HEPATITIS B VIRUS VACCINE COVERAGE AND PREVALENCE OF SEROCONVERSION IN HEALTH SCIENCE STUDENTS AT THE UNIVERSITY OF THE WITWATERSRAND, 2021

By: Nisha Makan

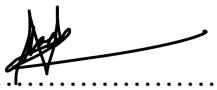
(307254)

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Science in Medicine in the field of Vaccinology

Johannesburg, 2022

DECLARATION

I, Nisha Makan, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Science in Medicine in the field of Vaccinology
(in the "submissible" format, together with my protocol) at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

Signature: 

20 day of June 2022

DEDICATION

This work is the culmination of the life-long effort, support and love I have received from my family (Bipin '*dad'*, Panna '*mom'* and Suraj '*kuks'*). To my loving and ever-so-patient husband, *Shane*, this project is dedicated to you – for being my rock, my cheerleader, and my midnight coffee-runner – I could not have done this without you. To my mentors and teachers without whom I would not have had the courage to begin or complete this work, for believing in me and inspiring me every step of the way, I am forever grateful.

PRESENTATIONS

Poster Presentations

1. Hepatitis B Virus Vaccine Coverage and Prevalence of Seroconversion in Health Science Students at Wits, 2021
   Wits School of Clinical Medicine, Biennial Research Day
   30 September 2021, (Virtual)
   First Prize Winner, Category: MSc/Medical Scientist/Researcher

2. Hepatitis B Virus Vaccine Coverage and Prevalence of Seroconversion in Health Science Students at Wits, 2021
   Conference on Liver Disease in Africa (COLDA)
   9 – 11 September 2021, (Virtual)

Oral (GradFlash) Presentation

1. Hepatitis B Virus Vaccine Coverage and Prevalence of Seroconversion in Health Science Students at Wits, 2021
   The Molecular Biosciences Research Thrust
   9 December 2021, (Virtual)
   https://www.youtube.com/watch?v=3ps11ydJ_Ys&list=PLyzwExOZMayrt6ICF0kPGkn4XjT8uLv0C&index=5

ACKNOWLEDGEMENTS

I would like to thank my supervisors Prof Anna Kramvis and Prof Ernest Song for their invaluable support and guidance throughout this journey, and for encouraging my curiosity and inspiring me to pursue my passions.

I would also like to acknowledge the work of Dr Constance Wose Kinge for her contribution to the seroprevalence study design. To Dr Alice Chien Chen for the many hours spent helping me recruit participants and for always offering her sage advice and words of wisdom that kept me going throughout the writeup process. A huge thank you to my colleagues within the HVDRU team for mentoring me throughout my research process.

My sincerest thanks also go to Dr Clare Cutland for offering me this wonderful (and rather 'serendipitous') opportunity to study a Masters in Vaccinology during trying times. To my UUME 'family', colleagues, friends, and mentors and in particular Dr Mantoa Mokhachane, for supporting and encouraging me to 'find my spark', and creating an environment for creativity, growth and self-reflection, I am truly grateful.

I would like to thank all the researchers who came before me and whose work I was able to build upon. Dr C. Le Roux and Prof A. Dramowski who's work on HBV vaccination practices at Stellenbosch was used to help build the questionnaire portion of this study.

I am indebted to Mr. Brian Jele and Sr. Maggie Moloi and the amazing staff at the Wits Campus Health and Wellness Center as well as Mr. Sipho Kunene and the National Health Laboratory Services without whom this study would not have been possible.

And finally, I would like to thank the students who graciously took the time to participate in this study, providing invaluable insights into our research questions, benefiting all those who come after.

Table of Contents

OVERVIEW

The structure of the following Master's research report has been adapted from the Postgraduate Information booklet and the Style Guide for Research Reports of the Faculty of Health Sciences at the University of the Witwatersrand. Additional guidance and instruction, due to the nature of the report, has been provided by the Faculty Research Office within the PV Tobias Building.

This research by 'publishable & submissible format' has two parts, and thus divided according to the separate articles for publication:

Article 1: 'Knowledge, attitudes and practices regarding hepatitis B vaccination policies among undergraduate medical and health-sciences students in a South African university.'

Published in South African Medical Journal June 2022

Article 2: 'Hepatitis B virus immunity prior to and after administration of a 'booster' dose of vaccine among health-care students at a South African University.'

Submissible format for publication in Vaccine Journal

Each article has been formatted according to the guidelines stipulated in the chosen Department of Higher Education and Training (DoHET) accredited journals. Journals were selected based on the scope and policies of the journals, our study findings, and relevance to these journals.

Each article is a stand-alone article (as submitted for publication), and includes an abstract, abbreviations, references, and sources pertinent to the respective study. The terms 'health-sciences students' and 'health-care students' are used interchangeably and were selected based on the likely audience for each respective journal. Local authors use the term 'health-sciences', while international counterparts prefer 'health-care'.

ARTICLE 1:

Knowledge, attitudes and practices of South African university undergraduate health-sciences students on hepatitis B vaccination highlight the need for improvement of policies, implementation and coordination.

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Published: South African Medical Journal (June 2022)

Key words:

Hepatitis B virus, Vaccine coverage, Health-sciences students; Vaccine practices

Abstract word count: 399 words (250-400)

Article word count: 3979 words (4000)

Abstract

Background: Hepatitis B virus (HBV) infection causes nearly 300 million chronic infections globally. Healthcare workers face up to four times the risk of HBV infection through occupational exposure to contaminated blood and bodily fluids. Health-sciences students (HSSs) are regarded at an even greater risk as they embark on their clinical training journey. While chronic hepatitis B is incurable, it can be prevented by the safe and effective hepatitis B vaccine (HepB). The South African National Department of Health recommends at least three doses of vaccine (HepB3) for HSSs before patient contact. However, data on policy implementation at training institutions, vaccine coverage and HBV immunity in HSSs are lacking/ limited.

Objectives: This study investigated knowledge, attitudes and practices of HSSs at the University of the Witwatersrand (Wits) in relation to international guidelines and institutional HepB programme included in the Wits vaccination policy. Sociodemographic factors predicting HepB uptake were also investigated.

Methods: A cross-sectional study was conducted between February and June 2021. An electronic, self-administered survey was emailed to all current HSSs (*N*=3785). The survey included questions on sociodemographic characteristics; knowledge of and attitudes towards HepB-related international guidelines and Wits policies; and HepB uptake and vaccine practices at Wits. Descriptive statistical analyses, followed by multivariable regression modelling, were used to identify factors associated with HepB uptake.

Results: A response rate of only 7.1% yielded 269 returned surveys, of which 221 were adequate for analysis. Most respondents were female (69.2%), with a mean (SD) age of 22.5 (3.5) years, and were studying a Bachelor of Medicine and Surgery (MBBCh) degree (76.9%). Only 78% of those students who reported a history of vaccination (89.1% of study sample) reported a completed vaccine series. The only significant predictor, when adjusted for interactions, was being enrolled in MBBCh compared to other courses (OR 4.69; *p*=0.026). Students displayed higher levels of knowledge around institutional (Wits) vaccine recommendations (94.1%) compared to international recommendations (75.6%). Most students were in favour of mandatory vaccination (91.4%) but not of serological testing following vaccination (42.5%). Half of our students received vaccinations in private facilities, but no

follow up or record was made of this by the designated Wits Campus Health and Wellness Centre (CHWC).

Conclusion: Institutional HepB policies are suboptimal with no centralised coordination or implementation strategy. Urgent efforts are required to create awareness around policy and management, ensure vaccination coverage in this high-risk group, and foster positive practices with adequate monitoring.

Abbreviations

AOR - adjusted odds ratio
BBF - blood and bodily fluids
CHWC - Campus Health and Wellness Centre
DoH - Department of Health
EPI - Expanded Programme on Immunization
FHS - Faculty of Health Science
HBV - hepatitis B virus
HCV - hepatis C virus
HCW - health-care worker
HepB – hepatitis B vaccine
HepB-BD - hepatitis B vaccine birth dose
HepB3 – minimum three dose series of hepatitis B vaccine
HF - health facility
HIV - human immunodeficiency virus
HPCSA - Health Professions Council of South Africa
HSS - health-sciences student
IQR - inter-quartile range
KAP - knowledge, attitude and practices
MBBCh - Bachelor of Medicine and Surgery
OR - odds ratio
SD - standard deviation
WHO - World Health Organization
Wits - University of the Witwatersrand

Introduction

Hepatitis B is a potentially life-threatening liver disease that is caused by the hepatitis B virus (HBV). It remains a major public health challenge, with approximately 296 million people chronically infected globally and around one million persons dying annually from consequent complications, such as liver cirrhosis and hepatocellular carcinoma.[1,2] HBV is estimated to be up to 100 times more infectious than human immunodeficiency virus (HIV),[3] and can survive outside of the body for up to 7 days, during which the virus is still capable of causing infection.[4,5] Transmission of HBV occurs through exposure to infected blood and other bodily fluids. The timing of exposure and transmission routes typically account for the geographic variation in severity and prevalence of HBV infection. Chronic HBV infection disproportionately affects low and middle income countries, including many in sub-Saharan Africa, where exposure typically occurs at an earlier age (infancy and early childhood) leading to hyperendemic levels.[6] With no 'curative' therapies currently available, the prevention and control of HBV infection depends on the effective implementation of policies ensuring the provision of the safe and highly effective hepatitis B vaccine (HepB) to at-risk populations.[7]

In 1991, the World Health Organization (WHO) recommended the inclusion of a three-dose hepatitis B vaccine schedule (HepB3) into routine infant immunization programs to reduce horizontal transmission in infants and young children.[8] In total, 190 WHO member states have introduced HepB3 with a current global coverage estimated at 83%.[9] Following this success, the WHO endorsed the addition of a first dose within 24 hours of birth (HepB-BD) to prevent mother-to-child transmission.[10] Although coverage remains short of the WHO target of >90% for HepB3 and HepB-BD, together these strategies have resulted in a global reduction in the proportion of children under 5 years becoming chronically infected from 4.7% to 1.3%,[1] and a prevention of more than 14 million potential cases.[11]

Another key strategy to achieving the goal of eliminating HBV as a global public health threat by 2030, is the need to endorse and strengthen similar prevention strategies among high-risk adult groups. One such group includes health-care workers (HCWs), whose risk of infection is estimated to be 2-4 times the level in the general population.[12–14] Occupational exposure to infectious blood and bodily fluids (BBF) through percutaneous or muco-cutaneous routes is a major cause of HBV infection amongst HCWs.[15] Annually, an

estimated 2.1 million HCWs are exposed to a 'sharp' injury, leading to ~66 000 work-related HBV infections globally.[13] In the unvaccinated individual, the risk of acquiring HBV infection after a single exposure approaches 30%.[15] Rates of accidental exposure to BBF are greater among health-sciences students (HSSs) when compared to their qualified counterparts,[16] particularly when clinical exposure occurs early in their respective curricula. Other factors contributing to the increased risk include inadequate knowledge around the risks of exposure and correct infection prevention methods, inexperience and a lack of confidence when performing procedural skills, and a reluctance to admit to accidental exposure in the workplace for fear of embarrassment.[17–19] The WHO therefore recommends that all HCWs and HSSs should be vaccinated with HepB3 if previously unvaccinated, followed by post-vaccination immunity testing 1-3 months after the last vaccine dose.[20] Globally, national policies regarding the vaccination of HCWs, and HSSs in particular, vary considerably, thus leading to marked differences in HepB coverage. Moreover, where national policies are not clearly stipulated, regional or institutional policies are used to govern vaccination practices, resulting in intra-national variations.[21]

In South Africa, universal HepB3 was integrated into the childhood Expanded Programme on Immunisation (EPI) schedule in 1995.[22] Two years later, vaccine coverage for HepB3 was estimated at just 74%, and it remains below the 90% target more than two decades later.[23] Consequently, a significant proportion of individuals born after 1995 remain inadequately vaccinated (incomplete HepB3 series or unvaccinated). In addition, universal HepB-BD was not routinely carried out in South Africa during that period. With regards to high-risk adult population groups, such as HCWs and HSSs, the South African National Department of Health (DoH) recommends pre-exposure vaccination – i.e. vaccination before engaging in any clinical activities.[24] However, guidelines for post-vaccination immunity testing are ambiguous, only stipulating 'high-risk HCWs' with no reference to HSSs.[24] In addition, HSSs are not provided with free vaccination,[25] leaving academic institutions to create and implement their own guidelines and policies for the protection of their students.[21] Two studies at other South African higher-education institutions show coverage levels exceeding 90% among HSSs, with one institution enforcing mandatory HBV vaccination, and the other providing free vaccination and serological testing services.[26,27]

Current guidelines at the University of the Witwatersrand (Wits) recommend HBV vaccination to all students registered within the Faculty of Health Science (FHS) during their

first year of study. HSSs born after the introduction of HepB3 in the South African EPI, receive a single 'booster' dose of HepB. with HepB3 reserved for only those students born before the introduction of HepB3 and non-South African residents who fail to provide proof of prior HepB3 receipt. There are no recommendations stipulated for HBV serological testing, to confirm immunity following vaccination, under the current Wits policy. The University's Campus Health & Wellness Centre (CHWC) provides health care services to Wits staff and students, including the administration of vaccines to HSSs for a nominal fee which is billed to the students account. The CHWC services are currently the only source of records for determining HBV vaccine coverage amongst HSSs at Wits. However, this record is incomplete as many students may choose to be vaccinated at other health facilities (HF), or remain unvaccinated without the knowledge of the University. At present, HBV vaccine coverage among FHS students at Wits remains unclear.

