatitis A in the country.

## 1.4 Policy question on Hepatitis A immunization in South Africa

The overall aim of this thesis was to support evidence-informed considerations to introduce routine hepatitis A immunization into the Expanded Program on Immunization of South African (EPI-SA). NAGI, which is well integrated within the South Africa policy-making framework, has been involved in this research from the early phase of conceptualization in 2017. The Hepatitis A Working Group within NAGI has been extensively involved in developing the policy question and decisions of critical factors needed to generate and synthesize contextually relevant evidence.

The specific aims of the research were built around generation of evidence that was deemed critical by the NAGI Hepatitis A Working Group following the World Health Organization's (WHO's) guidance for the development of evidence-based vaccination-related recommendations (3).

To support evidence-informed decision-making considerations to introduce hepatitis A vaccines into the EPI-SA, the critical factors of the disease epidemiology, clinical characteristics, and cost-effectiveness in the South African setting were generated and synthesized (**Table 1.1**). Evidence on hepatitis A vaccine safety and efficacy is well founded in the literature and, therefore, was not included in **Table 1.1** for generation of new evidence. In addition to generating the critical evidence to support the EIDM process, financial considerations will also be addressed while fostering political will is beyond the scope of this project.

*Table 1.1: Critical factors of evidence to be generated*

| Critical factor | Specific elements |
|---|---|
| Disease epidemiology | Definition of hepatitis A virus endemicity levels |
| Clinical characteristics | Description of hepatitis A clinical severity and outcomes<br>Burden of acute liver failure |
| Economic considerations | Cost-effectiveness of routine immunization scenarios<br>Budget impact of introducing routine immunization |

### 1.4.1 A systematic review of the epidemiology of hepatitis A in Africa

Comprehensive epidemiological evidence to guide public health policies of hepatitis A control in Africa was unavailable and deemed critical to guide recommendations on the introduction of routine immunization against HAV in South Africa. The WHO recommends that vaccination against HAV be integrated into the national immunization schedule for children aged ≥1 year if indicated on the basis of incidence of acute hepatitis A and hepatitis A epidemiology (13). In order to guide immunization policy

recommendations, it was essential to conduct research to estimate the burden of hepatitis A on a regional and national scale. To generate the missing epidemiological evidence, a study entitled “A systematic review of the epidemiology of hepatitis A in Africa” was conducted with special interest paid to South African data. The study underwent expedited ethics approval by the Human Research Ethics Committee at the University of Cape Town and was conducted in accordance with the protocol registered on PROSPERO (CRD42017079730).

### 1.4.2 A systematic review of the global epidemiology of viral-induced acute liver failure

Evidence on the epidemiology of the most severe hepatitis A outcome, acute liver failure, was missing not only in South Africa but also at a global level. In order to fully appreciate the burden of hepatitis A and to fully consider the potential cost-effectiveness of hepatitis A vaccination, it was deemed critical to generate evidence on the prevalence of viral-induced acute liver failure. To generate this missing evidence, a study entitled “A systematic review of the global epidemiology of viral-induced acute liver failure” was conducted in accordance with best evidence-informed decision-making practices to assess the burden of acute liver failure induced by hepatitis A virus infection. This study received ethics approval from the Human Research Ethics Committee at the University of Cape Town and was conducted in accordance with the published protocol (PROSPERO registration CRD42018110309) (17).

### 1.4.3 A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa

Anecdotal evidence in South Africa suggested that hospitalizations associated with hepatitis A infection were rising, however published data on this topic were unavailable. In order to understand the burden of hepatitis A on the South African healthcare system and to understand the costs associated with hepatitis A care, a study entitled “A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa” was conducted. The primary aim of this study was to describe the clinical severity and outcomes of hepatitis A cases presenting to two tertiary healthcare centres in Cape Town, South Africa. The secondary aim of this study was to estimate the average cost per hepatitis A case managed in the two relevant healthcare centres. The study was approved by the University of Cape Town's Research Ethics Committee and research clearance was granted by the two facility research committees (GSH HREC 485 and RCH RCC 153). All data were collected and analysed in accordance with the relevant ethics guidelines and regulations.

### 1.4.4 Modelling the cost-effectiveness and budget impact of hepatitis A vaccination in South Africa

To forecast the epidemiology of hepatitis A in South Africa and suggest the most effective vaccination strategies to mitigate morbidity and mortality, an age-structured dynamic transmission model was designed following the review of several existing hepatitis A dynamic transmission models. The model was parameterized using baseline demographic data from South Africa and epidemiological and vaccine parameter values were taken from the systematic reviews conduced in this body of work. The outcomes of the hepatitis A dynamic transmission model were analyzed to estimate and compare the cost and consequences of the baseline scenario (no vaccination) and potential vaccination scenarios outlined by the South African National Advisory Group on Immunization's (NAGI's) Hepatitis A Working Group. The study was approved by the University of Cape Town's Faculty of Science Research Ethics Committee (FSREC 106 – 2019).

*Table 1.2: Summary of thesis chapters, objectives, and manuscripts*

| Chapter | Objectives | Manuscript title and status |
|---|---|---|
| Chapter 2 | Primary:<br>• To describe the epidemiology of hepatitis A in Africa.<br><br>Secondary:<br>• To estimate HAV seroprevalence (the prevalence of IgG anti-HAV antibodies) in Africa<br>• To estimate the prevalence of IgM anti-HAV antibodies<br>• To estimate the acute hepatitis A hospitalization rate in Africa<br>• To estimate the acute hepatitis A case fatality rate in Africa | Patterson, J., Abdullahi, L., Hussey, G. D., Muloiwa, R., & Kagina, B. M. (2019). A systematic review of the epidemiology of hepatitis A in Africa. *BMC infectious diseases*, *19*(1), 651. https://doi.org/10.1186/s12879-019-4235-5. |
| Chapter 3 | Primary:<br>• To estimate the prevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with acute liver failure (ALF).<br><br>Secondary:<br>• To estimate the mortality rate for cases of ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvovirus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs<br>• To estimate the prevalence and incidence of liver transplantation for cases of ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvovirus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs | Patterson, J., Hussey, H. S., Silal, S., Goddard, L., Setshedi, M., Spearman, W., Hussey, G. D., Kagina, B. M., & Muloiwa, R. (2020). Systematic review of the global epidemiology of viral-induced acute liver failure. *BMJ open*, *10*(7), e037473. https://doi.org/10.1136/bmjopen-2020-037473. |
| Chapter 4 | Primary:<br>• To describe the clinical severity of hepatitis A cases presenting to two public sector tertiary healthcare centres in Cape Town, South Africa.<br><br>Secondary:<br>• To describe the costs of care for hepatitis A cases presenting to two public sector tertiary healthcare centres in Cape Town, South Africa. | Patterson, J., Cleary, S., Silal, S. P., Hussey, G. D., Enoch, A., Korsman, S., Goddard, E., Setshedi, M., Spearman, W. C., Kagina, B. M., & Muloiwa, R. (2022). A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa. *BMC infectious diseases*, *22*(1), 45. https://doi.org/10.1186/s12879-021-06993-w. |
| Chapter 5 | Primary:<br>• To evaluate the costs, outcomes, and cost-effectiveness of introducing routine hepatitis A immunization into the South African Expanded Program on Immunization. | Patterson, J., Cleary, S., Awine T., Norman, J., Mayet S., Kagina, B. M., Muloiwa, R., Hussey, G. D., Silal, S. P., Modelling the cost of hepatitis A vaccination in South Africa. *Being prepared for submission.* |

## 1.5 References


1. Steffen CA, Henaff L, Durupt A, Omeiri NE, Ndiaye S, Batmunkh N, et al. Evidence-informed vaccination decision-making in countries: Progress, challenges and opportunities. Vaccine. 2021;39(15):2146-52.
2. Buffardi AL, Njambi-Szlapka S. Questions for future evidence-informed policy initiatives: insights from the evolution and aspirations of National Immunization Technical Advisory Groups. Health Res Policy Syst. 2020;18(1):40.
3. World Health Organization. Guidance for the Development of Evidence-Based Vaccination-Related Recommendations. World Health Organization; 2017 31 January 2017.
4. Piso B, Wild C. Decision support in vaccination policies. Vaccine. 2009;27(43):5923-8.
5. University of Canberra. Evidence-Based Practice in Health 2018 [Available from: https://canberra.libguides.com/c.php?g=599346&p=4149722.
6. SP S, Africa MaSH. Operational research: A multidisciplinary approach for the management of infectious disease in a global context. Eur J Oper Res. 2021;291(3):929-34.
7. Avery C, Bossert W, Clark A, Ellison G, Ellison SF. An Economist's Guide to Epidemiology Models of Infectious Disease. Journal of Economic Perspectives. 2020;34(4):79-104.
8. World Health Organization. World report on knowledge for better health: strengthening health systems. Geneva: World Health Organization; 2004.
9. Dlamini NR, Maja P. The Expanded Programme on Immunisation in South Africa: A story yet to be told. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2016;106(7):675-7.
10. Delany-Moretlwe S, Kelley KF, James S, Scorgie F, Subedar H, Dlamini NR, et al. Human Papillomavirus Vaccine Introduction in South Africa: Implementation Lessons From an Evaluation of the National School-Based Vaccination Campaign. Global Health: Science and Practice. 2018;6(3).
11. Wiyeh AB, Sambala EZ, Ngcobo N, Wiysonge CS. Existence and functionality of national immunisation technical advisory groups in Africa from 2010 to 2016. Hum Vaccin Immunother. 2018;14(10):2447-51.
12. Guignard A, Praet N, Jusot V, Bakker M, Baril L. Introducing new vaccines in low- and middle-income countries: challenges and approaches. Expert Rev Vaccines. 2019;18(2):119-31.
13. World Health Organization. WHO position paper on hepatitis A vaccines - June 2012. Wkly Epidemiol Rec. 2012;87(28/29).
14. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653-7.
15. Solomons RS, Rabie H, Nel E, Cotton M. An overview of Hepatitis A at Tygerberg Children's Hospital. South African Journal of Child Health. 2008;2(2):43-5.
16. Enoch A, Hardie DR, Hussey GD, Kagina BM. Hepatitis A seroprevalence in the Western Cape Province, South Africa. Are we in epidemiological transition? South African Medical Journal. 2019;109(5):314-8.
17. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019;9(8).

# 2 Chapter 2: A systematic review of the epidemiology of Hepatitis A in Africa

Patterson, J., Abdullahi, L., Hussey, G. D., Muloiwa, R., & Kagina, B. M. (2019). A systematic review of the epidemiology of hepatitis A in Africa. *BMC infectious diseases*, *19*(1), 651. https://doi.org/10.1186/s12879-019-4235-5.

**Relevance of this paper to the thesis:**

Comprehensive epidemiological evidence is essential to guide public health policies of hepatitis A control. However, little is understood about the epidemiological profile of the hepatitis A virus in Africa. This paper presents a detailed synthesis of the epidemiology of hepatitis A in Africa, with special emphases on South African data.

**Contributions of the student and co-authors:**

BMK conceptualized this study. JP developed the study protocol under the supervision of BMK and RM. JP implemented the review under the supervision of BMK. JP and LA performed the search, screening, and data extraction under the guidance of BMK. GDH, RM and BMK provided content expertise for this review. All authors have provided comments on the final manuscript before publication. JP is the guarantor of this review

## 2.1 Abstract

Hepatitis A, caused by the hepatitis A virus (HAV), is a vaccine preventable disease. In Low and Middle-Income Countries (LMICs), poor hygiene and sanitation conditions are the main risk factors contributing to HAV infection. However, there have been notable improvements in hygiene and sanitation conditions in many LMICs. As a result, there are studies showing a possible transition of some LMICs from high to intermediate HAV endemicity. The World Health Organization (WHO) recommends that countries should routinely collect, analyse, and review local factors (including disease burden) to guide the development of hepatitis A vaccination programs. Up-to-date information on hepatitis A burden is, therefore, critical in aiding the development of country-specific recommendations on hepatitis A vaccination.

We conducted a systematic review and meta-analysis to present an up-to-date, comprehensive synthesis of hepatitis A epidemiological data in Africa.

The main results of this review include: 1) the reported HAV seroprevalence data suggests that Africa as a whole should not be considered as a high HAV endemic region; 2) the IgM anti-HAV seroprevalence data showed similar risk of acute hepatitis A infection among all age-groups; 3) South Africa could be experiencing a possible transition from high to intermediate HAV endemicity. The results of this review, however, should be interpreted with caution as the reported data represents research work with significant sociocultural, economic, and environmental diversity from 13 out of 54 African countries.

Our findings show that priority should be given to collecting HAV seroprevalence data and re-assessing the current hepatitis A control strategies in Africa to prevent future disease outbreaks.

## 2.2 Background

Hepatitis A is a vaccine preventable disease (VPD) caused by the hepatitis A virus (HAV). The hepatitis A virus is transmitted from person-to-person through the faecal-oral route primarily by ingestion of contaminated food or water and/or contact with infectious persons (1, 2). Poor hygiene and sanitation pose the greatest risk for HAV infection, particularly in Low and Middle-Income Countries (LMICs) (3). Infection with HAV causes an immune response which is assessed by measurement of specific antibodies: immunoglobulin class M (IgM) anti-HAV antibodies and immunoglobin class G (IgG) anti-HAV antibodies (4). Anti-HAV IgM antibodies are detectable following acute infection and antibody titres usually decline to zero within 3-6 months (5, 6). In contrast, anti-HAV IgG antibodies appear within 2-3 months after infection and persist for a long period of time conferring protective immunity against future infections (2). Therefore, a majority of hepatitis A seroprevalence studies often report anti-HAV IgG and not anti-HAV IgM seroprevalence data.

Common clinical symptoms of hepatitis A infection include jaundice, fever, malaise, anorexia, nausea, and abdominal discomfort (1, 4). Infection with HAV in early childhood is thought to be largely asymptomatic and results in the development of lifelong protective immunity (4). In contrast, infection with HAV after early childhood is associated with an increased risk of symptomatic, acute hepatitis A infection (1, 7, 8). The case fatality rate associated with acute hepatitis A in children and adults ≤ 50 years old ranges from 0.3 to 0.6%, while the case fatality rate in adults ≥ 50 years old ranges from 1.8 to 5.4% (9). The high costs associated with management of acute hepatitis A are well appreciated by healthcare providers. Hepatitis A patients typically miss several weeks of work or school and the costs of supportive medical care can be substantial (4). Therefore, vaccination against hepatitis A has been found to be cost-effective in many LMICs and should be prioritized in settings where hepatitis A is a public health concern (10). Routine hepatitis A vaccination policies can only be developed based on up-to-date and high-quality contextual evidence that includes the burden of the disease.

The latest global review of HAV endemicity was published in 2010 and included epidemiological data from 1990 to 2005. The review classifies Africa as a high HAV endemic region (11). Since 2005, many African countries have made significant improvements in water, sanitation, and developments in socio-economic status (SES). The improvements are likely to cause changes in the average age of first exposure and infection with HAV as well as in the prevalence of acute hepatitis A. Recent hepatitis A studies conducted in Africa, though few and far between, suggest that some regions on the continent

could be experiencing a transition in hepatitis A epidemiology. Our aim in this review is to provide an up-to-date synthesis of hepatitis A epidemiology in Africa.

The WHO does not recommend routine vaccination against hepatitis A in high endemic settings (2). As of 2018, no African country included routine hepatitis A vaccination as part of its' Expanded Program on Immunization (EPI). The WHO recommendation is that countries should routinely collect and review local factors and epidemiological data needed to guide the development of evidence-based recommendations on hepatitis A vaccination (2). To the best of our knowledge, an up-to-date, comprehensive synthesis of hepatitis A epidemiological data in Africa is lacking. Though there have been several primary studies on hepatitis A epidemiology published since 2005 in Africa, the review team is not aware of any recent publication that has synthesized data from this setting (12-15). The development of effective public health control strategies against hepatitis A require optimal characterization of the disease epidemiology. Therefore, this systematic review and meta-analysis aims to fill the existing knowledge gap to guide considerations of development of public health strategies to control hepatitis A in the region.

## 2.3 Methods

### 2.3.1 Objectives

To describe the epidemiology of hepatitis A in Africa.

#### *2.3.1.1 Primary objectives*

- To estimate the HAV seroprevalence (the prevalence of IgG anti-HAV antibodies) in Africa
- To estimate the prevalence of IgM anti-HAV antibodies
- To estimate the acute hepatitis A hospitalization rate in Africa
- To estimate the acute hepatitis A case fatality rate in Africa

#### *2.3.1.2 Secondary objective*

- To assess the impact of co-morbidities on hepatitis A epidemiology in Africa

### 2.3.2 Study eligibility criteria

Published and unpublished case-series, case-control, cross-sectional, cohort studies as well as randomized control trials (RCTs) and non-randomized control trials (nRCTs) in any language that reported the epidemiology of hepatitis A in children ≥1 year of age as well as in adults in any African

country were eligible for inclusion in this review. Studies were eligible for inclusion if they reported on any of the outcomes of this review, including seroprevalence of IgG anti-HAV antibody or prevalence of IgM HAV-antibody detection as well as hepatitis A disease incidence rates, hospitalization rates, case fatality rates as well as co-infections.

### 2.3.3 Search strategy

A combination of the following search terms (including the use of Medical Subject Headings (MESH)) was used: hepatitis A, acute hepatitis A, epidemiology, incidence, prevalence, morbidity, mortality, hospitalization, and case-fatality. An example of the search strategy as applied to PubMed is outlined in **Table 2.1**. The following electronic databases were searched for relevant published literature: EBSCOhost, MEDLINE via PubMed, ScienceDirect via SciVerse, Scopus via SciVerse, Ovid Discovery and Google Scholar. Grey literature was sourced by consulting with expert researchers in the field and by searching the following grey literature repositories: OpenUCT, OpenGrey, MEDNAR and CORE. The literature search was initially performed in February 2018 and updated in December 2018.

*Table 2.1: Search Strategy for PUBMED*

| Query # | Search Query |
|---|---|
| #1 | hepatitis A [MeSH Terms] OR hepatitis A [All Fields] OR acute hepatitis A [MeSH Terms] OR acute hepatitis A [All Fields] |
| #2 | epidemiology [MeSH Terms] OR epidemiology [All Fields] |
| #3 | incidence [MeSH Terms] or incidence [All Fields] |
| #4 | prevalence [MeSH Terms] or prevalence [All Fields] |
| #5 | morbidity [MeSH Terms] OR morbidity [All Fields] OR hospitalisation [MeSH Terms] OR hospitalization [All Fields] OR hospitalization [MeSH Terms] or hospitalization [All Fields] |
| #6 | mortality [MeSH Terms] OR mortality [All Fields] OR case-fatality [MeSH Terms] OR case-fatality [All Fields] |
| #7 | Africa [MeSH Terms] OR Africa [All Fields] OR Algeria [All Fields] OR Angola [All Fields] OR Benin [All Fields] OR Botswana [All Fields] OR Burkina Faso [All Fields] OR Burundi [All Fields] OR Cabo Verde [All Fields] OR Cameroon [All Fields] OR Central African Republic [All Fields] OR Chad [All Fields] OR Comoros [All Fields] OR Congo [All Fields] OR Cote d'Ivoire [All Fields] OR Djibouti [All Fields] OR Egypt [All Fields] OR Equatorial Guinea [All Fields] OR Eritrea [All Fields] OR Ethiopia [All Fields] OR Gabon [All Fields] OR Gambia [All Fields] OR Ghana [All Fields] OR Guinea [All Fields] OR Guinea-Bissau [All Fields] OR Kenya [All Fields] OR Lesotho [All Fields] OR Liberia [All Fields] OR Libya [All Fields] OR Madagascar [All Fields] OR Malawi [All Fields] OR Mali [All Fields] OR Mauritania [All Fields] OR Mauritius [All Fields] OR Morocco [All Fields] OR Mozambique [All Fields] OR Namibia [All Fields] OR Niger[All Fields] OR Nigeria [All Fields] OR Rwanda [All Fields] OR Sao Tome and Principe [All Fields] OR Senegal [All Fields] OR Seychelles [All Fields] OR Sierra Leone [All Fields] OR Somalia [All Fields] OR South Africa [All Fields] OR South Sudan [All Fields] OR Sudan [All Fields] OR Swaziland [All Fields] OR Tanzania [All Fields] OR Togo [All Fields] OR Tunisia [All Fields] OR Uganda [All Fields] OR Zambia [All Fields] OR Zimbabwe [All Fields] |
| #8 | 2005 [PDAT]: 2018 [PDAT] |
| #9 | #1 AND #2 AND #3 AND #4 AND # |
| **Note: Age of participants are included in search filter**<br>**Abbreviations: MeSH = Medical Subject Heading; PDAT = publication date.** | |

### 2.3.4 Data extraction

Study characteristics and outcomes of interests were extracted from the included studies on a pre-designed data extraction form by two independent reviewers (JP and LA). Prior to use by the two reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles that met the inclusion criteria. The study resolved any disagreements in data extraction through consensus in consultation with BMK. In cases where studies were not available in English, google translate was used to translate the article to English (16).

### 2.3.5 Data synthesis and meta-analysis

To conduct the meta-analysis, a random effects model was fitted to the study data as it includes estimates taken from a series of independently performed studies. Random effect models are an appropriate choice under the valid assumption that the observed prevalence estimates vary across studies because of real differences in the prevalence across settings as well as sampling variability. Where heterogeneity between included studies was found to be low in meta-analyses $(I^2 < 75)$, pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where heterogeneity was found to be high in meta-analyses $(I^2 \geq 75)$, narrative reporting was used to describe the prevalence ranges for each respective outcome.

### 2.3.6 Risk of bias

Each included study was assessed for risk of bias and quality using the Hoy *et al.,* 2012 tool for observational studies (17, 18). The scoring tool by Hoy examines the internal and external validity by considering study design, methodology and the presence of bias. For each included study, we reported our assessment of risk of bias together with a descriptive summary of the information that influenced our judgment. We judged the risk of bias in an included study as either 'low risk', 'high risk' or 'moderate risk' and presented a Risk of Bias table to summarize these assessments. All risk of bias judgements were made by JP and LA. In case of disagreement in risk of bias and quality assessment, a final decision was made through consensus in consultation with BMK.

### 2.3.7 Reporting of review

This systematic review and meta-analysis was registered with PROSPERO (registration number CRD42017079730) and the results are reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist (19).

## 2.4 Results

The initial database searches yielded 10,598 records, from which 4,334 duplicates were removed. No additional records were found when the search was updated in December 2018. A further 6,264 records were excluded following the screening of titles and abstracts (**Figure 2.1**). The full text of the remaining 121 records were screened from which 30 records met the final inclusion criteria. A further two unpublished studies at the time of the search were obtained through personal communication with hepatitis A researchers (20, 21). The second study, Enoch *et al*., has since been published. Therefore, a total of 32 studies were included in this review. The included studies were conducted in 13 African countries, a majority of these being from the North, West, and Southern regions of the continent (**Figure 3.2**). **Figure 2.2** displays the geographic location of 27 of the included studies conducted on the African continent. Five of the 32 included studies (not shown in **Figure 3.2**) reported hepatitis A data from expatriate communities (adults and children) from the African continent, living in Europe and North America (22-26).

*Figure 2.1: PRISMA flow diagram of study selection process.*

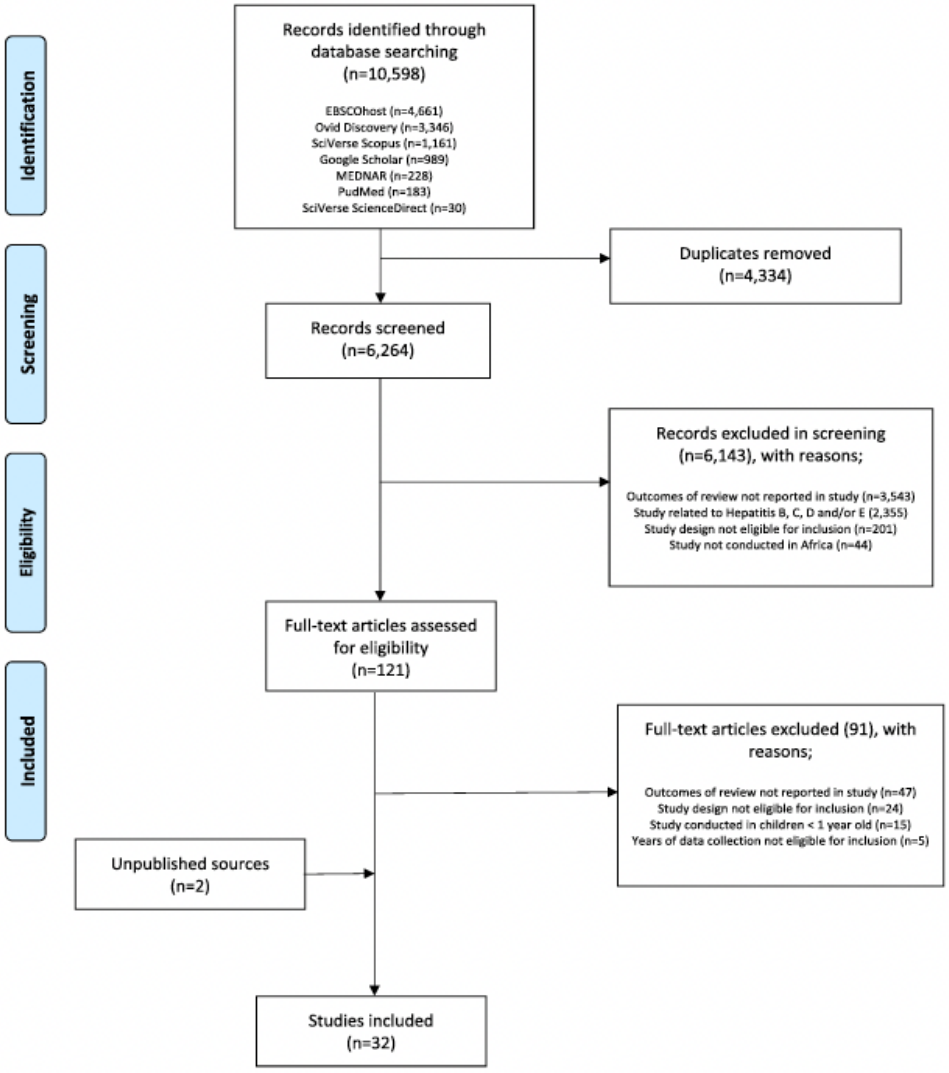
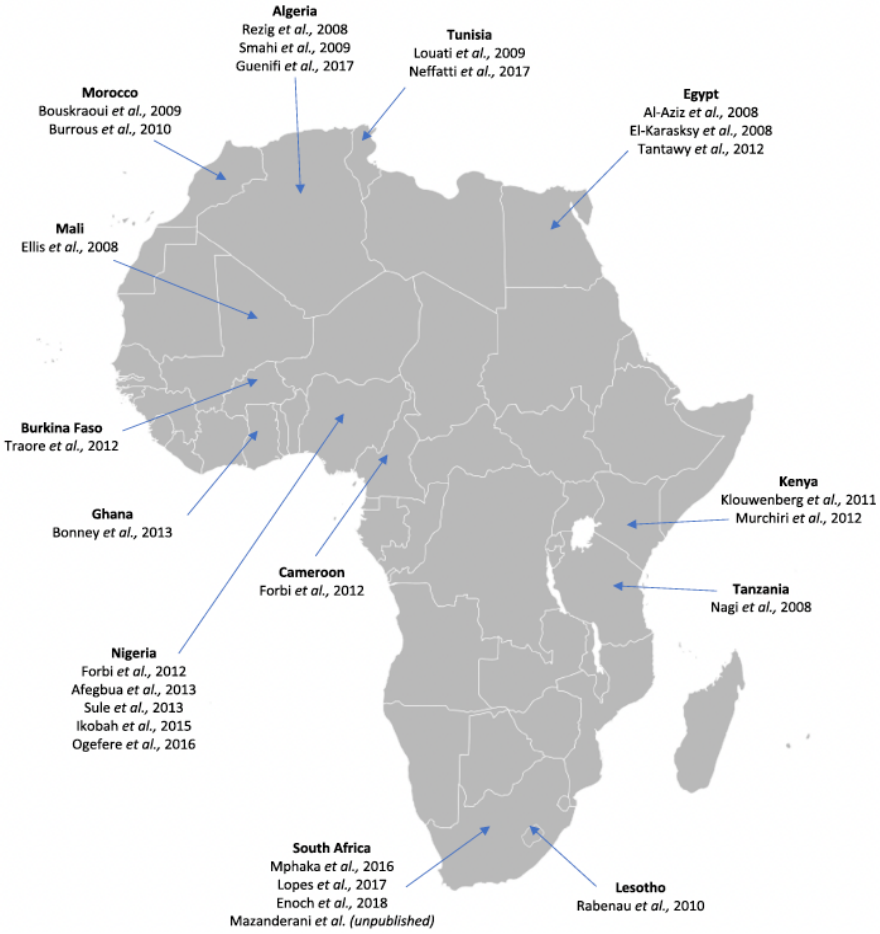


*Figure 2.2: Map of included studies*




Twenty-three of the included studies were cross-sectional studies (**Table 2.2**). Most of the included studies were conducted in the public healthcare sectors of lower-middle income countries. Of the 32 included studies, 17 provided data on anti-HAV IgG alone (referred to hereon as HAV seroprevalence), 11 provided data on anti-HAV IgM alone (referred to hereon as IgM anti-HAV seroprevalence) and 4 studies provided data together for IgG anti-HAV and IgM anti-HAV seroprevalence. Our analyses categorize the included studies according to the population age-groups [children & adolescents (1 to 18 years of age), adults (≥ 18 years of age) and all ages (1 to 99 years of age)], of which children and adolescent populations were most reported on (56% of included studies). Measurement of the anti-HAV antibodies was assessed using enzyme-linked immunosorbent assay (ELISA) for both IgG and IgM positivity in all studies. Reverse transcription polymerase chain reaction (RT-PCR) was used in 4 studies, in addition to the ELISA assay (**Table 2.3**). Details on the assay detection limits were missing from all included studies.