Data on current vaccination practices amongst HSSs at Wits is necessary to inform policy and protect this high-risk cohort. Surveys designed to assess the knowledge, attitude and practices (KAP) have been validated for the identification of knowledge gaps and behavioural patterns related to vaccination amongst at-risk population groups. Further, they provide baseline data that may be used to evaluate any proposed interventions. We aimed to investigate the HepB uptake and KAP of undergraduate HSSs in relation to international and institutional (Wits) HepB policies, and further, investigate factors associated with HepB uptake.

Methods

A cross-sectional analytical study was conducted at the Wits FHS Campus. An electronic, self-administered questionnaire was sent to all students registered with the FHS from February to June 2021. A total of 3 785 students were invited to participate via email through the undergraduate office. The questionnaire was created and managed using an electronic data capture system (REDCap Software, Vanderbilt University). Validation of the questionnaire was completed through a pilot study on 15 undergraduate students (not included in the final analysis) in February 2021. The amended questionnaire consisted of sections related to student sociodemographic characteristics and prior hepatitis B vaccination, both HepB and HepB3 uptake. In addition, three domains were included that assessed the

KAP of students towards HBV vaccination policies at Wits. The practice domain was limited to those students who had previously received HepB and included questions on the timing and setting of vaccination in the Wits context.

The responses within the questionnaires were analysed to determine the HBV vaccine coverage amongst our study population. Questionnaire items did not contain forced-choice formats due to the sensitive nature of some of the questions. Several variables also contained options for 'prefer not to say' or 'unsure'. Through the REDCap survey instrument we were able to create a branching logic to questions, depending on the options selected. This allowed a logical flow of targeted and congruous questions between students with different vaccination histories / statuses.

The invitation email included an information sheet that described the purpose of the study, guaranteed anonymity and strict confidentiality. Consent was obtained electronically from each participant prior to commencement of the questionnaire. Ethics approval was obtained from the Wits Human Research Ethics Committee (Medical) – ref: M201157 in February 2021.

All data was captured and stored on the encrypted REDCap online database. Completed questionnaires were anonymised, and personal identifiers were removed before importing the raw data into a password-protected Microsoft Excel document. The data was then cleaned and checked for the significance of missing values (no significance was detected). A final version of the data was then imported into SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) for analysis.

Statistical Analysis

Descriptive analysis of the dataset is presented as frequencies (*n*) and proportions (%) of the total study sample (*N*). Continuous variables are reported as means with standard deviation (SD) for normally distributed data and median and interquartile ranges (IQR) for non-normally distributed data.

Loglinear analysis, as a non-directional test, was used to determine if any significant associations existed between any categorical variables. The output of this analysis (K-way and higher order effects) showed that only main effects between variables were significant,

and no significant interactions were found between predictor variables. Following this, Pearson's chi-squared test (or Fisher's exact test where appropriate) was conducted on all variables that showed statistical significance in the loglinear analysis. Predictor variables that showed a significance of $p<0.20$ on chi-square testing were included in the final analysis. This multivariable binary logistic regression model was conducted to calculate the effect size (in the form of an adjusted odds ratio (OR) and 95% confidence interval (CI)) of predictor variables on the outcome (whether the respondent had been previously vaccinated coded as 1; or not vaccinated coded as 0). Responses recorded as 'unsure' were excluded from the binary logistic regression model.

All tests were two-tailed and a *p*-value of less than 0.05 was considered statistically significant. Data will be maintained and stored in the REDCap database for a period of 6 years, as per regulatory and institutional requirements.

Results

A total of 3 785 questionnaires were distributed electronically, of which 269 responses (7.1% response rate) were received, and 221 (82.2%) were regarded as satisfactorily completed for analysis – i.e. data on the primary outcome variable of vaccination history was entered.

Table 1 describes the participants characteristics. More than two-thirds of the 221 respondents were female (69.2%; 153/221), with a mean (SD) age of 22.5 (3.5) years. The majority (85.5%; 189/221) were born after 1995 when the HBV vaccine was introduced into the EPI in South Africa. Most of the respondents were of South African nationality (94.1%; 208/221), had grown up in urban settings (85.5%; 189/221) and were studying a Bachelor of Medicine and Surgery (MBBCh) degree (76.9%; 170/221).

Table 1: Sociodemographic characteristics of participants in the study (*N*=221)

Characteristics	Category	*n* (%)*
Date of birth†	Before (and including) 1995	19 (8.6)
	1996 onwards	189 (85.5)
Sex	Non-binary	4 (1.8)
	Male	62 (28.1)
	Female	153 (69.2)
Race	Black	72 (32.6)
	White	99 (44.8)
	Indian/ Asian	47 (21.3)
Marital Status	Single	211 (95.5)
	Married/ In a relationship	7 (3.2)
Children/ Dependents	None	214 (96.8)
	$\geq$ 1	5 (2.3)
Nationality	South African	208 (94.1)
	Foreign national	11 (5.0)
Place of birth	Home-birth	6 (2.7)
	Clinic	11 (5.0)
	Hospital	201 (91.0)
Childhood residence	Rural	30 (13.6)
	Urban	189 (85.5)
Course enrolment	Bachelor of Medicine and Surgery (MBBCh)	170 (76.9)
	Bachelor of Pharmacy	16 (7.2)
	Bachelor of Science in Physiotherapy	11 (5.0)
	Bachelor of Health Sciences	10 (4.5)
	Bachelor of Science in Occupational Therapy	7 (3.2)
	Bachelor of Dental Science	2 (0.9)
	Bachelor of Clinical Medical Practice	1 (0.5)
	Bachelor of Nursing	1 (0.5)

MBBCh (Bachelor of Medicine and Surgery)
*All values reported as frequency (*n*) and percentages (%). Percentages reflect proportion of total sample size (*N*=221) and account for any missing data when % values do not add up to 100%.
†Date of birth categorised according to timing of hepatitis B vaccine introduction into the Expanded Programme on Immunization.

Hepatitis B Vaccine History

Of the 221 students, 89.1% (197/221) reported having been vaccinated against HBV, with 78.2% (154/197) of these having received a complete vaccine schedule of at least three doses (HepB3). Those who were unsure of any previous vaccination account for 5.9% (13/221) of our study sample, with a further 8.6% (19/221) unsure of the number of doses received (Fig. 1).

Only 5% (*n*=11) of students had never been vaccinated. The most common reasons cited by participants, for either no vaccination or an incomplete series, were vaccine stock-outs (*n*=7), a lack of information around institutional vaccination policies (*n*=5), financial cost implications (*n*=4) and a fear of needles (*n*=2).

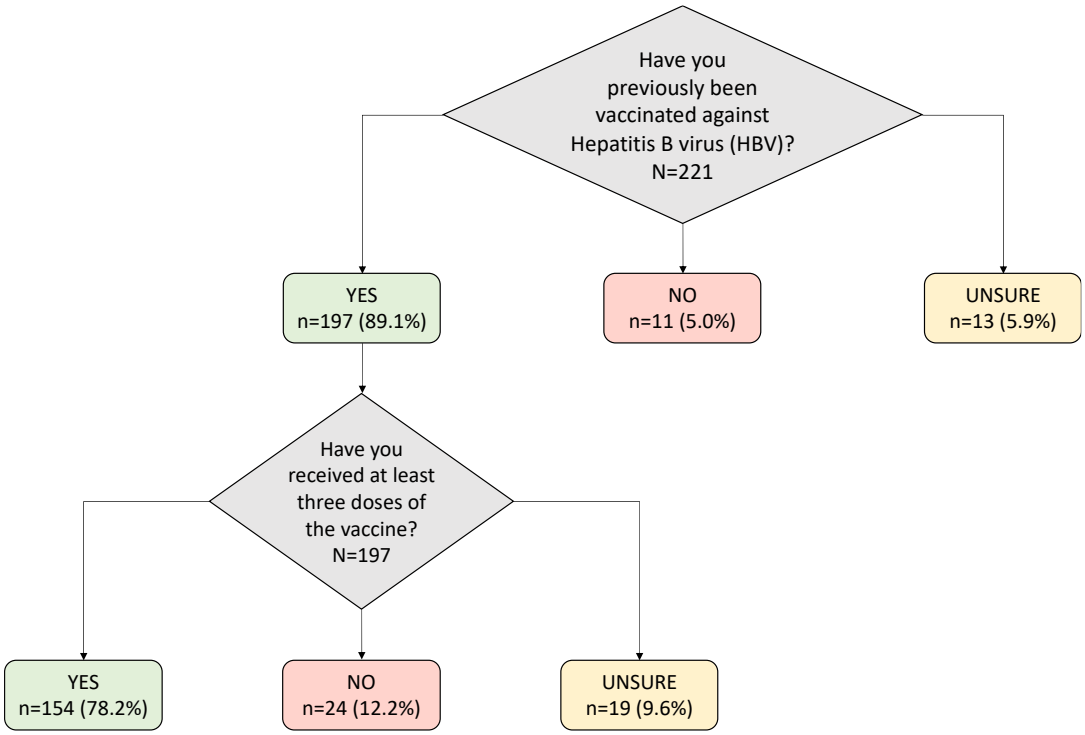

Fig. 1 – Flow diagram illustrating the prevalence of complete and partial vaccine coverage to hepatitis B virus infection, among study participants (*N*=221)

In order to identify any associations between predictor variables and a positive vaccination history, only students who reported previous vaccination (*n*=197) and those who reported no vaccination (*n*=11) were analysed. Students who were 'unsure' of their vaccine status (*n*=13) were excluded from this analysis as their impact did not change the outcome interpretation (separate independent analyses conducted) and could not be used as a stand-alone group by themselves due to the low sample size.

The following variables were significantly associated with a positive vaccine history as shown in Table 2: White students compared to Black students (OR 7.75; *p*=0.007); growing up in an urban setting (OR 4.74; *p*=0.011) and academic course enrolment - MBBCh

compared to all others (OR 8.54; $p<0.001$). Following multivariable binary logistic regression, course enrolment remained the only significant predictor of a positive vaccine history (adjusted OR 4.69; $p=0.026$). Sex ($p=0.502$), marital status ($p=1.000$) and the number of children ($p=1.000$) showed no significant association. All students born after 1995 were 1.17 times more likely to be vaccinated compared to those born during and before 1995, although this was not significant ($p=0.887$).

Table 2: Factors associated with HBV vaccination among Faculty of Health Science students at the University of the Witwatersrand (*N*=221)

Characteristics	Category	Univariable Analysis*			Multivariable Analysis§		
		OR	95% CI	*P* value	AOR	95% CI	*P* value
Date of birth†	Before (and including) 1995	1					
	1996 onwards	1.17	(0.14-9.87)	0.887			
Sex	Male	1					
	Female	1.53	(0.43-5.43)	0.502			
Race	Black	1			1		
	White	7.75	(1.62-37.19)	0.007	5.46	(0.97-30.86)	0.055‡
	Indian/ Asian	#					
Marital Status	Single	1					
	Married/ In a relationship	0.95	(0.91-0.98)	1.000			
Children/ Dependents	None	1					
	≥ 1	0.95	(0.91-0.98)	1.000			
Nationality	Foreign national	1			1		
	South African	4.59	(0.86-24.44)	0.052	2.93	(0.42-20.33)	0.278
Place of birth	Home-birth	1					
	Clinic	2.00	(0.10-41.00)				
	Hospital	5.06	(0.51-49.99)	0.240			
Childhood residence	Rural	1			1		
	Urban	4.74	(1.28-17.54)	0.011	2.25	(0.47-10.75)	0.308
Course enrolment	All other courses	1			1		
	MBBCh	8.54	(2.36-30.84)	<0.001	4.69	(1.20-18.28)	0.026

AOR (adjusted odds ratio); CI (confidence interval); MBBCh (Bachelor of Medicine and Surgery); OR (odds ratio)
***** Reference categories indicated with an OR of 1
† Date of birth categorised according to timing of hepatitis B vaccine introduction into the Expanded Programme on Immunization.
# Multicollinearity inhibited determination of significance as all respondents from this category answered 'yes'.
‡ Reference category (Black students); White students and Indian students combined in analysis due to low sample size numbers
§ Factors included in multivariable analysis on the basis of loglinear and chi square analysis where $p<0.20$ in univariable analysis. Among 9 variables, 4 variables were selected by stepwise method: $R^2= 0.237$ (Hosmer and Lemeshow Test); 0.095 (Cox and Snell); 0.277 (Nagelkerke); Test statistic = 20.319, $p<0.001$

Knowledge around HBV vaccination policy and implementation

A number of questions were posed to the students to determine their knowledge on HBV vaccination policy and implementation (Table 3). Respondents who stated that vaccinations form part of standard IPC precautions for HCWs were 5 times more likely to be vaccinated (p=0.009) when compared to those who disagreed or were unsure. Approximately half (52.5%) of the students knew that HepB3 vaccination does not necessarily equate to immunity while 24.9% (55/221) incorrectly viewed three vaccine doses as immunity and a further 21.7% (48/221) were unsure. Further, 29% did not know that antibody testing was required after vaccination to measure immunity, while nearly half (48.9%) were unsure.

Respondents displayed higher levels of knowledge around institutional (Wits) vaccine recommendations (94.1%) compared to international (WHO) recommendations (75.6%). Notably, HSSs who were aware of Wits vaccination policies were 12 times more likely to have been vaccinated than those who did not know the policy (p<0.001). However, less than one-quarter of students were aware of when (23.6%) or to whom (15.4%) they should submit proof of vaccination.

Table 3: Knowledge on hepatitis B vaccination policy and implementation (*N*=221)

Questions on Knowledge	Category	*n* (%)	OR[#]	95% CI	*P* value
A. International Policy					
1. Do hepatitis B vaccinations form part of standard Infection Prevention and Control precautions for HCWs?	No Yes* Unsure	4 (1.8) 191 (86.4) 24 (10.9)	5.00	(1.35-18.58)	0.009
2. Does receiving three doses of hepatitis B vaccine mean that you are immune to the disease?	No* Yes Unsure	116 (52.5) 55 (24.9) 48 (21.7)	0.91	(0.27-3.10)	0.885
3. Does the World Health Organisation (WHO) recommend routine hepatitis B vaccination for HCWs, including HSSs?	No Yes* Unsure	2 (0.9) 167 (75.6) 50 (22.6)	2.78	(0.81-9.53)	0.092
4. Does the WHO recommend serological testing after hepatitis B vaccination to confirm immunity?	No Yes* Unsure	64 (29.0) 48 (21.7) 108 (48.9)	1.15	(0.24-5.55)	0.858
B. Institutional Policy					
5. Does Wits recommend hepatitis B vaccination for HSSs?	No Yes*† Unsure	1 (0.5) 208 (94.1) 12 (5.4)	11.94	(2.52-56.58)	<0.001
6. By when should proof of hepatitis B vaccination be submitted to Wits? †	Before commencing first year studies Before the end of the first year of study* Before commencing clinical rotations Unsure	4 (1.9) 49 (23.6) 86 (41.3) 69 (33.2)	2.17	(0.26-18.13)	0.463
7. Where should proof of hepatitis B vaccination be submitted? †	CHWC* Faculty registrar office Head of Department HCW during the first clinical rotation HPCSA Unsure	32 (15.4) 21 (10.1) 13 (6.2) 1 (0.5) 5 (2.4) 136 (65.4)	0.28	(0.06-1.22)	0.072

CHWC (Campus Health and Wellness Centre); CI (confidence interval); HCW (health-care worker); HPCSA (Health Professions Council of South Africa); HSS (health-sciences student); OR (odds ratio); WHO (World Health Organization); Wits (University of the Witwatersrand);

* Correct response

† branching logic used to answer question on institutional policy taken from those who answered correctly in question 5. (*N*=208)

Reference categories included all categories not marked by * which were combined together to form one category.

Attitudes towards Hepatitis B Vaccination

From Table 4 it was apparent that the majority of respondents (84.6%) believed that HBV vaccination should be mandatory for all HSSs at Wits. Only 6.8% stated that it should not be mandatory, while 1.8% were uncertain. Qualitative inputs from some students (*n*=15; 6.8%) stated that mandatory policies should be limited to specific groups, including those students who 'have high clinical risk exposure', 'are patient-facing', or 'participate in laboratory dissections or other high-risk activities'. Fewer than two-thirds of the respondents (62%) thought post-vaccination antibody testing was necessary to confirm immunity, while less than half (42.5%) agreed that this practice should be made mandatory. No significant associations were noted between attitudes towards HBV vaccination and a history of having been vaccinated.

Table 4: Attitudes towards hepatitis B vaccination and serological testing (*N*=221)

Questions on Attitude	Category	*n* (%)	OR†	95% CI	*P* value
1. Do you believe it should be mandatory for all HSSs at Wits to be vaccinated against hepatitis B?	No	15 (6.8)	2.91	(0.57-14.76)	0.180
	Yes - all HSSs*	187 (84.6)			
	Yes - but only some*	15 (6.8)			
	Unsure	4 (1.8)			
2. Do you think it is necessary for HSSs to check if they have adequate immunity (using antibody tests) to hepatitis B after completing their vaccination schedule?	No	52 (23.5)	0.15	(0.02-1.19)	0.054
	Yes*	137 (62.0)			
	Unsure	32 (14.5)			
3. Do you think Wits should make it compulsory to submit antibody tests as proof of immunity against hepatitis B, before allowing students to have contact with patients?	No	91 (41.2)	0.59	(0.18-2.01)	0.399
	Yes*	94 (42.5)			
	Unsure	36 (16.3)			

CI (confidence interval); HSS (health-sciences student); OR (odds ratio); Wits (University of the Witwatersrand)
* Positive response
† Reference categories included all categories not marked by * which were combined together to form one category.

Vaccination Practices at Wits

Of the students who had been previously vaccinated against HBV infection (*n*=197), a significant majority of 170 (86.3%) students had received their most recent vaccine dose while attending university (Fig. 2). CHWC was responsible for vaccinating less than half of these students (78/170), with most using private health facilities (85/170). Up to 80% (73/91) of respondents who had not been vaccinated at CHWC did not provide evidence of their vaccination status to CHWC, and all 73 students reported that no follow-up was made by Wits authorities on confirming proof of vaccination.

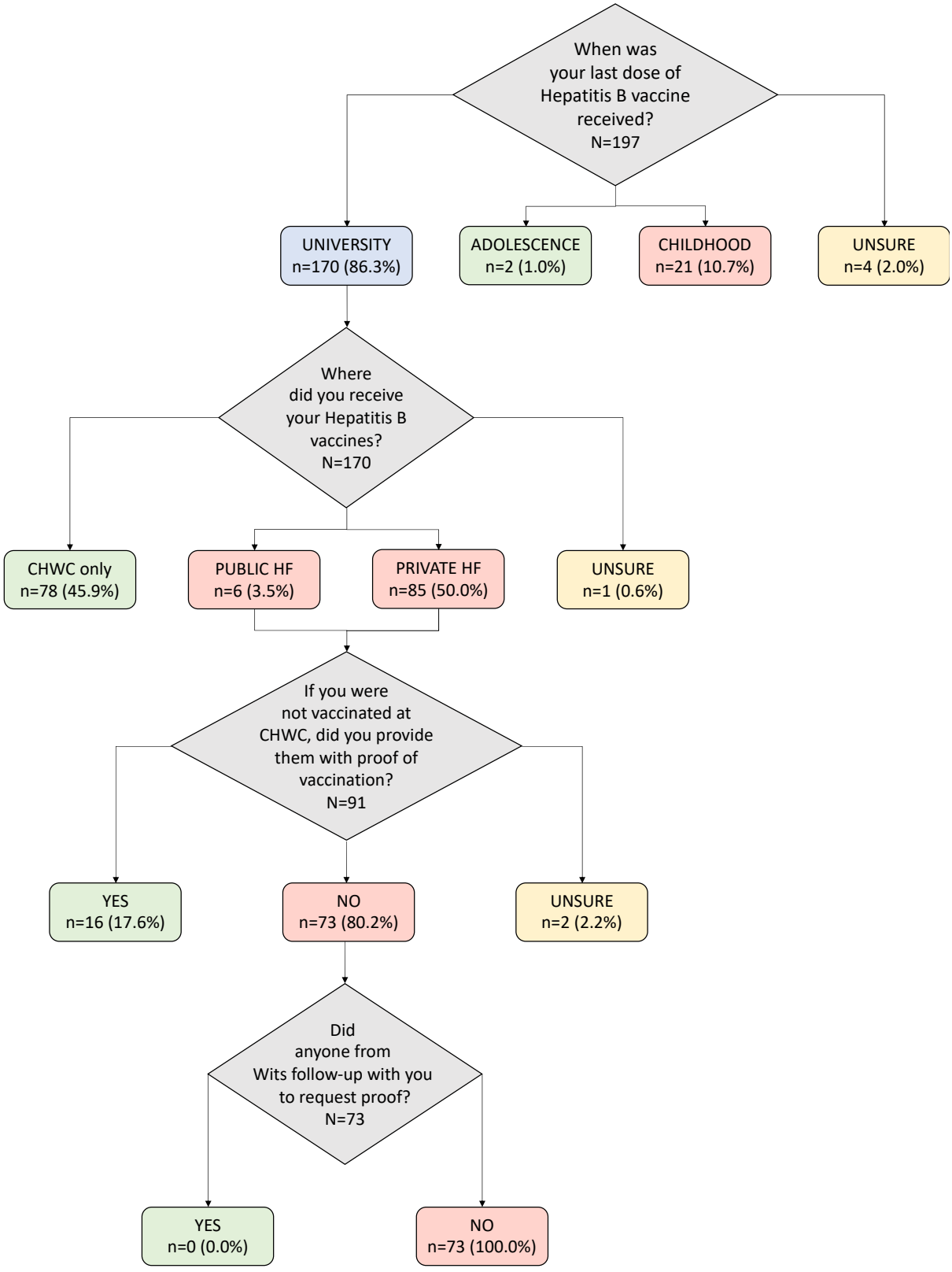

Fig. 2 – Hepatitis B vaccination practices among students who had self-reported previous vaccination at the University of the Witwatersrand, (*N*=197)

CHWC (Campus Health and Wellness Centre); HF – Health Facility; Wits (University of the Witwatersrand)

Discussion

This study sought to provide a cross-sectional description and understanding of the KAP of HBV vaccination in undergraduate FHS students at Wits. In addition, we sought to identify associations between sociodemographic characteristics and vaccination practices influencing HepB uptake among HSSs.

Due to Covid-19 regulations and the limited access to the university campus, questionnaire surveys were distributed electronically to students via university-linked emails. Despite several invitations to participate in the study, less than 10% of the HSSs responded to the questionnaire. This is not uncommon for digital surveys, which can be at least 10 percentage points lower than paper-based surveys, with response rates of approximately one quarter of the population.[28] However, our response rate was shown to be markedly lower than other studies conducted in higher-education institutions,[29] particularly amongst undergraduate students.[30] Several reasons for student non-participation in surveys have been suggested: including a general decrease in volunteerism amongst students; higher demands for participation (exponential increase in online survey methodology for research purposes) that results in over surveying, and preferential use of mobile devices (questionnaire functionality is not always optimised for mobile devices).[31] Additionally, concerns around safety and confidentiality may contribute to a reluctance to use web-based methods. Non-connectivity could not account for the lack of response, since all registered students received monthly data allowances, and the majority of teaching and learning occurred online during the 2021 academic year.

Although 89% of the respondents had received at least one dose of the hepatitis B vaccine, only 78% of those completed the vaccination series (HepB3). The 89% coverage in our study is similar to other South African studies which showed greater than 90% coverage among HSSs.[26,27] These findings are in stark contrast to other African institutions where coverage has been reported as low as 5%.[32] The major reasons for lack of vaccination within our cohort (5% of respondents) included vaccine stock-outs, inadequate education and information around the benefits and potential side effects of vaccination at Wits as well as the costs associated with vaccination. The financial burden of vaccination has also been the principal factor contributing to non-vaccination in other African and European institutions.[26,32,33] Therefore, the provision of free and accessible vaccines for high-risk

students, through either government or private donor funds, is a necessary means of protecting HSSs against HBV infection, and in turn the patients they care for. This recommendation is supported by other studies showing that the provision of free vaccination to students led to a significant increase of coverage from 9.4% to 48.8% (p<0.001).[33]

Although the poor response rate limited the statistical power of our study, several significant associations were found. Certain sociodemographic traits were positively associated with a participant's likelihood of previous vaccination. These factors include white race and growing up in urbanised areas. These associations are similar to studies from other low and middle income countries and reflect the institutionalized effects of marginalisation on select population groups, as well as a failure to provide redress to social determinants of health. The higher rates of vaccination in some race groups or those living in certain geographic locations, may reflect differences in access to centralized healthcare services as well as socioeconomic, educational and health literacy differences. A positive association with HBV knowledge and urban residence, for instance, has been documented in some studies,[34] but not in others.[35] However, these aspects were not evaluated directly in this study and future studies will be required to expound on this finding.