*Table 2.2: Characteristics of studies included in the review*

| Author, Year (Citation) | Study Design | Year(s) of Data Collection | Country | Population | Sample Size (n) | Outcome Measures | Study Objective |
|---|---|---|---|---|---|---|---|
| Abdulla et al., 2010 (22) | Cross-sectional | 2006 to 2008 | General Africa | Children & adolescents | 29 | IgG | To determine the prevalence of acute hepatitis A virus infection and immunity among internationally adopted children |
| Afegbua et al., 2013 (27) | Cross-sectional | 2009 | Nigeria | Children & adolescents | 403 | IgG | To determine seroprevalence of HAV among schoolchildren and adolescents in Kaduna State and identify factors associated with seropositivity |
| Al-Aziz et al., 2008 (28) | Cohort | 2008 | Egypt | Children & adolescents | 296 | IgG | To determine the seroprevalence of HAV antibodies among group of children |
| Blanchi et al., 2014 (23) | Cohort | 2009 to 2012 | General Africa | Children | 146 | IgM | To describe infectious diseases in internationally adopted children |
| Bonney et al., 2013 (29) | Cross-sectional | 2008 to 2011 | Ghana | All ages | 285 | IgM | To determine if viral haemorrhagic fevers and viral hepatitides contribute to hospital morbidity in the Central and Northern parts of Ghana |
| Bouskraoui et al., 2009 (30) | Cross-sectional | 2005 to 2006 | Morocco | Children & adolescents | 150 | IgG | To assess the prevalence of viral hepatitis A infection in febrile icteric children and to examine the main risk factors of transmission |
| Burrous et al., 2010 (31) | Cross-sectional | 2006 to 2008 | Morocco | Children & adolescents | 129 | IgM | To assess the prevalence of viral hepatitis A infection in febrile icteric children and to examine the main risk factors of transmission |
| El-Karasksy et al., 2008 (32) | Cohort | 2005 | Egypt | Children & adolescents | 172 | IgG | To determine the prevalence of anti-hepatitis A virus antibodies among 172 children with chronic liver disease |
| Ellis et al., 2008 (33) | Cohort | 2008 | Mali | Children | 36 | IgM | Phase 1 study in Malian children of the blood stage malaria vaccine |
| Enoch et al., 2019 (21) | Cross-sectional | 2009 to 2015 | South Africa | Children | 482 | IgG | To determine the seroprevalence of hepatitis A infection in the Western Cape Province of South Africa |
| Forbi et al., 2012 (34) | Cohort | 2012 | Cameroon | Children | 78 | IgM | To undertake genetic analysis of the hepatitis A virus associated with cases of acute diarrhoea among |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | children under five in Cameroon |
| Forbi et al., 2012_2 (35) | Cross-sectional | 2006 | Nigeria | Adults | 114 | IgM | To investigate HAV strains among apparently healthy adult Nigerian subjects |
| Guenifi et al., 2017 (36) | Cross-sectional | 2010 to 2011 | Algeria | Children | 1061 | IgG | To estimate the seroprevalence of hepatitis A virus infection in the district of Setif |
| Ikobah et al., 2015 (37) | Cross-sectional | 2012 | Nigeria | Children & adolescents | 406 | IgG | To determine the seroprevalence and predictors of viral hepatitis A in children aged 1 to 18 years |
| Jablonka et al., 2017 (38) | Cross-sectional | 2015 | General Africa | All ages | 55 | IgG | To determine the seroprevalence of anti-HAV IgG in refugees in Germany |
| Klouwenberg et al., 2011 (39) | Cohort | 2011 | Kenya | Children | 222 | IgM | To determine the temporal pattern of a co-infection of P. falciparum malaria and acute HAV in a cohort of Kenyan children under the age of five |
| Lopes et al., 2017 (40) | Cross-sectional | 2015 | South Africa | All ages | 300 | IgG | To determine the seroprevalence of HAV and HEV antibodies in blood donors giving at the Western Province Blood Transfusion Service |
| Louati et al., 2009 (41) | Cross-sectional | 2007 | Tunisia | Adults | 376 | IgG | To assess hepatitis A virus seroprevalence in blood donors from South Tunisia in two periods; 200 and 2007 |
| Majori et al., 2008 (26) | Cross-sectional | 2008 | General Africa | All ages | 182 | IgG & IgM | To assess the seroprevalence of viral hepatitis infections in sub-Saharan immigrants living in Italy |
| Mazanderani et al., 2019 (20) | Cross-sectional | 2005 to 2015 | South Africa | All ages | 501083 | IgG & IgM | To assess seroprevalence rates among specimens tested for HAV serology within South Africa's public health sector |
| Mphaka et al., 2016 (42) | Cross-sectional | 2016 | South Africa | Children & adolescents | 46 | IgM | To respond to an increase in blood samples testing positive for HAV IgM |
| Murchiri et al., 2012 (43) | Cross-sectional | 2007 to 2008 | Kenya | Adults | 100 | IgM | To determine seroprevalence of HAV, HBV HCV and HEV among patients with acute hepatitis in Nairobi Kenya |
| Nagu et al., 2008 (44) | Cross-sectional | 2006 | Tanzania | Adults | 260 | IgM | To determine the prevalence and predictors of viral hepatitis co-infection among HIV-infected individuals presenting at the HIV care |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | and treatment clinics in the country |
| Neffatti et al., 2017 (45) | Cross-sectional | 2014 to 2015 | Tunisia | Adults | 216 | IgG | To supplement lacking data on hepatitis A and E from rural areas of South Tunisia |
| Ogefere et al., 2016 (46) | Cross-sectional | 2016 | Nigeria | All ages | 200 | IgM | To determine the seroprevalence of anti-HAV IgM in an at-risk population in Benin City and to identify the social, demographic and other risk factors |
| Raabe et al., 2014 (24) | Cross-sectional | 2014 | General Africa | Children | 656 | IgM | To assess the need to recommend routine HAV vaccination in internationally adopted children |
| Rabenau et al., 2010 (47) | Cohort | 2007 | Lesotho | Adults | 205 | IgG | To screen international adoptees for acute HAV infection |
| Rezig et al., 2008 (48) | Cross-sectional | 2008 | Algeria | Children & adolescents | 3357 | IgG | To assess the seroprevalence of coinfecting viruses in a cohort of 205 HIV-infected individuals |
| Smahi et al., 2009 (49) | Cross-sectional | 2006 | Algeria | Children | 252 | IgG | To determine the seroprevalence of hepatitis A and E infections |
| Sule et al., 2013 (50) | Cross-sectional | 2010 to 2011 | Nigeria | All ages | 91 | IgG | To determine the prevalence of anti-hepatitis A virus IgG antibody and associated factors among residents of Osogbo |
| Tantawy et al., 2012 (51) | Case-control | 2009 to 2010 | Egypt | Children & adolescents | 182 | IgG | To evaluate the seroprevalence of hepatitis A in Egyptian patients with haemophilia A |
| Traore et al., 2012 (52) | Cross-sectional | 2010 to 2012 | Burkina Faso | Adults | 91 | IgG & IgM | To assess the seroprevalence of antibodies to both HAV and HEV in central Burkina Faso in the absence of a recorded hepatitis epidemic |
| **Abbreviations: HAV = hepatitis A virus; IgG = immunoglobin class G; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus.** | | | | | | | |

*Table 2.3: Assays used in included studies*

| Author, Year | Assay | Brand |
|---|---|---|
| Abdulla et al., 2010 (22) | ELISA | DiaSorin |
| Afegbua et al., 2013 (28) | ELISA | Asia-lion Bitechnology |
| Al-Aziz et al., 2008 (35) | ELISA | DiaSorin |
| Blanchi et al., 2014 (23) | Serology | NR |
| Bonney et al., 2013 (36) | RT-PCR | RealStar |
| Bouskraoui et al., 2009 (37) | ELISA | NR |
| Burrous et al., 2010 (38) | ELISA | DiaSorin |
| El-Karasksy et al., 2008 (39) | ELISA | DiaSorin |
| Ellis et al., 2008 (40) | Serology & ALT levels | NR |
| Enoch et al., 2019 (21) | ELISA | Siemens |
| Forbi et al., 2012 (41) | RT-PCR | Applied Biosystems |
| Forbi et al., 2012_2 (42) | RT-PCR | NR |
| Guenifi et al., 2017 (43) | ELISA | Roche |
| Ikobah et al., 2015 (44) | EIA | DRG International Inc. |
| Jablonka et al., 2017 (45) | ELISA | Abbott ARC |
| Klouwenberg et al., 2011 (46) | ELISA | BioChain |
| Lopes et al., 2017 (47) | ELISA | Abbott ARC |
| Louati et al., 2009 (48) | ELISA | DiaSorin |
| Majori et al., 2008 (26) | ELISA | Abbott ARC |
| Mazanderani et al., 2018 (11) | Serology | NR |
| Mphaka et al., 2016 (49) | Serology | NR |
| Murchiri et al., 2012 (50) | ELISA | NR |
| Nagu et al., 2008 (51) | ELISA | Adaltis |
| Neffatti et al., 2017 (52) | RT-PCR | Wantani |
| Ogefere et al., 2016 (53) | Serology | Qingdao High-top Biotech |
| Raabe et al., 2014 (24) | Serology | N/A |
| Rabenau et al., 2010 (54) | ELISA | AxSYM MEIA |
| Rezig et al., 2008 (55) | ELISA | Bio-Rad |
| Smahi et al., 2009 (56) | Serology | NR |
| Sule et al., 2013 (57) | ELISA | DiaSorin |
| Tantawy et al., 2012 (58) | ELISA | DiaSorin |
| Traore et al., 2012 (59) | ELISA | DiaSorin |

**Abbreviations: NR=Not reported, ELISA=enzyme-linked immunosorbent assay, RT-PCR=reverse transcription polymerase chain reaction, EIA=competitive enzyme immunoassay, ALT=Alanine aminotransferase.**

## HAV seroprevalence in Africa from 2008 to 2018

Heterogeneity was high ($I^2$ = 99.21%) among the 15 studies pooled for analysis of IgG seroprevalence in all age groups. This was not surprising considering the diversity of the included studies; thus, we categorized the analysis of HAV seroprevalence by age-groups (**Figure 2.3**). The estimated average of the reported HAV seroprevalence for children and adolescents among included studies was 57.0% (Estimate (ES) = 0.57; 95% CI = 0.40, 0.73) as compared to compared to 95.0% (ES = 0.98; 95% CI = 0.85, 1.00) for adults. Data reported by Mazanderani *et al.,* (2018) presented a unique opportunity to further explore of HAV seroprevalence by age-groups in South Africa from 2005 to 2015 (**Figure 2.4**). The data displayed in **Figure 2.4** shows that HAV seroprevalence for children, adolescents ≤15 years old remained below 90% for any given year between 2005 and 2015. Additionally, **Figure 2.4** shows that HAV seroprevalence for adolescents ≥15 and adults ≤20 reduced from its highest in 2011 (92.8%) to 83.5% in 2015.

*Figure 2.3: Hepatitis A virus seroprevalence by population in Africa, 2008-2018*

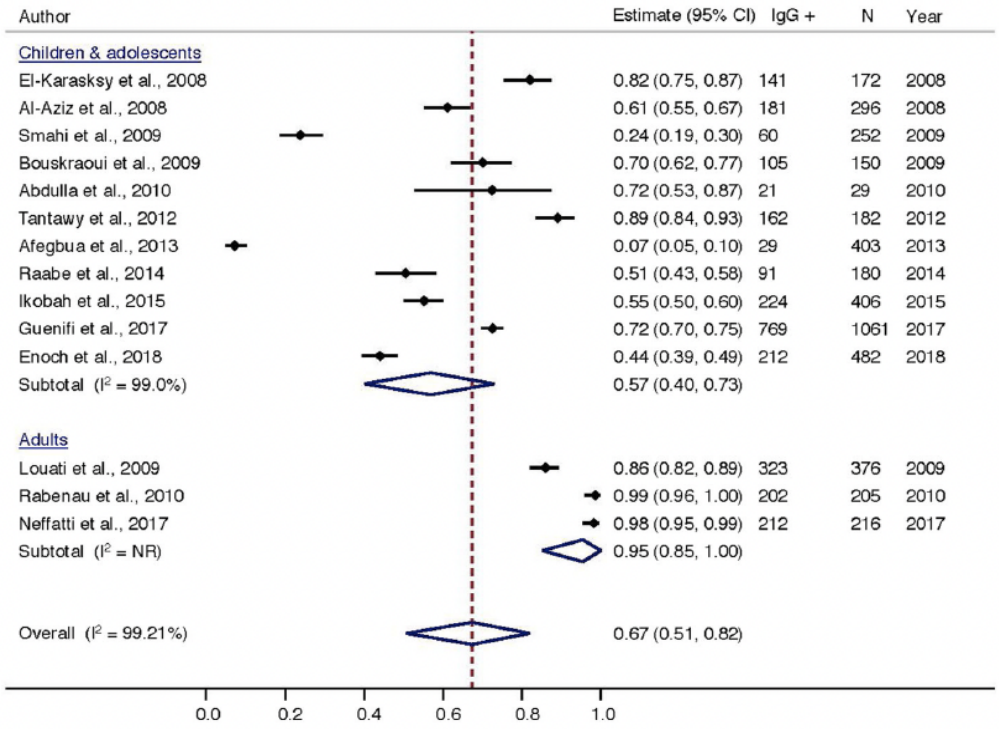
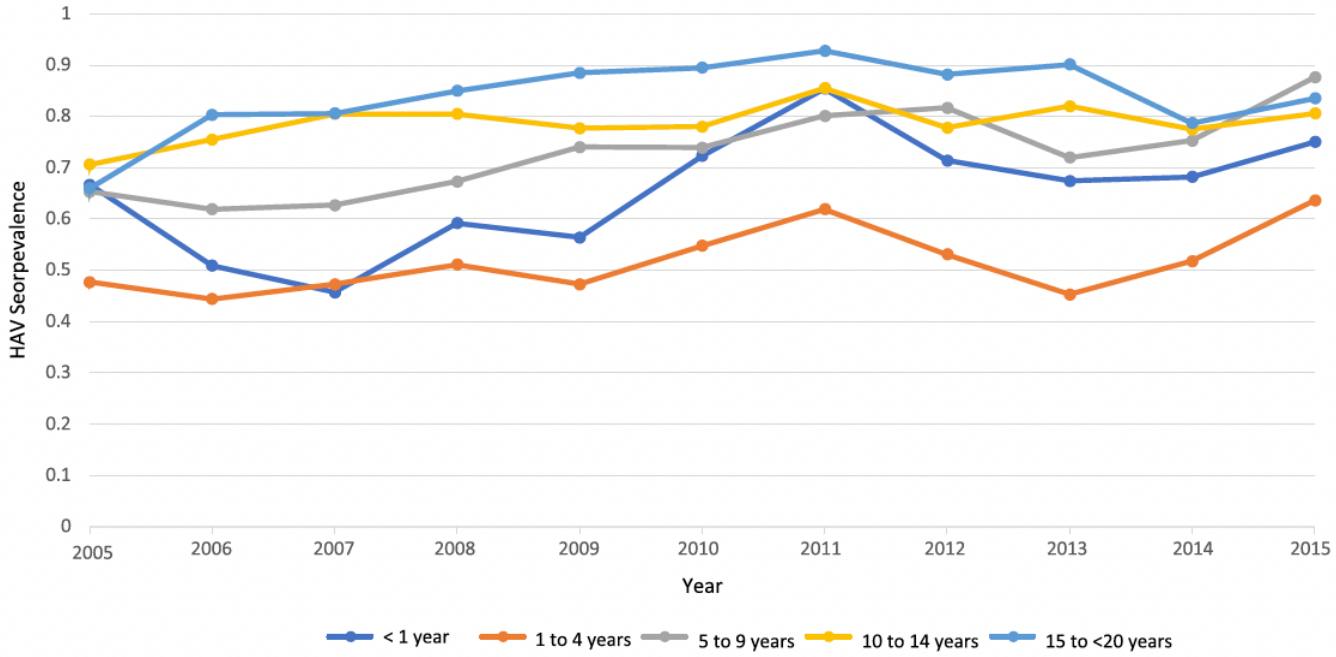


*Figure 2.4: Hepatitis A virus seroprevalence estimates by age-group in South Africa, 2005-2015*




### 2.4.1 IgM anti-HAV seroprevalence in Africa from 2008 to 2018

We have used IgM anti-HAV seroprevalence as a marker for acute hepatitis A infection in this review (53). Pooled acute hepatitis A prevalence for 2008 to 2018 showed high heterogeneity ($I^2$ = 98.1%) (**Figure 2.5).** An outlier in the data (Burros et al., 2010) reported acute hepatitis A prevalence in a population of febrile icteric children [91.0% (ES = 0.91; 95% CI = 0.85, 0.96)] and removed from the analysis. With removal of the outlier from the dataset, the average annual acute hepatitis A prevalence was reported to be approximately 5.0% (ES = 0.05; 95% CI = 0.03, 0.08). We further explored the age-related risk of acute hepatitis A infection in Africa. When assessing IgM anti-HAV seroprevalence by age-group, the heterogeneity between studies was found to be relatively low $(I^2 = 74.73)$ (**Figure 2.6**). The estimated average IgM anti-HAV seroprevalence for children and adolescents among included studies was 7.0% (ES = 0.07; 95% = 0.04, 0.12) (**Figure 3.6**). The estimated average IgM anti-HAV seroprevalence for adults among included studies was 5.0% (ES = 0.05; 95% = 0.03, 0.07) (**Figure 2.6**). The similarity in the estimated IgM anti-HAV seroprevalences among children, adolescents and adults is not expected in a high HAV endemic region such as Africa.

*Figure 2.5: Immunoglobulin M hepatitis A seroprevalence in Africa, 2008-2018*

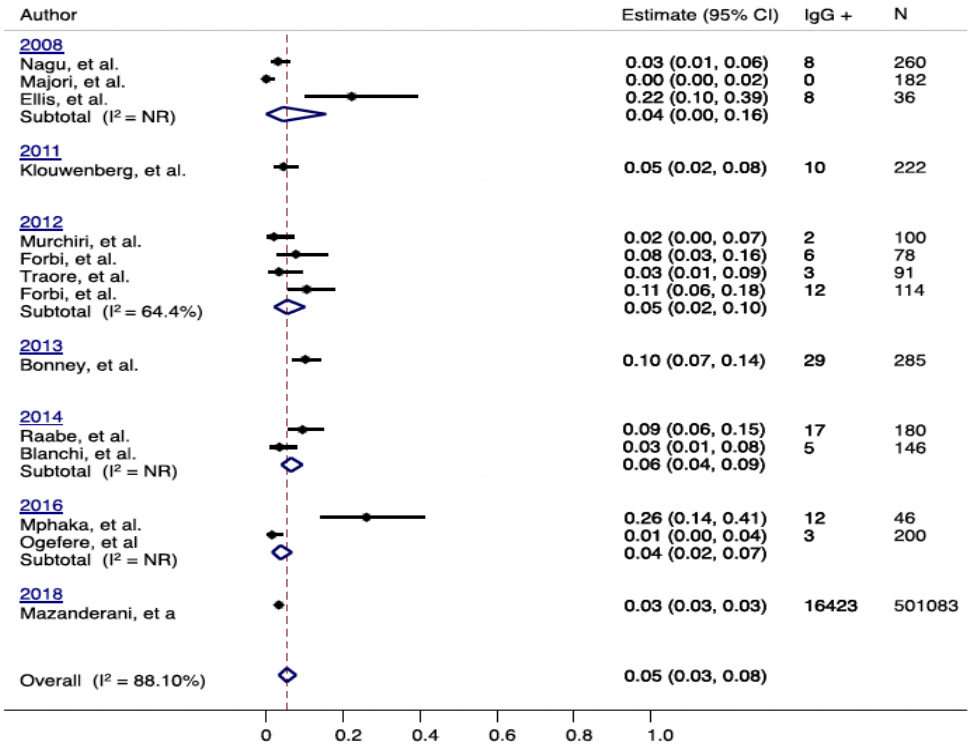
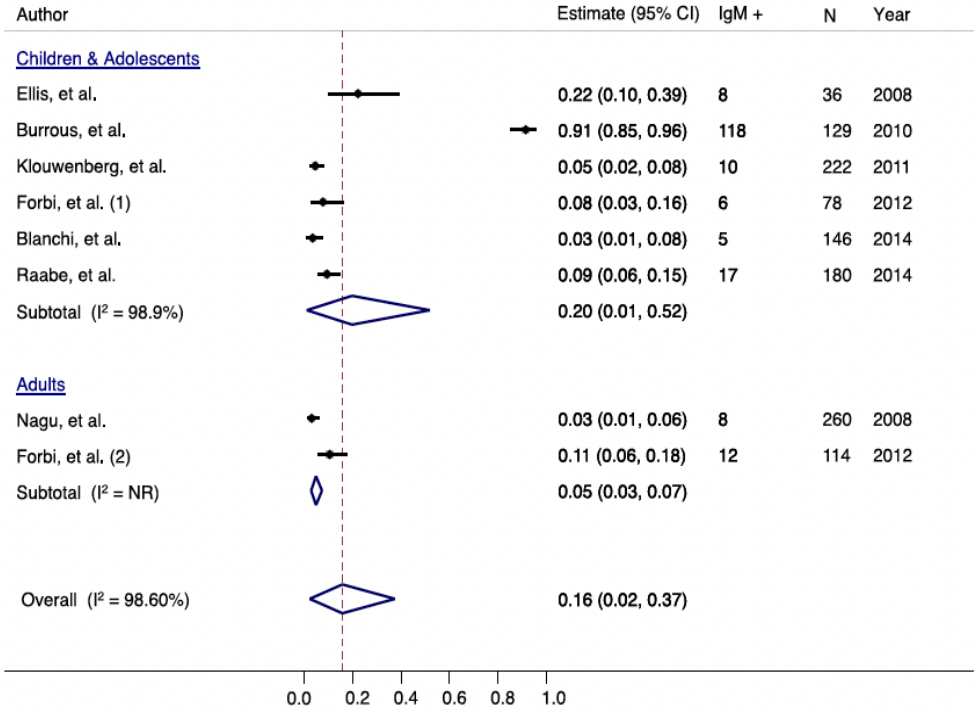


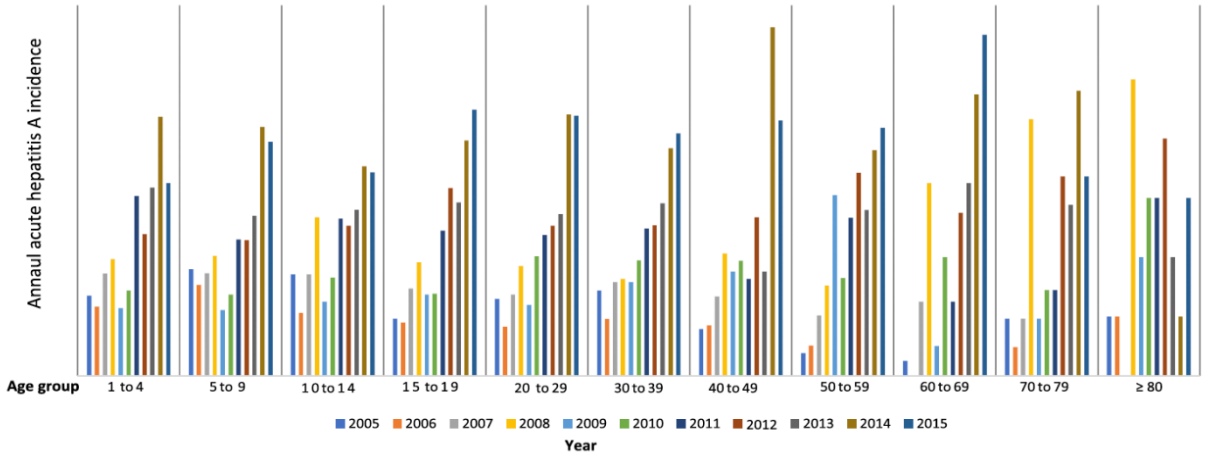

*Figure 2.6: Immunoglobulin M hepatitis A seroprevalence by population group in Africa, 2008-2014*



### 2.4.2 IgM anti-HAV seroprevalence in South Africa

Data reported by Mazanderani *et al.,* (2018) allowed us to further explore age-related IgM anti-HAV seroprevalence in South Africa, a country with no routine hepatitis A vaccination (20). **Figure 2.7** shows the annual IgM anti-HAV seroprevalence by age-group between 2005 and 2015 in South Africa, in which the overall IgM anti-HAV seroprevalence was found to be highest in children ≤ 15 years of age. Acute hepatitis A infection rates over the decade for age groups ≤ 10 years of age and 10 to 14 years of age were approximately 16.5% and 15.0%, respectively. The prevalence of acute hepatitis A in South Africa appeared to increase for all reported age-groups between 2005 and 2015.

*Figure 2.7: Immunoglobulin M seroprevalence estimates by age-group in South Africa, 2005-2015*




### 2.4.3 Methodological quality

For each included study, risk of bias and quality assessments were conducted using the Hoy *et al.,* risk of bias tool that examines internal and external validity of observation studies. Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if scored 5-7 and 'high risk' if scored 0-5. Scores were assigned by two (JP and LA) reviewers and the reasons for the assigned score was provided (**Table 2.4**). The scores assigned by the two reviewers we then compared. Where the assigned score made by JP and LA differed, these differences were resolved through consensus in consultation with BMK. For any score below 10, a descriptive summary of the information that influenced our judgments was provided. Majority of the studies were scored either 10 or 8 due to one or a combination of the following reasons: 1) selection of the research location was not justified; 2) Selection of study participants was not generalizable to the entire population; 3) Selection bias may be present.

*Table 2.4: Risk of Bias assessment for included studies*

| Author, Year | Risk of Bias | Hoy *et al*. tool Score | Score Description |
|---|---|---|---|
| Abdulla et al., 2010 (22) | Low | 10 | |
| Afegbua et al., 2013 (28) | Low | 8 | 1) Selection of research location was convenience and not justified as generalizable to entire population; 2) No description of how survey was conducted is given |
| Al-Aziz et al., 2008 (35) | Low | 9 | 1) Selection of research location was convenience and not justified as generalizable to entire population |
| Blanchi et al., 2014 (23) | Low | 10 | |
| Bonney et al., 2013 (36) | Low | 9 | 1) Selection of research location was convenience and not justified as generalizable to entire population |
| Bouskraoui et al., 2009 (37) | Low | 10 | |
| Burrous et al., 2010 (38) | Low | 10 | |
| El-Karasksy et al., 2008 (39) | Low | 9 | 1) Selection of research location was convenience and not justified as generalizable to entire population |
| Ellis et al., 2008 (40) | Low | 10 | |
| Enoch et al., 2019 (21) | Low | 10 | |
| Forbi et al., 2012 (41) | Low | 9 | 1) Selection of research location was convenience and not justified as generalizable to entire population |
| Forbi et al., 2012_2 (42) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Guenifi et al., 2017 (43) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Ikobah et al., 2015 (44) | Low | 9 | 1) Selection of total anti-HAV antibody testing may confound results |
| Jablonka et al., 2017 (45) | Low | 10 | |
| Klouwenberg et al., 2011 (46) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Lopes et al., 2017 (47) | Low | 9 | 1) Years of data collection not described in publication |
| Louati et al., 2009 (48) | Low | 10 | |
| Majori et al., 2008 (26) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Mazanderani et al., 2018 (11) | Low | 10 | |
| Mphaka et al., 2016 (49) | Low | 8 | 1) Selection of research population was not justified as generalizable to entire population; 2) No random selection or census undertaken |
| Murchiri et al., 2012 (50) | Low | 8 | 1) Purposive sampling leads to selection bias; 2) Selection of research population was not justified as generalizable to entire population |
| Nagu et al., 2008 (51) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Neffatti et al., 2017 (52) | Low | 10 | |
| Ogefere et al., 2016 (53) | Low | 9 | 1) Sampling method may have led to selection bias |
| Raabe et al., 2014 (24) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Rabenau et al., 2010 (54) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |

| | | | |
|---|---|---|---|
| Rezig et al., 2008 (55) | Low | 10 | |
| Smahi et al., 2009 (56) | Low | 10 | |
| Sule et al., 2013 (57) | Low | 9 | 1) Selection of research population was not justified as generalizable to entire population |
| Tantawy et al., 2012 (58) | Low | 10 | |
| Traore et al., 2012 (59) | Low | 9 | 1) Selection of research location was convenience and not justified as generalizable to entire population |

## 2.5 Discussion

This systematic review and meta-analysis evaluated the epidemiology of hepatitis A in participants ≥1 year of age in Africa. The main findings of the review include: 1) the reported HAV seroprevalence data suggests that Africa, as a whole, should not be considered as a high HAV endemic region; 2) the IgM anti-HAV seroprevalence data showed similar risk of acute hepatitis A infection among all age-groups; 3) South Africa could be experiencing a possible transition from high to intermediate HAV endemicity. The results of this review were limited due to lack of detailed age-grouped data from the included studies. Additionally, no included review reported data on the hospitalization and case fatality rates or co-morbidities occurring with acute hepatitis A which did not allow for the objectives of the paper to be met fully.

Only 13 (24%) out of 54 countries in Africa contributed to the data synthesized in this review which significantly limits the ability of this systematic review and meta-analysis to represent the epidemiology of hepatitis A for the entire African continent. Furthermore, the data included in this review was collected mainly in hospital settings as opposed to from community surveys. A recent study on trends of childhood immunization research in Africa reported lack of hepatitis A research on the continent (54). Based on these findings, we believe that more up-to-date research on hepatitis A epidemiology in Africa is needed and will be critical to generate evidence needed to re-think hepatitis A control strategies in the region.

Although limited, the HAV seroprevalence data in this review appear to meet the WHO's definition of intermediate HAV endemic setting (< 90% IgG seroprevalence by 10 years of age and ≥ 50% IgG seroprevalence by 15 years of age) (55). The reported HAV seroprevalence estimates for children and adolescents age-groups indicate that the presumed "natural immunization" during the early childhood is not sufficient to imply high HAV endemicity for the entire continent. Secondly, the reported similarity of IgM anti-HAV seroprevalence among children and adolescents compared with adults was a surprising

finding as we expected lower IgM anti-HAV seroprevalence in adults than children due to prior exposure in a high endemic setting. A recent study in China and conducted in a setting undergoing a hepatitis A epidemiological transition, adults aged 20 years and older showed higher disease incidence than children (56). Thus, our findings corroborate the notion of a HAV epidemiological transition in the African region.

Current global recommendations on hepatitis A vaccination appear to take African countries as homogeneous settings (55). Our review results showed a large spread in HAV seroprevalence rates as well as IgM anti-HAV seroprevalence rates across the continent. This indicates the heterogeneity of hepatitis A epidemiology, and highly likely, the epidemiology of other VPDs among African countries. For example, in South Africa where comprehensive dataset was available, we reported an increase in IgM anti-HAV seropositivity among all age groups from 2005 to 2015. These results indicate that South Africa is most likely transitioning from high to intermediate endemicity. Previous classifications of South Africa as a high endemic region have been based on limited data published between 1986 and 2002 (57). This data showed variable HAV seroprevalence rates that were dependent on SES. High HAV seropositivity rates were reported in low SES groups, while high SES groups that were less represented in the data showed low HAV seropositivity rates. Given this and the gradual socio-economic improvements in South Africa since the collapse of apartheid, it is likely that the HAV epidemiological transition in South Africa has been taking place even before 2005. It would be irrational to extrapolate findings from South Africa to all other African countries as hepatitis A epidemiology is highly influenced by economic as well as healthcare developments (58). Our findings suggest that African countries with similar SES developments as South Africa should prioritize generating evidence to guide recommendations on introducing routine immunization against the disease.

The results of this review must be interpreted with caution due to several limitations. Firstly, the included studies have significant sociocultural, economic, and environmental diversity. Secondly, because only 13 of 54 countries in Africa contributed to the data synthesized in this review, we were not able to present data for all sub-regions of the continent or by country income category. Thirdly, as data included in this review were collected mainly in hospital settings as opposed to from community surveys, we were unable to stratify our results to urban versus rural areas to assess whether hygiene and sanitation affect the current epidemiology of HAV in Africa. Lastly, although trends in publication of the immunization research is growing, a lot of research work in Africa still remains unpublished and

access to such information is limited (59). Regardless of these limitations, it is noteworthy to mention that most included studies focused on hepatitis A data in childhood and adolescent populations, which may attest to the anecdotal evidence that children and adolescents are increasingly at risk for acute hepatitis A infection in Africa.

The results of this paper may be an over-estimate of HAV seroprevalence for the general population in Africa as those seeking private healthcare services were not included in this review. Populations seeking private healthcare services are more likely to be of higher social economic status. Higher social economic populations have access to optimal sanitation and are likely to show lower HAV seroprevalence although some may be vaccinated against the disease (60). Furthermore, the extent of HAV vaccine use in the private sector of Africa is unknown. Future research should include populations seeking both private and private healthcare. Measurement of both IgG and IgM as immunological outcomes should be incorporated in future studies as well as details of the assay detection limits used. Additional missing data such as morbidity, comorbidities, and mortality due to hepatitis A disease should be a research priority. Collectively, complete, and high-quality hepatitis A epidemiology data would allow for better pooling of results and meta-analyses. The review team also encourages future studies to incorporate mathematical modelling where the data permits as such an approach could possibly assist health policy decision-makers to better design hepatitis A control strategies in Africa.

## 2.6 Conclusion

Due to the paucity of data available on the epidemiology of hepatitis A, this study utilized data from the African continent but did not compromise the primary intention to synthesize South African data. Given the perspective and despite the limitations, this systematic review and meta-analysis successfully generated up-to-date available epidemiological evidence of hepatitis A in Africa. There were evidence gaps on hospitalization, case fatality rates, and comorbidities. The results indicate the historical grouping of hepatitis A endemicity on the continent should be revised. In addition, the results underscore that countries should routinely collect and monitor contextually relevant hepatitis A epidemiological data to assess possible transitions of endemicity. In South Africa where hepatitis A is a notifiable disease, epidemiological data signalled that there could be an ongoing transition from high to intermediate or low HAV endemicity. The evidence of a transition from high to intermediate or low HAV endemicity in South Africa was graded as moderate in the **Supplementary Table S2.1**. Given this moderate evidence and the risk of acute hepatitis A infection being similar among all age-groups in

South Africa, there is merit for collecting additional evidence to guide policy makers in the development of an evidence-based recommendation for introduction of routine immunization against HAV in South Africa. Further evidence should include a description of hepatitis A clinical severity and outcomes among hospitalized cases, a deeper understanding of the burden of acute liver failure, cost-effectiveness estimates of routine immunization strategies, and a budget impact analysis of introducing routine immunization in South Africa.