The strongest predictor of a student's vaccination status was the course in which they were enrolled. Students enrolled in the medical course (MBBCh) were 8.5 times more likely to have been vaccinated than other HSSs (OR=8.54; p<0.001). These findings concur with those in other studies,[36] which attribute the higher levels of vaccine coverage among medical students to more clinical experience, as well as greater knowledge around HBV infection and prevention measures. A study by Ochu et al.[37] found that HCWs (i.e. persons with greater health literacy) exhibited higher perceptions of both susceptibility to contracting HBV and disease severity of HBV, if contracted. These health beliefs in turn drove positive health-related behaviours, such as vaccination, in this subgroup.[37] Thus, improving health literacy on HBV can directly improve one's health behaviour.[35]

The majority of students displayed good knowledge of both institutional (94.1%) and international (75.6%) recommendations for hepatitis B vaccination. However, only institutional knowledge was significantly associated with HepB uptake (OR 11.94, p<0.001). Despite this, most students were still not aware of where or by when proof of vaccination needed to be submitted to the health authorities at Wits. It is clear that the Wits policy on

HepB is not implemented effectively. Increasing awareness of Wits HepB policy, coupled with earlier education on the risk of HBV exposure and infection and benefits of timely and appropriate vaccination, will improve vaccine uptake and HSS engagement in positive vaccination behaviours.

Uncertainty around concepts of vaccination and immunity following vaccination ('immunization') was noted amongst our student cohort. Approximately half of the students (52.5%) knew that a complete primary series (HepB3) did not necessarily equate to immunity. Levels of knowledge on post-vaccination immunity showed no significant association with a student's prior vaccine status. This is not a surprising finding, as a study of South African higher-education institutions found a poor understanding of what constituted adequate immunity following vaccination among academic principals and heads of departments at these universities and nursing colleges.[21] Authority figures such as these have been shown to influence a student's decision to vaccinate with improved uptake amongst those who are better informed by professional sources or medical teachers.[38] The introduction of formal training by academic authorities for newly admitted HSSs could address the shortfalls in knowledge surrounding hepatitis B vaccination and immunity.

More than 90% of the students in our study stated that 'mandatory' policies for hepatitis B vaccination should be implemented by the university. This shows that students understand and value the importance of vaccines in preventing HBV infection and transmission. Similarly, strong recommendations and mandates have been shown to improve vaccine coverage, while other studies show that one of the principal reasons behind non-vaccination (cited by HSSs) was the 'non-compulsory' nature of HepB policies.[39]

In addition, the majority of students (62%) felt that HSSs should confirm their immune status following vaccination, despite the omission thereof from current Wits HepB policy. Less than half agreed that this practice should be made mandatory by the institution. The lower response in favour of mandatory policy could be the result of suspected financial implications for the students, who are expected to pay for their own vaccines, and may have assumed similar costs would be incurred by them if additional mandates come into effect. The study by Le Roux and Dramowski,[26] at another South African university, saw their HSSs calling for vaccination and immunity testing to be subsidised by the University funders or the National DoH, a sentiment not examined in our study. When vaccination and immunity

testing are provided free of charge, more than 90% of students complete their vaccination schedules and at least 80% receive immunity testing.[27] The subsidisation of vaccination and serological testing to confirm immunity to HBV should be considered by both institutional and national health authorities.

Limitations

This study was conducted in a single academic institution within South Africa, which limits the generalizability of the results found. In addition, the questionnaire relied upon self-reported HBV vaccination practices, without documented proof of prior vaccine receipt, which is subject to recall bias particularly for vaccines received in childhood. Despite guaranteeing and safeguarding the anonymity of our participants, several students were not comfortable with answering questions around vaccine practices as seen by those choosing to select the option 'prefer not to say' or omitting the options altogether. The contribution of the Covid-19 pandemic to the remote online teaching and learning interface may have also contributed to "survey fatigue", leading to a low response rate for the online survey used. Questions referring to knowledge may be subject to social desirability bias as students may have searched for the correct answers online during the survey – no time limits or website browser restrictions were implemented. The use of an electronically-distributed questionnaire in our study may have introduced a volunteer bias whereby the characteristics of respondents may differ systematically from non-respondents and thus the greater target population. This volunteer bias is likely inflated by the poor response rate in our study (7.1%) as well as the skewed sampling distribution towards medical students (76.9%). Furthermore, the lack of record-keeping and corroborating data from the Wits CHWC prevents a true understanding of the potential over- or under-estimation of HepB uptake within our sample compared to the total HSS population at Wits. It is therefore not possible to generalise these findings to our target population or similar populations at other tertiary institutions.

Conclusion

As students play an important role in the dissemination of knowledge and raising awareness among their communities, more opportunities to improve education and drive awareness around hepatitis B should be provided to the students themselves. Further, HBV-related educational and empowerment initiatives should occur, to improve health-seeking behaviour

and create a culture of health advocacy amongst the HSS communities at Wits. It is apparent from our study that policies regarding HepB at Wits require strengthening and reform. The current CHWC facility serves as the principal provider for preventive care services for students actively seeking assistance. However, both the FHS and CHWC facilities are currently not equipped to monitor and evaluate the vaccination practices of HSSs , and as a result may overlook those students who are unvaccinated and thus remain at high-risk for infection when entering clinical practice. The responsibility to ensure completed vaccine series should not be left to students, but rather current policy should be enforced, centralised, and the CHWC should be provided with sufficient powers and resources for monitoring, follow-up and facilitation of completed three-dose vaccination. In addition, Wits HepB policies should include serological testing to confirm immunity following vaccination as well as to identify potential vaccine non-responders or those who may be infected, with these services and costs subsidised by the institution. We further recommend collaboration with the National DoH to assist with the following: identify prior vaccination status through national immunization records; create a central electronic repository for hepatitis B vaccination and immunity testing for all HSSs; provide extensive training, knowledge and up-to-date research for the prevention and management of exposure to HSSs through institutional authorities; offer subsidies and incentives for complete vaccination and immunity testing, given the potential for non-immune healthcare personnel to transmit infection to vulnerable patients and pose a risk to their own well-being. Future research that samples a greater proportion of the target population of HSSs are needed to validate and expand on the findings of this study as well as facilitate the generalisability of our conclusions.

Author Contributions

Conceived the study: AK, NM; Designed the questionnaire: NM, AK; Analysed the data: NM, ES, AK; Wrote the paper: NM, AK; Read, contributed to and critically revised the paper: NM, ES, AK. All authors read and approved the final manuscript.

Conflicts of Interest

None

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ARTICLE 2:

Hepatitis B virus immunity prior to and after administration of a 'booster' dose of vaccine among health-care students at a South African university

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Format: As per Vaccine Journal

(Authors Guide - https://www.elsevier.com/journals/vaccine/0264-410X/guide-for-authors)

Conflict of interest: None declared

Funding: Professor E Song, Administered Fund, University of the Witwatersrand

Key words: Hepatitis B virus, Health-care student, Vaccination, Immunity

Abstract word count: 301 words (300)

Article word count: 4930 words (5000)

Abstract

Background: Health-care students (HCSs) are at risk of occupational exposure to hepatitis B virus (HBV) infection despite an effective hepatitis B vaccine (HepB) being available. The majority of current HCSs are born after HepB was introduced into the South African Expanded Programme on Immunisation in 1995. Thus, it is assumed that having received HepB in infancy, a single 'booster' dose would suffice. This study aimed to investigate HBV immunity prior to and after administration of a HepB 'booster' dose.

Methods: In 2021, hepatitis B surface antibody (anti-HBs) levels were determined in first year HCSs at the University of the Witwatersrand, before and after receiving the 'booster'. Participant demographics and HepB history were captured using a structured questionnaire.

Results: Before receiving the 'booster', 56% (101/180) had anti-HBs <10 mIU/mL and were non-immune. A further 35% had anti-HBS levels of 10 – 99 mIU/mL, and 9% had ≥100 mIU/mL. Less than 30% of HCSs self-reported completion of a three-dose primary series, which was significantly associated with higher baseline anti-HBs levels compared to those with a partial schedule (p=0.045). Following vaccination, 39% (71/180) returned for follow-up with a significant median (IQR) increase of 476 (151 – 966) mIU/mL (p<0.001). Of the 45 students who had non-immune baseline levels, 73% (33/45) responded with ≥100 mIU/mL, 16% (7/45) with 10 – 99 mIU/mL and 11% (5/45) remained non-immune. Levels of ≥100 mIU/mL were achieved by 100% of students with baseline levels ≥10 mIU/mL (n=26).

Conclusion: A significant proportion of HCSs were not immune to HBV prior to receiving the recommended 'booster' dose. After receiving the 'booster', 7% (5/71) remained unprotected. This study highlights that in the absence of vaccination records and without confirming the immune status of HCSs, it cannot be assumed that HCSs will be protected following a 'booster'. Policy reform and inclusion of serological tests for immunity prior to HCSs initiating clinical exposure are recommended.

Abbreviations

anti-HBs - hepatitis B surface antibody
BBF - blood and bodily fluids
CHWC - Campus Health and Wellness Centre
CLIA - chemiluminescent immunoassay
DoH - Department of Health
EPI - Expanded Programme on Immunisation
FHS - Faculty of Health Science
HBV – hepatitis B virus
HCS - health-care student
HCW - health-care worker
HepB – hepatitis B vaccine
HepB-BD - hepatitis B vaccine birth dose
HepB3 - third dose of hepatitis B vaccine
IPC - infection prevention and control
IQR - inter-quartile range
NHLS - National Health Laboratory Services
SD - standard deviation
SST - serum separator tube
WHO - World Health Organization
Wits - University of the Witwatersrand

Introduction

Hepatitis B Virus (HBV) infection is a global health problem that accounts for nearly one million deaths annually through complications of HBV-induced liver diseases, such as hepatocellular carcinoma and cirrhosis [1]. Despite the availability of a safe and highly effective vaccine for the past three decades, HBV remains endemic in many regions, including sub-Saharan Africa, where vaccine coverage remains sub-optimal [2].

Since the early 1990's, the World Health Organization (WHO) has recommended universal vaccination of all infants against HBV, with a minimum of three doses of HepB administered at least four weeks apart [3]. Furthermore, the WHO recommends that an additional dose be administered to neonates within 24 hours of birth (HepB-BD) as the risk of developing chronic HBV infection is greatest amongst infants infected during the first year of life (80 - 90%) – this risk decreases exponentially if infection is acquired in adulthood (1 - 5%) [4,5]. Therefore, global efforts towards HBV infection prevention and control have primarily focused on this younger cohort, resulting in significant reductions in children under 5 years becoming chronically infected from 4.7% to 1.3% [6].

Despite these successes, the prevalence of HBV infection amongst high-risk groups, such as health-care workers (HCWs) and those with immune-compromised states, remains high in many parts of the world [7,8]. These groups include persons who are at increased risk of exposure to HBV because of occupational, behavioural, and biological susceptibility. To reduce the likelihood of infection among these high-risk groups, the WHO has further endorsed at least three doses of HepB in previously unvaccinated persons and booster vaccine doses in previously vaccinated individuals to reinstate immunity [1]. In addition, global organizations recommend serological testing to confirm immunity following vaccination, particularly in HCWs and students in training, prior to potential occupational exposure [9]. A measurement of antibodies to hepatitis B surface antigen (anti-HBs) of ≥10 mIU/mL, measured 1-3 months after administration of the last vaccine dose, confers immunity [10]. This value is commonly cited as the correlate of protection among healthy vaccinees in most countries. However, some countries regard higher anti-HBs levels of ≥100 mIU/mL as adequate immunity in high-risk groups – particularly HCWs [11]. This higher threshold-value has been adopted on the basis of observational studies where, several years after vaccination, significantly fewer breakthrough infections were seen in the 'high-responder'

cohort (≥100 mIU/mL), when compared to lower threshold values in the 'low-responder' cohort (10 – 99 mIU/mL) [12].

Occupational exposure to infectious blood and bodily fluids (BBF) through muco-cutaneous or percutaneous routes are the major cause of HBV infection among susceptible HCWs [13,14], occurring at rates up to four times that of the general population [15]. Annually, an estimated 2.1 million HCWs (5.9%) globally, are exposed to HBV through contaminated sharp objects, leading to an estimated 66 000 infections [16]. HCWs from developing countries, largely in Asia and Africa, account for more than 90% of these infections, with an annual prevalence of occupational exposure to infectious BBF among African HCWs reported at almost 50% [17,18].

Health-care students (HCSs) are exposed to clinical situations alongside their professional counterparts and are thus at similar risk of HBV exposure during their academic training years [19]. Some studies have cited higher rates of needle stick injuries among trainees as a result of their zealous nature, coupled with a lack of procedural skills, incorrect use of personal protective equipment, and poor safety and infection control practices [20,21]. In addition, students' fear of repercussions, shame and personal lack of knowledge on post-exposure practices, may further prevent them from reporting the incident and in turn receiving the appropriate management [22].

While several African countries have strengthened policies for the control and prevention of HBV infection amongst HCWs, vaccine coverage in the region has remained sub-optimal [23,24]. A pooled analysis reported a completed vaccination series in just under 25% of African HCWs, as low as 1% in some regions [23]. Interestingly, recent studies have shown increasing trends in vaccine uptake amongst HCSs - largely attributed to the introduction of national and institutional policies recommending (and in some instances, mandating) vaccination prior to clinical exposure [25,26]. However, substantial variations are seen in knowledge, timing and provision of vaccination between academic institutions, even when standard national policies exist [27].

In South Africa, HepB was first introduced into the national Expanded Programme on Immunisation (EPI) in 1995 [28], and has seen a significant reduction in HBsAg prevalence from highly endemic levels (>8%) to low carriage levels ranging from 0.0 to 2.7%, even

among HIV-positive infants [29,30]. Despite this, vaccine coverage, officially recorded two years after HepB introduction was 74%, and remained at less than 90% over the following two decades [31]. Consequently, nearly one-quarter of children born during that period (the current age-group of newly enrolled HCSs) are inadequately protected against HBV infection. In lieu of the anticipated poor vaccination coverage, as well as local HBV endemicity, the South African Department of Health (DoH) recommends the provision of three doses of HepB to previously unvaccinated HCWs and HCSs at-risk of HBV exposure [32]. However, national policy fails to translate these recommendations into practical and cost-effective strategies, leaving many local health authorities and academic institutions to create and implement their own guidelines. Despite protocols and guidelines to protect HCSs from occupational exposure to blood and blood products, up to one quarter of HCSs have reported occupational exposure to infectious during their academic training, with more than a third of those exposed admitting to not having followed universal precautions or the recommended post-exposure prophylaxis guidelines [33]. Where vaccine coverage among HCWs in South Africa has been sub-optimal [24], HepB coverage appears promising among HCSs in South Africa (>90%) [34,35].

The majority of HCSs enrolled in the 2021 health-related courses at the University of the Witwatersrand (Wits) were born after the introduction of HepB in 1995 and are thus presumed to have received adequate vaccination in childhood. On this basis, current vaccination policy at Wits stipulates the need for a single booster dose of the HepB to all HCSs during their first year of study [36]. A three-dose schedule is reserved for those born before the introduction of hepatitis vaccine into the EPI, unless they can provide proof of completed HepB three-dose vaccination [36]. The coordination of the vaccination policy and administration of recommended vaccines, including HBV, is undertaken by the Wits student health clinic - Campus Health and Wellness Centre (CHWC). The financial cost of the vaccine is incurred by the HCS and billed to their respective fees account, providing the university with the only source of vaccine record for its HCSs. Post-vaccination serological testing is not currently offered nor recommended within the Wits policy.

The paucity of data on vaccination practices and the apparent under-appreciation for the need to confirm immunity following vaccination, requires further exploration and analysis [27]. Limited serological studies have been conducted amongst dental undergraduate HCSs in South Africa to evaluate immunity against HBV [34]. Our study thus aimed to quantify the

levels of immunity to HBV among all first year HCSs across the Faculty of Health Science (FHS) at Wits, prior to them receiving the recommended single 'booster' dose of HepB (to establish baseline immunity). In addition, we aimed to analyse the effects of the 'booster' dose by comparing pre- and post-vaccination immunity levels.

Methods

Study population and recruitment site

We conducted a prospective cohort study of first year HCSs registered at Wits during the 2021 academic year. All registered students (*N*=924) over the age of 18 years in the FHS were invited via email to participate in a survey which included a structured questionnaire, and blood sample collection to assess anti-HBs levels prior to ('pre-vaccination'), and more than 1 month following vaccination ('post-vaccination'). Data collection took place from March to November 2021. All students who took part in the study were actively recruited at the CHWC facility on the day of their scheduled vaccination. Eligible participants were taken through the study protocol to ensure their understanding of the risks and benefits of participation. Written informed consent was obtained from all willing participants.

Ethical approval

This study received ethical approval from the Wits Human Research Ethics Committee (medical) in February 2021 – reference number: M201157. All activities were conducted in compliance with the Declaration of Helsinki. Venesection was performed by registered health personnel in accordance with the National Infection Prevention and Control (IPC) Strategic Framework (2019) as set out by the South African DoH [37]. Any personal identifying information was coded and password-protected, accessible to the approved study researchers only.

Data collection

The structured questionnaire was used to determine participant demographics as well as HepB history. Questions regarding age, gender, childhood living environment and course of study were included in Section 1. Questions pertaining to HepB were included in Section 2. Despite a request by CHWC staff for all attending students to provide documentation of vaccination history, the majority of students did not comply. Therefore, details pertaining to

Section 2, relied largely on student or caregiver recall and are reported herein without distinction.

For serological testing, approximately 3-5 mL of venous blood was drawn from each participant and collected in the appropriate serum separator tube (SST). CHWC nursing staff then administered a single dose of HepB [36]. A dose of 1.0mL (20µg HBsAg) of Euvax B™ Inj. (LG co., Korea) was injected into the participant's non-dominant deltoid muscle [38].

All samples were delivered to the National Health Laboratory Services (NHLS), on-campus testing facility, within three hours of collection. Quantification of anti-HBs was done using validated chemiluminescent immunoassay (CLIA) technology. The assay used throughout this study was the Roche Elecsys® Anti-HBs II (Roche Diagnostics, Germany) according to the manufacturer's instructions. Overall sensitivity and specificity of this assay is estimated at 100% and 99.45%, respectively [39].

Participants with non-reactive anti-HBs concentrations of <10 mIU/mL were considered 'non-immune'. Those with reactive sample levels of ≥10 mIU/mL were stratified into two immune groups: 10 – 99 mIU/mL ('immunity') and levels ≥100 mIU/mL ('high immunity') baseline categories. Levels of anti-HBs ≥1000 mIU/mL were not quantified further due to assay limitations. Official anti-HBs results, including interpretation of the findings, were emailed to the respective participants. At this time, participants were invited for post-vaccination anti-HBs testing (scheduled at least one month following vaccination) to assess the peak antibody response to the vaccine dose. Returning participants were again classified into three categories based on their anti-HBs response levels: <10 mIU/mL ('non-immune'), 10 – 99 mIU/mL ('low responders'), ≥100 mIU/mL ('high responders'). The term 'non-immune' rather than 'non-response' was chosen in the case following vaccination, as prior vaccine history could not be verified. The term 'non-response' is reserved and internationally used for participants with non-reactive anti-HBs levels following exclusion of chronic hepatitis B infection and two three-dose courses of HepB, measured four weeks after the sixth HepB dose [40].

In cases where the anti-HBs concentrations remained <10 mIU/mL after administration of the vaccine, respective participants were contacted and advised to return for further testing and management (offered through the study protocol).

Data Capture

For each participant, pre- (baseline) and post- vaccination (if available) anti-HBs results, together with the coded responses from the corresponding questionnaire, were captured into an encrypted Microsoft® Excel (2021) document. De-identified hard copies of the questionnaires were scanned and stored on two electronic devices with the original copies held in a sealed cabinet at Wits.

Statistical Analysis

Cleaned data was imported into SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA) for analysis. Continuous variables were expressed as mean and standard deviation (SD) where appropriate, or median and inter-quartile range (IQR) where the distribution of data deviated from normal. All categorical variables were summarized as frequencies (*n*) and percentages (%). Pearson's chi-squared test or Fisher's exact test (where appropriate) were used to evaluate for significant associations between categorical variables and the main outcome of interest (anti-HBs 'immune' categories). Spearman's rho was calculated to determine the correlation between pre- and post-vaccination anti-HBs levels. Due to the low sample size of returning participants, McNemar's test for paired nominal data was used to determine the change from pre- to post- vaccination immune categories. Wilcoxon signed-rank tests for paired data were used to determine the significance of changes to anti-HBs levels following vaccination within immune categories. These tests were chosen as data was not normally distributed as raw values or when log-transformed. All tests were two-tailed, and a *p*-value of less than 0.05 was considered statistically significant. Graphs and tables were compiled using the GraphPad Prism software (version 5, USA).

Results

Invitations were emailed to 924 HCSs, of which 230 were screened at the CHWC. Of these, 222 participants met the eligibility criteria for inclusion in the study. Following discussion and written informed consent, 191 (86.0%) students were enrolled in the study. Anti-HBs results were not available for six students, and a further five did not complete the questionnaire portion of the study (Fig. 1). As a result, 180 (81.1%) students were included in the pre-vaccination analysis. Only 71 of these students (39.4%) returned following vaccination and completed both pre- and post- vaccination procedures as stipulated in the study protocol (Fig. 1).

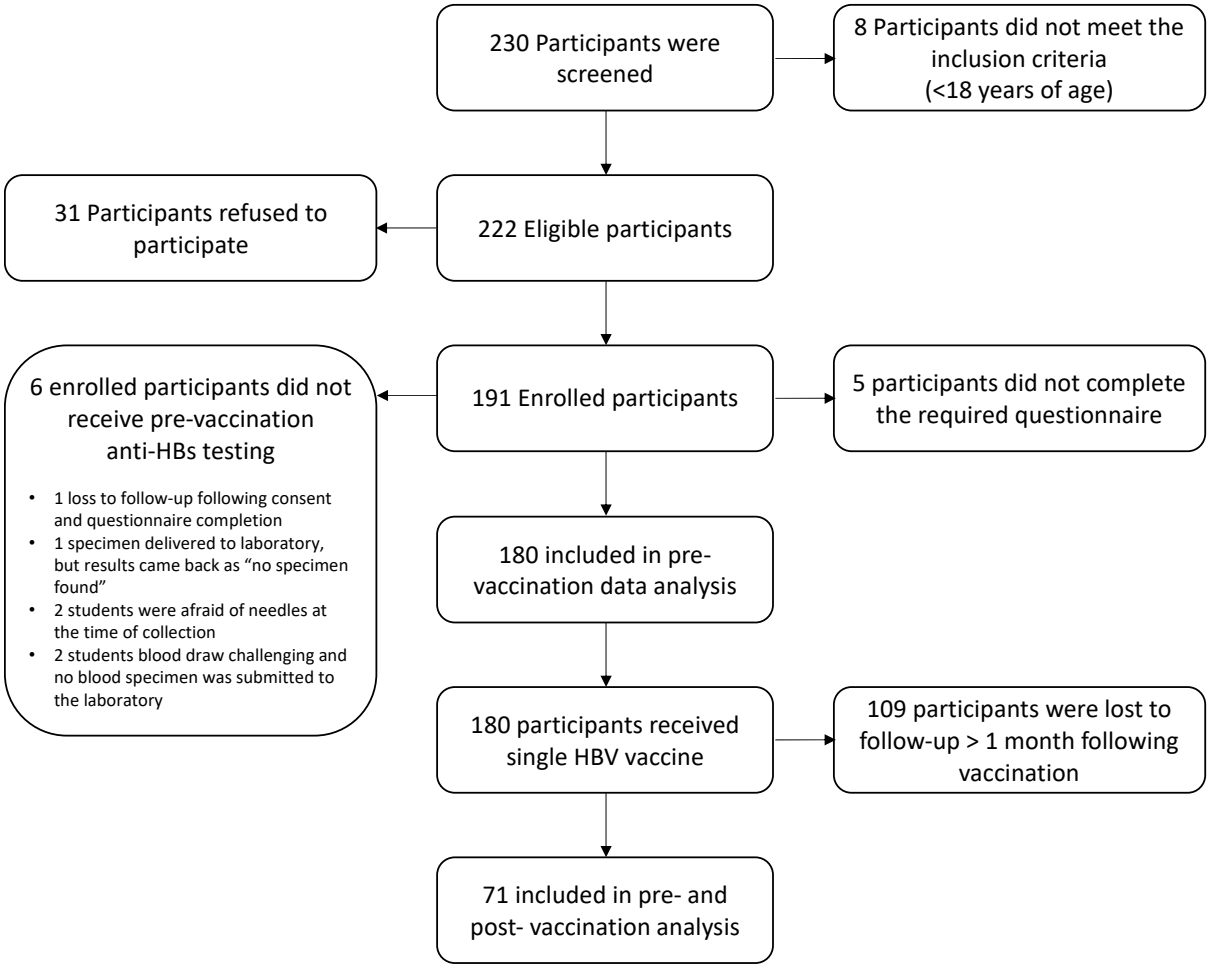

Fig. 1 – Flow diagram of study participants for inclusion in pre-vaccination (*N*=180) and post-vaccination (*N*=71) data analysis

anti-HBs (hepatitis B surface antibody); HBV (hepatitis B virus)

Pre-vaccination findings

The mean (SD) age of the study population was 19.0 (1.3) years, with the majority identifying as female (70%). Black students accounted for 80% (144) of the sample, and most of the participants (96.7%) were born in South Africa. Six of the nine undergraduate health-related courses at Wits were represented in the study, with no participants from nursing, physiotherapy, or occupational therapy disciplines (Table 1).