## 2.7 References


1. de Jong G. Guidelines for the Control of Hepatitis A in South Africa. South Africa: National Institiue of Communicable Disease; 2007.
2. World Health Organization. Hepatitis A vaccines. 2012.
3. Heathcote J, Elewaut A, Fedail S, Gangl A, Hamid S, Shah M, et al. Managment of acute viral hepatitis. 2003.
4. Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. Curr Opin Infect Dis. 2015;28(5):488-96.
5. Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. Vaccine. 2012;31:3-11.
6. Wasley A, Fiore A, Bell BF. Hepatitis A in the Era of Vaccination. Epidemiologic Reviews. 2006;28.
7. Ellis A, Rüttimann RW, Jacobs J, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Pan Am J Public Health. 2007;21(6).
8. Rajan E, Shattock AG, Fielding JF. Cost-Effective Analysis of Hepatitis A Prevention in Ireland. American Journal of Gastroenterology. 2000;95(1).
9. Lemon SM, Ott JJ, Van Damme P, Shouval D. Type A viral hepatitis: A summar and update on the molecular virology, epidemiolgy, pathogenesis and prevention. Journal of Hepatology. 2017;68:167-84.
10. Anonychuk AM, Tricco A, Bauch CT, Pham B, Gilca V, Duval B, et al. Cost-Effectiveness Analyses of Hepatitis A Vaccine: A Systematic Review to Explore the Effect of Methodological Quality on the Economic Attractiveness of Vaccination Strategies. Pharmaeconomics. 2008;21(1).
11. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653-7.
12. Itani T, Jacobsen KH, Nguyen T, Wiktor SZ. A new method for imputing country-level estimates of hepatitis A virus endemicity levels in the Eastern Mediterranean region. Vaccine. 2014;32(46):6067-74.
13. Melhem NM, Talhouk R, Rachidi H, Ramia S. Hepatitis A virus in the Middle East and North Africa region: a new challenge. J Viral Hepat. 2014;21(9):605-15.
14. Jacobsen KH. Hepatitis A virus in West Africa: Is an epidemiological transition beginning. Nigerian Medical Journal. 2014;55(4):279-84.
15. Koroglu M, Jacobsen KH, Demiray T, Ozbek A, Erkorkmaz U, Altindis M. Socioeconomic indicators are strong predictors of hepatitis A seroprevalence rates in the Middle East and North Africa. J Infect Public Health. 2017;10(5):513-7.
16. Balk E, Ching M, Chen M, Trikalinos T, L KWC. Assessing the Accuracy of Google Translate to Allow Data Extraction From Trials Published in Non-English Languages. Rockville, USA: Agency for Healthcare Research and Quality; 2013 Jan 2013. Contract No.: EHC145-EF.
17. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater aggreement. Journal of Clinical Epidemiology. 2012;65:934-9.
18. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
20. Mazanderani AH, Motaze VN, McCarthy K, Suchard M, du Plessis NM. Hepatitis A Virus Seroprevalence in South Africa-Estimates using Routine Laboratory Data, 2005-2015. PloS one. 2018;26(12).
21. Enoch A, Hardie DR, Hussey GD, Kagina BM. Hepatitis A seroprevalence in the Western Cape Province, South Africa. Are we in epidemiological transition? South African Medical Journal. 2019;109(5):314-8.
22. Abdulla RY, Rice MA, Donauer S, Hicks KR, Poore D, Staat MA. Hepatitis A in internationally adopted children: screening for acute and previous infections. Pediatrics. 2010;126(5):e1039-e44.
23. Blanchi S, Chabasse D, Pichard E, Darviot E, de Gentile L. Post-international adoption medical follow-up at the Angers university hospital between 2009 and 2012. Medecine et maladies infectieuses. 2014;44(2):69-75.
24. Raabe VN, Sautter C, Chesney M, Eckerle JK, Howard CR, John CC. Hepatitis a screening for internationally adopted children from hepatitis A endemic countries. Clinical pediatrics. 2014;53(1):31-7.
25. Jablonka A, Solbach P, Wobse M, Manns MP, Schmidt RE, Wedemeyer H, et al. Seroprevalence of antibodies and antigens against hepatitis A-E viruses in refugees and asylum seekers in Germany in 2015. European journal of gastroenterology & hepatology. 2017;29(8):939-45.
26. Majori S, Baldo V, Tommasi I, Malizia M, Floreani A, Monteiro G, et al. Hepatitis A, B, and C infection in a community of sub-Saharan immigrants living in Verona (Italy). Journal Of Travel Medicine. 2008;15(5):323-7.
27. Afegbua SL, Bugaje MA, Ahmad AA. Seroprevalence of hepatitis A virus infection among schoolchildren and adolescents in Kaduna, Nigeria. Trans R Soc Trop Med Hyg. 2013;107(10):627-30.

28. Al-Aziz AMA, Awad MAM. Seroprevalence of hepatitis A virus antibodies among a sample of Egyptian children. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit. 2008;14(5):1028-35.
29. Bonney JH, Osei-Kwasi M, Adiku TK, Barnor JS, Amesiya R, Kubio C, et al. Hospital-based surveillance for viral hemorrhagic fevers and hepatitides in Ghana. PLoS neglected tropical diseases. 2013;7(9):e2435.
30. Bouskraoui M, Bourrous M, Amine M. Prévalence des anticorps de l'hépatite A chez l'enfant dans la région de Marrakech. Prevalence of anti-hepatitis A virus antibodies in chidren in Marrakech. 2009;16:S132-S6.
31. Bourrous M, Drais G, Amine M, Adabbous A, Admou I, Bouskraoui M. Séroprévalence de l'hépatite virale A dans les ictères fébriles chez les enfants de la région de Marrakech, Maroc. Seroprevalence of the viral hepatitis A in febrile icteric children living in the area of Marrakech, Morroco. 2010;23(2):76-81.
32. El-Karaksy H, El-Sayed R, El-Raziky M, El-Koofy N, Mansour S. Cost-effectiveness of prescreening versus empirical vaccination for hepatitis A in Egyptian children with chronic liver disease. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit. 2008;14(4):804-9.
33. Ellis RD, Dicko A, Sagara I, Kamate B, Guindo O, Niambele MB, et al. Short report: elevated levels of alanine aminotransferase and hepatitis A in the context of a pediatric malaria vaccine trial in a village in Mali. The American journal of tropical medicine and hygiene. 2008;79(6):980-2.
34. Forbi JC, Agwale SM, Ndip LM, Esona MD. Genetic analysis of hepatitis A virus variants circulating among children presenting with acute diarrhea in Cameroon. J Med Virol. 2012;84(5):728-32.
35. Forbi JC, Iperepolu OH, Zungwe T, Agwale SM. Prevalence of Hepatitis B e Antigen in Chronic HBV Carriers in North-central Nigeria. Journal of Health, Population & Nutrition. 2012;30(4):377-82.
36. Guenifi W, Laouamri S, Lacheheb A. Changes in prevalence of hepatitis A and associated factors in Setif-Algeria. Revue d'epidemiologie et de sante publique. 2017;65(6):437-42.
37. Ikobah JM, Okpara HC, Ekanem EE, Udo JJ. Seroprevalence and predictors of hepatitis A infection in Nigerian children. The Pan African medical journal. 2015;20:120.
38. Jablonka Aad, Solbach Pbcd, Wobse Mb, Manns MPbde, Schmidt REad, Wedemeyer Hb, et al. Seroprevalence of antibodies and antigens against hepatitis A-E viruses in refugees and asylum seekers in Germany in 2015. European journal of gastroenterology & hepatology. 2017;29(8):939-45.
39. Klouwenberg PK, Sasi P, Bashraheil M, Awuondo K, Bonten M, Berkley J, et al. Temporal Association of Acute Hepatitis A and Plasmodium falciparum Malaria in Children. PloS one. 2011;6(7):1-5.
40. Lopes T, Cable R, Pistorius C, Maponga T, Ijaz S, Preiser W, et al. Racial differences in seroprevalence of HAV and HEV in blood donors in the Western Cape, South Africa: a clue to the predominant HEV genotype? Epidemiol Infect. 2017;145(9):1910-2.
41. Louati N, Feki L, Rekik H, Feki H, Chaabouni M, Hammami A, et al. Comparison of hepatitis A seroprevalence in blood donors in South Tunisia between 2000 and 2007. Archives de l'Institut Pasteur de Tunis. 2009;86(1-4):69-74.
42. Mphaka MR, Ntshiqa T, Majake L, Mugero C, Maphele A, Van Der Westhuizen M, et al. Hepatitis A virus outbreak in a compound in Tshwane district, Gauteng, South Africa: October 2014-March 2015. International Journal of Infectious Diseases. 2016;45:447-8.
43. Murchiri I, Okoth FA, Ngaira J, Tuei S. Seroprevalence of HAV, HBV, HCV, and HEV Among Acute Hepatitis Patients at Kenyatta National Hospital in Nairobi, Kenya. East African medical journal. 2012;89(6):199-205.
44. Nagu TJ, Bakari M, Matee M. Hepatitis A, B and C viral co-infections among HIV-infected adults presenting for care and treatment at Muhimbili National Hospital in Dar es Salaam, Tanzania. BMC public health. 2008;8:416.
45. Neffatti H, Lebraud P, Hottelet C, Gharbi J, Challouf T, Roque-Afonso AM. Southern Tunisia: A still high endemicity area for hepatitis A. PloS one. 2017;12(4):e0175887.
46. Ogefere HO, Egbe CA. Seroprevalence of IgM antibodies to hepatitis A virus in at-risk group in Benin City, Nigeria. The Libyan journal of medicine. 2016;11:31290.
47. Rabenau HF, Lennemann T, Kircher C, Gurtler L, Staszewski S, Preiser W, et al. Prevalence- and gender-specific immune response to opportunistic infections in HIV-infected patients in Lesotho. Sexually transmitted diseases. 2010;37(7):454-9.
48. Rezig D, Ouneissa R, Mhiri L, Mejri S, Haddad-Boubaker S, Ben Alaya N, et al. Séroprévalences des infections à hépatite A et E en Tunisie. Seroprevalences of hepatitis A and E infections in Tunisia. 2008;56(3):148-53.
49. Smahi MC, Rahmoun L, Ghomari SM, Benmansour S, Sendani H, Bendeddouche AS, et al. [Seroprevalence and risk factors of hepatitis A among children in Tlemcen (north-west Algeria)]. Archives de pediatrie : organe officiel de la Societe francaise de pediatrie. 2009;16(6):844-6.
50. Sule WF, Kajogbola AT, Adewumi MO. High prevalence of anti-hepatitis A virus immunoglobulin G antibody among healthcare facility attendees in Osogbo, Nigeria. J Immunoassay Immunochem. 2013;34(1):75-82.
51. Tantawy AA, Sallam TH, Ibrahim DM, Sallam MT, Ragab IA. Pathogenesis and prognosis of neutropenia in infants and children admitted in a university children hospital in Egypt. Pediatric hematology and oncology. 2013;30(1):51-9.

52. Traoré KA, Rouamba H, Nébié Y, Sanou M, Traoré AS, Barro N, et al. Seroprevalence of fecal-oral transmitted hepatitis A and E virus antibodies in Burkina Faso. PloS one. 2012;7(10):e48125-e.
53. Nainan OV, Xia G, Vaughan G, Margolis HS. Diagnosis of hepatitis a virus infection: a molecular approach. Clin Microbiol Rev. 2006;19(1):63-79.
54. Haddison E, Machingaidza S, Wiysonge C, Hussey G, Kagina B. An update on trends in the types and quality of childhood immunization researchoutputs from Africa 2011-2017: Mapping the evidence base. Vaccine. 2018.
55. World Health Organization. WHO position paper on hepatitis A vaccines - June 2012. Wkly Epidemiol Rec. 2012;87(28/29).
56. Wang Z, Chen Y, Xie S, Lv H. Changing Epidemiological Characteristics of Hepatitis A in Zhejiang Province, China: Increased Susceptibility in Adults. PloS one. 2016;11(4):e0153804.
57. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. Vaccine. 2010;28(41):6653-7.
58. Jacobsen KH. Globalization and the Changing Epidemiology of Hepatitis A Virus. Cold Spring Harb Perspect Med. 2018.
59. Machingaidza S, Huddey GD, Wiysonge CS. Trends in the types and qualitiy of childhood immunisations research output from Africa 1970-2010: mapping the evidence. BMC Health Services Research. 2014;14(52).
60. Karim A, Coutsoudis A. Sero-epidemiology of hepatitis A in black South African children. South African Medical Journal. 1993;83.

# 3 Chapter 3: A systematic review of the global epidemiology of viral-induced acute liver failure

Patterson, J., Hussey, H. S., Silal, S., Goddard, L., Setshedi, M., Spearman, W., Hussey, G. D., Kagina, B. M., & Muloiwa, R. (2020). Systematic review of the global epidemiology of viral-induced acute liver failure. *BMJ open*, *10*(7), e037473. https://doi.org/10.1136/bmjopen-2020-037473.

**Relevance of this paper to the thesis:**

Comprehensive evidence on the epidemiology of the most severe hepatitis A outcome, acute liver failure, is missing not only in South Africa but also at a global level. This paper presents a detailed synthesis of the prevalence of viral-induced acute liver failure, with special interest paid to hepatitis A induced liver failure.

**Contributions of the student and co-authors:**

BMK conceptualized this study. JP implemented the review under the supervision of BMK and RM. JP and HSH performed the study search, screening, and extraction of data under the guidance of RM. GDH, BMK, and RM provided methodological expertise for this review. SS, LG, MS, and WS provided content expertise for this review and all authors will provide comments on the final manuscript before publication. JP is the guarantor of this review.

## 3.1 Abstract

The etiology and burden of viral-induced acute liver failure remains unclear, globally. It is important to understand the epidemiology of viral-induced acute liver failure to plan for clinical case management and case prevention.

This systematic review was conducted to synthesize data on the relative contribution of different viruses to the aetiology of viral-induced acute liver failure in attempt to compile evidence that is currently missing in the field. EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science were searched for relevant literature published from 2009 to 2019. The initial search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include. Twenty-five eligible studies were included in the results of this review.

This systematic review estimated the burden of acute liver failure following infection with hepatitis A, hepatitis B, hepatitis C, hepatitis E, herpes simplex virus-1, herpes simplex virus-2, human herpesvirus 6, Epstein Barr virus, cytomegalovirus, and parvo-virus B19. Data were largely missing for acute liver failure following infection with varicella-zoster virus, human parainfluenza viruses, yellow fever virus, coxsackievirus and/or adenovirus. The prevalence of hepatitis A-induced acute liver failure was markedly lower in countries with routine hepatitis A immunization vs no routine hepatitis A immunization. Hepatitis E virus was the most common etiological cause of viral-induced acute liver failure reported in this review. In addition, viral-induced acute liver failure had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries.

Immunization against hepatitis A and hepatitis B should be prioritized in low- and middle-income countries to prevent high viral-induced acute liver failure mortality rates, especially in settings where resources for managing acute liver failure are lacking. The expanded use of hepatitis E immunization should be explored as hepatitis E was the most common cause of acute liver failure.

## 3.2 Background

Acute liver failure (ALF) refers to the development of encephalopathy and synthetic function impairment following acute liver injury in an individual without pre-existing liver disease (1). The presence of encephalopathy is not required to define ALF in paediatrics but is an essential component of the definition in adults (1). Possible causes of ALF include viral infections, drugs and toxins, pregnancy related liver diseases, vascular causes and/or malignancies. Acute viral hepatitis has been identified as the most common cause of ALF among all ages in Asia and Africa and one of the most common causes of ALF in children in Asia and South America (2, 3). The incidence of viral-induced ALF has substantially declined in Europe following the introduction of universal immunization against the hepatitis B virus (HBV), with only 19% of all ALF cases now attributable to viral infection in the European population (4). The introduction of routine immunization against the hepatitis A virus (HAV) in Argentina has reduced the number of hepatitis A induced ALF cases by more than 25% (4).

Fatality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care (5, 6). Liver transplantation plays a central role in the management of ALF and remains the only definitive treatment for patients who fail to demonstrate spontaneous recovery (7). A large proportion of patients with ALF in both high and low resource settings, however, are deemed to have contraindications to transplantation or deteriorate beyond transplantation before a liver donor is found (8-10).

The burden of viral-induced ALF around the world remains unclear, with little to no data collected regarding the disease incidence (3). Establishing the aetiology of viral-induced ALF is important for early initiation of treatment, determining the prognosis of the liver failure and identifying potential contraindications to liver transplantation. Most importantly, understanding the epidemiology of vaccine-preventable aetiologies of ALF should be prioritised in under-resourced regions with limited access to facilities for transplantation. This review aims to synthesize data on the relative contribution of different viruses to the aetiology of viral-induced ALF in attempt to compile evidence that is currently missing in the field. *Bernal et al. 2010* completed a review of the burden of acute and fulminant liver failure based on literature published between 1997 and 2009. The review became the bases for guidelines for clinical practice (5). In this systematic review, we assess whether data have changed following the Bernal publication, and whether there is evidence to warrant a review of clinical practice.

## 3.3 Methods

This systematic review was registered with PROSPERO (registration number CRD42017079730) and the methods for its conduction have been published (11). The results of the review are reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines checklist.

### 3.3.1 Objectives

- To estimate the prevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackievirus (CA16) and/or adenovirus (HAdVs) among patients with ALF.
- To estimate the mortality rate for cases of ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvovirus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs.
- To estimate the prevalence and incidence of liver transplantation for cases of ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvovirus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs.

### 3.3.2 Study eligibility criteria

Published cross-sectional, surveillance and cohort studies reporting the outcomes of interest in patients with ALF following infection with HAV, HBV, HCV, HDV, HEV, EBV, HSV1, HSV2, VZV, parvovirus B19, HPIVs, YFV, HHV-6, CMV, CA16 and/or HAdVs were eligible for inclusion in this study. Studies were eligible for inclusion if they had clearly stated case definitions of viral-induced ALF and confirmed ALF cases using both clinical and serological, molecular or culture diagnostic methods.

#### *3.3.2.1 Acute Liver Failure Case definition*

Included studies must have a clearly stated case definition of viral-induced acute liver failure. Cases must be confirmed by both clinical and laboratory diagnostic methods. Clinical diagnosis of ALF was be defined as follows for children and adults presenting with an acute liver injury:

- Children – The absence of known, chronic liver disease with liver-based coagulopathy not responsive to parenteral vitamin K and an international normalised ratio (INR) ≥ 1.5 in the

presence of clinical evidence of encephalopathy or INR of ≥ 2.0 without clinical signs of encephalopathy (2, 3).

- Adults – Liver-based coagulopathy (INR ≥ 1.5) and any grade of hepatic encephalopathy (HE) as defined by the West Haven criteria within 26 weeks after the onset of symptoms but with no evidence of chronic liver disease, including cirrhosis (1).
- Serological, molecular or culture laboratory confirmation of infection with HAV, HBV, HCV, HDV, HEV, EBV), HSV1, HSV2, VZV, parvo-virus B19, HPIVs, YFV, HVV-6, CMV, CA16 or HAdVs.

### 3.3.3 Search strategy

A combination of the following search terms (including the use of Medical Subject Headings (MESH)) was used and adapted for each of the relevant electronic databases: epidemiology, prevalence, incidence, burden, mortality, morbidity, fulminant hepatic failure, fulminant liver failure, acute hepatic failure, acute liver failure, Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), Epstein Barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), varicella-zoster virus (VZV), parvo-virus B19, human parainfluenza viruses (HPIVs), yellow fever virus (YFV), human herpesvirus 6 (HHV-6), cytomegalovirus (CMV), coxsackie virus and adenovirus. The following electronic databases were searched for relevant literature published from 2009 to 2019: EBSCOhost, PubMed, ScienceDirect, Scopus and Web of Science. The search was run on 9 April 2019 and updated via PubMed on 30 September 2019 with no new eligible studies to include.

### 3.3.4 Data extraction

Study characteristics and outcomes of interests were extracted from the included studies on a pre-designed data extraction form by two independent reviewers (JP and HH). Prior to use by the two reviewers, the reliability of the extraction form was assessed by piloting 10 randomly selected articles that met the inclusion criteria. The study team resolved any disagreements in data extraction through consensus in consultation with RM. In cases where studies were in German, HH provided translation. In cases where studies were not available in English or German, google translate was used to translate the article to English (12).

The following information was be extracted from the included studies:

- Study characteristics: year of publication, study design, sample size and objectives of study

- Study population: country, WHO region, country income level, hepatitis A vaccination program (yes or no)
- Case definition: clinical case definition and laboratory confirmation methods and the type of virus or viruses indicated as the causative agent for the condition
- Case characteristics: age, gender, hepatitis A vaccination status, country of residence and immune suppressive conditions (e.g. HIV, cancer and diabetes, immunosuppression, chemotherapy)

### 3.3.5 Data synthesis and analysis

A random-effects model was fitted to the study data as it included data taken from a series of independently performed studies in different populations. We assessed heterogeneity by calculating $I^2$ statistics (threshold $I^2 > 40\%$). The values of $I^2$ were categorized for heterogeneity as follows: "not important" ($\leq 40\%$), "moderate" ($> 40\%$ to $\leq 60\%$) and "considerable" ($> 60\%$ to $\leq 80\%$) and "substantial" ($> 80\%$ to $\leq 100\%$). Where "not important" or "moderate" heterogeneity existed between studies ($I^2 \leq 60\%$), pooled outcome measures were reported with 95% confidence intervals for each respective outcome. Where "considerable" or "substantial" heterogeneity exists between studies ($I^2 > 60\%$), forest plots and prevalence ranges calculated using the random-effects model were used to narratively describe each outcome.

### 3.3.6 Risk of bias assessment

Each included study was assessed for risk of bias and quality using the Hoy *et al.,* 2012 tool for observational studies (13, 14). Studies were judged as having 'low risk' if scored 8-10, 'moderate risk' if scored 5-7 and 'high risk' if scored 0-5. All risk of bias judgements were made by both JP and HH. In case of disagreement in risk of bias and quality assessment, a final decision was made through consensus in consultation with RM.

### 3.3.7 Patient and public involvement

This review was developed as part of an ongoing project by the research team that aims to generate evidence to facilitate evidence-based decision-making of introducing routine hepatitis A vaccination in South Africa. The findings of this review contribute to the knowledge base that aims to enhance global vaccination strategies against viral-associated ALF. As this is a systematic review, no patient involvement

was required; however, it is hoped that the findings of this review will help to highlight the burden that ALF places on populations without routine vaccination.

## 3.4 Results

The initial database searches yielded 6,952 records, from which 3,545 duplicates were removed. A further 3,263 were excluded following the screening of titles and abstracts (**Figure 3.1**). The full text of the remaining 144 records were screened by JP and HH, from which 25 studies were deemed to meet the final inclusion criteria. Twenty-four (96%) of the included studies were cohort studies. As detailed in **Table 3.1**, the included studies were published between 2009 and 2017. Included studies were conducted globally, with 7 studies and 3 studies conducted in India and Pakistan, respectively. The populations represented by the included studies spanned all age groups and included participants primarily from hospital settings. As the data in this review was sourced from a variety of countries, age groups and settings, the heterogeneity was considerable and/or substantial for all results. Thus, we narratively and graphically reported estimates of combined prevalence rates and the spreads of prevalence.

*Figure 3.1: PRISMA flow diagram for selection of studies*

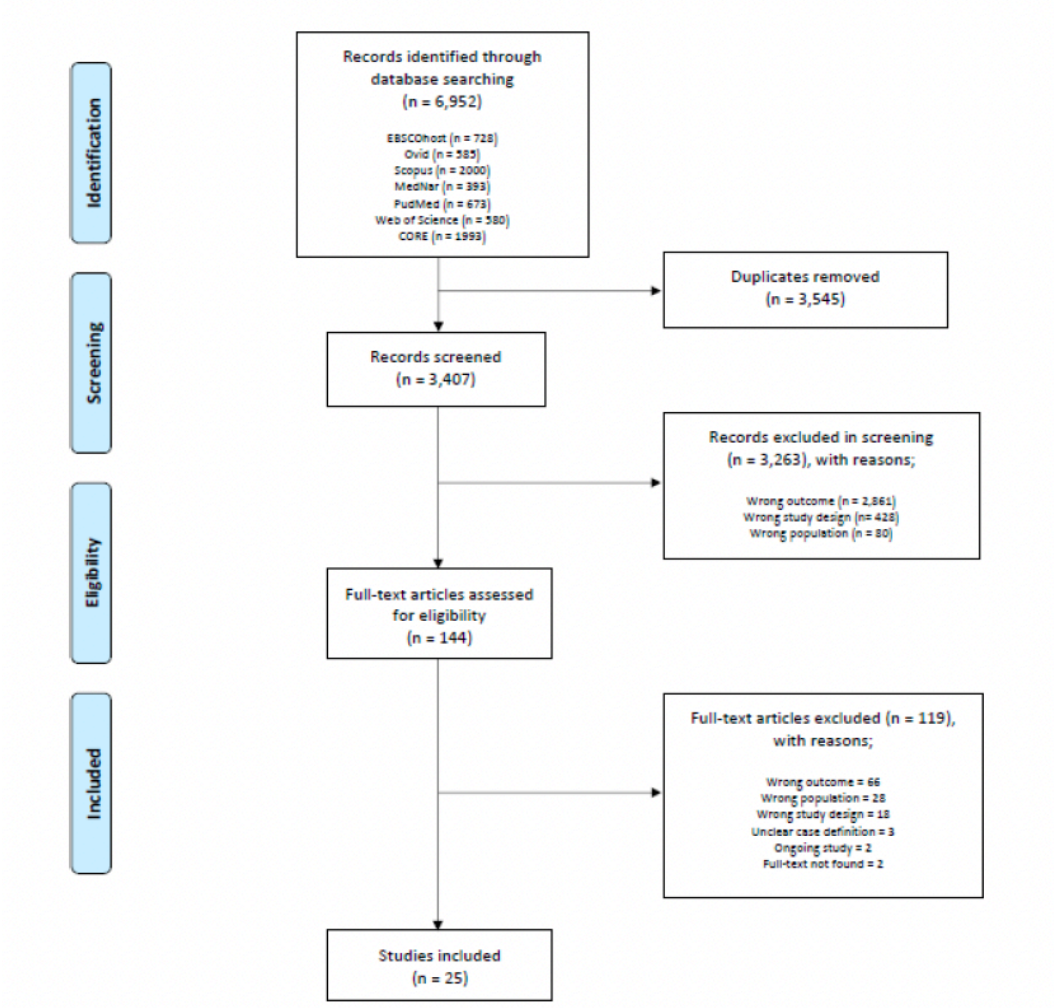


*Table 3.1: Characteristics of included studies*

| Study | Study Design | Aim | Country | Income Level | Start of Data Collection | End of Data Collection | ALF Case Definition |
|---|---|---|---|---|---|---|---|
| Alam et al., 2009 (15) | Prospective cohort | To evaluate the aetiology, complications, and outcome of FHF | Bangladesh | Lower middle | 3-Nov | 8-May | Occurrence of hepatic encephalopathy within 8 weeks of onset of jaundice in patients with no previous liver disease and the presence of coagulopathy as proved by a PT > 15 s or INR > 1.5 |
| Asim et al., 2009 (16) | Cross-sectional | To analyse serum samples from patients with ALF for hepatitis A-G viral markers | India | Lower middle | 1-Jun | 4-May | Patient become deeply jaundiced and went into hepatic encephalopathy within 8 weeks of onset of the disease, with no history of chronic hepatitis |
| Bechmann et al., 2014 (17) | Retrospective cohort | To identify currently predominant aetiologies of ALF at a transplant centre | Germany | High | 1-Jan | 12-Feb | *Acute Liver Failure Study Group Germany* case definition: INR > 1.5 and encephalopathy of any grade. Pre-existing liver disease and systemic cause of liver failure were excluded |
| Bhatia et al., 2013 (18) | Prospective cohort | To analyse clinical features, liver function tests, hepatitis viral markers and clinical outcomes in patients with ALF | India | Lower middle | Jun-99 | 1-Jan | Development of hepatic encephalopathy within 26 weeks of the first symptoms of acute hepatitis-like illness without any history of underlying liver disease |
| Borkakoti et al., 2013 (19) | Prospective cohort | To determine the viral load of HEV and its association with the disease severity in patients with ALF in comparison with patients with ALF due to other hepatides | India | Lower middle | 6-Jan | 11-Dec | Development of encephalopathy within 8 weeks of the onset of jaundice without any history of chronic liver disease; diagnosed as a self-limiting disease and a serum aspartate aminotransferase elevation of at least fivefold or clinical jaundice or both |
| Bravo et al., 2012 (20) | Prospective & retrospective cohort | To investigate the aetiology, outcomes, and incidence of AHF among children 0-18 years old | Philippines | Lower middle | Jan-00 | 6-Dec | Onset of coagulopathy and/or encephalopathy ≤4 weeks after the onset of symptoms, a prothrombin time > 2, an increased bilirubin and evidence for liver failure complicated by encephalopathy |
| Cervio et al., 2011 (4) | Retrospective cohort | To investigate the impact of HAV UI on the trends in the occurrence of FHF in children | Argentina | High | Mar-93 | 5-Jul | *Mieli-Vergani* case definition: a multisystem disorder in which severe impairment of liver function, with or without encephalopathy, occurs in |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | association with hepatocellular necrosis in a patient with or without recognized underlying chronic liver disease (**Cheeseman & Mieli-Vergani, 2004**) |
| Das et al., 2016 (21) | Prospective cohort | To determine the profile of ALF aetiologies | India | Lower middle | 7-Jan | 15-Dec | History of development of encephalopathy within 8 weeks of disease onset |
| Gupta et al., 2015 (22) | Retrospective cohort | To determine the profile of Hepatitis A, B, C and E as a cause of AHF in children in a tertiary care hospital | India | Lower middle | 11-Jan | 14-Dec | Elevated ALT levels or AST of at least five-fold with clinical jaundice and without evidence of chronic liver disease. Patients who had INR > 1.5 with encephalopathy or INR > 2 without encephalopathy |
| Ho et al., 2014 (23) | Prospective cohort | To investigate the incidence, aetiology, outcomes, and prognostic factors of ALF | Taiwan | High income | 5-Jan | 7-Sep | International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 570.0 |
| Latif et al., 2010 (24) | Prospective cohort | To identify the risk factors for FHF and their relationship with the outcome in children | Pakistan | Lower middle | 6-Sep | 7-Feb | Development of encephalopathy within 8 weeks of the onset of jaundice having evidence of coagulopathy i.e., PT deranges > 4 s of control and deranged liver function i.e., TSB > 1.5 mg/dl, AT > 40 IU/L |
| Mamun et al., 2009 (25) | Retrospective cohort | To assess the burden of HEV as a cause of ALF | Bangladesh | Lower middle | 4-Jun | 6-Dec | Previously healthy patients who presented with severe impairment of hepato-cellular function, i.e., encephalopathy, coagulopathy, and jaundice, within six months of onset of symptoms |
| Manka et al., 2015 (26) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | Germany | High | 6-Nov | 13-Dec | Significant liver dysfunction with pathologically increased laboratory parameters [AST, ALT, AP], an existing coagulopathy in terms of an INR > 1.5, and with the concomitant presence of any degree of encephalopathy |
| Mendizabal et al., 2014 (27) | Retrospective cohort | To determine the causes and short-term outcomes of ALF | Argentina | High | 5-Jun | 11-Dec | Presence of coagulopathy [INR > 1.5 or prothrombin index < 50%] and any grade of HE within 26 weeks of the first symptoms without a known underlying liver disease |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mishra et al., 2016 (28) | Retrospective cohort | To assess the relative efficacy of HEV antigen detection by ELISA in patients with ALF | India | Lower middle | 13-Nov | 15-Jan | Any evidence of coagulation abnormality, generally INR >1.5 and any degree of mental alteration (encephalopathy) without pre-existing cirrhosis and with an illness of < 4 weeks duration |
| Mumtaz et al., 2009 (29) | Prospective cohort compared to historical control | To assess the aetiology, prothrombin time (PT), alanine aminotransferase, creatinine, albumin for non-acetaminophen-induced ALF | Pakistan | Lower middle | Jan-00 | 7-Mar | Rapid development of acute liver injury with impaired synthetic function and encephalopathy in a person who previously had a normal liver |
| Pandit et al., 2015 (30) | Retrospective cohort | To assess the frequency of hepatotropic viruses as etiological agents of ALF | India | Lower middle | 3-Jan | 5-Dec | Onset of encephalopathy ≤28 days after the onset of symptoms with INR > 2 and increased bilirubin complicated by encephalopathy in patients without a previous history of liver disease |
| Poovorawan (31) et al., 2013 | Prospective cohort | To determine the causes and outcomes of Thai children with AHF | Thailand | Upper middle | 2-Jan | 5-Sep | *International Association for the Study of the Liver* case definition: (**Tandon et al, 1999)** |
| Schwarz et al., 2014 (32) | Retrospective cohort - Patient registry | To analysed results of viral testing among non-acetaminophen ALF study participants | USA/Canada/UK | High | Dec-99 | 12-Dec | No known evidence of chronic liver disease, with evidence of acute liver injury, and hepatic-based coagulopathy not corrected by vitamin K with the follow parameters: PT ≥ 15 s or INR ≥ 1.5 in the presence of clinical HE or a PT ≥ 20 s or INR ≥ 2.0 regardless of the presence or absence of clinical HE |
| Shalimar et al., 2017 (33) | Retrospective cohort | To assess the differences in the course of HEV-ALF as compared to other aetiologies of ALF | India | Lower middle | Jan-86 | 15-Dec | *International Association for the Study of Liver* (IASL) case definition: Occurrence of encephalopathy within 4 weeks from the onset of symptoms in the absence of pre-existing liver disease |
| Silverio et al., 2015 (34) | Retrospective cohort | To describe the clinical features of children treated for ALF | Cuba | Upper middle | 5-Jan | 11-Dec | Evidence of liver damage in the absence of prior known chronic liver disease; altered coagulation, expressed as PT >15 s with encephalopathy; or PT > 20 s with or without encephalopathy—all this within eight weeks of onset of clinical symptoms |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Somasekar et al., 2017 (35) | Retrospective cohort | To investigate the causes of previously diagnosed indeterminate cases ALF | United States | High | Jan-98 | 10-Dec | *United States Acute Liver Failure Study Group* case definition |
| Uddin Jamro et al., 2013 (36) | Retrospective cohort | To study the aetiology, outcome, and risk factors for FHF in children at a tertiary care hospital | Pakistan | Lower middle | 7-Jul | 12-Jun | Presence of acute liver failure (coagulopathy PT > 20 s or INR > 2), HE without pre-existing liver disease, within 8 weeks of the onset of clinical liver disease |
| Tsunoda et al., 2017 (37) | Prospective cohort | To identify the roles of CMV, EBV and HHV in immunocompetent children with acute liver failure not resulting from hepatitis virus | Japan | High | 7-Jan | 13-Dec | Liver dysfunction with elevated AST and ALT > 30 IU/L |
| Zhao et al., 2014 (38) | Retrospective cohort | To investigate aetiologies and outcomes of children with ALF | China | Middle | 7-Jan | 12-Dec | Coagulopathy [PTA ≤40% or INR ≥ 1.5 excluding hematologic diseases] and jaundice [Tbil ≥ 171 µmol/L] within 4 weeks in a child without pre-existing liver diseases |

**Abbreviations:** ALF = acute liver failure; FHF = fulminant hepatic failure; AHF = acute hepatic failure; HEV = hepatitis E virus; CMV = cytomegalovirus; EBV = Epstein Barr virus; HHV = human herpesvirus; ELISA = enzyme-linked immunosorbent assay; INR = international normalized ratio; PT = prothrombin time; s = second; TSB = total serum bilirubin; HE = hepatic encephalopathy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AP = alkaline phosphatase; PTA = plasma thromboplastin antecedent

### 3.4.1 Vaccine-preventable viral-induced ALF

We narratively report the prevalence of HAV- and HBV-induced ALF by country immunization status. It should be noted that countries included in the review had a variety of hepatitis A immunization strategies ranging from universal single-dose immunization for children in Argentina to targeted adult immunization strategies in the United States. Countries were only noted as having universal hepatitis A immunization strategies if they had implemented hepatitis B vaccines into their childhood immunization schedules. The point prevalence of HAV-induced ALF in countries with no routine HAV immunization at the time of data collection ranged from 2% to 81% with an average point prevalence of 27% (95% CI 13, 43), while the prevalence in countries with routine HAV immunization at the time of data collection ranged from 1% to 2% with an average point prevalence of 2% (95% CI 1, 3) (**Figure 3.2**). In Argentina, the prevalence of HAV-induced ALF prior to routine immunization was approximately 50% (95% CI 45, 55), compared to approximately 1% (95% CI 0, 5) after immunization was introduced. The point

prevalence of HBV-induced ALF in countries without universal HBV immunization at the time of data collection ranged from 16% to 27% with an average point prevalence of 22% (95% CI 16, 30) (**Figure 3.3**). The point prevalence of HBV-induced ALF in countries with universal HBV immunization at the time of data collection ranged from 0% to 83% with an average point prevalence of 20% (95% CI = 8, 35).

*Figure 3.2: Prevalence of hepatitis A virus induced acute liver failure by country hepatitis A immunization status*

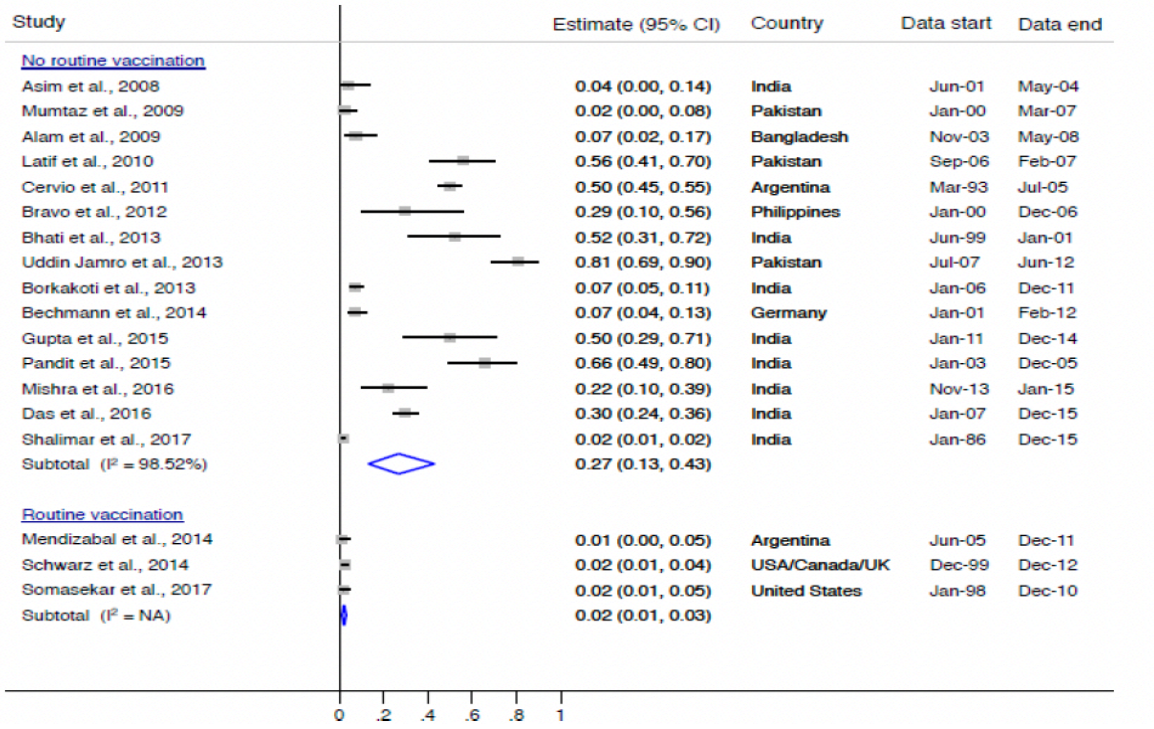
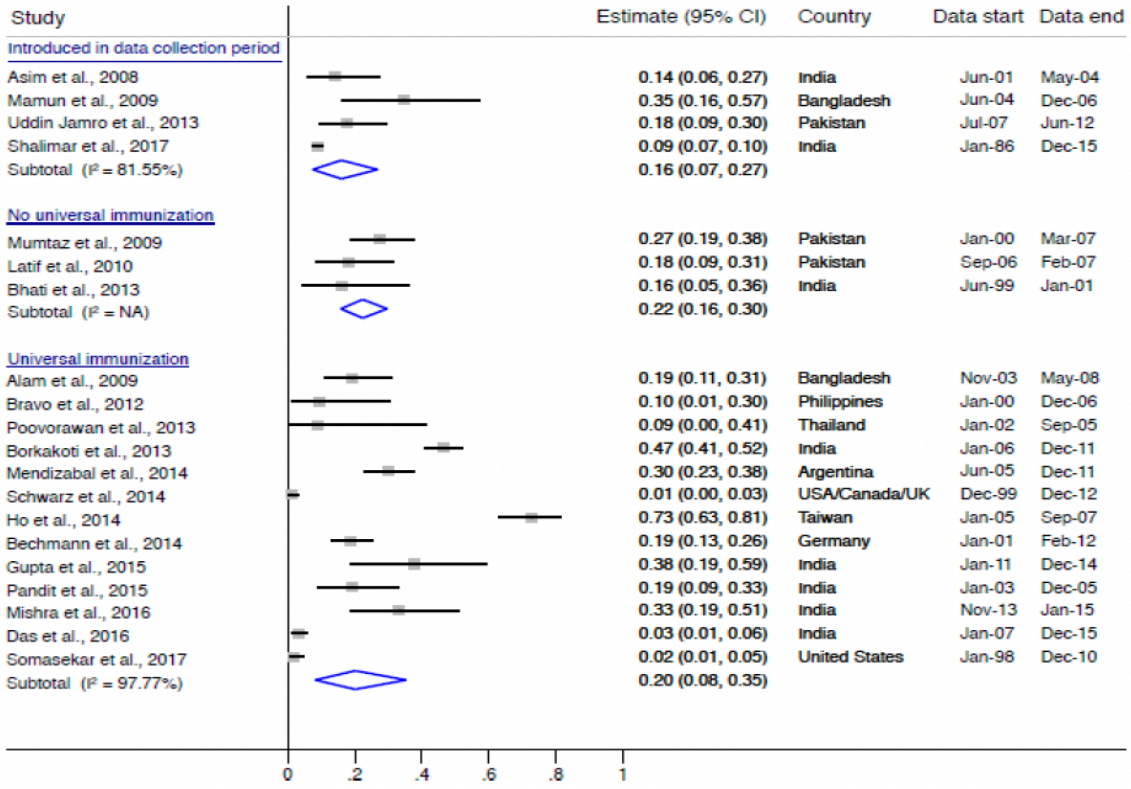


*Figure 3.3: Prevalence of hepatitis B virus induced acute liver failure by country hepatitis B immunization status*




### 3.4.2 ALF attributable to non-vaccine-preventable viral infections

The point prevalence of HCV-induced ALF ranged from 2% to 25% with a combined of 9% (95% CI = 1, 21) (**Supplementary Figure S3.1**). The point prevalence of HEV-induced ALF ranged from 3% to 70% with a combined of 32% (95% CI 24, 41) (**Supplementary Figure S3.2**). The point prevalence of HDV-, HHV/HSV-, CMV-, and EBV-induced ALF were estimated to have the average prevalence of 4% (95% CI 0, 13), 6% (95% CI 1, 12), 13% (95% CI 1, 35) and 6% (95% CI 0, 24), 10% (95% CI 2, 22), 2% (95% CI 0, 5), and 1% (95% CI 0, 5), respectively (**Supplementary Figure S4.3**). Data was not available to estimate the burden of ALF following infection with HDV, VZV, HPIVS, YFV, CA16 and/or HAdVs as outlined per the published protocol (11).

### 3.4.3 Outcomes of viral-induced ALF

The narratively reported outcomes of viral-induced ALF were found to be severe. The mortality rates associated with viral-induced ALF in lower-middle income countries ranged from 18% to 91% with a combined mortality rate of 50% (95% CI 36, 64) (**Figure 3.4A**). The mortality rates associated with viral-induced ALF in upper-middle income countries ranged 3% to 45% with a combined mortality rate of 26%

(95% CI 1, 63) (**Figure 434A**). The mortality rates associated with viral-induced ALF in high income countries ranged from 12% to 40% with an average mortality rate of 29% (95% CI 17, 43) (**Figure 3.4A**). The rate of encephalopathy associated with viral-induced ALF cases in children ranged from 69% to 100% with a combined rate of 89% (95% CI 79, 97) (**Figure 3.4B**). The need for liver transplantation with viral-associated ALF ranged from 4% to 62% with a combined rate of 25% (95% CI 6, 53) (**Figure 3.4B**). The need for renal transplant in viral-associated ALF cases ranged from 4% to 34% with a combined rate of 18% (95% CI 2, 43) (**Figure 3.4B**).

*Figure 3.4A: Prevalence of mortality rates associated with viral-induced acute liver failure*

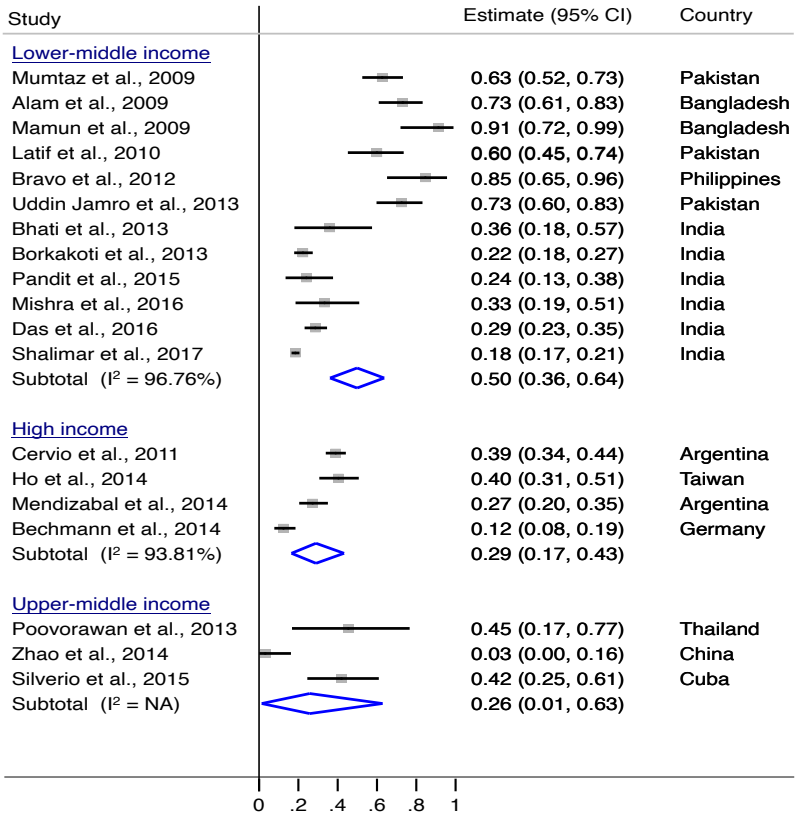
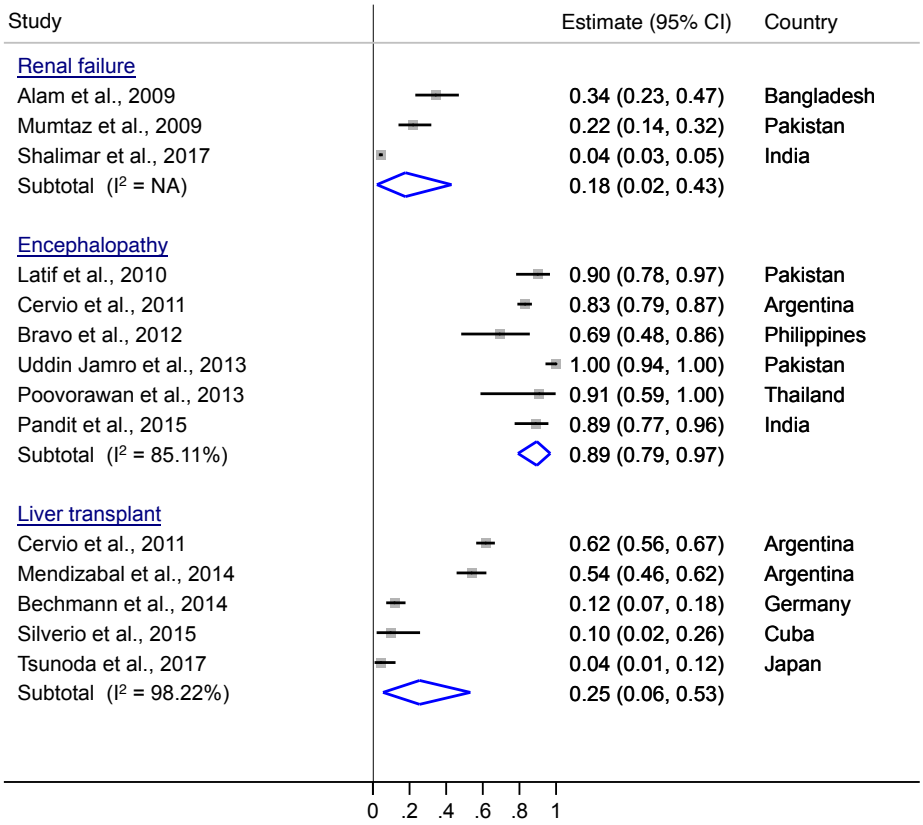


*Figure 3.4B: Prevalence of clinical outcomes associated with viral-induced acute liver failure*




### 3.4.4 Methodological quality

Risk of bias scores were assigned by two reviewers (JP and HH) and are described in **Supplementary Table S3.1**. Overall, most of the included studies were judged as having 'low risk' of bias. Only one included study was judged as having 'moderate risk' of bias due to lack of clarity around the representativeness of the study population to the national population, methods of participant selection and methods employed to reduce the likelihood of non-response.

## 3.5 Discussion

This systematic review estimated the burden of ALF following infection with HAV, HBV, HCV, HEV, HSV/HHV, CMV, EBV, and parvovirus B19. The prevalence of HAV-induced ALF is markedly lower in countries with routine HAV immunization while HEV was the most common etiological cause of viral-induced ALF reported in this review. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which seem to increase with poor economic status of the studied countries.

The estimated prevalence of HAV-induced ALF in countries with routine HAV immunization was lower than the estimated prevalence in countries without routine HAV immunization. When looking at countries with data before and after the introduction of routine HAV immunization, the lower prevalence of HAV-induced ALF due is highlighted for further investigation to establish causality. The combined prevalence of HBV-induced ALF was the same in settings with or without universal HBV immunization. Countries without universal HBV immunization programs are likely to have weak healthcare systems; thus, the reported prevalence of HBV-induced ALF is assumed to be an underestimate of the true burden in these populations due to weak routine testing and reporting systems. Currently, there is one HEV vaccine (Hecolin) licensed in China that has shown promise with a high degree of efficacy in preventing HEV genotype IV infection in healthy individuals 16 to 65 years (39). Further exploration of the efficacy of this vaccine for prevention of infection with genotypes I and II in different populations should to explore it's application in different countries and HEV endemicity settings (40).

This review estimated the mortality rate for viral-induced ALF to be approximately 50% in low- and middle- income countries (LMICs) and less than 30% in upper-middle- and high-income countries. Previous studies have estimated that mortality rates associated with ALF vary between 60% and 80%, depending on the disease aetiology as well as a patient's access to care. Our review shows that although viral-induced ALF still carries a significant mortality, though possibly lower than that reported for other ALF aetiologies (5, 6). Mortality data largely comes from hospitals with the capacity to diagnose viral-induced ALF, thus deaths outside of the hospital system or ALF deaths without virological testing may not be captured in these mortality estimates. Liver transplantation is required by approximately 25% of viral-induced ALF cases and approximately 18% of viral-induced ALF cases required renal transplantation, globally. In addition to general lack of resources for transplantation, a significant proportion of potential candidates have contraindications to transplant related to poor socioeconomic status in LMICs. The transplant data included in this review may only reflect successful and unsuccessful transplants, not those that were needed but not carried out due to resource constraints or contraindications.

This review is limited by lack of data for many of the viral aetiologies of ALF including for HDV, HSV/HHV, VZV, HPIVs, YFV, CA16 and/or HAdVs, which may have led to an underestimation of the global burden of viral-induced ALF. Additionally, we believe that our findings underestimate the global burden of viral-

induced ALF as some important causes of ALF (e.g., HSV/HHV) are believed to be underrecognized as they require PCR testing for diagnosis. The included studies also used varying methods of virus detection including serology and molecular tests which further added to the heterogeneity in the results of our review. This is a well-recognized limitation in studies of ALF where diagnostics are often limited by cost in under-resourced regions where viral causes of ALF are more prevalent. It should be noted that no data from Africa was included in this review likely due to these cost prohibitive diagnostic testing techniques which may lead to regional data being used for health policy setting within Africa. The limited availability of data, including lack of same country data on burden of disease before and after introduction of immunization, hindered most of the planned sub-group analyses outlined in the study protocol. Where data were available, high heterogeneity of the data led to planned meta-analyses and meta-regression analyses not being possible and results were reported in narrative form. Estimates of the mortality rates for each aetiological agent were not statistically significant and were grouped by country income level. In addition, estimates of clinical outcomes for each aetiological agent were not statistically significant and were grouped by outcome type. Lastly, the diversity of viruses attributable to ALF cases led to low statistical power in meta-analyses conducted.

Future research should assess the burden of viral-induced ALF following infection with HDV, HSV/HHV, VZV, HPIVS, YFV, CA16 and HAdVs. Collectively, high-quality data on all viral aetiologies of ALF would allow for better pooling of results. The review team encourages future studies to incorporate health economic estimates and mathematical modelling where data permits to assist health policy decision-makers to better design strategies for the prevention and management of viral-induced ALF. Epidemiological-economic modelling of immunization against HAV, HBV and HEV may well show that introduction of vaccination could lead to future cost savings in the long run due to prevented medical care and liver failure.

## 3.6 Conclusion

Due to the paucity of data available on the burden of viral-induced ALF, this study utilized global data but did not compromise the primary intention to synthesize South African data. Given the global perspective of this study, the review successfully addressed the outlined aims although data on VZV, HPIVs, YFV, CA16 and/or HAdVs were missing. Notwithstanding the noted limitations, HAV, HBV, and HEV – vaccine-preventable ALF aetiologies – account for a large proportion of ALF (approximately 21%, 20%, 32% of viral-induced ALF cases, respectively). The burden of ALF that is associated with vaccine-

preventable ALF aetiologies should be used in conjunction with other available key evidence to inform practice and policies on immunization, particularly in LMICs. Routine HAV immunization in LMICs is lacking and more data on the burden of hepatitis A is urgently needed to guide routine use of the vaccine in prevention of morbidity and mortality caused by the virus. Where contextually relevant data on hepatitis A is missing, future studies should evaluate the severity of hepatitis A cases and cost of care. Such studies are critical to generate evidence on the potential cost-savings that may be attained through vaccination to prevent costs as well as impacts associated with medical care and acute liver failure in absence of vaccination. There was no single study that evaluated ALF in South Africa. Thus, in the absence of this local (South African) evidence, there is reason to generate evidence on the clinical severity of hepatitis A and associated healthcare costs in the country.

## 3.7 References


1. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017;66(5):1047-81.
2. Morabito V, Adebayo D. Fulminant Hepatitis: Definitions, Causes and Management. Health. 2014;06(10):1038-48.
3. European Association for the Study of the Liver. Electronic address eee, Clinical practice guidelines p, Wendon J, Panel m, Cordoba J, Dhawan A, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.
4. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Armoni J, et al. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. Hepat Med. 2011;3:99-106.
5. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet (London, England). 2010;376(Seminar):190-201.
6. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure - one disease, more than 40 definitions. Aliment Pharmacol Ther. 2012;35(11):1245-56.
7. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology. 2012;55(3):965-7.
8. Spearman CW, McCulloch M, Millar AJ, Burger H, Numanoglu A, Goddard E, et al. Liver transplantation at Red Cross War Memorial Children's Hospital. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 2006;96(9 Pt 2):960-3.
9. O'Grady JG. Acute liver failure. Postgraduate medical journal. 2005;81(953):148-54.
10. O'Grady J. Liver transplantation for acute liver failure. Best Pract Res Clin Gastroenterol. 2012;26(1):27-33.
11. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019;9(8).
12. Balk E, Ching M, Chen M, Trikalinos T, L KWC. Assessing the Accuracy of Google Translate to Allow Data Extraction From Trials Published in Non-English Languages. Rockville, USA: Agency for Healthcare Research and Quality; 2013 Jan 2013. Contract No.: EHC145-EF.
13. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C. Assessing risk of bias in prevalence studies: Modification of an existing tool and evidence of interrater aggreement. Journal of Clinical Epidemiology. 2012;65:934-9.
14. Werfalli M, Musekiwa A, Engel ME, Ross I, Kengne AP, Levitt NS. The prevalence of type 2 diabetes mellitus among older people in Africa: a systematic review study protocol. BMJ Open. 2014.
15. Alam S, Azam G, Mustafa G, Azad AK, Haque I, Gani S, et al. Natural course of fulminant hepatic failure: the scenario in Bangladesh and the differences from the west. Saudi J Gastroenterol. 2009;15(4):229-33.
16. Asim M, Singla R, Gupta RK, Kar P. Clinical & molecular characterization of human TT virus in different liver diseases. Indian Journal of Medical Research. 2010;131(4):545-54.
17. Bechmann LP, Manka P, Best J, Saner FH, Paul A, Canbay A, et al. Drug-induced liver injury as predominant cause of acute liver failure in a monocenter study. Deutsche Medizinische Wochenschrift. 2014;139(17):878-82.
18. Bhatia V, Dhawan A, Arora NK, Mathur P, Das MK, Irshad M. Urinary potassium loss in children with acute liver failure and acute viral hepatitis. J Pediatr Gastroenterol Nutr. 2013;57(1):102-8.
19. Borkakoti JH, R. K.; Mohammad, A.; Kumar, A.; Kar, P. Does high viral load of hepatitis E virus influence the severity and prognosis of acute liver failure during pregnancy? Journal of Medical Virology. 2013;85(4):620-6.
20. Bravo LC, Gregorio GV, Shafi F, Bock HL, Boudville I, Liu Y, et al. Etiology, incidence and outcomes of acute hepatic failure in 0-18 year old Filipino children. Southeast Asian J Trop Med Public Health. 2012;43(3):764-72.
21. Das AK, Begum T, Kar P, Dutta A. Profile of Acute Liver Failure from North-east India and Its Differences from other Parts of the Country. Euroasian J Hepatogastroenterol. 2016;6(2):111-5.
22. Gupta P, Mittal M, Bhat NK, Agarwal RK, Gupta P, Mittal G. A hospital based retrospective study on hepatotropic viruses as a cause of acute viral hepatitis in children in Uttarakhand, India. Indian Journal of Community Health. 2015;27(4):451-5.
23. Ho CM, Lee CH, Wang JY, Lee PH, Lai HS, Hu RH. Nationwide longitudinal analysis of acute liver failure in taiwan. Medicine (Baltimore). 2014;93(4):e35.
24. Latif N, Mehmood K. Risk factors for fulminant hepatic failure and their relation with outcome in children. J Pak Med Assoc. 2010;60(3):175-8.
25. Mamun Al M, Rahman S, Khan M, Karim F. HEV infection as an aetiologic factor for acute hepatitis: experience from a tertiary hospital in Bangladesh. J Health Popul Nutr. 2009;27(1):14-9.
26. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E Virus Infection as a Possible Cause of Acute Liver Failure in Europe. Clin Gastroenterol Hepatol. 2015;13(10):1836-42.e2; quiz e157-8.

27. Mendizabal MM, S.; Videla, M. G.; Anders, M.; Zerega, A.; Balderramo, D. C.; Chan, D.; Barrabino, M.; Gil, O.; Mastai, R.; Yantorno, S.; Gadano, A.; Silva, M. O. Changing etiologies and outcomes of acute liver failure: Perspectives from 6 transplant centers in Argentina. Liver Transplantation. 2014;20(4):483-9.
28. Mishra SB, J.; Kumar, S.; Kar, P. Role of HEV antigen detection in HEV-related acute viral hepatitis and acute liver failure. Journal of Medical Virology. 2016;88(12):2179-85.
29. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Ali Shah H, et al. Role of N-acetylcysteine in adults with non-acetaminophen-induced acute liver failure in a center without the facility of liver transplantation. Hepatology International. 2009;3(4):563-70.
30. Pandit A, Mathew LG, Bavdekar A, Mehta S, Ramakrishnan G, Datta S, et al. Hepatotropic viruses as etiological agents of acute liver failure and related-outcomes among children in India: a retrospective hospital-based study. BMC Res Notes. 2015;8:381.
31. Poovorawan Y, Chongsrisawat V, Shafi F, Boudville I, Liu Y, Hutagalung Y, et al. Acute hepatic failure among hospitalized Thai children. Southeast Asian J Trop Med Public Health. 2013;44(1):50-3.
32. Schwarz KBO, Dominic Dell; Lobritto, Steven J.; Lopez, M. James; Rodriguez-Baez, Norberto; Yazigi, Nada A.; Belle, Steven H.; Zhang, Song; Squires, Robert H.; for the Pediatric Acute Liver Failure Study, Group. Analysis of Viral Testing in Nonacetaminophen Pediatric Acute Liver Failure. Journal of Pediatric Gastroenterology & Nutrition. 2014;59(5):616-23.
33. Shalimar, Kedia S, Gunjan D, Sonika U, Mahapatra SJ, Nayak B, et al. Acute Liver Failure Due to Hepatitis E Virus Infection Is Associated with Better Survival than Other Etiologies in Indian Patients. Dig Dis Sci. 2017;62(4):1058-66.
34. Silverio CE, Smithen-Romany CY, Hondal NI, Diaz HO, Castellanos MI, Sosa O. Acute liver failure in Cuban children. MEDICC Rev. 2015;17(1):48-54.
35. Somasekar SL, D.; Rule, J.; Naccache, S. N.; Stone, M.; Busch, M. P.; S.; ers, C.; Lee, W. M.; Chiu, C. Y. Viral Surveillance in Serum Samples from Patients with Acute Liver Failure by Metagenomic Next-Generation Sequencing. Clinical Infectious Diseases. 2017;65(9):1477-85.
36. Uddin Jamro BMC, S.; Mal Makheja, P.; Ahmed Soomro, A. Etiology, outcome and risk factors for fulminant hepatic failure in children at a tertiary care hospital, Sukkur, Pakistan. Rawal Medical Journal. 2013;38(3):219-22.
37. Tsunoda T, Inui A, Iwasawa K, Oikawa M, Sogo T, Komatsu H, et al. Acute liver dysfunction not resulting from hepatitis virus in immunocompetent children. Pediatr Int. 2017;59(5):551-6.
38. Zhao P, Wang CY, Liu WW, Wang X, Yu LM, Sun YR. Acute liver failure in Chinese children: a multicenter investigation. Hepatobiliary Pancreat Dis Int. 2014;13(3):276-80.
39. Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. Hum Vaccin Immunother. 2015;11(4):908-14.
40. Wu X, Chen P, Lin H, Hao X, Liang Z. Hepatitis E virus: Current epidemiology and vaccine. Human Vaccines and Immunotherapeutics. 2016;12(10):2603-10.

# 4 Chapter 4: A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa

Patterson, J., Cleary, S., Silal, S. P., Hussey, G. D., Enoch, A., Korsman, S., Goddard, E., Setshedi, M., Spearman, W. C., Kagina, B. M., & Muloiwa, R. (2022). A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa. *BMC infectious diseases*, *22*(1), 45. https://doi.org/10.1186/s12879-021-06993-w.

**Relevance of this paper to the thesis:**

Published data describing the burden of hepatitis A on the South African healthcare system is missing. This paper presents the health outcomes and costs associated with hepatitis A cases presenting to two tertiary healthcare facilities in Cape Town, South Africa.

**Contributions of the student and co-authors:**

BMK conceptualized this study. JP developed the study protocol under the guidance of BMJ, SC, and RM. JP implemented the research under the supervision of BMK, SC, and RM. JP conducted all analyses, developed this manuscript, and is the guarantor of this research. All authors read and approved the final manuscript.

## 4.1 Abstract

While some evidence has been demonstrated the cost-effectiveness of routine hepatitis A vaccination in middle-income countries, the evidence is still limited in other settings including in South Africa. Given this, the evidence base around the cost of care for hepatitis A needs to be developed towards considerations of introducing hepatitis A vaccines in the national immunization schedule and guidelines. This paper aims to describe the severity, clinical outcomes, and cost of hepatitis A cases presenting to two tertiary healthcare centres in Cape Town, South Africa.

We conducted a retrospective folder review of patients presenting with hepatitis A at two tertiary level hospitals providing care for urban communities of metropolitan Cape Town, South Africa. Patients included in this folder review tested positive for hepatitis A immunoglobulin M between 1 January 2008 and 1 March 2018.

In total, 239 folders of hepatitis A paediatric patients < 15 years old and 212 folders of hepatitis A adult patients ≥ 15 years old were included in the study. Before presenting for tertiary level care, more than half of patients presented for an initial consultation at either a community clinic or general physician. The mean length of hospital stay was 7.45 days for adult patients and 3.11 days for paediatric patients. Three adult patients in the study population died as a result of hepatitis A infection and 29 developed complicated hepatitis A. One paediatric patient in the study population died as a result of hepatitis A infection and 27 developed complicated hepatitis A, including 4 paediatric patients diagnosed with acute liver failure. The total cost per hepatitis A hospitalization was $1,935.41 for adult patients and $563.06 for paediatric patients, with overhead costs dictated by the length of stay being the largest cost driver.

More than 1 in every 10 hepatitis A cases (13.3%) included in this study developed complicated hepatitis A or resulted in death. Given the severity of clinical outcomes and high costs associated with hepatitis A hospitalization, it is important to consider the introduction of hepatitis A immunization in the public sector in South Africa to potentially avert future morbidity, mortality, and healthcare spending.

## 4.2 Background

The epidemiology of hepatitis A remains unclear globally. The World Health Organization (WHO) describes the epidemiology of hepatitis A according to hepatitis A virus (HAV) endemicity levels measured by the proportion of people with anti-HAV Immunoglobulin G (IgG) antibodies (1). In areas where there is high exposure to the virus (high HAV endemicity), a large percentage of the population is assumed to have been asymptomatically infected by 10 years old (1). Due to improvements in water, sanitation, and developments in socioeconomic status, low- and middle-income countries may transition from high to intermediate or low HAV endemicity. In areas of intermediate or low HAV endemicity, a lower proportion of the respective populations will have been infected during childhood, and the likelihood of symptomatic infection during adulthood increases (2). In these cases, WHO recommends the consideration of introducing hepatitis A vaccines to reduce morbidity and mortality due to the disease (1).

Since 2005, there has been a documented shift in hepatitis A epidemiology in South Africa with a rise in the number of clinically symptomatic hepatitis A cases indicated by high anti-HAV Immunoglobulin M (IgM) positivity rates, especially among children and adolescents < 15 years old (2-5). Analyses of routine HAV laboratory data between 2005 and 2015 in South Africa suggest that children < 5 years old carry the largest burden of acute hepatitis A compared to other age groups. Additionally, these analyses point out that the seroprevalence of anti-HAV reaches levels >90% only in individuals > 25 years old, suggesting South Africa should be classified as a country with intermediate HAV endemicity.

Despite South Africa's intermediate HAV endemicity status, hepatitis A vaccines are not currently included in the National Expanded Program on Immunization (EPI) even as the cost-effectiveness of universal hepatitis A vaccination is well documented in low and intermediate HAV endemicity regions such as Argentina, Brazil, Chile, and Mexico (6-8). It has, therefore, become important to consider the local hepatitis A morbidity, mortality, and costs of care to bolster considerations of introducing the vaccine in South Africa.

## 4.3 Methods

### 4.3.1 Objective

The aim of this study is to describe the clinical severity and costs of care for hepatitis A cases presenting to two public sector tertiary healthcare centres in Cape Town, South Africa. The results of this study will be used together with other ongoing research to forecast the health impacts and cost-effectiveness of different hepatitis A vaccination strategies to be considered for inclusion in the EPI.

### 4.3.2 Setting and participants

We conducted a retrospective folder review of patients presenting with hepatitis A to two tertiary level hospitals providing care for urban communities of metropolitan Cape Town, South Africa. The hospitals included Red Cross War Memorial Children's Hospital (RCH) serving paediatric patients < 15 years old and Groote Schuur Hospital (GSH) serving adult patients ≥ 15 years old.