Table 1: Sociodemographic characteristics of study participants from the Faculty of Health Science at the University of the Witwatersrand - Pre-vaccination survey (*N*=180)

Characteristics	Category	*n* (%)
Date of birth	Before (and including) 1995	2 (1.1)
	1996 onwards	178 (98.9)
Sex	Female	126 (70.0)
	Male	54 (30.0)
Race	Black	144 (80.0)
	White	18 (10.0)
	Coloured	6 (3.3)
	Indian	12 (6.7)
Nationality	South African	174 (96.7)
	Foreign national	6 (3.3)
Childhood residence*	Urban	110 (61.1)
	Rural	69 (38.3)
Course enrolment	Bachelor of Health Sciences	59 (32.8)
	Bachelor of Medicine and Bachelor of Surgery	48 (26.7)
	Bachelor of Pharmacy	28 (15.6)
	Bachelor of Clinical Medical Practice	20 (11.1)
	Bachelor of Dental Science	14 (7.8)
	Bachelor of Oral Health Sciences	11 (6.1)

Values reported as frequency (*n*) and percentages (%)
**N*=179 for childhood residence (single data point missing)

The results of the pre-vaccination testing revealed that most students (*n*=101; 56.1%) had no immunity to HBV, with non-reactive (<10 mIU/mL) anti-HBs levels (Table 2). Of those students with reactive anti-HBs levels (*n*=79), 16 students (20.3%) had high levels of immunity (≥100 mIU/mL) with the remainder of 63 (79.7%) students having lower levels of immunity (10 – 99 mIU/mL). Pre-vaccination anti-HBs levels showed no association with

sex (p=0.743), nationality (p=0.664) or childhood residence (p=0.396). A significant association was found between race and baseline anti-HBs (p=0.034). Further subgroup analysis (through pairwise comparisons) revealed this difference was primarily due to higher pre-vaccination levels seen among the Indian students compared to the Black students (p=0.009; adjusted by the Bonferroni correction for multiple tests) (Table 2 – Section 1).

The majority of students (96/180; 53.3%) were uncertain of their prior vaccination status, with 36.7% (66/180) students stating they had been previously vaccinated, and 10% (18/180) never having been vaccinated. A minority provided proof of vaccination (data not shown). No significant difference was seen in level of anti-HBs and previous vaccination status (p=0.226) among these participants (n=84). Accounting for the additional 96 students who were 'unsure' of their vaccine history, again no association was found between self-reported vaccine status (vaccinated, unvaccinated and unsure) and baseline anti-HBs levels when compared across all three groups (n=180; p=0.262) (Table 2 – Section 2).

Among students who reported that they were previously vaccinated (n=66), the majority (51; 77.3%) had completed a three-dose schedule and were more likely to have reactive pre-vaccination anti-HBs levels ($\geq$10 mIU/mL) compared to those who had not completed the schedule (p=0.045). This difference was most notable in the lower immunity group (10 - 99 mIU/mL). Recent vaccination was significantly associated with higher immunity levels (p=0.028). However, only two students had received a dose within the past five years, with both displaying immunity to HBV, compared to 54 students who received their last vaccine dose more than 10 years prior (Table 2 – Section 2).

Table 2: Pre-vaccination anti-HBs immunity described according to sociodemographic characteristics and hepatitis B vaccine history (*N*=180)

Category		Pre-vaccination anti-HBs titre			***P* value**[†]	
		non-immune (<10 mIU/mL)	*low immunity* (10 - 99 mIU/mL)	*high immunity* (≥100 mIU/mL)		
SECTION 1 – Demographics of Whole Population (*N* = 180)						
Sex	Female	73 (72.3)	42 (66.7)	11 (68.8)	0.743	
	Male	28 (27.7)	21 (33.3)	5 (31.2)		
Race	Black	88 (87.1)	45 (71.4)	11 (68.8)	0.034[‡] (0.009)[§]	
	White	8 (7.9)	9 (14.3)	1 (6.3)		
	Coloured	2 (2.0)	2 (3.2)	2 (12.5)		
	Indian	3 (3.0)	7 (11.1)	2 (12.5)		
Nationality	South African	98 (97.0)	61 (96.8)	15 (93.8)	0.664	
	Foreign national	3 (3.0)	2 (3.2)	1 (6.3)		
Childhood residence	Urban	58 (58,0)	40 (63.5)	12 (75.0)	0.396	
	Rural	42 (42.0)	23 (36.5)	4 (25.0)		
Previously vaccinated against HBV	Yes[*]	38 (37.6)	24 (38.1)	4 (25.0)	0.226[¶]	0.262[#]
	No	14 (13.9)	3 (4.8)	1 (6.3)		
	Unsure	49 (48.5)	36 (57.1)	11 (68.8)		
	Total 180	101 (56.1)	63 (35.0)	16 (8.9)		
SECTION 2 - Vaccine History of Previously Vaccinated (*n* = 66[*])						
Completed three-dose schedule	Yes	27 (71.1)	22 (91.7)	2 (50.0)	0.045	
	No	11 (28.9)	2 (8.3)	2 (50.0)		
Time since last dose	1-5 years ago	0 (0.0)	1 (4.2)	1 (25.0)	0.028[‖]	0.019[**]
	>10 years ago	33 (86.8)	20 (83.3)	1 (25.0)		
	Unsure	5 (13.2)	3 (12.5)	2 (50.0)		
	Total 66	38 (57.6)	24 (36.4)	4 (6.0)		

Anti-HBs (hepatitis B surface antibody); HBV (hepatitis B virus)
All values reported as frequency (*n*) and percentages (%); *n* (%)
* branching logic used to answer question on completion of vaccine schedule and timing since last dose, taken from those who answered 'yes' to previous vaccination (*n*=66)
† Chi square testing (or Fischer's exact test where needed) to determine *p*-value for all variables
‡ Chi square test to determine significance between all categories of race and pre-vaccination immune category
§ Pair-wise analysis between each race group and pre-vaccination immune category Chi-square test to determine significance adjusted with Bonferroni correction for multiple tests
¶ Test included those who were previously vaccinated in the category 'yes' and 'no' only (*n*=84)
# Test included those who were previously vaccinated in the category 'yes', 'no' and 'unsure' (*N*=180)
|| Test included those who knew the time elapsed since their last dose in the category '1-5 years' and '>10 years' only (*n*=56)
** Test included those who knew the time elapsed since their last dose in the category '1-5 years', '>10 years' and 'unsure' (*n*=66)

Post-vaccination findings

Following vaccination, all students were invited to return for post-vaccination anti-HBs testing, regardless of their baseline levels. Approximately 40% (*n*=71) of students returned for follow-up after a median (IQR) interval of 48 (41 - 57) days.

The mean (SD) age of the follow-up study population was 18.7 (0.6) years. Similar socio-demographic characteristics were seen in these students compared to the baseline, apart from students in the Bachelor of Oral Health Science discipline not being represented in post-vaccination analysis (Table 3).

Table 3: Sociodemographic characteristics of study participants from the Faculty of Health Science at the University of the Witwatersrand - Post-vaccination survey (*N*=71)

Characteristics	Category	*n* (%)
Date of birth	Before (and including) 1995	0 (0)
	1996 onwards	71 (100)
Sex	Female	49 (69.0)
	Male	22 (31.0)
Race	Black	59 (83.1)
	White	7 (9.9)
	Coloured	3 (4.2)
	Indian	2 (2.8)
Nationality	South African	69 (97.2)
	Foreign national	2 (2.8)
Childhood residence	Urban	44 (62.0)
	Rural	27 (38.0)
Course enrolment	Bachelor of Health Sciences	32 (45.1)
	Bachelor of Medicine and Bachelor of Surgery	21 (29.6)
	Bachelor of Pharmacy	8 (11.3)
	Bachelor of Clinical Medical Practice	6 (8.5)
	Bachelor of Dental Science	4 (5.6)
	Bachelor of Oral Health Sciences	0 (0.0)

Values reported as frequency (*n*) and percentages (%)

Similar to the pre-vaccination results, post-vaccination anti-HBs groups showed no association with sex, nationality or childhood residence. In contrast to baseline results, no associations between post-vaccination anti-HBs groups and race, prior completion of the three-dose vaccine schedule, or timing of the last received dose were noted (Table 4).

Pre-vaccination anti-HBs categorisation was the only factor that was significantly associated with post-vaccination anti-HBs categorisation ($p<0.001$) when using McNemar's test.

Following vaccination, a significant median (IQR) increase of 476 (151 – 966) mIU/mL was noted ($p<0.001$). Of the 71 students who returned post-vaccination, 45 were non-immune at baseline with an overall median (IQR) increase within this group of 198 (66 - 781) mIU/mL ($p<0.001$). Classification into immune response categories revealed 33 of the 45 students (73.3%) achieved high levels of immunity ($\geq$100 mIU/mL) while 7 (15.6%) students had lower levels (10 - 99 mIU/mL). Of the 45 non-immune students, five (11.1%) remained non-reactive following vaccination. This equates to 7% of the total study sample ($n=5/71$) who returned following vaccination. Table 5 below describes the characteristics of these five participants.

Students with reactive baseline anti-HBs levels who returned post-vaccination, regardless of lower (10 - 99 mIU/mL) or higher ($\geq$ 100 mIU/mL) baseline immunity, all achieved high levels of immunity following the single vaccine dose ($n=26$) (Fig. 2). A median (IQR) change of 946 (773 - 975) mUI/mL ($p<0.001$) and 884 (311 - 891) mIU/mL ($p=0.125$) was noted in the two groups, respectively. A statistically significant moderate correlation ($r_s = 0.566$, $p<0.001$) was seen between all pre- and post-vaccination anti-HBs levels (Fig. 3).

Table 4: Post-vaccination anti-HBs response described according to sociodemographic characteristics and hepatitis B vaccine history in students registered to the Faculty of Health Science, at the University of the Witwatersrand (*N*=71)

Category		Post-vaccination anti-HBs titre			*P* value†	
		non-immune (<10 mIU/mL)	*low responder* (10 - 99 mIU/mL)	*high responder* (≥100 mIU/mL)		
SECTION 1 – Demographics of Whole Population (*N* = 71)						
Sex	Female	3 (60.0)	6 (85.7)	40 (67.8)	0.682	
	Male	2 (40.0)	1 (14.3)	19 (32.2)		
Race	Black	4 (80.0)	6 (85.7)	49 (83.0)	0.601	
	White	0 (0)	1 (14.3)	6 (10.2)		
	Coloured	1 (20.0)	0 (0)	2 (3.4)		
	Indian	0 (0)	0 (0)	2 (3.4)		
Nationality	South African	5 (100.0)	7 (100.0)	57 (96.6)	0.811	
	Foreign national	0 (0)	0 (0)	2 (3.4)		
Childhood residence	Urban	1 (20.0)	4 (57.1)	39 (66.1)	0.109	
	Rural	4 (80,0)	3 (42.9)	20 (33.9)		
Previously vaccinated against HBV	Yes*	38 (37.6)	24 (38.1)	4 (25.0)	0.086‡	0.023§
	No	14 (13.9)	3 (4.8)	1 (6.3)		
	Unsure	49 (48.5)	36 (57.1)	11 (68.8)		
	Total 71	5 (7.0)	7 (9.9)	59 (83.1)		
SECTION 2 - Vaccine History of Previously Vaccinated (*n* = 28*)						
Completed three-dose schedule	Yes	0 (0.0)	2 (66.7)	19 (79.2)	0.253	
	No	1 (100.0)	1 (33.3)	5 (20.8)		
Time since last dose	1-5 years ago	0 (0.0)	0 (0.0)	1 (4.2)	0.937¶	0.270#
	>10 years ago	1 (100)	2 (66.7)	23 (95.8)		
	Unsure	0 (0.0)	1 (33.3)	0 (0.0)		
	Total 28	1 (3.6)	3 (10.7)	24 (85.7)		

anti-HBs (hepatitis B surface antibody); HBV (hepatitis B virus)
All values reported as frequency (*n*) and percentages (%); *n* (%)
* branching logic used to answer question on completion of vaccine schedule and timing since last dose, taken from those who answered 'yes' to previous vaccination (*n*=66)
† Chi square testing (or Fischer's exact test where needed) to determine *p*-value for all variables
‡ Test included those who were previously vaccinated in the category 'yes' and 'no' only (*n*=84)
§ Test included those who were previously vaccinated in the category 'yes', 'no' and 'unsure' (*N*=180)
¶ Test included those who knew the time elapsed since their last dose in the category '1-5 years' and '>10 years' only (*n*=56)
# Test included those who knew the time elapsed since their last dose in the category '1-5 years', '>10 years' and 'unsure' (*n*=66)

Table 5: Socio-demographic characteristics and vaccine history for students who remained non-reactive (anti-HBs <10 mIU/mL) following a single dose of hepatitis B vaccine