Patients included in this folder review were identified by flagging all positive hepatitis A immunoglobulin M (IgM) tests between 1 January 2008 and 1 March 2018 through the South African National Health Laboratory Services database. Once folder numbers corresponding to positive IgM tests were identified, patient folders were reviewed for inclusion eligibility. Patients with clinically confirmed hepatitis A and without evidence of concomitant hepatitis E infection were selected for inclusion in this study.

### 4.3.3 Hepatitis A case definition

Included cases needed to meet both the clinical description and laboratory confirmation of acute hepatitis A, as defined by the Centres for Disease Control and Prevention (CDC) (9).

- Clinical description: An acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis and either a) jaundice, or b) elevated serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels. Symptoms of acute viral hepatitis include fever, headache, malaise, anorexia, nausea, vomiting, diarrhoea, and abdominal pain.
- Laboratory criteria: Positive sera identification of immunoglobulin M (IgM) antibody to the hepatitis A virus.

At the time of admission, evidence of acute liver injury was assessed through analysis of international normalized ratio (INR), elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase

(AST), alkaline phosphatase (ALP), and total bilirubin (10, 11). Patient clinical outcomes were classified as uncomplicated, complicated, or deceased within further analysis.

### 4.3.4 Hepatitis A outcome definitions

Complications included the development of relapsing hepatitis, prolonged cholestasis, acute liver failure, or had comorbidities that complicated care and recovery.

- Relapsing hepatitis A was defined in all patients as being re-admitted for hepatitis A within 6 months of first admission.
- Prolonged cholestasis was defined in all patients with prolonged jaundice lasting longer than 14 days and conjugated bilirubin > 10 IU/L.
- Acute liver failure in paediatric patients was defined as INR ≥ 1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy or INR ≥ 2.0 regardless of the presence or absence of clinical hepatic encephalopathy (10, 12).
- Acute liver failure in adult patients was defined as hepatic encephalopathy and coagulopathy INR ≥ 1.5, in patients without pre-existing cirrhosis, and an illness of <26 weeks duration (13).

### 4.3.5 Data collection

Data were extracted from folders and corresponding electronic records by a clinical registrar using a pre-designed piloted data extraction form. The data extraction form was piloted using 50 patient folders before the start of the study. The following data elements were included in the data extraction form: demographic information, hepatitis A risk factors, hospital admission and discharge dates, clinical signs and symptoms of hepatitis A, bloods drawn, medicines and products used for case management, medicines prescribed at discharge, clinical outcome, and length of stay in varying hospital wards. In addition, data on the patient account were extracted from the folders to estimate the percentage of the cost of hepatitis A cases carried by the national governments as the ultimate fee payer for the included facilities.

During data extraction, study IDs were generated to identify patients so that names and/or any patient identifying information were not included in the data extraction process. Data were analysed in STATA version 16.0 (14). Clinical characteristics, demographics, and clinical variables were summarised using descriptive statistics. Means, medians, and interquartile ranges were calculated for continuous variables, while counts and percentages were calculated for categorical variables.

All study data were subsequently removed from Kobo Toolbox and have been saved on a password-protected hard drive which will be kept by the first author for 5 years. The study was approved by the University of Cape Town's Research Ethics Committee and research clearance was granted by GSH (HREC 485) and RCH's Research Committees (RCC 153).

### 4.3.6 Costing

Costing for hepatitis A cases was conducted following recommendations for conducting and reporting of economic evaluations as per the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (15). To estimate the cost of care for hepatitis A cases, this study calculated the mean cost per hepatitis A hospitalization from a health care provider's perspective. Costing of hepatitis A cases entailed the multiplication of counts of health service utilization against unit costs. Counts of service utilization were achieved using data extracted from folders. Thereafter, unit costs were established using a combination of the ingredients and step-down methods, as appropriate. In this process, the ingredients approach was first applied to cost the items directly used for the diagnosis and treatment of hepatitis A cases, including laboratory investigations, procedures, medications, and blood products (16). Laboratory and blood unit costs were provided by the National Health Laboratory Services. Medicine unit costs were obtained from the 2018 National Tender Price List (17). Radiology and other imaging investigation costs were derived from the 2018 National Uniform Patient Fee Schedule (18).

Overhead resources that could not be costed from the folder review were costed using the step-down approach. In the step-down approach, overhead expenditures were established from facility accounting records and were allocated to routine patient activity data to establish an overhead cost per inpatient day.

All costs were expressed in September 2018 prices and converted to US dollars using an average exchange rate over the same period (US$1 = 14.75 South African Rand) (19). One-way deterministic sensitivity analyses were conducted on the three largest patient-specific cost components including blood tests, medicines, and radiology tests to explore the impact on the mean cost per hepatitis A hospitalization. Each component was varied using the 90% CI and the results are displayed in tornado diagrams.

## 4.4 Results

### 4.4.1 Demographics and risk factor characteristics of the study population

In total, 239 folders of hepatitis A paediatric patients < 15 years old (median = 6.6 years old) and 212 folders of hepatitis A adult patients ≥ 15 years old (median = 27.4 years old) were included in the study. A total of 8 adult patients and 6 paediatric patients included in the study were confirmed as HIV positive. Five adult patients and one paediatric patient were also positive for hepatitis B surface antigen (HBs-Ag), while one adult patient was also positive for hepatitis C. For patients where this information was reported, regular use of toilets without plumbing and sharing of communal taps were the most frequent hepatitis A risk factors among both adult and paediatric patients. The demographic and risk factor characteristics of the patients are further summarized in **Table 4.1**.

*Table 4.1: Demographics and risk factors for hepatitis A patients among the study patient population*.

| Variable | Number of adult patients (%) | Number of paediatric patients (%) |
|---|---|---|
| **Number of patients** | 212 | 239 |
| **Median age (interquartile range)** | 27.4 (21.5, 34.3) | 6.6 (4.4, 8.9) |
| **Demographics** | | |
| **Gender** | | |
| Female | 94 (44.3%) | 125 (52.3%) |
| Male | 118 (55.7%) | 114 (47.7%) |
| **Patient account class** | | |
| Patient pays nominal fees | 169 (79.7%) | 194 (81.2%) |
| Patient pays a portion of fees | 12 (5.7%) | 24 (10.0%) |
| Patient pays fees in full | 22 (10.4%) | 14 (5.9%) |
| Not recorded | 9 (4.2%) | 7 (2.9%) |
| **Known co-morbidities** | | |
| HIV positive | 8 (0.04%) | 6 (0.03%) |
| Hepatitis B positive | 0 (0.00%) | 1 (0.004%) |
| Hepatitis C positive | 1 (0.005%) | 0 (0.00%) |
| **Risk Factors** | | |
| **Known contact with hepatitis A case** | 20 (9.4%) | 16 (6.7%) |
| **Housing** | | |
| Informal housing | 9 (4.3%) | 9 (3.8%) |
| Formal housing | 9 (4.3%) | 48 (20.1%) |
| Housing type not reported | 194 (91.5%) | 182 (76.1%) |

| | | |
|---|---|---|
| **Water source** | | |
| Water source from outside dwelling | 11 (5.2%) | 58 (24.3%) |
| Water source not reported | 201 (94.8%) | 181 (75.7%) |
| **Sanitation** | | |
| Toilet without plumbing | 19 (9.0%) | 56 (23.44%) |
| Toilet type not reported | 193 (91.0%) | 183 (76.6%) |
| **Additional risk factors*** | | |
| Alcohol use | 46 (21.7%) | ---- |
| IV drug use | 20 (9.4%) | ---- |
| Travel history | 10 (4.7%) | 7 (3.0%) |
| All variables are presented as N (%).<br>*Additional risk factor information including alcohol and IV drug use was not collected for paediatric patients. | | |

### 4.4.2 Clinical presentation and severity

Clinical signs and symptoms of hepatitis A at the time of admission are summarized in **Table 4.2**. More than half of patients in the study reported vomiting and abdominal pain as symptoms of hepatitis A before presentation for care at respective facilities. More than half of adult patients presented for care with clinical signs of jaundice, while more than half of paediatric patients presented for care with clinical signs of jaundice and enlargement of the liver. As displayed in **Table 4.3**, > 80% of adult patients and > 90% of paediatric patients who developed complicated hepatitis A displayed evidence of acute liver injury at the time of admission. All patients who died from hepatitis A infection displayed evidence of prolonged INR at the time of admission.

*Table 4.2: Hepatitis A clinical presentation*

| Variable | Number of adult patients (%) | Number of paediatric patients (%) |
|---|---|---|
| **Prevalence of clinical symptoms** | | |
| Abdominal pain | 110 (51.9%) | 121 (50.6%) |
| Anorexia | 58 (27.4%) | 90 (37.7%) |
| Dark urine | 83 (39.2%) | 105 (43.9%) |
| Diarrhoea | 26 (12.3%) | 62 (25.9%) |
| Drowsiness | 4 (1.9%) | 16 (6.7%) |
| Fatigue | 49 (23.1%) | 37 (15.5%) |
| Fever ≥ 38 ℃ | 68 (32.1%) | 71 (29.7%) |
| Headache | 21 (9.9%) | 15 (6.3%) |
| Jaundice | 155 (73.1%) | 198 (82.9%) |
| Joint ache | 8 (3.8%) | 0 (0.0%) |
| Nausea | 84 (39.6%) | 20 (8.4%) |
| Pale stool | 15 (7.1%) | 13 (5.4%) |
| Pruritis | 103 (48.6%) | 58 (24.3%) |
| Respiratory symptoms | 10 (4.7%) | 22 (9.2%) |

| | | |
|---|---|---|
| Vomiting | 140 (66.0%) | 166 (69.5%) |
| **Prevalence of clinical signs** | | |
| Enlarged liver | 60 (28.3%) | 137 (57.3%) |
| Upper-right abdominal tenderness | 104 (49.1%) | 105 (43.9%) |

*Table 4.3: Hepatitis A clinical outcomes and evidence of acute liver injury*

| **Adult patients** | | | | |
|---|---|---|---|---|
| **Evidence of acute liver injury** | **All patients (N=212)** | **Uncomplicated hepatitis (n=180, 84.9%)** | **Complicated hepatitis A (n=29, 13.7%)** | **Deceased (n=3, 1.4%)** |
| INR ≥ 1.5 | 12 (5.6%) | 9 (5.0%) | 0 (0.0%) | 3 (100.0%) |
| ALT > 40 U/L | 199 (93.9%) | 168 (93.3%) | 27 (93.1%) | 3 (100.0%) |
| AST > 40 U/L | 197 (92.9%) | 168 (93.3%) | 26 (89.7%) | 3 (100.0%) |
| ALP > 128 U/L | 192 (90.6%) | 165 (91.7%) | 24 (82.8%) | 3 (100.0%) |
| Total bilirubin > 21 U/L | 188 (88.7%) | 160 (88.9%) | 25 (86.2%) | 3 (100.0%) |
| **Paediatric patients** | | | | |
| **Evidence of acute liver injury** | **All patients (N=239)** | **Uncomplicated hepatitis (n=211, 88.3%)** | **Complicated hepatitis A (n=27, 12.8%)** | **Deceased (n=1, 0.4%)** |
| INR 1.50 – 1.99 | 9 (3.8%) | 8 (3.8%) | 1 (3.7%) | 0 (0.0%) |
| INR ≥ 2.0 | 4 (1.7%) | 0 (0.0%) | 3 (11.1%) | 1 (100.0%) |
| ALT > 40 U/L | 239 (100.0%) | 211 (100.0%) | 27 (100.0%) | 1 (100.0%) |
| AST > 40 U/L | 238 (99.6%) | 211 (100.0%) | 26 (96.3%) | 1 (100.0%) |
| ALP > 128 U/L | 233 (97.5%) | 207 (98.1%) | 25 (92.6%) | 1 (100.0%) |
| Total bilirubin > 21 U/L | 232 (97.1%) | 206 (97.6%) | 25 (92.6%) | 1 (100.0%) |

All variables are presented as N (%).
Abbreviations: alanine aminotransferase (ALT), AST, alanine aminotransferase (ALT), Units per Litre (U/L)

### 4.4.3 Clinical outcomes

Among the study population, 4 patients (0.9%) died as a result of hepatitis A infection [GSH 3/212 (1.4%); RCH 1/239 (0.4%)]. In addition to these deaths, 56 patients (12.4%) developed complicated hepatitis A [GSH 29/212 (13.7%); RCH 27/239 (11.3%)]. Of the 14 HIV+ patients included in the study, 7 of these patients (50%) developed complicated hepatitis. One adult patient and two paediatric patients developed relapsing hepatitis A. Four paediatric patients developed prolonged cholestasis. Four paediatric patients and one adult patient included in this study developed acute liver failure from hepatitis A infection. One of these paediatric acute liver failure patients died during hospitalization, however, no ALF patients in the study population were sent for transplant.

### 4.4.4 Hepatitis A patient clinical service utilization

Before presenting for tertiary level care, 332 patients (73.6%) [GSH 149/212 (70.3%); RCH 183/239 (76.6%)] presented for an initial consult at either a community health centre, clinic, or general physician (**Figure 4.1**). Following presentation for care at the primary level, the mean time for adults to present to

GSH tertiary clinic or emergency room was 34.3 hours (median = 17.1 hours) and the mean time for paediatric patients to present to RCH tertiary level clinic or emergency room was 20.0 hours (median = 17.0 hours). The mean times spent in the emergency room or outpatient consulting room in the tertiary hospital prior to admission for adult patients were 6 hours (median = 6.2 hours) and 19.2 hours (median = 6.2 hours), respectively. The mean times spent in the tertiary facility clinic and emergency rooms before hospital admission for paediatric patients were 6 hours (median = 5.5 hours) and 6 hours (median = 4.7 hours), respectively. The mean length of inpatient hospital stay was 7.45 days (median = 0.8 days) for adult patients and 3.11 days (median = 0.3 days) for paediatric patients, which was largely influenced by the clinical outcome as displayed in **Figure 4.2** and **Supplementary Table S4.1**.

*Figure 4.1: Hepatitis A outcomes for adults and children presenting for care*

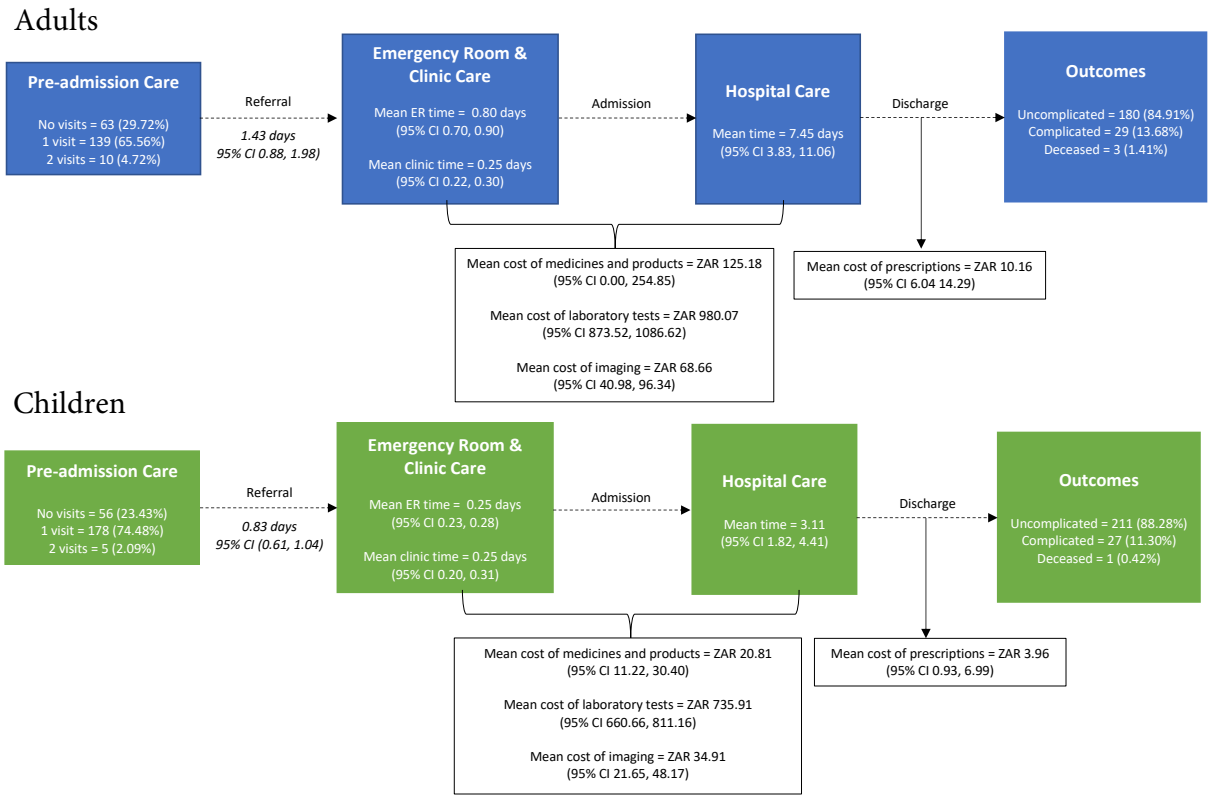
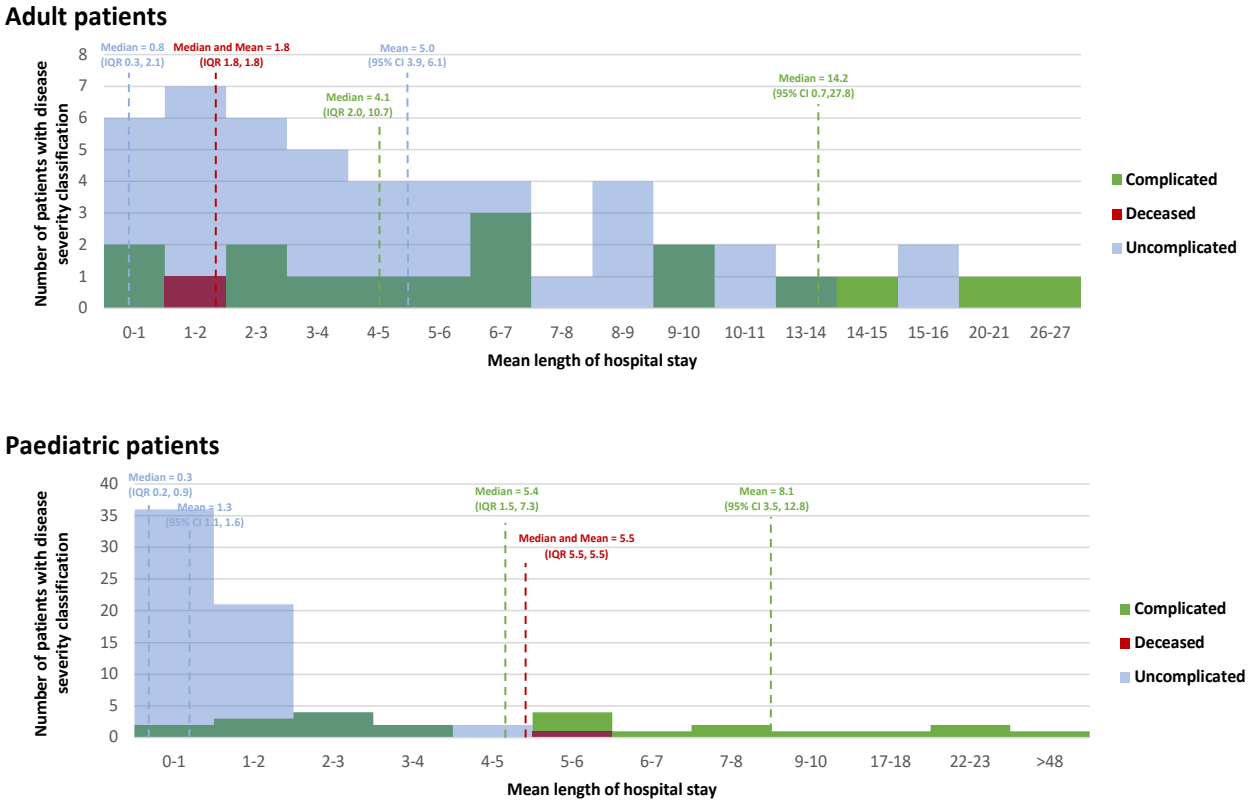


*Figure 4.2: Length of hospitalization by hepatitis A patient outcomes*




### 4.4.5 Hepatitis A costing

Using 2018 financial reports for each of the included facilities, overhead costs are presented in **Table 4.4**. Disaggregated expenditures in **Table 4.4** and the patient volumes reported per facility in 2018 yielded a cost per patient day equivalent of $249.00 for GSH and $163.71 for RCH.

The mean patient-specific hepatitis A costs per hospitalization/episode including investigations, radiology, and medication were estimated to be $80.34 (95% CI 68.83, 91.86) for adult patients and $53.94 (95% CI 48.81, 59.07) for paediatric patients (**Table 4.5)**. **Supplementary Table S4.2** provides detail on the utilization and unit costs of the investigations, radiology, and medicines and products. The most expensive blood and radiological tests conducted in these patient groups were antibody tests ($8.96) and gastroscopies ($74.92). The most expensive medicines and products were fresh frozen plasma for adult patients ($618.97) and prescriptions at discharge ($13.52) for paediatric patients.

*Table 4.4: Cost per patient day equivalent at included facilities in USD*

| Overhead line item | Groote Schuur Hospital serving adult patients | Red Cross Children's War Memorial Hospital serving paediatric patients |
|---|---|---|
| Compensation of employees | $119,892,542.40 | $9,548,135.59 |
| Employee benefits | $556,000.00 | $175,457.63 |
| Goods and services | $27,203,728.81 | $9,441,423.73 |
| Machinery and equipment | $1,715,050.85 | $878,983.05 |
| Software and intangible equipment | $16,949.15 | $0.00 |
| **Total overhead costs** | **$149,384,271.20** | **$20,044,000.00** |
| **Total patient days** | **599,931** | **122,439** |
| **Overhead cost per patient day equivalent*** | **$249.00** | **$163.71** |
| *To obtain the cost per patient day equivalent, the total overhead costs were divided by the total patient days per facility. | | |

*Table 4.5: Hepatitis A patient-specific costs per hospitalization/episode at facilities in USD*

| Patient-specific cost | Mean adult cost in USD (95% CI) | Mean paediatric cost in USD (95% CI) |
|---|---|---|
| Laboratory tests | 66.45 (59.2, 73.7) | 49.89 (44.79, 55.0) |
| Radiology | 4.65 (2.8, 6.5) | 2.37 (1.47, 3.3) |
| Medications | 9.24 (0.5, 18.0) | 1.68 (0.99, 2.4) |
| **Total** | **80.34 (68.8, 91.9)** | **53.94 (48.8, 59.1)** |

Using 95% CIs, sensitivity analyses were conducted to explore changes in the mean cost per admission associated with the three largest components of the patient-specific hepatitis A costs (blood tests, medicines, and radiology). Results are presented using tornado diagrams for adult and paediatric patients in **Figure 4.3** and **Figure 4.4**, respectively. As displayed in these tornado plots, blood tests were the main cost driver for patient-specific hepatitis A costs in both adult and paediatric patients. Given the mean lengths of hospital stay for adult patients (7.45 days) and paediatric patients (3.11 days), the mean total cost per hepatitis A hospitalization was $1,935.41 for adult patients and $563.06 paediatric patients. The overhead costs dictated by the length of hospital stay were the main driver of total cost per hepatitis A hospitalization as depicted in **Figure 4.5**.

*Figure 4.3: Sensitivity of patient-specific hepatitis A costs for adult cases*

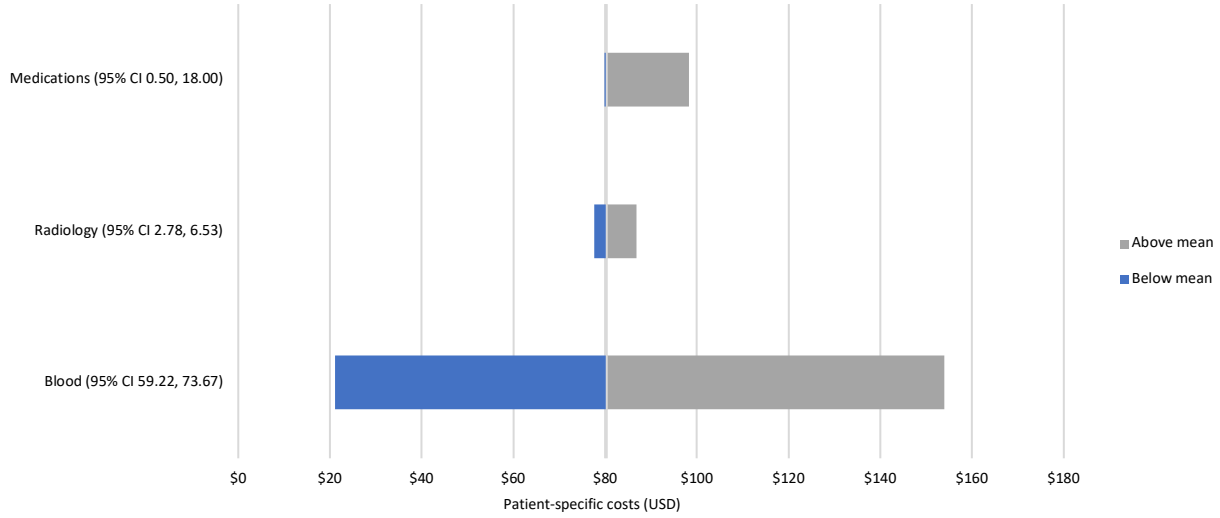



*Figure 4.4: Sensitivity of patient-specific hepatitis A costs for paediatric cases*

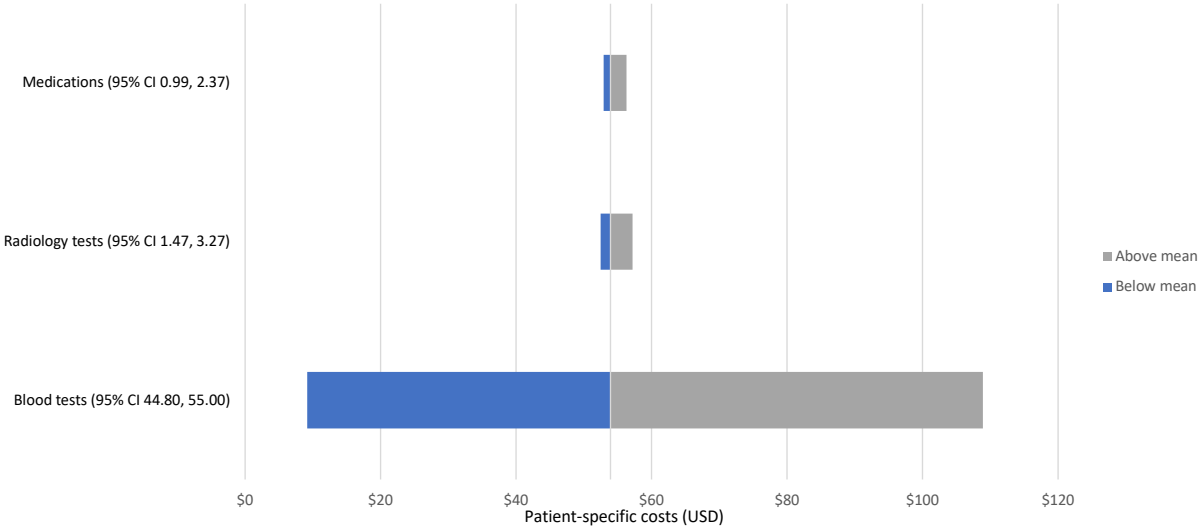
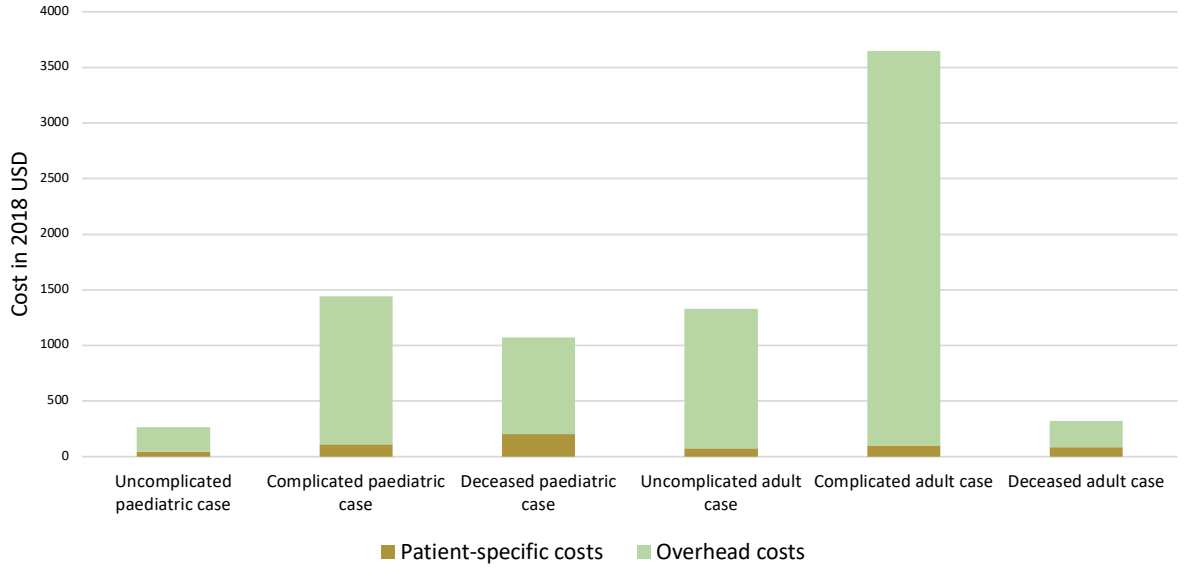


*Figure 4.5: Components of total hepatitis A hospitalization costs by patient clinical outcomes*




## 4.5 Discussion

The results of this study indicate that hepatitis A causes severe disease in adults and children with 13.3% of the study population having suffered death (4 patients) or complication (56 patients). Of the patients who developed complications, almost all displayed evidence of acute liver injury at the time of admission. Of the patients who were HIV positive (14 patients), half developed complications due to hepatitis A infection. None of the acute liver failure patients included in this study population were referred for a liver transplant. To qualify for a transplant, social and socioeconomic criteria are used exclusion criteria for patients as transplant requires adherence to lifelong treatment and the presence of social support structures for positive outcomes.

The median length of hospital stay for hepatitis A cases included in this study was largely influenced by clinical outcomes. It is worrisome that patients who died under care had significantly shorter hospital stays meaning that these patients likely presented for care at a very late stage of infection. If patients did not die as a result of hepatitis A infection, they required significant resources for case management and treatment.

Blood tests were the main cost driver for patient-specific hepatitis A costs in both adult and paediatric patients, with an average of 3 blood panels ordered per hepatitis A case. The mean total cost per

hepatitis A hospitalization was $1,935.41 for adult patients and $563.06 for paediatric patients. The overhead costs dictated by the length of hospital stay were the main driver of total cost per hepatitis A hospitalization. Notably, a large majority of adult and paediatric patients included in this study paid a nominal daily fee for hospitalization and the government was responsible for paying > 90% of the cost of treatment in more than 75% of cases included in this study. Further work should include an analysis of the impact of hepatitis A hospitalization costs on the national health budget.

At large, the patient-specific hepatitis A cost estimates presented in this study are likely underestimates of the true costs of care. This folder review was conducted at tertiary level facilities, therefore, the study was unable to capture costs incurred for care at the primary level, which was utilized by approximately 70% of patients before presenting for tertiary care. The folder review also did not capture costs at non-tertiary hospitals, where patients (particularly severe patients who died under care at GSH and RCH) may have sought care before presenting at the tertiary levels facilities included in this study. Additionally, the adoption of a provider's perspective in this study led to the exclusion of costs incurred by patients for care and did not allow for the opportunity costs of accessing care including out-of-pocket payments and loss of productivity. Lastly, the folder review did not include additional costs of providing prophylaxis to close contacts of hepatitis A cases with HAV vaccine or immunoglobulin according to clinical guidelines in South Africa (20).

Additional limitations of this study include that the underlying epidemiological characteristics of the study population were not well described as comorbidities were not well documents and not all patients were tested for HIV, hepatitis B, or hepatitis C at the time of admission. Information on hepatitis A risk factors such as housing, sanitation, and water source were also not routinely reported in patient folders. Patients presenting to the included tertiary facilities cannot be considered representative of the general South African population, however, the clinical outcome and cost data collected in this study provides a better local context than is currently represented in published literature.

Notwithstanding the noted limitations, this is the first study to describe the clinical severity and costs of care for hepatitis A cases in South Africa. The study highlights the notable severity of hepatitis A infection experienced by many patients in South Africa and the high burden of cost on the national health budget for case management and treatment of the disease. This study is part of an ongoing body of work to determine the cost-effectiveness of introducing hepatitis A vaccines into the South African

Expanded Program on Immunization. The ongoing work includes a dynamic model to estimate the epidemiological and economic outcomes for different hepatitis A vaccination strategies in the country.

## 4.6 Conclusion

More than 1 in 10 hepatitis A cases included in this study developed complicated hepatitis A or died because of infection. Given the evidence generated thus far including data on the epidemiology of hepatitis A, clinical severity of hepatitis A, cost of care for hepatitis A patients in South Africa, a modelling approach is recommended to further interrogate the hypothetical merits and cost-effectiveness of making an evidence-based recommendation on routine immunization against hepatitis A in South Africa.

## 4.7 References


1. World Health Organization. WHO position paper on hepatitis A vaccines - June 2012. Wkly Epidemiol Rec. 2012;87(28/29).
2. Mazanderani AH, Motaze VN, McCarthy K, Suchard M, du Plessis NM. Hepatitis A Virus Seroprevalence in South Africa-Estimates using Routine Laboratory Data, 2005-2015. PloS one. 2018;26(12).
3. Enoch A, Hardie DR, Hussey GD, Kagina BM. Hepatitis A seroprevalence in the Western Cape Province, South Africa. Are we in epidemiological transition? South African Medical Journal. 2019;109(5):314-8.
4. Solomons RS, Rabie H, Nel ED, Cotton MF. An overview of hepatitis A at Tygerberg Children's Hospital. South African Medical Journal. 2008;2(2):43-5.
5. Patterson J, Hussey HS, Abdullahi LH, Silal S, Goddard L, Setshedi M, et al. The global epidemiology of viral-induced acute liver failure: a systematic review protocol. BMJ Open. 2019;9(8).
6. Anonychuk AM, Tricco A, Bauch CT, Pham B, Gilca V, Duval B, et al. Cost-Effectiveness Analyses of Hepatitis A Vaccine: A Systematic Review to Explore the Effect of Methodological Quality on the Economic Attractiveness of Vaccination Strategies. Pharmaeconomics. 2008;21(1):17-32.
7. Sartori AM, de Soarez PC, Novaes HM. Cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine into the universal immunisation of infants in Brazil. J Epidemiol Community Health. 2012;66(3):210-7.
8. Ellis A, Rüttimann RW, Jacobs J, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Rev Panam Salud Publica. 2007;21(6):345-56.
9. Centers for Disease Control and Prevention. Hepatitis A, Acute 2019 Case Definition. Atlanta, GA: Centers for Disease Control and Prevention; 2019. Report No.: 18-ID-07.
10. Bhatt H, Rao GS. Management of Acute Liver Failure: A Pediatric Perspective. Current Pediatric Reports. 2018;6(3):246-57.
11. Shin EC, Jeong SH. Natural history, clinical manifestations, and pathogenesis of hepatitis A. Cold Spring Harbor Perspectives in Medicine. 2018;8(9).
12. Squires JE, McKieran P, Squires RH. Acute Liver Failure: An Update. Clinical Liver Disease. 2018;22(4):773-805.
13. Arshad MA, Murphy N, Bangash MN. Acute liver failure. Clinical Medicine. 2020;20(5):505-8.
14. StataCorp, inventorStata Statistical Software: Release 16. USA2019.
15. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force. . Value Health. 2013;16(2):231-50.
16. Walker DG, Hutubessy R, Beutels P. WHO Guide for standardisation of economic evaluations of immunization programmes. Vaccine. 2010;28(11):2356-9.
17. National Health Laboratory Service. NHLS State Price List 2018. South Africa: National Health Laboratory Service Republic of South Africa; 2018.
18. National Department of Health. Uniform Patient Fee Schedule. South Africa: Department of Health Republic of South Africa; 2018.
19. X-Rates. Monthly Average 2018 2021 [Available from: https://www.x-rates.com/average/?from=ZAR&to=USD&amount=1&year=2018.
20. de Jong G, Schoub B, Blumberg L. Guidelines for the Control of Hepatitis A in South Africa. South Africa: National Institiue of Communicable Disease; 2007 January 2007.

# 5 Chapter 5: Modelling the cost-effectiveness of hepatitis A vaccination in South Africa

Patterson, J., Cleary, S., van Zyl H., Awine T., Mayet S., Norman, J., Kagina, B. M., Muloiwa, R., Hussey, G. D., Silal, S. P., Modelling the cost-effectiveness of hepatitis A vaccination in South Africa. *Being prepared for submission.*

**Relevance of this paper to the thesis:**

While data was collected on the epidemiology, costs, and health outcomes associated with hepatitis A, an analytical tool to bring all findings together was needed to support evidence-informed considerations to introduce routine hepatitis A immunization into the EPI-SA. This paper presents a detailed analysis forecasting the epidemiology of hepatitis A in South Africa and modelling the cost-effectiveness of several potential routine hepatitis A vaccination strategies.

**Contributions of the student and co-authors:**

BMK and SPS conceptualized this study. JP developed the study protocol and implemented the study under the supervision of SC, SPS, and BMK. JP, TA, JN, SM, and SPS developed the model code and accompanying Rshiny application under the Modelling and Simulation Hub Africa (MASHA) team. JP implemented the economic analysis under the supervision of SC. JP is leading in the ongoing development of this manuscript.

## 5.1 Abstract

The World Health Organization (WHO) recommends the consideration of introducing routine hepatitis A vaccination into national immunization schedules for children ≥ 1 years old in countries with intermediate HAV endemicity. Recent data suggest that South Africa is transitioning from high to intermediate HAV endemicity, thus it is important to consider the impact and cost of potential routine hepatitis A vaccination strategies in the country.

An age-structured compartmental model of hepatitis A transmission was calibrated with available data from South Africa, incorporating direct costs of hepatitis A treatment and vaccination. We used the calibrated model to evaluate the impact and costs of several childhood hepatitis A vaccination scenarios from 2023 to 2030. We assessed how each scenario impacted the burden of hepatitis A (symptomatic hepatitis A cases and mortality) as well as calculated the incremental cost per DALY averted as compared to the South African cost-effectiveness threshold. All costs and outcomes were discounted at 5%.

For the modelled scenarios, the median estimated cost of the different vaccination strategies ranged from $1.71 billion to $2.85 billion over the period of 2023 to 2030, with the cost increasing for each successive scenario and approximately 39-52% of costs being due to vaccination. Scenario 1, which represented the administration of one dose of the hepatitis A vaccine in children < 2 years old, requires approximately 5.3 million vaccine doses over 2023-2030 and is projected to avert a total of 136,042 symptomatic cases [IQR: 88,842-221,483] and 31,106 [IQR: 22,975- 36,742] deaths due to hepatitis A over the period of 2023 to 2030. The model projects that Scenario 1 would avert 8,741 DALYs over the period of 2023 to 2030, however is not cost-effective against the South African cost-effectiveness threshold with an ICER per DALY averted of $21,006. While Scenario 3 and 4 included the administration of more vaccine doses and averted more symptomatic cases of hepatitis A, these scenarios were absolutely dominated owing to the population being infected before vaccination through the mass campaigns at older ages.

The model was highly sensitivity to varying access to liver transplant in South Africa. When increasing the access to liver transplant to 100% for baseline and Scenario 1, the ICER for Scenario 1 becomes cost-effective against the CET (ICER = $2,425). Given these findings, we recommend further research is conducted to understand the access to liver transplants in South Africa to better estimate the cost of

liver transplant care for hepatitis A patients. The modelling presented in this paper has been used to develop a user-friendly application for vaccine policy makers to further interrogate the model outcomes and consider the costs and benefits of introducing routine hepatitis A vaccination in South Africa.

## 5.2 Background

Over the last two decades, South Africa has been assumed to have high hepatitis A virus (HAV) endemicity with seroprevalence ≥ 90% by 10 years old. Data suggests, however, that South Africa has transitioned from high to intermediate or low hepatitis A virus (HAV) endemicity with less children acquiring hepatitis A infection and developing natural immunity at a young age. With this shift and a rise in age of people susceptible to HAV infection in the population, the risk for serious outbreaks and significant burden of disease increases.

The World Health Organization (WHO) recommends the consideration of introducing routine hepatitis A vaccination into national immunization schedules for children ≥ 1 years old in countries with intermediate HAV endemicity. Previously published studies have found routine hepatitis A vaccination strategies to be cost-effective in countries with existing childhood immunization programs, however an analytical framework to assess the impact and cost of different routine hepatitis A vaccination strategies in South Africa has not yet been developed (1-10). A new dynamic transmission model was deemed necessary to develop so that South Africa's hepatitis A force of infection could be robustly estimated and population-level clinical outcome and cost data collected in previous studies could be properly implemented.

While the Expanded Program on Immunization in South Africa (EPI-SA) has been a leader in adopting new vaccines on the African continent, there are considerable economic obstacles facing the introduction of new vaccines into the EPI-SA. Implementation of new vaccines requires large upfront investment, and the success of new vaccination programs is often uncertain in low- and middle-income countries (LMICs). In countries with health budgets that have little room for expansion, it is important for economic evaluations to deliver strong evidence for opportunities of cost-effectiveness. We evaluated the cost, outcomes, cost-effectiveness of different potential routine hepatitis A vaccination strategies in South Africa. This model was developed with the aim to support the South African National Advisory Group on Immunization (NAGI) Hepatitis A Working Group's consideration of introducing routine hepatitis A vaccination into the EPI-SA.

## 5.3 Methods

### 5.3.1 Transmission model

Ordinary differential equations were used to develop an age-structured model for hepatitis A transmission dynamics in South Africa. The model diagram is displayed in **Figure 5.1** and the differential equations are presented in **Supplementary Table S5.1**. In the model, the South African population is divided into 18 distinct hepatitis-A specific epidemiological compartments (**Table 5.1**), which are further stratified by 19 age groups (annual ages until 9 years old followed by 5-year age groups). The population is modelled over time through the birth rate, aging rate, and age-specific death rate.

Births are classified according to the presence of maternal antibodies (*propM*) into the ***M*** (maternal antibody) and ***S*** (susceptible) compartments. Hepatitis A infection occurs in the ***E*** compartment with the age-specific force of infection given by $lambda_i = \beta_{ij} * \frac{I}{P} * Prel * betaE_i * prevE * Erel$, where infection is determined by the number of contacts, the proportion of infected contacts, the transmission probability per contact, the environmental presence of HAV, and the nature of mixing between age groups. The contact pattern between age groups is determined by the conditional probability contact matrix $B_{ij}$ for South Africa adapted from *Prem et al. 2017* (**Supplementary Table S5.2)** (11).

The ***A*** (asymptomatic) and ***S*** (symptomatic) compartments represents active hepatitis A infections with anti-HAV IgM antibodies following an incubation period *nu*. ***O*** and $\boldsymbol{H_i}$ represent the treatment sought for uncomplicated hepatitis A cases, while the ***ALF*** compartment represents the treatment sought for viral-induced acute liver failure. Acute liver failure cases spontaneously recover from liver injury into compartment $\boldsymbol{ALF_R}$, indicate the need for liver transplant and move into compartment $\boldsymbol{ALF_T}$, or die due to liver injury without transplant in compartment $\boldsymbol{ALF_D}$. Liver transplant cases recover in compartment $\boldsymbol{T_R}$ at rate *gammaT* or die following the transplant procedure in compartment $\boldsymbol{T_D}$ at rate *TDrate*. Hospitalized and outpatient cases lose infectivity at the rate of *gamma* and move into the ***N*** compartment representing previous hepatitis A cases with anti-HAV IgG antibodies that may still have present anti-HAV IgM antibodies. ***R*** represents fully recovered hepatitis A cases with anti-HAV IgG antibodies and no anti-HAV IgM antibodies, while ***D*** represents all death due to hepatitis A infection.

*Figure 5.1: Flow diagram of hepatitis A transmission and vaccination model*

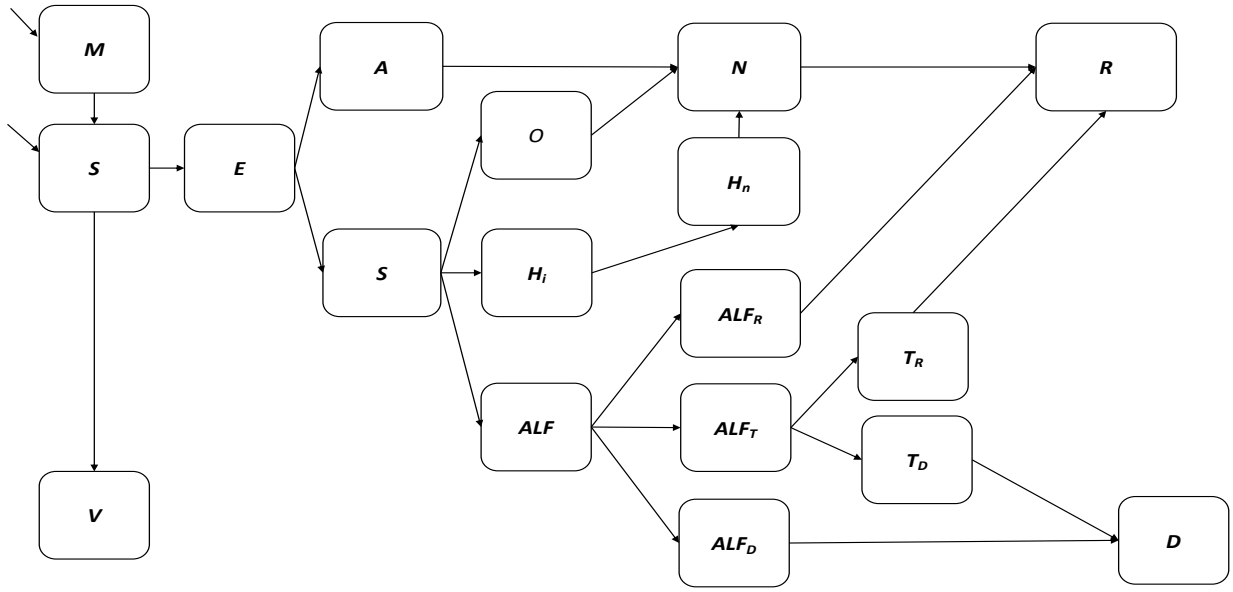



*Table 5.1: Model compartments and description*

| Abbreviation | Compartment | Description |
|---|---|---|
| M | Maternal antibodies | Presence of maternally acquired anti-HAV IgG antibodies |
| S | Susceptible | No presence of anti-HAV IgG antibodies |
| E | Exposed | Exposed to the hepatitis A virus with the risk of infection |
| A | Asymptomatic | Infected with the hepatitis A virus following the incubation period |
| S | Symptomatic | Infected with the hepatitis A virus following the incubation period |
| O | Outpatient case | Hepatitis A case requiring outpatient care at a tertiary level facility |
| $H_i$ | Hospitalized infectious case | Hepatitis A case requiring hospitalization at a tertiary level facility while shedding HAV |
| $H_n$ | Hospitalized non-infectious case | Hepatitis A case requiring hospitalization at a tertiary level facility after shedding HAV |
| N | Recovering case | Hepatitis A case with waning anti-HAV IgM antibodies |
| R | Recovered and immune | Previous hepatitis A case with anti-HAV IgG antibodies developed through infection |
| ALF | Viral-induced acute liver failure | Hepatitis A case resulting in acute liver failure defined as the development of encephalopathy and synthetic function impairment following acute liver injury in an individual without pre-existing liver disease |
| $ALF_R$ | Spontaneous recovery from acute liver failure | Viral-induced acute liver case that recovers without liver transplant |
| $ALF_D$ | Death due to acute liver failure | Viral-induced acute liver case that dies due to any cause |
| $ALF_T$ | Liver transplant case | Viral-induced acute liver transplant case that requires liver transplant for recovery |
| $T_R$ | Liver transplant recovery | Viral-induced acute liver transplant case that requires and receives liver transplant |
| $T_D$ | Liver transplant death | Liver transplant case that dies due to any cause |
| D | Hepatitis A death | Hepatitis A case that dies due to any cause |

| | | |
|---|---|---|
| V | Vaccinated | Vaccinated with one or two doses of hepatitis A vaccine with sufficient development of anti-HAV IgG antibodies for protection against infection |

### 5.3.2 Model calibration

The model is fitted to annual South African hepatitis A seroprevalence (anti-HAV IgG) data between 2005 to 2015 from the National Institute of Communicable Diseases (NICD) (12, 13). Ethical approval for the use of this data was obtained from the University of Cape Town Human Research Ethics Committee and the National Institute of Communicable Diseases (NICD). The observed rising trend in hepatitis A seroprevalence data suggests an increase in the incidence of hepatitis A infections (anti-HAV IgM) in South Africa across all age groups. The increase in hepatitis A seroprevalence, however, is not enough to reach the definition of high HAV endemicity as seroprevalence remains <90% for children and adolescents <15 years old between 2005-2015.

The model was run from 2000 with parameters in **Table 5.2** to reach a steady state before being fitted through maximum likelihood estimation to the seroprevalence data from 2005 to 2015. The incidence of HAV seroprevalence in 2015 was considered as baseline for future predictions and all parameters from 2015 were held constant for scenario testing. The NICD seroprevalence data and model seroprevalence outputs are compared by age group in **Figure 5.2**.

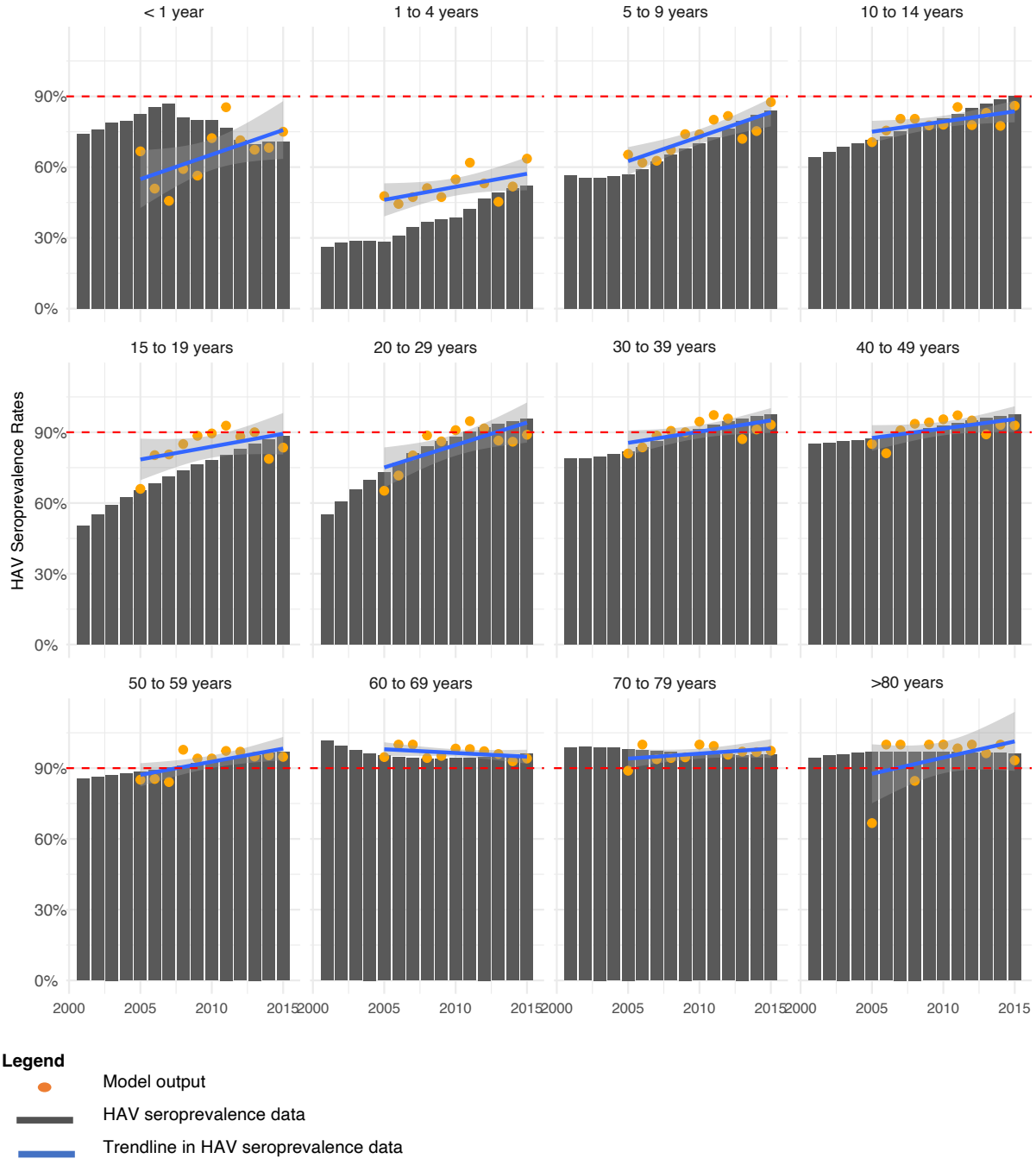
*Table 5.2: Parameter values and distributions*

| Parameter | Symbol | Baseline value or fitted range when stated [Uncertainty distribution/Range] | Source |
|---|---|---|---|
| Proportion of population born with maternal anti-HAV antibodies | $propM$ | $t \leq$2005: 0.72<br>$t:$2006: 0.76<br>$t:$2007: 0.79<br>$t:$2008: 0.81<br>$t:$2009: 0.77<br>$t:$2010: 0.77<br>$t:$2011: 0.76<br>$t:$2012: 0.71<br>$t:$2013: 0.66<br>$t:$2014: 0.63<br>$t \geq$2015: 0.64 | Calculated based on annual female population aged 15-49, fertility rates for ages 15-49, age specific annual HAV seroprevalence rates for ages 15-49, and annual birth rates |
| Rate of maternal anti-HAV antibody waning (years) | $tau$ | 1 | *Guzelkucuk et al. 2019* (14) |
| Incubation period (days) | $nu$ | 28 [15,50] | *Foster et al. 2021* (15) |
| Probability of asymptomatic hepatitis A infection in age group $i$ | $propA_i$ | $i \leq 6 = 0.7$<br>$i \geq 7 = 0.3$ | *Foster et al. 2021* (15) |

| | | | |
|---|---|---|---|
| Probability of outpatient care due to hepatitis A infection in age group $i$ | $propO_i$ | $1 \geq i \leq 12 = 0.68$<br>$13 \geq i \leq 14 = 0.7262$<br>$15 \geq i \leq 16 = 0.6662$<br>$17 \geq i \leq 19 = 0.7362$ | Calculated as $(1 - propH + propF)$ |
| Probability of hospitalization due to hepatitis A infection in age group $i$ | $propH_i$ | $1 \geq i \leq 12 = 0.21$<br>$13 \geq i \leq 14 = 0.17$<br>$15 \geq i \leq 16 = 0.23$<br>$17 \geq i \leq 19 = 0.16$ | *Canuel et al. 2007* (16) |
| Probability of viral-induced acute liver failure in age group $i$ | $propF_i$ | $1 \geq i \leq 12 = 0.11$<br>$i \geq 12 = 0.1038$ | *Keles et al. 2021* & *Jiang et al. 2018* (17, 18) |
| Probability of spontaneous recovery from acute liver failure in age group $i$ | $propFr_i$ | 0.25 | *Mendizabal et al. 2016* (19) |
| Probability of liver transplant due to hepatitis A infection in age group $i$ | $propT_i$ | 0.26 | *Mendizabal et al. 2016* (19) |
| Probability of death due to acute liver failure in age group $i$ | $propFD_i$ | 0.49 | *Mendizabal et al. 2016* (19) |
| Probability of death due to liver transplant in age group $i$ | $propTD$ | 0.16 | *Mendizabal et al. 2016* (19) |
| Recovery from hepatitis A infectious period (days) | $gamma$ | 21 [14, 180] | *Foster et al. 2021* (15) |
| Days for hepatitis A cases to seek care | $trt$ | 2 [1,3] | *Patterson et al. 2022* (20) |
| Days for hospitalized hepatitis A cases to develop acute liver failure | $Frate$ | 2 [1,3] | *Patterson et al. 2022* (20) |
| Days for acute liver failure cases to die | $FDrate$ | 16 [1, 20] | *Allen et al. 2016* (21) |
| Days for acute liver failure cases to spontaneously recover | $gammaF$ | 21 [14, 180] | *John Hopkins 2021* (22) |
| Days for acute liver failure cases to be diagnosed as liver transplant cases | $Trate$ | 3 [1, 10] | *Allen et al. 2016* (21) |
| Days for liver transplant cases to die (years) | $TDrate$ | 1 | Based on mortality probabilities reported annually |
| Days for liver transplant cases to recover | $gammaT$ | 21 [14, 180] | *John Hopkins 2021* (22) |
| Days for hepatitis A cases to lose IgM antibodies and develop IgG antibodies marking immunity (months) | $Rrate$ | 180 [90, 365.25] | *Prabdial-Sing et al. 2021* (13) |
| Person-to-person contact scaling factor | $Prel$ | 0.002 [0, 0.01] | Calibrated to fit national HAV seroprevalence data set |
| Person-to-environment contact scaling factor | $Erel$ | 0.0007 [0, 0.01] | Calibrated to fit national HAV seroprevalence data set |
| Prevalence of hepatitis A in environment | $PrevE$ | $t \leq 2005$: 0.3 [0, 1]<br>$2005 > t \leq 2010$: 0.5 [0, 1]<br>$t > 2010$: 0.8 [0, 1] | Calculated from supplementary data files associated with *Kuodi et al. 2020* (23) |
| Age-specific number of infective contacts per year | $betaE_i$ | $i: 1$ = 1,084.79 $i: 2$ = 1,139.04<br>$i: 3$ = 813.61. $i: 4$ = 678.02<br>$i: 5$ = 542.42 $i: 6$ = 813.66<br>$i: 7$ = 542.42 $i: 8$ = 271.29<br>$i: 9$ = 105.90 $i: 10$ = 2,169.59<br>$i: 11$ = 189.84 $i: 12$ = 162.72<br>$i: 13$ = 678.02. $i: 14$ = 542.42<br>$i: 15$ = 406.83 $i: 16$ = 271.24 | Baseline values from *Venter et al. 2007* calibrated to fit national HAV seroprevalence data set (24) |

| | | | |
|---|---|---|---|
| | | $i: 17$ = 135.64 $i: 18$ = 52.96<br>$i: 19$ = 52.96 | |

*Figure 5.2: Model fitting to HAV seroprevalence (anti-HAV IgG) data by age group*

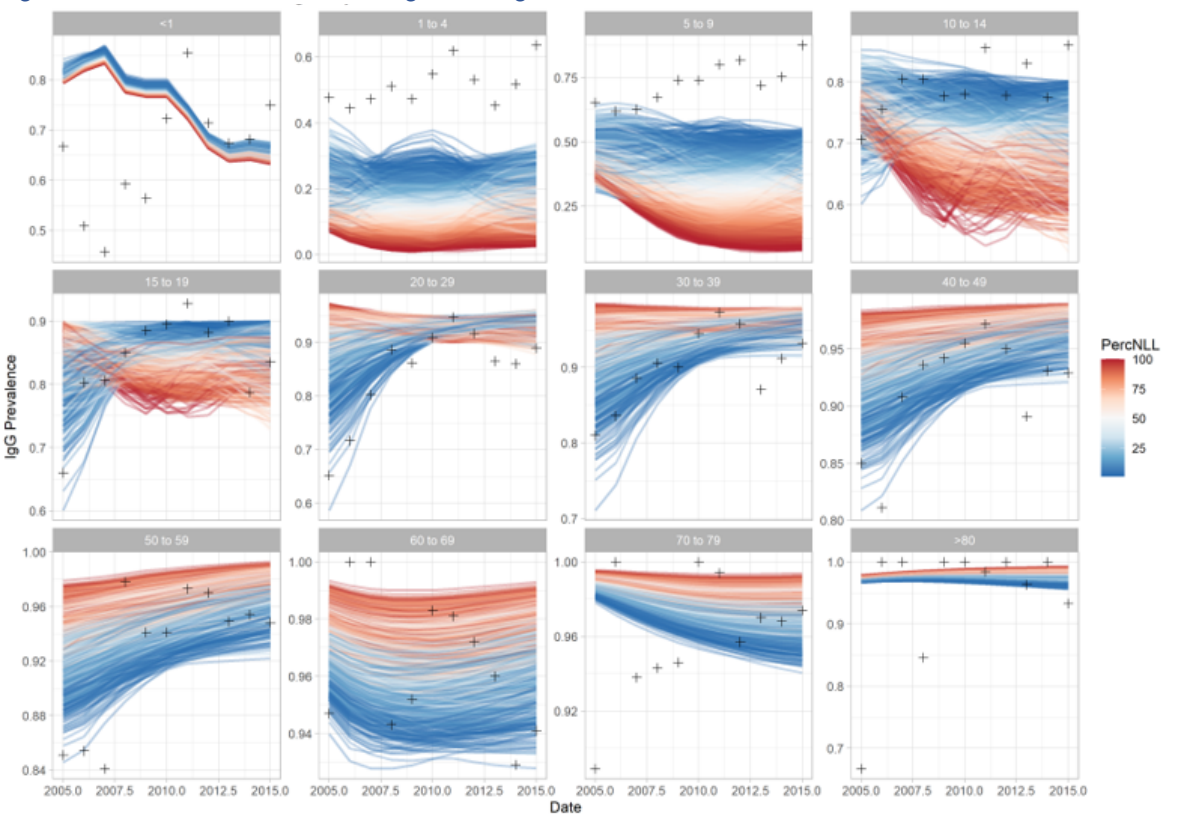


Owing to uncertainty in the dataset and a large number of unknown parameters, a simulation approach was selected for data fitting We simulated 100,000 Latin Hypercube Sampled parameter combinations to calibrate the model to key features in the dataset. As the South African testing volumes, IgM positivity rates, and age specific anti-HAV seroprevalence rates varied by year, the model was calibrated to three conditions (features) estimated from the NICD seroprevalence data. As the volume of anti-HAV total antibody tests and proportion of positive total antibody results was highest in 2011, this was chosen as the most reliable year of reporting (12). Only those parameter sets from model runs that reproduced the following criteria were deemed suitable for further analysis:

- seroprevalence below 90% for individuals <20 years old between 2005-2015; and
- seroprevalence to only reach ≥90% in individuals 20-29 years old in 2011 and 2012; and
- seroprevalence below 60% for individuals <5 years old after 2012.

We accepted 1,513 of the 100,000 parameter combinations used to simulate the model reproduced the epidemiological criteria above. The calibration negative log likelihood results are displayed in **Figure 5.3**.

*Figure 5.3: Model calibration negative log likelihood results*




Model output IgG prevalence over time for each age group in the model. Colours show the goodness of fit with red representing a better fit. Black crosses represent data.

### 5.3.3 Scenario analyses

We used the calibrated model with accepted parameter sets to evaluate various hepatitis A vaccination scenarios from 2023 to 2030. Nested vaccination scenarios were built in line with existing hepatitis A immunization strategies in LMICs and feedback South African National Advisory Group on Immunization's (NAGI's) Hepatitis A Working Group. We assessed how each scenario impacted the number of symptomatic hepatitis A cases, hepatitis A mortality, total costs, and total DALYs as compared to the baseline of no vaccination until 2030. The median values are reported for all model outcomes with associated interquartile ranges. In each scenario, the administration of vaccine doses 1 and 2 began in 2023 and catch-up doses began in 2027. The vaccination coverage rates were assumed to be equal to average performance estimates of the EPI-SA in 2019 in relevant age groups and were estimated to be 80%, 60%, and 40% for dose 1, dose 2, and catch-up doses, respectively (25). Vaccine efficacy estimates taken from published literature for dose 1 and subsequent doses were estimated to be 98% and 95%, respectively (26).

**Baseline Scenario:** No vaccination

**Scenario 1:** Dose 1 administered in children < 2 years old

**Scenario 2:** Dose 1 administered in children < 2 years old + Dose 2 administered in children < 3 years old

**Scenario 3:** Dose 1 administered in children < 2 years old + Dose 2 administered in children < 3 years old + Catch-up dose administered in children < 5 years old

**Scenario 4:** Dose 1 administered in children < 2 years old + Dose 2 administered in children < 3 years old + Catch-up dose administered in children < 10 years old

### 5.3.4 Estimation of hepatitis A treatment and routine immunization costs

We conducted the economic evaluation in accordance with CHEERS Guidelines (27). We adopted a provider's perspective that requires the inclusion of direct health care costs to estimate the cost-effectiveness of the scenarios. The direct costs included treatment costs of HAV and the costs of vaccination. Treatment costs included costs for outpatient care, hospitalization, and liver transplants. Cost inputs displayed in **Table 5.3** were taken from published literature. Where costs were reported in South African Rands (ZAR), they were adjusted to ZAR 2020 using the South African medical consumer price index (CPI) and converted to 2020 United States Dollars (USD) using an average exchange rate over 2020 (US$ 1= ZAR$ 16.61) (28, 29). Where costs were reported in USD, they were converted to ZAR

using the relevant exchange rate and adjusted to ZAR 2020 using the South African medical CPI, and then converted back to USD using the 2020 exchange rate.

The cost inputs displayed in **Table 5.3** for hepatitis A outpatient and inpatient treatment at tertiary healthcare facilities were taken from *Patterson et al. 2022* (20). The cost of liver transplant was broken down into treatment of transplant cases and cost of transplant procedures at tertiary healthcare facilities. The cost of treatment for liver transplant cases was calculated by multiplying the cost per inpatient day equivalent (PDE) ($539.86 for patients $<$ 15 years and $821.12 for patients $\geq$ 15 years old) by the average length of stay (LOS) (26 days) (20, 30). The cost of liver transplant was taken from the Department of Health Uniform Patient Fee Schedule (UFPS) 2020 to include the procedure and specialist practitioner fee for liver transplants at public tertiary facilities (31). We applied an access parameter of 30% to the cost of liver transplant as not all patients who indicate the need for liver transplant in South Africa will receive one due to social contraindications. To qualify for a transplant, social and socioeconomic criteria are used as exclusion criteria for patients as transplant requires adherence to lifelong treatment and the presence of social support structures for positive outcomes.