ID Code	Age	Sex	Race	Nationality	Childhood residence	Course enrolment	Previous HepB Vaccination	Completed three-dose schedule*	Time since last dose*
1	18	Female	Coloured	South African	Urban	Bachelor of Clinical Medical Practice	Unsure	N/A	N/A
2	18	Female	Black	South African	Rural	Bachelor of Health Sciences	Unsure	N/A	N/A
3	18	Male	Black	South African	Rural	Bachelor of Health Sciences	Unsure	N/A	N/A
4	19	Male	Black	South African	Rural	Bachelor of Pharmacy	Unsure	N/A	N/A
5	19	Female	Black	South African	Rural	Bachelor of Health Sciences	Yes	No	>10 years ago

anti-HBs (hepatitis B surface antibody); HBV (hepatitis B virus); N/A (not applicable)
*N/A – responses to 'completion of a three-dose schedule' and 'time since last dose' only apply to students who respond 'yes' to having received previous HepB

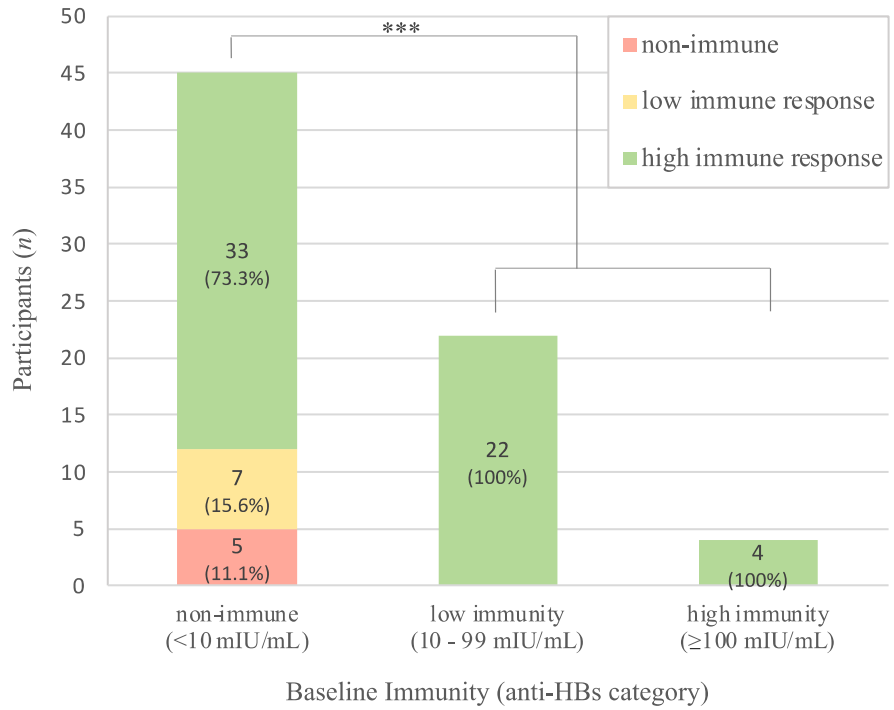

Fig. 2 – Hepatitis B immune response following vaccination with a single 'booster' dose, grouped according to pre-vaccination (baseline) hepatitis B surface antibody (anti-HBs) immune category

Participants in various categories post vaccination reported as frequency (*n*) and percentages (%)
Non-immune (anti-HBs <10 mIU/mL), low immunity (anti-HBs 10 - 99mIU/mL), high immunity (≥100 mIU/mL)
***McNemar's test for significance ($p<0.001$) for paired categorical data

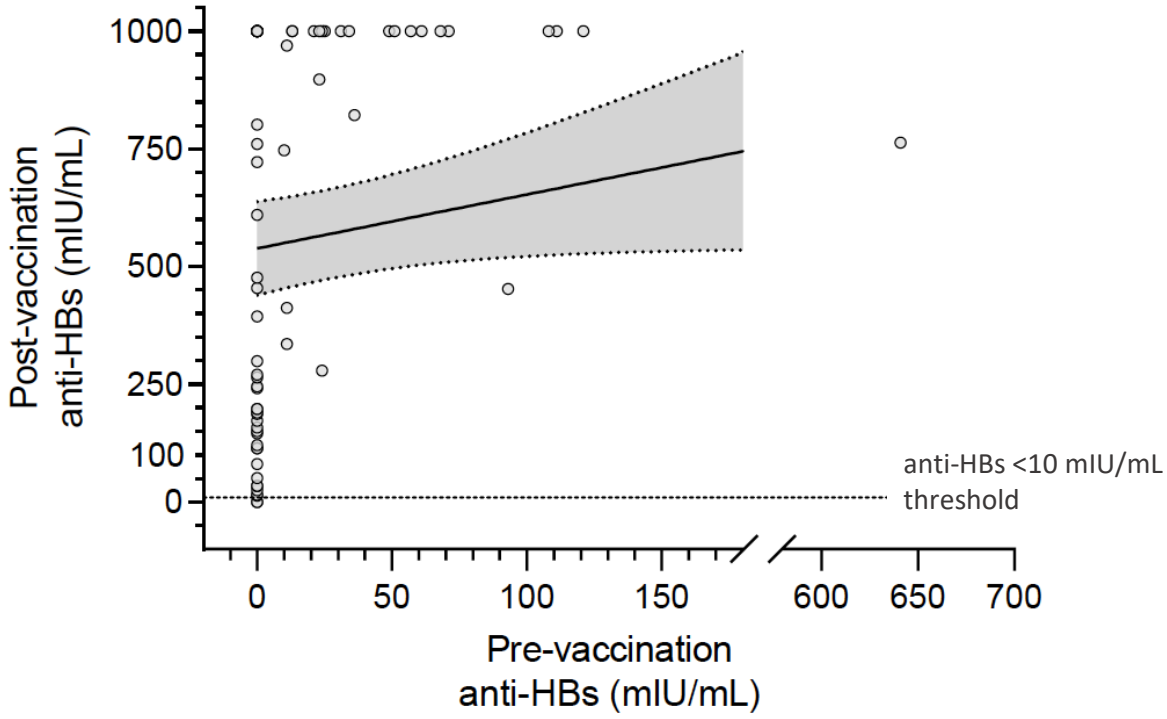

Fig. 3 – Post-vaccination anti-HBs level in comparison with pre-vaccination anti-HBs level (Spearman's rank correlation (rho) $r_s = 0.566$, $p<0.001$)

Shaded area includes 95% confidence interval for linear plot; horizontal dotted line indicates anti-HBs <10 mIU/mL (below which values are non-reactive)
anti-HBs (hepatitis B surface antibody)

Discussion

This study aimed to determine the effect of a single 'booster' dose of HepB administered by the Wits CHWC to all FHS undergraduate students in their first year of study. A pre-vaccination questionnaire was completed by participants, and their baseline anti-HBs titres determined. During the second phase of the study, serology was repeated to evaluate individual pairwise differences in anti-HBs levels stratified according to previous vaccination status.

At the start of the 2021 academic year, more than 900 students registered for various first year health science programs, all of whom were instructed to receive HepB as stipulated by the Wits health policy for the prevention of HBV infection [36]. Approximately 25% of the 900 registered FHS students (n=230) were sampled for participation in this study at CHWC, with 222 satisfying the selection criteria. This implies that the remainder of HCSs (~75%) may have received their vaccination on alternative dates (when the study team was unavailable), at private health facilities, or not at all. The CHWC has no current mechanism to record the vaccination practices of the latter two groups, and no active investigation or follow-up is made on their vaccine status by CHWC or other Wits administrators. Pre-vaccination (baseline) anti-HBs testing and analysis was performed on 180 students (81% of the eligible participants, Fig. 1), with only 71 (39%) of these returning for post-vaccination testing. The poor follow-up may be because of a lack of awareness and appreciation for the potential risk of HBV among young HCSs.

The mean age of participants was 19 years and most participants were female, characteristics consistent with the current admission statistics in the FHS undergraduate programs at Wits. The distribution of the different race groups was representative of national South African demographics (80.6% Black and 8.0% White) [41]. No students registered to nursing, physiotherapy and occupational therapy disciplines participated in this study. The reason for this is unclear and raises concerns particularly with regards to nurses, who represent one of the highest exposure-prone HCW groups [42]. Further, the lack of representation limits the generalizability of our results and what inferences we can make about the target population.

Less than half of the participants (44%) had reactive anti-HBs samples pre-vaccination. Further when compared to European anti-HBs threshold values for adequate immunity among HCSs (anti-HBs ≥100 mIU/mL), only 9% of our study population met this criteria [11,12]. These values were selected based on studies which identified lower rates of break-through infection among people with anti-HBs ≥100 mIU/mL compared to those in a lower immune group of 10 – 99 mIU/mL. However, these studies were conducted in regions with contrasting hepatitis B variants, endemicity and population characteristics [43,44]. Further studies would be needed to determine the utility of these thresholds in the South African setting.

Most participants (56%) had non-reactive samples, with anti-HBs levels of <10 mIU/mL at baseline, and were thus considered not immune to HBV. Baseline levels showed no significant association with sex, nationality, or childhood residence. However, a statistically significant difference between race groups was found. These results should be viewed with caution due to the lower representation of non-Black students. In addition our study does not account for potential confounding factors such as socio-economic status, access to health-care facilities, or other social factors which may account for the race differences seen here rather than any biological or genetic reasons.

The high proportion of non-immune students in our study (56%) could be due to inadequate vaccination (no previous vaccination or incomplete schedules) or the result of waning immunity in those who were previously vaccinated. Anti-HBs titres have been shown to wane from as early as one year following vaccination in immunocompetent responders [1,45]. Similarly, waning levels of anti-HBs have been seen across various HCS populations several decades following successful complete three-dose HepB schedules. In countries where HBV endemicity is low, including those with higher vaccine coverage, better health infrastructure and explicit safety and prevention policies, individuals show persistent immunity lasting up to 20 years following vaccination [46–48]. Comparatively, in countries where HBV endemicity ranges from intermediate to high levels, similar to that found among South African populations, immune levels are seen to wane earlier [49,50]. Newly enrolled HCSs in Hong Kong showed persistent levels of anti-HBs in just 18.9% of previously vaccinated students more than 10 years later [51]. The challenge of waning immunity can be addressed by additional booster vaccination to stimulate immunological memory and elicit an anamnestic response in persons who previously responded. Following booster vaccination

with either a single or three booster doses, 85% and 100% of individuals with baseline anti-HBs <10 mIU/mL responded positively, respectively [51]. A key difference between the latter studies and ours, is the inclusion of only participants who had received documented proof of a complete HepB series , which was not possible in the present study, but rather highlights key weaknesses in current policy.

Despite the request by CHWC for all students receiving vaccination to bring a copy of their childhood immunisation cards to the scheduled vaccination appointment, only a minority of students were able to comply with this request. As such, the vaccinators only administer a single 'booster' dose to all students born after the introduction of HepB in the South African EPI, under the assumption that these students had received at least three-doses of HepB in childhood [28]. Considering that vaccine coverage for the third dose of HepB (HepB3) in South Africa, from the time of introduction (1995) up until 2003 (age of the youngest enrolled study participant), has fluctuated between 74% and 80% [31], this policy may be based on inaccurate presumptions and the single 'booster' dose of vaccine may be insufficient for at least a quarter of HCSs.

Data on vaccine status was largely dependent upon the participant's (or their caregiver's) memory. The dependence on recall introduced bias into our study, meaning our data is less reliable than those corroborated with records and should thus be interpreted with caution. Unfortunately, the absence of health records is not a unique finding to our study, as many low and middle income countries report similar findings. In cases where health records are available, information is often inaccurate and/or incomplete and thus solely relying on records alone is not feasible either [52–55].

Our study revealed no significant differences between vaccination status ('yes', 'no' or 'unsure') and baseline anti-HBs levels. However, it is difficult to draw conclusions from this finding due to potential biases in self-reported vaccination status. Reasons include the large number of students who were uncertain of their vaccine status, as well as the potential misclassification by some participants (who reported either 'yes' or 'no') due to recall or social desirability bias. Epidemiological studies such as ours are particularly susceptible to this, where a power dynamic between researcher and participant occurs and information given tends to overestimate 'good' health behaviours. In our case, participants may have been reluctant to disclose a history of no or incomplete prior vaccination [56].

Most of the participants (77,2%) who reported previous vaccination had completed a three-dose HepB series. Within this group, significantly higher pre-vaccination anti-HBs titres were found in those with a complete schedule when compared to students with a partial schedule (p=0.045), accounting for a baseline immune-prevalence of 47% and 27%, respectively. This finding supports the conclusions of other studies which demonstrate significant positive correlations between anti-HBs titres and completion of HepB series up to 20 years following childhood vaccination [47,48].

Post-vaccination analysis was limited to 71 students who returned between 1- and 3-months following vaccination (39% of study sample). Despite the high number of students who were lost to follow-up (n=109), there were no significant differences in student characteristics between those who returned and those who did not. The only exception included those enrolled in the Bachelor of Oral Health Sciences course who were not represented in the post-vaccination analysis.