Vaccination cost inputs were comprised of the cost per vaccine dose and cost of vaccine administration (clinic visit). The mean cost per vaccine dose was calculated as the average of the single exit prices reported for *Havrix junior single dose vial 0.5ml* and *Avaxim prefilled syringe 80 0.5ml* (32). As the vaccination scenarios modelled did not include the administration combined with vaccines in the EPI, the cost per vaccine clinic visit was sourced from the District Health Barometer 2020 Public Health Clinic (PHC) expenditure and added to the cost per dose (33).

We calculated disability-adjusted life-years (DALYs) by adding the years lived with disability (YLD) and years of life lost (YLL) The YLD were calculated by applying the disease state incidence, disability weight, and time lived in each disease state. The YLL were calculated by applying the number of deaths due to hepatitis A by the remaining life expectancy at time of death. We assumed a disability weight of 0.051 (95% CI 0.032, 0.074) for all outpatient hepatitis A cases based on the Global Burden of Disease Study 2017 disability weigh estimate for moderate acute hepatitis A (34). We assumed a disability weight of 0.133 (95% CI 0.008, 0.190) for all hospitalized patients based on the Global Burden of Disease Study 2017 disability weigh estimate for severe acute hepatitis A (34). We assumed a disability weight of 0.54 from all patients with liver transplant based on the Global Burden of Disease Study 2017 disability

weight estimate for terminal phase of liver cancer due to hepatitis B infection (34). Future costs and outcomes (i.e. DALYs) modelled were discounted at 5% as recommended by the Health Technology Assessment (HTA) guidelines in South Africa (35).

The results of the economic evaluation for each scenario are reported as incremental cost-effectiveness ratios (ICERs) calculated by comparing each scenario to the baseline given that the vaccination scenarios were nested scenarios. The cost-effectiveness of scenarios was judged against the South African cost-effectiveness threshold (CET) of $3,276 per DALY averted (36). The South African CET reported was reported in 2015 and adjusted to ZAR 2020 using the South African medical CPI and then converted to USD using the 2020 exchange rate.

*Table 5.3: Cost inputs*

| Cost | Cost ($US 2020) | Source |
|---|---|---|
| Outpatient treatment of hepatitis A cases in patients < 15 years | $177.88 | *Patterson et al. 2022* (20) |
| Outpatient treatment of hepatitis A cases in patients ≥ 15 years old | $264.94 | *Patterson et al. 2022* (20) |
| Inpatient treatment of hepatitis A cases in patients < 15 years | $1,856.79 | *Patterson et al. 2022* (20) |
| Inpatient treatment of hepatitis A cases in patients ≥ 15 years old | $6,382.37 | *Patterson et al. 2022* (20) |
| Inpatient treatment of liver transplant patients < 15 years | $11,337.14 | *Calculated value based on PDE and LOS* |
| Inpatient treatment of liver transplant patients ≥ 15 years old | $21,329.20 | *Calculated value based on PDE and LOS* |
| Liver transplant procedure (all ages) | $1,787.74 | *UPFS 2020 (31)* |
| Dose of paediatric hepatitis A vaccine | $19.71 | *MedicinePrices.org (32)* |
| Clinic visit for vaccine administration | $136.15 | *Massyn et al. 2020 (33)* |

*Table 5.4: DALY inputs*

| Variable | Value | Source |
|---|---|---|
| DW outpatient hepatitis A cases | 0.051 | *GBD 2018 (34)* |
| DW hospitalized hepatitis A cases | 0.133 | *GBD 2018 (34)* |
| DW liver transplant | 0.54 | *GBD 2018 (34)* |
| YLD hepatitis A outcomes, excluding liver failure (days) | 21 | *Johns Hopkins 2021* (22) |
| YLD liver transplant (days) | 180 | *Johns Hopkins 2021* (22) |
| *Abbreviations: DW = disability weight; YLD = years lived with disability* | | |

### 5.3.5 Sensitivity analyses

We ran several one-way sensitivity analyses on key cost and DALY parameters for the most desirable vaccination scenario. We conducted sensitivity analyses on the baseline scenario to determine how the total costs of the scenario would vary for the below changes in cost assumptions and discount rates and display the results in a tornado diagram.

- Remove costs of clinic visit for vaccine administration ($136.15)
- Vary the access to liver transplant procedures to 0% and 100%

- Vary the discount rate between 0% and 10%

## 5.4 Results

### 5.4.1 Baseline scenario

Without implementation of any hepatitis A vaccination strategy from 2023, hepatitis A seroprevalence (anti-HAV IgG) in children < 10 years old is estimated to reach 95.87% [IQR: 93.42%-96.11%] by 2030. However, even with this increase in HAV seroprevalence among children < 10 years old, our model projects that the annual number of symptomatic hepatitis A cases is expected to decline by less than 2% from an expected 49,778 [IQR: 31,546, 87,872] symptomatic case in 2023 to 48,878 [31,057, 87,067] symptomatic cases in 2030. In addition, our model projects that annual hepatitis A mortality will decline by less than 4% from an expected 11,924 [IQR: 8,621-16,446] deaths due to hepatitis A in 2023 to 11,536 [IQR: 8,342, 16,076] deaths in 2030.

**Table 5.5** shows the impact of each vaccination scenario on symptomatic hepatitis A cases and mortality over the period of 2023-2030.

**Scenario 1:** Administration of one dose of the hepatitis A vaccine in children < 2 years old requires approximately 5.3 million vaccine doses over 2023-2030. The model projects Scenario 1 would avert a total of 136,042 symptomatic cases [IQR: 88,842-221,483] and 31,106 [IQR: 22,975- 36,742] deaths due to hepatitis A over the period of 2023 to 2030. Under Scenario 1, one symptomatic case would be averted for approximately every 39 vaccines administered. Similarly, one death due to hepatitis A would be averted for approximately every 171 vaccines administered.

**Scenario 2:** Administration of a first dose of the hepatitis A vaccine in children < 2 years old and a second dose in children < 3 years old requires approximately 7.8 million vaccine doses over 2023-2030. The model projects Scenario 2 would avert a total of 255,857 [IQR: 159,721-225,065] symptomatic cases and 31,585 [IQR: 23,388-37,240] deaths due to hepatitis A over the period of 2023 to 2030. Under Scenario 2, one symptomatic case would be averted for approximately every 56 vaccines administered. Similarly, one death due to hepatitis A would be averted for approximately every 247 vaccines administered.

**Scenario 3:** Administration of a first dose of the hepatitis A vaccine in children < 2 years old and a second dose in children < 3 years old with a catch-up dose administered to children < 5 years old that are not already vaccinated requires approximately 9.2 million vaccine doses over 2023-

2030. The model projects that Scenario 3 would avert a total of 259,318 [IQR: 162,828-477,574] symptomatic cases and 30,982 [IQR: 22,502-37,488] deaths due to hepatitis A over the period of 2023 to 2030. Under Scenario 3, one symptomatic case would be averted for approximately every 68 vaccines administered. Similarly, one death due to hepatitis A would be averted for approximately every 298 vaccines administered.

**Scenario 4:** Administration of a first dose of the hepatitis A vaccine in children < 2 years old and a second dose in children < 3 years old with a catch-up dose administered to children < 10 years old not already vaccinated requires approximately 11.7 million vaccine doses over 2023-2030. The model projects that Scenario 4 would avert a total of 267,947 [IQR: 169,625-482,796] symptomatic cases and 29,890 [IQR: 21,235-37,309] deaths due to hepatitis A over the period of 2023 to 2030. Under Scenario 4, one symptomatic case would be averted for approximately every 86 vaccines administered. Similarly, one death due to hepatitis A would be averted for approximately every 392 vaccines administered.

*Table 5.5: Impact of modelled vaccination scenarios on the burden of hepatitis A (2023-2030)*

| Scenario | Total Cost | Number of Vaccines Required | Symptomatic Cases Averted | Deaths Averted |
|---|---|---|---|---|
| 1 | $1,714,015,277 | 5.3 million | 136,042 | 31,106 |
| 2 | $2,009,207,209 | 7.8 million | 255,857 | 31,585 |
| 3 | $2,195,073,864 | 9.2 million | 259,318 | 30,982 |
| 4 | $2,851,373,642 | 11.7 million | 267,947 | 29,890 |

### 5.4.2 Cost-effectiveness of vaccination

For the modelled scenarios, the median estimated cost of the different vaccination strategies ranged from $1.71 billion to $2.85 billion over the period of 2023 to 2030, with the cost increasing for each successive scenario and approximately 39-52% of costs being due to vaccination. The ICERs for the vaccination scenarios in **Table 5.3** were calculated by comparing each scenario to the baseline. In **Supplementary Table S5.3**, we also present ICERS calculated by comparing each scenario to the previous undominated and less costly scenario. The cost-effectiveness of scenarios was judged against the South African CET of $3,276 per DALY averted (36).

The model suggests that implementation of all potential vaccination scenarios would deliver health gains in the population, with the lowest incremental cost per DALY averted against baseline for Scenario 1. The model projects that Scenario 1, representing administration of a single dose of hepatitis A vaccine

in children < 2 years old from 2023 to 2030, would avert 8,741 DALYs, however is not cost-effective against the CET with an ICER per DALY averted of $21,006. In **Supplementary Table S5.3**, the results of our model show that Scenarios 3 and 4 were absolutely dominated in that they produced less health gains and were more expensive than Scenarios 1 and 2. These results signal that the timing of vaccination is critical in the roll-out of potential hepatitis A prevention programs. While Scenario 3 and 4 include the administration of more vaccine doses and avert more symptomatic cases of hepatitis A, the total health gains are smaller than in Scenarios 1 and 2 owing to the population being infected before vaccination through the mass campaigns at older ages. With our results, the model suggests that natural exposure to HAV may begin as early as 3 years old in South Africa.

*Table 5.6: Cost-effectiveness of modelled scenarios referencing across a common baseline (2023-2030)*

| Scenario | Total Costs | Incremental Costs | Total DALYs | DALYs averted | Incr. Cost per DALY averted |
|---|---|---|---|---|---|
| Baseline | $1,530,392,760 | --- | 27,137 | --- | --- |
| 1 | $1,714,015,277 | $183,622,517 | 18,396 | 8,741 | $21,007 |
| 2 | $2,009,207,209 | $478,814,449 | 18,266 | 8,871 | $53,975 |
| 3 | $2,195,073,864 | $664,681,104 | 18,440 | 8,697 | $76,426 |
| 4 | $2,851,373,642 | $1,320,980,882 | 19,151 | 7,986 | $165,412 |

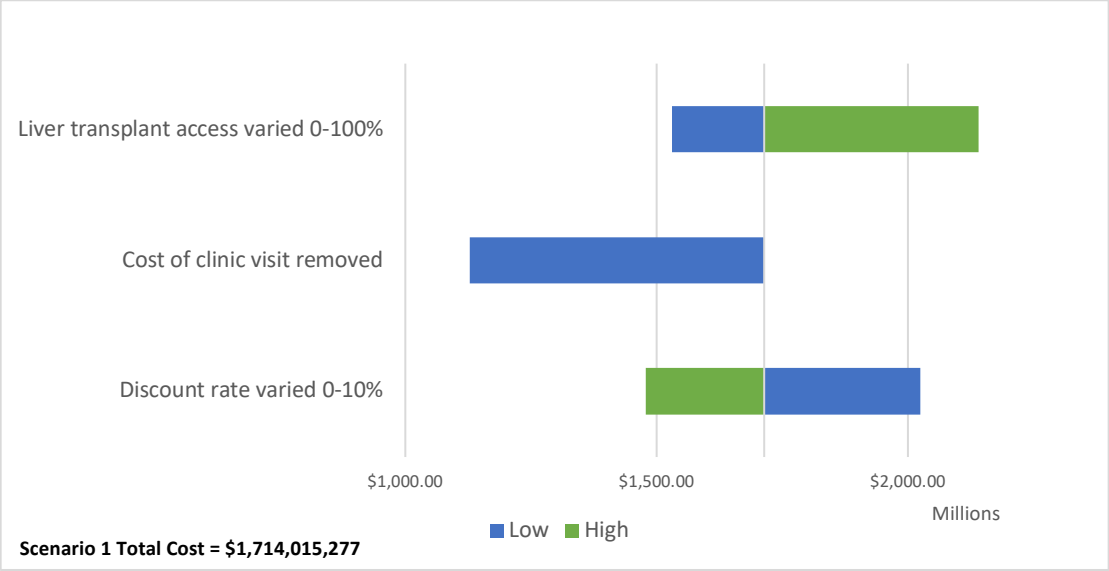
*The Incremental costs and DALYs averted presented in this table are calculated by referencing across the common baseline.*

*Abbreviations: Incr. = incremental; DALYs = Disability adjusted life years*

### 5.4.3 Sensitivity analysis

Our one-way sensitivity analysis on the total cost of Scenario 1 reported in **Figure 5.5** shows that varying access to liver transplant between 0% and 100% has the largest impact in results (total cost delta = $609,302,599). When increasing the access to liver transplant to 100% for baseline and Scenario 1, the ICER for Scenario 1 becomes cost-effective against the CET (ICER = $2,425) (**Supplementary Table S5.4).**

*Figure 5.5: One-way sensitivity analysis impact on Scenario 1 total costs*




## 5.5 Discussion

Our results indicate that administration of a single dose of the hepatitis A vaccine in children < 2 years old in South Africa between the period of 2023 to 2030 would produce significant health gains. The implementation of this vaccination strategy between 2023 and 2030 has the potential to avert a total of 136,042 symptomatic cases [IQR: 88,842-221,483] and 31,106 [IQR: 22,975- 36,742] deaths due to hepatitis A. The model projects that for every 39 hepatitis A vaccines administered, one symptomatic case of hepatitis A would be averted. Similarly, for every 171 hepatitis A vaccines administered, one death due to hepatitis A would be averted. Our results show that the implementation of a single dose of the hepatitis A vaccine in children < 2 years old in South Africa would avert 8,741 DALYs over the period of 2023-2030, however is not cost-effective against the South African CET of $3,276 per DALY averted with an ICER per DALY averted of $21,006.

The total cost of implementing a single dose of the hepatitis A vaccine for children < 2 years old over the eight-year intervention period is estimated to be $1.71 billion, with approximately 39% of the cost due to the 5.3 million vaccine doses required. When reviewing the total cost of modelled scenarios, it is notable that less than 50% of the total costs were due to vaccination. These results indicate that the burden of hepatitis A in the baseline scenario is heavy for the healthcare system and national health budget in South Africa.

Our study signals that the timing of hepatitis A vaccine administration is important as Scenarios 3 and 4 were absolutely dominated by Scenarios 1 and 2. While Scenario 3 and 4 include the administration of more vaccine doses and avert more symptomatic cases of hepatitis A, the total health gains are less than in Scenarios 1 and 2 owing to the population being infected before vaccination through the mass campaigns at older ages.

In regard to patient outcomes, we applied a liver transplant access parameter of 30% in our economic evaluation as not all patients who indicate the need for liver transplant in South Africa will receive one due to social contraindications. To qualify for a transplant, social and socioeconomic criteria are used as exclusion criteria for patients as transplant requires adherence to lifelong treatment and the presence of social support structures for positive outcomes. Our sensitivity analysis shows that the cost-effectiveness of vaccination was highly sensitivity to varying access to liver transplant. When increasing the access to liver transplant to 100% for baseline and Scenario 1, the ICER for Scenario 1 becomes cost-effective against the CET (ICER = $2,425). Given these findings, we recommend further research is conducted to understand the access to liver transplants in South Africa to better estimate the cost of liver transplant care for hepatitis A patients and cost-effectiveness of vaccination.

The main strength of this study is that, to the best of our knowledge, it is the first to utilize a dynamic modelling approach to understand the epidemiology of hepatitis A in South Africa and to conduct a cost-effectiveness analysis of routine hepatitis A vaccination in the country. Our study uses local cost data drawn from a retrospective folder review of hepatitis A cases requiring outpatient care or hospitalization in South Africa and this contextually relevant data leads to the derivation of more realistic cost projections in the country.

The modelling presented in this paper has been used to develop a user-friendly application for vaccine policy makers to further interrogate the model outcomes and consider the costs and benefits of introducing routine hepatitis A vaccination in South Africa. The application allows users to vary clinical parameters in the model such as the proportion of hepatitis A patients that require hospitalisation or develop viral-induced liver failure as well as associated costs. Once the user has varied these parameters, they have the opportunity to develop vaccination programs and compare outcomes to assess the potential cost-effectiveness. The application has been developed in R using the Rshiny package and can be accessed using this link (https://masha-app.shinyapps.io/HepA-VacExplorer/).

Several limitations must be considered in the interpretation of our results from the hepatitis A transmission model. It is important to take into account that incidence rates for hepatitis A are likely underreported due to the circumstances and mild nature with which the disease can present. In addition, the transmission model assumes that all symptomatic cases seek treatment for infection, which may not be the case. As these estimates were missing from the literature, we recommend more research be conducted on treatment seeking behaviours for patients with hepatitis A.

It should also be noted that the projected increase in hepatitis A seroprevalence among children < 10 years old in South Africa is unexpected and these results should be interpreted with caution. While the model was calibrated using the largest description of HAV seroprevalence within South Africa to date, the HAV seroprevalence data published by the NICD was unable to determine yearly seroprevalence trends due to the low volumes of anti-HAV total antibody testing and uneven distribution among age groups (12). The data that we used to calibrate the model was available only until 2015, which means caution should be applied when interpreting forecasted results until 2030. In addition, we were unable to determine a trend in the environmental presence of HAV which plays a large part in childhood hepatitis A transmission. To validate and update the model's seroprevalence projections, new data on anti-HAV IgG and IgM positivity and the environmental presence of HAV in South Africa should be included in the model as it comes available. Further analysis should include fitting the model to a decreasing trend in HAV seroprevalence between 2005 and 2015. Other limitations of this study include that the cost of hepatitis A inpatient treatment is likely overestimated as it is drawn from a tertiary hospital setting.

## 5.6 Conclusion

The results of this study indicate that implementation of a single dose of the hepatitis A vaccine in South African children < 2 years old between 2023 and 2030 generates health gains in comparison to the baseline approach, however, is not cost-effective against the CET with an ICER per DALY averted of $21,006. Given the sensitivity of the model to varying access to liver transplant, we recommend further research is conducted to understand the access parameters in order to better inform considerations of hepatitis A vaccination policies. In addition, further analysis using this model might include fitting the model to a decreasing trend in HAV seroprevalence between 2005 and 2015.

## 5.7 Funding

Funding for this research was provided by the Vaccines for Africa Initiative (VACFA) and the Department of Science and Innovation and the National Research Foundation (NRF). Any opinion, finding, and conclusion or recommendation expressed in this material is that of the authors and the NRF does not accept any liability in this regard.

## 5.8 Acknowledgements

Many thanks to Nishi Prabdial-Sing for providing raw IgM data from the publication "*Establishment of Outbreak Thresholds for Hepatitis A in South Africa Using Laboratory Surveillance, 2017–2020*".

## 5.9 Reference List


1. Suwantika AA, Yegenoglu S, Riewpaiboon A, Tu HA, Postma MJ. Economic evaluations of hepatitis A vaccination in middle-income countries. Expert Rev Vaccines. 2013;12(12):1479-94.
2. Sartori AM, de Soarez PC, Novaes HM. Cost-effectiveness of introducing the 10-valent pneumococcal conjugate vaccine into the universal immunisation of infants in Brazil. J Epidemiol Community Health. 2012;66(3):210-7.
3. Quezada A, Baron-Papillon F, Coudeville L, Maggi L. Universal vaccination of children against hepatitis A in Chile: a cost-effectiveness study. Pan American Journal of Public Health. 2008;23(5).
4. Lopez E, Debbag R, Coudeville L, Baron-Papillon F, Armoni J. The cost-effectiveness of universal vaccination of children against hepatitis A in Argentina: results of a dynamic health-economic analysis. J Gastroenterol. 2007;42(2):152-60.
5. Valenzuela MT, Jacobs RJ, Arteaga O, Navarrete MS, Meyerhoff AS, Innis BL. Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. Vaccine. 2005;23(32):4110-9.
6. Van Effelterre T, De Antonio-Suarez R, Cassidy A, Romano-Mazzotti L, Marano C. Model-based projections of the population-level impact of hepatitis A vaccination in Mexico. Hum Vaccin Immunother. 2012;8(8):1099-108.
7. Van Effelterre T, Marano C, Jacobsen KH. Modeling the hepatitis A epidemiological transition in Thailand. Vaccine. 2016;34:555-62.
8. Van Effelterre T, Guignard A, Marano C, Rojas R, Jacobsen KH. Modeling the hepatitis A epidemiological transition in Brazil and Mexico. Human Vaccines & Immunotherapeutics. 2017;13(8):1942.
9. Suwantika AA, Beutels P, Postma MJ. Cost-effectiveness of hepatitis A vaccination in Indonesia. Hum Vaccin Immunother. 2014;10(8):2342-9.
10. Ellis A, Rüttimann RW, Jacobs J, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. Pan Am J Public Health. 2007;21(6).
11. Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLoS Comput Biol. 2017;13(9):e1005697.
12. Mazanderani AH, Motaze VN, McCarthy K, Suchard M, du Plessis NM. Hepatitis A Virus Seroprevalence in South Africa-Estimates using Routine Laboratory Data, 2005-2015. PloS one. 2018;26(12).
13. Prabdial-Sing N, Motaze V, Manamela J, McCarthy K, Suchard M. Establishment of Outbreak Thresholds for Hepatitis A in South Africa Using Laboratory Surveillance, 2017-2020. Viruses. 2021;13(12).
14. Guzelkucuk Z, Duyan Camurdan A, Beyazova U, Bozdayl G, Civil F, Altay Kocak A. Waning Time of Maternally Derived Anti-Hepatitis A and Anti-Varicella Zoster Virus Antibodies. Journal of Pediatric Infectious Diseases. 2019;14(3):116-20.
15. MA F, P H, NP N. Hepatitis A. Centers for Disease Control and Prevention; 2021.
16. Canuel M, De Serres G, Duval B, Gilca R, De Wals P, Gilca V. Trends of hepatitis A hospitalization and risk factors in Quebec, Canada, between 1990 and 2003 DBP - 20070418. BMC infectious diseases. 2007;7:31.
17. Keles E, Hassan-Kadle MA, Osman MM, Eker HH, Abusoglu Z, Baydili KN, et al. Clinical characteristics of acute liver failure associated with hepatitis A infection in children in Mogadishu, Somalia: a hospital-based retrospective study. BMC infectious diseases. 2021;21(1):890.
18. Jiang QQ, Han MF, Ma K, Chen G, Wan XY, Kilonzo SB, et al. Acute kidney injury in acute-on-chronic liver failure is different from in decompensated cirrhosis. World Journal of Gastroenterology. 2018;24(21):2300-10.
19. Mendizabal M, Silva MO. Liver transplantation in acute liver failure: A challenging scenario. World J Gastroenterol. 2016;22(4):1523-31.
20. Patterson J, Cleary S, Silal SP, Hussey GD, Enoch A, Korsman S, et al. A retrospective study assessing the clinical outcomes and costs of acute hepatitis A in Cape Town, South Africa. BMC infectious diseases. 2022;22(1):45.
21. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. Hepatology. 2016;64(6):2165-72.
22. Medicine JH. Hepatitis A. John Hopkins Medical University; 2022.
23. Kuodi P, Patterson J, Silal S, Hussey GD, Kagina BM. Characterisation of the environmental presence of hepatitis A virus in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open. 2020;10(9):e036407.
24. Venter JM, van Heerden J, Vivier JC, Grabow WO, Taylor MB. Hepatitis A virus in surface water in South Africa: what are the risks? Journal of water and health. 2007;5(2):229-40.
25. World Health Organization, United Nations Children's Fund. South Africa: WHO and UNICEF estimates of immunization coverage. 2019.
26. Irving G, Holden J, Yang R, Pope D. Hepatitis A immunisation in persons not previously exposed to hepatitis A (Review). Cochrane Database of Systematic Reviews. 2012(7).
27. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force. . Value Health. 2013;16(2):231-50.

28. South African Rand per US Dollar Monthly Average 2020 2021 [Available from: https://www.x-rates.com/average/?from=USD&to=ZAR&amount=1&year=2020.
29. STATS SA. Consumer Price Index. Departnemtn of Statistics South Africa; 2020.
30. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time spent in hospital after liver transplantation: Effects of primary liver disease and comorbidity. World J Transplant. 2016;6(4):743-50.
31. Uniform Patient Fee Schedule. Department of Health Republic of South Africa; 2020.
32. MedicinePrices.org. Hepatitis A: OpenUp; 2021 [Available from: https://medicineprices.org.za/#search:hepatitis%20A.
33. Massyn N, Day C, Ndlovu N, Padayachee T. District Health Barometer 2019/2020. Health Systems Trust; 2020.
34. Network GBoDC. Global Burden of DIsease Study 2017 Disability Weights. Seattle, USA: Institute for Health Metrics and Evaluation; 2018.
35. Wilkinson T, Wilkinson M, MacWuilkan K. Health Techonolgy Assessment Methods Guide. South Africa: Essential Drugs Program, National Department of Health; 2021.
36. Edoka I, Stacey N. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. Health Policy and Planning. 2020;35:546-55.

# 6 Chapter 6: Recommendations for Hepatitis A Vaccine for Preexposure Prophylaxis in South Africa

## 6.1 Overview

This document has been prepared for the South African National Advisory Group on Immunization's (NAGI's) in considerations of introducing routine hepatitis A immunization into the South African Program on Immunization (SA-EPI). In order to support a systematic and transparent process for decision making and to ensure that all important criteria are considered, this recommendation follows the Gradings of Recommendations Assessment, Development, and Evaluation (GRADE) Evidence to Recommendations (EtR) Framework. Judgements made in the GRADE Framework presented in the text below and summarized in **Table 6.1** represent the opinions of the research team and are subject to changes as further data becomes available.

## 6.2 GRADE Framework

### 6.2.1 Is the problem a priority?

The World Health Organization (WHO) recommends that countries should routinely collect, analyse, and review local factors to guide the development of hepatitis A vaccination programs. To collect contextually relevant evidence on the burden of hepatitis A, we conducted a systematic review of hepatitis A epidemiological data in Africa. The results of this review indicate that Africa, as a whole, should not be considered as a high HAV endemic region. In addition, our results indicate that South Africa is likely experiencing a transition from high to intermediate HAV endemicity, with the IgM anti-HAV seroprevalence data showing a similar risk of acute hepatitis A infection among all age-groups. The results of this review indicate that priority should be given to re-assessing the current hepatitis A control strategies to reduce the burden of hepatitis A.

Given the similar profile of acute hepatitis A infection among all age groups, we found it was important to understand the epidemiology of viral-induced ALF to plan for clinical case management and case prevention in South Africa. We conducted a systematic review to synthesize data on the relative contribution of different viruses to the etiology of viral-induced ALF and compile evidence which was missing from the field. Our results indicate that the prevalence of HAV-induced ALF was markedly lower

in countries with routine HAV immunization versus no routine HAV immunization. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries.

In order to describe the severity, clinical outcomes, and cost of acute hepatitis A cases presenting in South Africa, we conducted a retrospective folder review of patients presenting with hepatitis A at two tertiary level hospitals providing care for urban communities of metropolitan Cape Town, South Africa. Before presenting for tertiary level care, more than half of patients presented for an initial consultation at either a community clinic or general practitioner. The mean length of hospital stay was 7.45 days for adult patients and 3.11 days for paediatric patients and the total cost per hepatitis A hospitalization was $1,935.41 for adult patients and $563.06 for paediatric patients.

More than 1 in every 10 hepatitis A cases included our retrospective folder review developed complicated hepatitis A or resulted in death. Given the severity of clinical outcomes and high costs associated with hepatitis A hospitalization, it is important to consider the introduction of hepatitis A immunization in the public sector in South Africa to potentially avert future morbidity, mortality, and excess healthcare spending.

### 6.2.2 How substantial are the desirable anticipated effects?

To estimate the potential impacts of hepatitis A vaccination in South Africa, we developed an age-structured model for hepatitis A transmission dynamics. Using this model, we assessed the impact of four potential scenarios on the number of symptomatic hepatitis A cases, hepatitis A mortality, total costs, and total DALYs as compared to the baseline of no vaccination until 2030. The model results project that implementation of a single-dose hepatitis A vaccination program for children < 2 years old between 2023-2030 would avert a total of 36,042 symptomatic cases [IQR: 88,842-221,483] and 31,106 [IQR: 22,975- 36,742] deaths due to hepatitis A over the period. Under the scenario of a single dose of hepatitis A vaccine given to children < 2 years old, the model projects the following outcomes: for every 39 hepatitis A vaccines administered, one symptomatic case of hepatitis A would be averted; for every 171 hepatitis A vaccines administered, one death due to hepatitis A would be averted.

### 6.2.3 How substantial are the undesirable anticipated effects?

Our work did not directly assess any undesirable effects of introducing a hepatitis A vaccination program in South Africa. Potential undesirable effects of the introduction of any new vaccine program could include low uptake or increased vaccine hesitancy. The implementation of routine childhood hepatitis A immunization in other LMICs has not shown to have any particular risk associated as the proposed policy does not place significant risk on any particular group in the population.

### 6.2.4 What resources are required?

Administration of single dose of the hepatitis A vaccine in South African children < 2 years old between 2023-2030 is projected to require approximately 5.3 million vaccine doses. The total discounted cost of vaccine acquisition and administration is estimated to be $670,103,181 using current market prices.

### 6.2.5 Are the net benefits worth the incremental cost?

Our model projects that the implementation of a single dose routine childhood hepatitis A vaccination program administration would produce significant health gains in South Africa. The suggested vaccination program is projected to require an additional $183,622,517 than is expected to be spent on hepatitis A care under the status quo in South Africa. This additional investment in hepatitis A vaccination is projected to avert $8,741, leading to the incremental cost per DALY averted of $21,007. The implementation of the suggested vaccination strategy is judged as not cost-effective against the South African CET with an ICER of $3,276 per DALY averted.

### 6.2.6 What would the impact be on health equity?

The implementation of a hepatitis A vaccination program into the EPI-SA would increase health equity among children in South Africa as the vaccine is routinely offered to children seeking healthcare in the private sector in the country.

## 6.3 Recommendation

Prior to the results of our study, the cost-effectiveness of a one-dose hepatitis A vaccination strategy has been demonstrated in several LMICs transitioning from high to intermediate HAV endemicity. While the overall cost of the proposed vaccination strategy would require additional investment, our results indicate that implementation of a one-dose hepatitis A vaccination strategy has the potential to offer

significant healthcare gains and to reduce healthcare spending on the management and treatment of hepatitis A. While the implementation of a single dose of hepatitis A vaccines in children < 2 in South Africa was found to be not cost-effective against the South African CET, we suggest that further evidence is collected to establish the HAV seroprevalence trends and environmental presence of HAV in South Africa.

*Table 6.1: GRADE Evidence to Recommendation Framework*

| GRADE Framework Question | Research Evidence | Judgement | Quality of Evidence | Strength of Evidence |
|---|---|---|---|---|
| Is the problem a priority? | • South Africa is experiencing a transition from high to intermediate HAV endemicity, with the IgM anti-HAV seroprevalence data showing a similar risk of acute hepatitis A infection among all age-groups (Chp 2).<br>• The prevalence of HAV-induced ALF was found to be markedly lower in countries with routine HAV immunization vs no routine HAV immunization. In addition, viral-induced ALF had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries (Chp 3).<br>• Given the severity of clinical outcomes and high costs associated with hepatitis A hospitalization, it is important to consider the introduction of hepatitis A immunization in the public sector in South Africa to potentially avert future morbidity, mortality, and healthcare spending (Chp 4). | Yes | High | Strong |
| How substantial are the desirable anticipated effects? | • Implementation of a single-dose hepatitis A vaccination program for children < 2 years old between 2023-2030 would avert a total of 136,042 symptomatic cases and 31,106 deaths due to hepatitis A over the period (Chp 5).<br>• In addition, this vaccination strategy has the potential to avert a total of 8,741 DALYS between 2023-2030 (Chp 5).. | Moderate | Moderate | Moderate |
| How substantial are the undesirable anticipated effects? | • Potential undesirable effects of the introduction of any new vaccine program could include low uptake or increased vaccine hesitancy | Probably favors the intervention | Low | Low |
| What resources are required? | • Administration of single dose of the hepatitis A vaccine in South African children < 2 years old between 2023-2030 is projected to require approximately 5.3 million vaccine doses (Chp 5).<br>• The total discounted cost of vaccine acquisition and administration is estimated to be $670,103,181 (Chp 5). | Moderate costs | Moderate | Moderate |
| Are the net benefits worth the incremental cost? | • The suggested vaccination program is projected to require an additional $183,622,517 than is expected to be spent on hepatitis A care under the status quo in South Africa (Chp 5).<br>• This additional investment in hepatitis A vaccination is projected to avert $8,741, leading to the | Probably favors the comparison | Moderate | Moderate |

| | | | | |
|---|---|---|---|---|
| | incremental cost per DALY averted of $21,007 (Chp 5).<br>• The implementation of the suggested vaccination strategy is judged as not cost-effective against the South African CET with an ICER of $3,276 per DALY averted (Chp 5). | | | |
| What would the impact be on health equity? | • The implementation of a hepatitis A vaccination program into the EPI-SA would increase health equity among children in South Africa as the vaccine is routinely offered to children seeking healthcare in the private sector in South Africa. | Increased | High | Strong |

# 7 Chapter 7: Highlights and Conclusions

The thesis aimed to generate evidence for decision making on whether a routine vaccination program against HAV should be considered for introduction into the EPI-SA using principals of evidence-based vaccinology and EtR frameworks. This included descriptions of the epidemiologic features of hepatitis A, clinical characteristics of the disease, hepatitis A vaccine characteristics and cost of case management in South Africa. Using this evidence, the PhD estimated the future epidemiology of hepatitis A and cost-effectiveness of routine childhood hepatitis A vaccination in the country.

The systematic reviews included in the thesis clarify the epidemiology of hepatitis A in the region and warns of adverse outcomes without the implementation of routine HAV vaccination. The results of the systematic review of the epidemiology of hepatitis A in Africa indicate that South Africa is transitioning from high to intermediate HAV endemicity, with a similar risk of acute hepatitis A infection in all age groups. These results contradict previous thinking that the risk of acute hepatitis A infection in South Africa was highest among adults and show that priority should be given to re-assessing the current hepatitis A control strategies. In addition, the results of the systematic review of the global epidemiology of viral-induced acute liver failure indicate that viral-induced acute liver failure was highest in countries with no routine HAV vaccination programs. Worryingly, the absence of HAV vaccination programs increases the need for liver transplantation – a service for which access is low in South Africa.

The primary data collection included in the thesis highlights the burden of hepatitis A on the healthcare system in South Africa. Before presenting for tertiary level care, more than half of patients included in the retrospective folder review presented for an initial consultation at either a community clinic or general physician. The mean length of hospital stays for admitted patients was > 3 days, which brought total costs for case management to range between $500 to $1,5000. Additionally, the folder review found that more than 1 in every 10 hepatitis A cases developed complicated hepatitis A or resulted in death. These results reiterate the possibility of severe outcomes as a result of HAV infection and, again, highlight the risks of no vaccination coupled with low access to liver transplantation services in the country.

The systematic reviews and primary study were used to parameterize a dynamic transmission model developed for hepatitis A in South Africa. The model was fit to South Africa HAV seroprevalence data and assessed the impact of several childhood hepatitis A vaccination strategies. While the preferred scenario of implementing a single dose hepatitis A vaccination strategy was found to not be cost-effective against the current South African CET, the results of the modelling study highlight important considerations.

The first important consideration highlighted by the modelling study is that the timing of vaccine administration is critical in the success of hepatitis A vaccination strategies. The model findings suggest that exposure to the HAV is happening as early as 3 years old in South Africa. Given the equal risk in acute HAV infection across all age groups, the DALYs due to HAV infection have the potential to rise as HAV seroprevalence is projected to increase without the implementation of any vaccination strategy. Secondly, the modelling study points to the sensitivity of vaccine cost-effectiveness in regard to liver transplant care. If all patients who developed HAV-induced ALF received the liver transplant care necessary for recovery, then the cost-effectiveness of a single dose of hepatitis A vaccination strategy would be a clear win. This highlights the need for more research to be done on access to transplant care in South Africa, a topic which is attracting more attention both in the health and governance space.

The results of the thesis indicate a further need to deliberate the introduction of routine hepatitis A immunization in South Africa and to continue to collect data to understand the true HAV seroprevalence in the country. The evidence collected in this thesis, the dynamic transmission model developed, and accompanying user-friendly Rshiny application will be taken forward to NAGI by the Hepatitis A Working Group, for which I have been a part of during my PhD studies.

# 8 Appendices

## 8.1 Ethics approval documents

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room E53-46 Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6338
**Email:** lamees.emiedl@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

06 July 2018

**Ms J Patterson**
Public Health & Family Medicine
Epidemiology & Biostatistics
Falmouth Building
Medical School

Dear Ms Patterson

Thank you for your email to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC confirm that Ethics is not needed for the following chapters of your research:

Chapter 1: The Epidemiology of Hepatitis A in Africa
-Systematic Review and meta-analysis will use existing published and unpublished data
Chapter 2: Hepatitis A Immunisation in Persons Not Previously Exposed to Hepatitis A
-Systematic Review and meta-analysis will use existing published data
Chapter 4: Epidemiological-Economic Model for Hepatitis A in South Africa
-Modelling study will use data generated in Chapters 1-3 as well as exiting, publicly available data from sources such as literature and databases

However, Ethics is needed for Chapter 3: Clinical Outcomes and Healthcare Costs of Hepatitis A Cases in Cape Town, South Africa: A Retrospective Folder Review Protocol -Retrospective folder review will require data collection from 500 folders (250 children, 250 adults) having presented to care at two tertiary hospitals in Cape Town.

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE**

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room E53-46 Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6626
**Email:** shuretta.thomas@uct.ac.za
**Website:** www.health.uct.ac.za/fhs/research/humanethics/forms

14 September 2018

**HREC REF: 485/2018**

**Dr Rudzani Muloiwa**
Vaccines for Africa Initiative (VACFA)
IIDMM
Werner Belt Building North N2.09A

Dear Dr Muloiwa

**PROJECT TITLE: CLINICAL OUTCOMES AND HEALTHCARE COSTS OF HEPATITIS A CASES IN CAPE TOWN, SOUTH AFRICA (PHD CANDIDATE - MS A PATTERSON)**

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee dated 13 September 2018.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**Approval is granted for one year until the 30 September 2019.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

**Please quote the HREC REF in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

***The HREC acknowledge that the student Jenna Patterson will also be involved in this study.***

***Yours sincerely***

**PROFESSOR M BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Western Cape Government
Health

**GROOTE SCHUUR HOSPITAL**
**Enquiries**: Dr Bernadette Eick
**E-mail** : Bernadette.Eick@westerncape.gov.za

Dr R. Muloiwa
**GENERAL PAEDIATRICS & HIV CLINICAL SERVICES**

E-mail: Rudzani.muloiwa@uct.ac.za / PTTJEN005@myuct.ac.za / Wendy.Spearman@uct.ac.za

Dear Dr Muloiwa

**RESEARCH PROJECT: Clinical Outcomes and Healthcare Costs of Hepatitis-A Cases in Cape Town, South Africa (PhD. Ms. A. Patterson**

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 September 2019.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
**g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
**l) Kindly submit a copy of the publication or report to this office on completion of the research.**

I would like to wish you every success with the project.

Yours sincerely

**DR BERNADETTE EICK**
**CHIEF OPERATIONAL OFFICER**
**Date:** 14 January 2019

C.C. Mr. L. Naidoo
Dr H. Aziz

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.capegateway.go.v.za

Western Cape Government
Health

**DR AN PARBHOO**
**Manager: Medical Services**
**Red Cross War Memorial Children's Hospital**
Email: Anita.Parbhoo@westerncape.gov.za
Tel: +27 21 658 5430 Fax: +27 21 658 5006/5166

**17 October 2018**

Ms J Patterson
Vaccines for Africa Initiative

Dear Ms Patterson,

**RESEARCH: RXH: RCC 153**

**PROJECT TITLE: Clinical Outcomes and Healthcare Costs of Hepatitis A Cases in Cape Town, South Africa: A Retrospective Folder Review Protocol**

It is a pleasure to inform you that approval is hereby granted to conduct above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

**DR AN PARBHOO**
**MANAGER: MEDICAL SERVICES**

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

**Faculty of Science**
University of Cape Town
Rondebosch
South Africa 7701

**E-mail: shari.daya@uct.ac.za**
**Tel: 021 650-2880**

14 November 2019

Jenna Patterson
School of Public Health and Family Medicine

**Epidemiologic-economic model of hepatitis A in South Africa**

Dear Jenna Patterson

I am pleased to inform you that the Faculty of Science Research Ethics Committee has approved the above-named application for research ethics clearance, subject to the conditions listed below.

- Implement the measures described in your application to ensure that the process of your research is ethically sound; and
- Uphold ethical principles throughout all stages of the research, responding appropriately to unanticipated issues: please contact me if you need advice on ethical issues that arise.

Your approval code is: **FSREC 106 - 2019**

I wish you success in your research.

Yours sincerely

**Dr Shari Daya**
Chair: Faculty of Science Research Ethics Committee

**Cc:** **Dr Sheetal Silal (Supervisor)**

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

**22 March 2019**

**Applicant:** Ms Jenna Patterson
**Institution:** University of Cape Town
**Department:** Public Health and Family Medicine
**Email:** PTTJEN005@myuct.ac.za
**Cell:** 076 204 9483

**Re: Approval to access National Health Laboratory Service (NHLS) Data**

Your application to undertake a research project "**Epidemiological-Economic Model for Hepatitis A in South Africa**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***without patient names*** to conduct the proposed study as outlined in the submitted application.

Please note that final approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

PP. Bhabwandlela

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

## 8.2 Supplementary tables

*Supplementary Table S2.1 - GRADE Table*

| **Outcome: Epidemiological transition from high to intermediate or low HAV endemicity in South Africa** | | | |
|---|---|---|---|
| | **Rating** | **Footnotes** | **Quality of evidence** |
| **Study design** | High | Systematic review | Moderate |
| **Risk of bias** | Low | Minimal risk of bias among included studies | |
| **Inconsistency** | Low | Minimal inconsistency for South African data | |
| **Indirectness** | Very low | Not detected | |
| **Imprecision** | Very low | Not detected | |
| **Publication bias** | Very low | Not detected | |

*Supplementary Table S3.1: Risk of bias judgements for included studies*

| Study ID | Representation of the national population | Representation of target population | Random selection or census | Minimal likelihood of non-response bias | Data collected directly from participants | Acceptable case definition | Valid measurement | Same mode of data collection | Appropriate length | Appropriate numerator(s) and denominator(s) | Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alam et al., 2009 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Asim et al., 2009 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Bechmann et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Bhati et al., 2013 | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Borkakoti et al., 2013 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Bravo et al., 2012 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Cervio et al., 2011 | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Das et al., 2016 | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Gupta et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Ho et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Latif et al., 2010 | No | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Mamun et al., 2009 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Manka et al., 2015 | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | 8 |
| Mendizabal et al., 2014 | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Mishra et al., 2016 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |
| Mumtaz et al., 2009 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Pandit et al., 2015 | No | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Poovoraw an et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |
| Schwarz et al., 2014 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | 9 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Shalimar et al., 2017 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Silverio et al., 2015 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Somasekar et al., 2017 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |
| Uddin Jamro et al., 2013 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 10 |
| Tsunoda et al., 2017 | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 9 |
| Zhao et al., 2014 | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 8 |

*Supplementary Table S4.1: Mean and median lengths of hospitalization by patient outcome*

| **Adult patients** | | |
|---|---|---|
| **Patient Outcome** | **Mean length of stay in days (95% CI)** | **Median length of stay in days (IQR)** |
| Uncomplicated (n=180) | 5.0 (3.9, 6.1) | 0.8 (0.3, 2.1) |
| Complicated (n=29) | 14.2 (0.7, 27.8) | 4.1 (2.0, 10.7) |
| Deceased (n=3) | 1.8 (1.8, 1.8) | 1.8 (1.8, 1.8) |
| **Paediatric patients** | | |
| **Patient Outcome** | **Mean length of stay in days (95% CI)** | **Median length of stay in days (IQR)** |
| Uncomplicated (n=211) | 1.3 (1.1, 1.6) | 0.3 (0.2, 0.9) |
| Complicated (n=27) | 8.1 (3.5, 12.8) | 5.4 (1.5, 7.3) |
| Deceased (n=1) | 5.3 (5.3, 5.3) | 5.5 (5.5, 5.5) |

*Supplementary Table S4.2: Unit counts and cost (2018 USD) for patient-specific hepatitis A items*

| **Blood tests** | | | | | |
|---|---|---|---|---|---|
| **Test** | **Unit counts for adult hepatitis A patient population** | **Unit counts for paediatric hepatitis A patient population** | **Unit cost in USD** | **Total cost USD for adult hepatitis A patient population** | **Total cost USD for paediatric hepatitis A patient population** |
| HAV IgG | 9 | 3 | 8.96 | 80.65 | 26.88 |
| HAV IgM | 219 | 224 | 8.96 | 1962.54 | 2007.34 |
| HBsAg | 128 | 105 | 8.96 | 1147.05 | 940.94 |
| HBC | 63 | 62 | 8.96 | 564.57 | 555.60 |
| HCV | 94 | 82 | 8.96 | 842.37 | 734.83 |
| ALT | 358 | 288 | 3.23 | 1157.74 | 931.36 |
| AST | 306 | 234 | 3.23 | 989.57 | 756.73 |
| ALP | 309 | 214 | 3.08 | 951.93 | 659.27 |
| Albumin | 201 | 145 | 2.86 | 575.61 | 415.24 |
| Total bilirubin | 325 | 243 | 2.51 | 816.14 | 610.22 |
| Conjugated bilirubin | 275 | 208 | 1.91 | 525.95 | 397.81 |
| GGT | 299 | 206 | 3.23 | 966.94 | 666.18 |
| Fibrinogen | 23 | 41 | 2.43 | 56.00 | 99.82 |
| INR | 273 | 247 | 3.37 | 919.50 | 831.93 |
| HB | 230 | 199 | 1.28 | 295.18 | 255.39 |
| FBC Differential Count | 229 | 192 | 2.26 | 518.55 | 434.77 |
| Full Blood Count Inch Platelet | 222 | 190 | 4.13 | 916.75 | 784.60 |
| Neutrophils | 37 | 43 | 2.26 | 83.78 | 97.37 |
| Na | 197 | 166 | 2.16 | 425.65 | 358.67 |
| K+ | 207 | 167 | 2.16 | 447.26 | 360.83 |
| Urea | 191 | 161 | 2.16 | 412.69 | 347.87 |
| Creatine | 224 | 184 | 2.16 | 483.99 | 397.56 |
| HIV | 57 | 67 | 3.93 | 223.90 | 263.19 |
| **Radiology** | | | | | |
| **Test** | **Unit counts for adult hepatitis A patient population** | **Unit counts for paediatric hepatitis A patient population** | **Unit cost in USD** | **Total cost USD for adult hepatitis A patient population** | **Total cost USD for paediatric hepatitis A patient population** |
| AXR | 5 | 2 | 4.47 | 22.37 | 8.95 |
| Abdominal ultrasound | 50 | 36 | 12.68 | 633.90 | 456.41 |
| Liver ultrasound | 1 | 1 | 7.86 | 7.86 | 7.86 |

| | | | | | |
|---|---|---|---|---|---|
| Gastroscopy | 1 | 1 | 74.92 | 74.92 | 74.92 |
| Brain CT | 4 | 0 | 60.75 | 242.98 | 0.00 |
| **Medicines and products** | | | | | |
| **Medicines and products** | **Number of prescriptions in adult hepatitis A patient population** | **Number of prescriptions in paediatric hepatitis A patient population** | **Mean unit cost USD per prescription** | **Total cost USD for prescriptions in adult hepatitis A population** | **Total cost USD for prescriptions in paediatric hepatitis A population** |
| Antibiotics | 27 | 31 | 5.33 | 1524.56 | 3019.70 |
| Antifungals | 11 | 5 | 0.79 | 112.13 | 74.75 |
| Antiemetics | 41 | 2 | 0.97 | 38.56 | 575.28 |
| Lactulose | 14 | 3 | 1.31 | 251.08 | 77.51 |
| Steroid | 2 | 2 | 4.71 | 75.84 | 202.22 |
| Vitamin K | 33 | 24 | 2.97 | 1770.66 | 729.50 |
| Other medicines | 128 | 53 | 0.98 | 1841.09 | 785.13 |
| Fresh frozen plasma | 1 | 0 | 157.79 | 2327.44 | NA |
| Platelets | 2 | 0 | 618.97 | 18247.26 | NA |
| Prescriptions at discharge | 145 | 84 | 13.52 | 2149.74 | 946.64 |

*Supplementary Table S5.1: Ordinary differential equations*

$$\frac{dM}{dt} = propM * mu * N - tau * M - d_1 * M - (1 - d_1) * age_1 * M$$

$$\frac{dS_i}{dt} = (1 - propM) * mu * N + tau * M - propV * S_i * Vrate * (1 - propVF) - lambda_i * S_i - d_i * S_i - (1 - d_i) * age_i * S_i$$

$$\frac{dV_i}{dt} = propV * S_i * Vrate * (1 - propVF) - d_i * V_i - (1 - d_i) * age_i * V_i$$

$$\frac{dE_i}{dt} = lambda_i * S_i - nu * propA_i * E_i - nu * (1 - propA_i) * E_i - d_i * E_i - (1 - d_i) * age_i * E_i$$

$$\frac{dA_i}{dt} = nu * propA_i * E_i - gamma * A_i - d_1 * A_i - (1 - d_i) * age_i * A_i$$

$$\frac{dSy_i}{dt} = nu * (1 - propA_i) * E_i - trt * propO_i * Sy_1 * trt * propH_i * Sy_1 - propF_i * trt * Sy_1 - d_i * Sy_i - (1 - d_i) * age_i * A_i$$

$$\frac{dO_i}{dt} = trt * propO_i * Sy_i - gamma * O_i - d_i * O_i - (1 - d_i) * age_i * O_i$$

$$\frac{dHi_i}{dt} = trt * propH_i * Sy_i - gamma * Hi_i - d_i * Hi_i - (1 - d_i) * age_i * Hi_i$$

$$\frac{dHn_i}{dt} = gamma * Hi_i - gamma * Hn_i - d_i * Hn_i - (1 - d_i) * age_i * Hn_i$$

$$\frac{dALF_i}{dt} = propF_i * trt * Sy_i - (1 - propT_i) * propFD_i * Frate * Fu_i - propFR_i * Frate * Fu_i - propT_i * Frate * Fu_i - d_i * Fu_i - (1 - d_i) * age_i * Fu_i$$

$$\frac{dALFd_i}{dt} = propFD_i * Frate * ALF_i - FDrate * ALFd_i - d_i * ALFd_i - (1 - d_i) * age_i * ALFd_i$$

$$\frac{dALFr_i}{dt} = propFr_i * Frate * Fu_i - gammaF * ALFr_i - d_i * ALFr_i - (1 - d_i) * age_i * ALFr_i$$

$$\frac{dALFt_i}{dt} = propT_i * Frate * Fu_i - propTD_1 * Trate * ALFt_i - (1 - propTD_i) * rate * T_i - d_i * T_i - (1 - d_i) * age_i * ALFt_i$$

$$\frac{dTd_i}{dt} = propTD_i * Trate * T_i - TDrate * Td_i - d_i * Td_i - (1 - d_i) * age_i * Td_i$$

$$\frac{dTr_i}{dt} = (1 - propTD_i) * Trate * T_i - gammaT * Tr_i - d_i * Tr_i - (1 - d_i) * age_i * Tr_i$$

$$\frac{dD_i}{dt} = TDrate * Td_i + FDrate * ALFd_i$$

$$\frac{dN_i}{dt} = gamma * A_i + gamma * O_i + gamma * Hn_i - Rrate * N_i - d_i * N_i - (1 - d_i) * age_i * N_i$$

$$\frac{dR_i}{dt} = Rrate * N_i + gammaF * Fr_i + gammaT * Tr_i - d_i * R_i - (1 - d_i) * age_i * R_i$$

## *Supplementary Table S5.2: Daily contact matrix*

| Age | | Age | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 to 14 | 15t o 19 | 20 to 29 | 30 to 39 | 40 to 49 | 50 to 59 | 60 to 69 | 70 to 79 | 80+ |
| | 0 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 | 0.17 | 0.11 | 0.46 | 0.52 | 0.20 | 0.13 | 0.06 | 0.02 | 0.00 |
| | 1 | 0.13 | 0.13 | 0.12 | 0.12 | 0.12 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 | 0.17 | 0.11 | 0.46 | 0.52 | 0.19 | 0.13 | 0.06 | 0.02 | 0.00 |
| | 2 | 0.13 | 0.12 | 0.12 | 0.12 | 0.12 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 | 0.17 | 0.11 | 0.45 | 0.51 | 0.19 | 0.13 | 0.06 | 0.02 | 0.00 |
| | 3 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.17 | 0.11 | 0.45 | 0.51 | 0.19 | 0.13 | 0.06 | 0.02 | 0.00 |
| | 4 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.12 | 0.11 | 0.17 | 0.11 | 0.44 | 0.50 | 0.19 | 0.13 | 0.06 | 0.02 | 0.00 |
| | 5 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.05 | 0.41 | 0.12 | 0.27 | 0.47 | 0.26 | 0.09 | 0.05 | 0.01 | 0.00 |
| | 6 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.41 | 0.12 | 0.28 | 0.48 | 0.26 | 0.09 | 0.05 | 0.01 | 0.00 |
| | 7 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.05 | 0.41 | 0.12 | 0.27 | 0.47 | 0.26 | 0.09 | 0.05 | 0.01 | 0.00 |
| | 8 | 0.06 | 0.06 | 0.06 | 0.05 | 0.05 | 0.06 | 0.06 | 0.06 | 0.05 | 0.05 | 0.40 | 0.11 | 0.27 | 0.46 | 0.25 | 0.09 | 0.05 | 0.01 | 0.00 |
| | 9 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.06 | 0.05 | 0.05 | 0.05 | 0.38 | 0.11 | 0.26 | 0.44 | 0.24 | 0.09 | 0.05 | 0.01 | 0.00 |
| | 10 to 14 | 0.12 | 0.12 | 0.12 | 0.11 | 0.11 | 0.12 | 0.12 | 0.12 | 0.11 | 0.11 | 12.55 | 1.31 | 1.22 | 1.60 | 1.46 | 0.42 | 0.17 | 0.07 | 0.02 |
| | 15 to 19 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 0.07 | 3.74 | 9.68 | 3.30 | 1.56 | 1.75 | 0.58 | 0.16 | 0.04 | 0.01 |
| | 20 to 29 | 0.13 | 0.13 | 0.13 | 0.13 | 0.12 | 0.13 | 0.13 | 0.13 | 0.12 | 0.12 | 0.95 | 5.04 | 16.20 | 6.20 | 3.84 | 2.04 | 0.53 | 0.08 | 0.02 |
| | 30 to 39 | 0.24 | 0.24 | 0.23 | 0.23 | 0.23 | 0.24 | 0.24 | 0.24 | 0.23 | 0.22 | 2.37 | 1.38 | 6.41 | 8.32 | 4.64 | 1.84 | 0.68 | 0.10 | 0.02 |
| | 40 to 49 | 0.23 | 0.22 | 0.22 | 0.22 | 0.21 | 0.22 | 0.23 | 0.22 | 0.22 | 0.21 | 2.25 | 2.50 | 3.75 | 4.94 | 5.00 | 1.79 | 0.53 | 0.10 | 0.02 |
| | 50 to 59 | 0.20 | 0.20 | 0.20 | 0.19 | 0.19 | 0.20 | 0.20 | 0.20 | 0.19 | 0.19 | 1.93 | 1.89 | 3.57 | 3.18 | 3.11 | 2.19 | 0.67 | 0.11 | 0.03 |
| | 60 to 69 | 0.14 | 0.14 | 0.14 | 0.14 | 0.13 | 0.14 | 0.14 | 0.14 | 0.14 | 0.13 | 1.11 | 0.84 | 1.92 | 2.61 | 1.84 | 1.33 | 0.96 | 0.18 | 0.02 |
| | 70 to 79 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.08 | 0.09 | 0.08 | 0.08 | 0.08 | 1.20 | 0.95 | 0.65 | 0.98 | 1.13 | 0.77 | 0.56 | 0.34 | 0.09 |
| | 80+ | 0.10 | 0.09 | 0.09 | 0.09 | 0.09 | 0.10 | 0.10 | 0.09 | 0.09 | 0.09 | 0.60 | 0.48 | 0.26 | 0.41 | 0.51 | 0.38 | 0.19 | 0.12 | 0.04 |

*Supplementary Table S5.3 Cost-effectiveness of modelled scenarios referencing previous undominated approach (2023-2030)*

| Scenario | Total Costs | Incremental Costs | Total DALYs | DALYs averted | Incr. Cost per DALY averted |
|---|---|---|---|---|---|
| Baseline | $1,530,392,760 | | 27,137 | | |
| 1 | $1,714,015,277 | $183,622,517 | 18,396 | 8,741 | $21,007 |
| 2 | $2,009,207,209 | $295,191,932 | 18,266 | 130 | $2,270,707 |
| 3 | $2,195,073,864 | $185,866,655 | 18,440 | -174 | ($1,068,199) |
| 4 | $2,851,373,642 | $656,299,778 | 19,151 | -711 | ($923,066) |

*The Incremental costs and DALYs averted presented in this table are calculated by referencing the previous undominated and less costly scenario.*

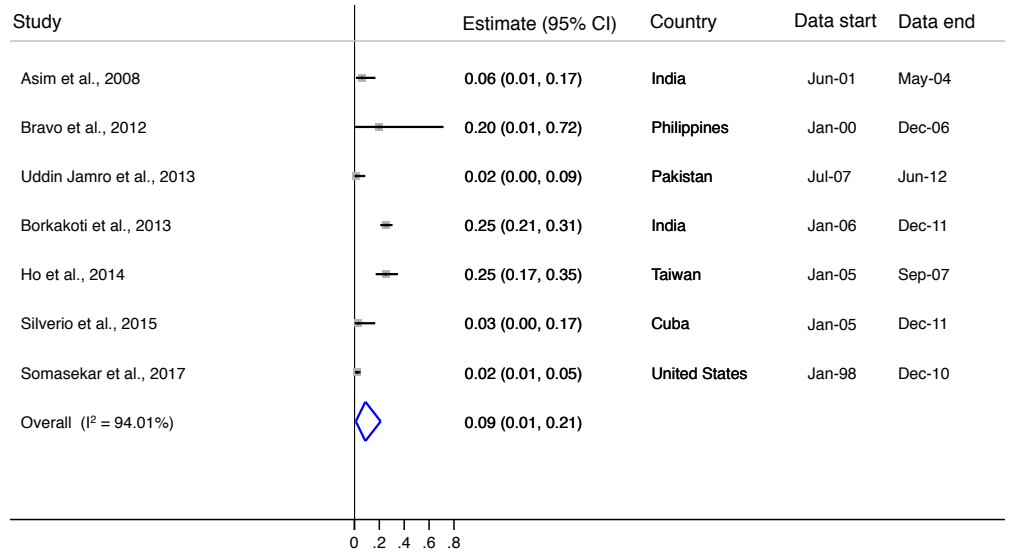
*Abbreviations: Incr. = incremental; DALYs = Disability adjusted life years*

*Supplementary Table S5.4: One-way sensitivity analysis for Scenario 1 ICER Results*

| One-way sensitivity analysis | Scenario 1 Total Cost | DALYS averted against baseline | Incr. cost per DALY averted against baseline |
|---|---|---|---|
| Cost of clinic visit removed | $1,128,653,105 | 18,396 | $45,958 |
| Access to liver transplant at 0% | $1,531,224,497 | 18,396 | -$31,048 |
| Access to liver transplant at 100% | $2,140,527,097 | 18,396 | $2,426 |
| Discount rate at 0% | $2,025,301,242 | 20,984 | -$19,972 |
| Discount rate at 10% | $1,477,986,262 | 16,406 | -$22,079 |

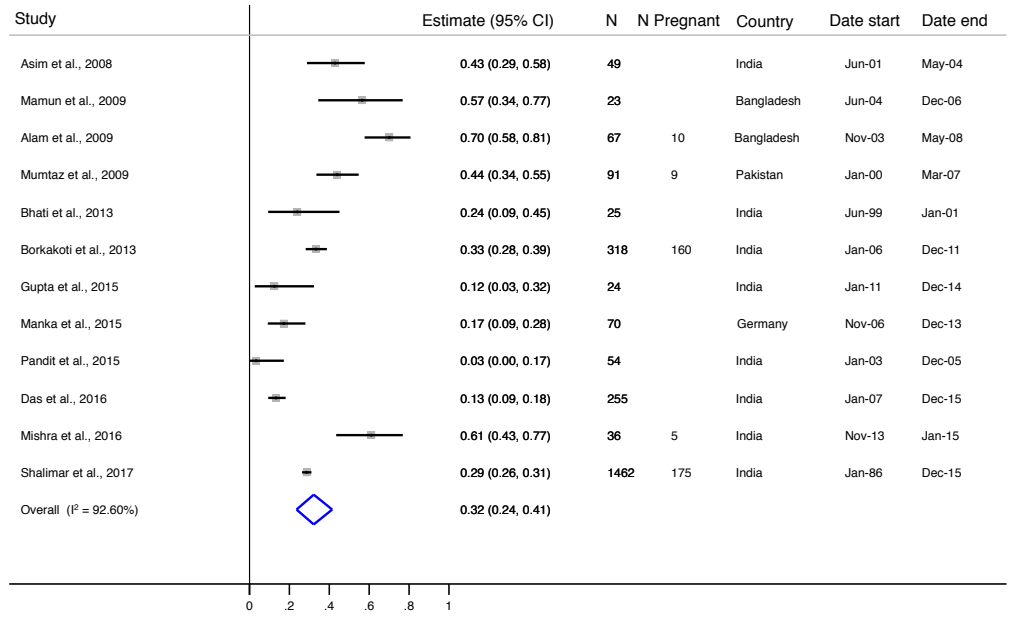
## 8.3 Supplementary figures

### *Supplementary Figure S3.1: Prevalence of hepatitis C virus induced acute liver failure*



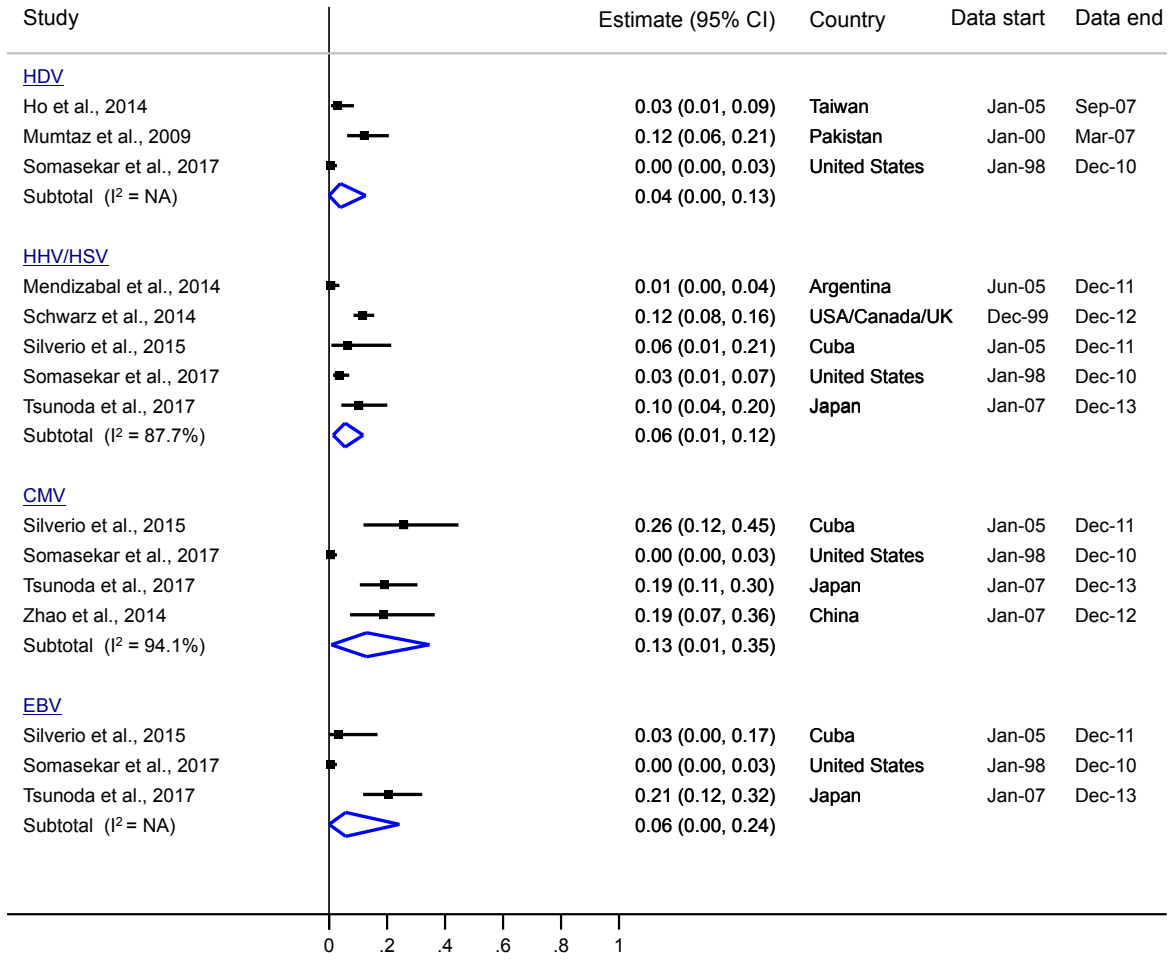

Abbreviations: HCV = hepatitis C virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

### *Supplementary Figure S3.2: Prevalence of hepatitis E virus induced acute liver failure*




Abbreviations: HEV = hepatitis E virus, ALF = acute liver failure, CI = confidence interval, $I^2$ = heterogeneity statistic

*Supplementary Figure S3.3: Prevalence of hepatitis D virus, herpes simplex virus, cytomegalovirus, and Epstein Barr virus induced acute liver failure*




Abbreviations: HDV = hepatitis D virus, HHV/HSV = Human Herpes virus/Herpes Simplex Virus, CMV = Cytomegalovirus, EBV = Epstein-Barr virus,