Of concern, this study revealed that 7% (5/71) of students returning for follow-up remained non-reactive following the 'booster' dose. All were sero-negative at baseline, and only one student reported receiving a partial vaccine schedule more than 10 years prior. The other four students (80%) were unsure of their previous vaccination status. The absence of any history of vaccination prohibits the attribution of non-response to any particular factors. It is not known whether participants have completed the primary three-dose schedule necessary to accurately define HepB non-response [57]. Furthermore, HBV infection, which may confound the interpretation of serological testing, was not evaluated in this study. Current Wits vaccination policy does not include the testing of HCSs for hepatitis B infection nor immunity following vaccination [36]. As such, students and faculty are not aware of susceptible individuals prior to clinical exposure and urgent policy reform to include such tests are needed. As per this study protocol, all five students were referred to a hepatologist for further investigations and management.

Previous vaccine status, completion of the three-dose schedule (partial or complete) and timing of the last dose prior to receiving the 'booster' vaccine had no effect on post-vaccination anti-HBs levels. This disconnect may be due to recall bias and misclassification mentioned earlier. Pre-vaccination anti-HBs (baseline immunity) was the only variable that

was significantly associated with an immune response following vaccination (p<0.001) with a moderate positive correlation for the entire returning cohort (r_s = 0.566). The anti-HBs levels of students with non-reactive pre-vaccination serology (<10 mIU/mL) were not reported quantitatively, and thus all taken to be 0 mIU/mL. Consequently, tests of correlation within this subset could not be performed. These findings underscore the utility of pre-vaccination anti-HBs testing as a predictive factor for the effectiveness of a 'booster' dose in re-establishing immunity (in the presence of waning immunity), as well as preventing the unnecessary administration of a booster dose in those with already elevated levels of anti-HBs. However, a cost-effectiveness analysis should be conducted to compare universal adult HepB vaccination to the costs of anti-HBs testing prior to vaccination among HCSs.

Limitations

Less than half the students enrolled returned for post-vaccination testing introducing attrition bias into the study. Together with the potential of recall and social desirability bias (previously described), the results reported here may not be generalizable to HCSs within the FHS at Wits or at other academic institutions. Factors, such as obesity, chronic illness, immune compromised states, tobacco use, genetic haplotypes [57–59], known to affect the immunogenicity of the vaccine, were not investigated in the present study. Finally, serological markers of either previous, acute, occult or chronic HBV infection were not evaluated in this study. Therefore, immune status at baseline and following vaccination cannot be attributed to vaccination alone. Despite these limitations, this study provides valuable insights into current practices and policies at a South African tertiary institution, assessing the immune status and effect of 'booster' vaccination in at-risk students.

The way forward: recommendations

After receiving a 'booster' HepB dose, 7% of HCSs remained non-immune, highlighting that despite receiving the "booster" dose the HCSs were unprotected against HBV. Testing for immunity after receiving the booster is an important step in monitoring and ensuring adequate protection. We therefore recommend strengthening institutional vaccination policies and record keeping systems within the FHS and CHWC at Wits. Childhood vaccination records do not provide reliable proof of protection because immunity is expected to wane

with time after a successful primary series. Nevertheless, digital platforms to centralize and store student historical and current vaccine records can provide a database to ensure completion of primary schedules, guide further management for students at risk and assist in quantifying true vaccine coverage rates for HBV amongst FHS students at Wits. Immunity testing prior to administration of HepB vaccination will avoid the administration of unnecessary booster doses to those who are adequately protected. However, a cost-effectiveness study will be required to determine the best approach. On the other hand, the inclusion of timely post-vaccination testing for immunity is highly recommended to ensure adequate protection of students before they enter clinical training. 'Non-responders' should be tested for HBsAg and those who are chronically infected counselled, and not employed in positions where they are a risk to their patients. HBsAg-negative non-responders should receive a total of 6 HepB doses to be classified as true non-responders and must receive hepatitis B immunoglobulin post-exposure. Institutional subsidy of immunity testing and immunization will ensure higher vaccine coverage and adequate immunity to ensure that HCSs are adequately protected when undertaking their clinical duties.

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APPENDICES

Appendix 1: Approved Research Protocol

UNIVERSITY OF WITWATERSAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

SCHOOL OF PATHOLOGY

HEPATITIS B VIRUS VACCINE COVERAGE AND PREVALENCE OF SEROCONVERSION IN HEALTH SCIENCE STUDENTS AT THE UNIVERSITY OF THE WITWATERSRAND, 2021

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Abbreviations

Anti-HBs - antibody to HBsAg

BBF - blood and bodily fluids

CH - Campus Health

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

FHS - Faculty of Health Science

HBsAg - hepatitis B surface antigen

HBV - hepatitis B virus

HCWs – health-care workers

HIV - human immunodeficiency virus

HVDRU - Hepatitis Virus Diversity Research Unit

ICF – Informed Consent Form

NHLS - National Health Laboratory Service

PIS - Participant Information Sheet

SANAS - South African National Accreditation System

SSA - sub-Saharan Africa

Wits - University of Witwatersrand

Introduction

2.1 Background and Literature review

Hepatitis B virus (HBV) is a major global public health concern with over 257 million people chronically infected, a third residing in Africa (1). In 2015, ~887,220 persons died as a result of complications of chronic HBV infection, including cirrhosis and hepatocellular carcinoma (1). Prevalence of HBV, determined by the number of individuals who are hepatitis B surface antigen (HBsAg)-positive, varies globally. In many parts of sub-Saharan Africa (SSA) HBV is hyperendemic (>8%) (2). HBV is estimated to be up to 100 times more infectious than human immunodeficiency virus (HIV) (3) and can survive outside the body for up to 7 days while retaining its capacity to cause infection (4).

Globally, occupational exposure to infectious blood and bodily fluids (BBF), through percutaneous or muco-cutaneous routes, have been implicated as a major cause of HBV infection among susceptible HCWs (5). Annually, an estimated 2.1 million HCWs are exposed to a sharps injury, contaminated with HBV from infected patients, leading to ~66,000 work-related HBV infections (6). In an unvaccinated individual, the risk of acquiring HBV infection after only a single exposure, ranges from 6-30% (5).

During their tertiary education, university health science students are exposed to clinical situations similar to those of their professional counterparts. As such, accidental exposure to BBF can occur within this population. In fact, due to their lack of confidence and experience in clinical procedures and insufficient training in the correct use of personal protective equipment, rates of exposure may be greater among medical and nursing students than their respective qualified counterparts (7).

According to the World Health Organisation, all HCWs and students in training should be vaccinated against HBV, if they have not received a complete primary series (8). In addition, post-vaccination serological testing is recommended 1-2 months after the administration of the last vaccine dose (8): antibody to HBsAg (anti-HBs) level of >10mIU/mL heralds immunity (9).

There is a paucity of data regarding vaccination practices and policies in higher education institutions in South Africa. The self-reported vaccination status and the perceptions around vaccinations of health science students at Stellenbosch University, South Africa were investigated. Of the 403 students who participated, 90% of students reported having completed or were in the process of completing their HBV primary vaccination series, but only 60% had provided proof to the university. Though HBV vaccination is mandatory, the university had no formal follow-up system and many students remained confused about the process (10).

In the United States, vaccine coverage is very high amongst health professional students: with more than 90% of students having documented proof of having received the 3 primary vaccine doses. Amongst these students 83.9% - 92.6% showed protective anti-HBs seroconversion (11). Those who did not mount an adequate immune response to the complete vaccine series are known as vaccine “non-responders” and would require further HBV testing, repeat vaccination and additional preventative measures before any protection against HBV is assumed. Of the students who did not receive a complete vaccine series, a significantly lower proportion of students (75.9% - 84.6%) had adequate seroconversion values (11). These results indicate the need for complete HBV vaccination as well as post-vaccination serology testing in order to identify those who did not respond to the vaccine to effectively manage thereafter.

2.2 Statement of the problem

The University of the Witwatersrand (Wits) requires for all first year undergraduate students registered to the Faculty of Health Science (FHS) to be vaccinated against HBV and Measles, Mumps and Rubella (12).

Students born after 1998 are expected to bring their Road-to-health-cards (childhood immunization cards) to the university’s Campus Health (CH) as evidence of receipt of the complete primary HBV vaccine series included in the national EPI. If students have proof of this, one booster dose of HBV vaccine is administered at CH. International or South African students without proof of a completed vaccination series should receive 3 doses of HBV vaccine given at 0, 1 month and 6 months apart. However, due to resource constraints, any student born after 1998 is given only one booster dose, regardless of proof of previous vaccine receipt. Three-dose schedule is reserved for those born before 1998.

CH maintains the confidential records for students who receive on-campus vaccination. Students may choose to get their vaccinations done off-campus but no record of this is kept. The true numbers of those vaccinated cannot be known. Furthermore, a lack of post-vaccination serological tests prevents students from being able to confirm immunity, leaving some vulnerable to infection despite vaccination.

To date, few serological studies have been done in African health science students to confirm immunity or identify those who remain at risk of HBV infection. To overcome this paucity of data, this study aims to determine the HBV vaccine coverage among all FHS students at Wits and determine the proportion of first-year FHS students who are serologically immune pre- and post-vaccination. Findings within this study may aid in the development of guidelines and policies within the university and the wider country to ensure all health science students are adequately protected against HBV infection before any clinical exposure.

Study Objectives

3.1 Research Questions

1. What knowledge and practices do undergraduate FHS students possess regarding HBV vaccination at the University of Witwatersrand?
2. What is the proportion of undergraduate students registered within the Faculty of Health Sciences that have received the three-dose HBV vaccine?
3. What proportion of first-year undergraduate FHS students are immune-protected pre- and post- HBV vaccination?

3.2 Hypothesis

Although a mandatory policy states that all students registered within the Wits FHS must be vaccinated against HBV in their first year, no robust record keeping exists to enforce this policy, and as such vaccine coverage remains unknown. Of those who

are vaccinated, a proportion of students may not have mounted an adequate seroprotective response and without post-vaccination serological tests, the number of students who remain at risk of infection remains unknown. We therefore hypothesize that a proportion of students remain susceptible to HBV infection as a result of incomplete vaccination or non-responsiveness to a completed vaccine series.

3.3 Aims & Objectives

The main aim of the study is to determine the HBV vaccination coverage in all students registered to the Wits FHS and determine the proportion of first-year students who have anti-HBs seroprotective levels pre- and post- HBV vaccination from January 2021 to June 2021.

The specific objectives will be to:

1. Determine knowledge and practices regarding HBV vaccination in all undergraduate students registered to the FHS at the Wits between January and June 2021
2. Describe the Hepatitis B vaccine coverage (complete, partial or unvaccinated) in all undergraduate FHS students between January and June 2021, stratified by year and program of study.
3. Determine the proportion of first-year undergraduate students registered to the FHS at Wits, between January and June 2021, who are sero-protected against HBV infection pre- and post- HBV vaccination stratified by previous vaccine status.

Methodology

4.1 Study Setting

This study will be conducted at the Faculty of Health Sciences, University of Witwatersrand. All laboratory testing will be performed at a SANAS (South African

National Accreditation System) approved laboratory, the National Health Laboratory Services (NHLS), by trained and experienced personnel.

4.2 Study Design

(Objective 1 and 2) This component of the study will be cross-sectional in design conducted on all undergraduate students enrolled in the FHS from January to June 2021. It will consist of an electronic self-administered questionnaire sent to all students, to determine HBV vaccine coverage and students' knowledge and practices regarding vaccination.

(Objective 3) The seroprevalence component of the study will be longitudinal and offered to all first-year undergraduate FHS students enrolled at Wits from January to June 2021 before vaccination and 1-2 months after receiving their booster dose.

4.3 Study Population

(Objective 1 and 2) The study will involve all undergraduate students enrolled in the Faculty of Health Science at Wits from January 2021 to June 2021. According to the university records, a total of 3,785 students are enrolled in the Faculty of Health Science (Appendix 1) in 2020.

(Objective 3) The seroprevalence part of the study will consist of registered first-year undergraduate students with an approximate total of 924 students (2020 value).

4.3.1 Inclusion criteria

- Registered undergraduate student in the Faculty of Health Science, University of Witwatersrand over the age of 18 years.
- (Specifically to objective 3 only – born in 1998 or later)
- Must provide written informed consent
- Students of all Nationalities

4.3.2 Exclusion criteria

- Unable or unwilling to give informed consent

4.4 Sampling, Sample Size and Power Calculation

4.4.1 Sampling

A pretested, semi-structured self-administered questionnaire will be sent to all students who fulfil the eligibility criteria (poor response rate expected with electronic surveys (10)).

All registered first-year FHS students will be invited to participate in the collection of blood samples pre- and post- HBV vaccination to determine their anti-HBs levels.

4.4.2 Sample size and power

(Objective 1 and 2) The questionnaire will be sent to all students via university email however the minimum number of responses required is calculated using the following single population proportion formula:

$$n = \left(\frac{z}{d}\right)^2 \hat{p}\left(1 - \hat{p}\right)$$

$where, z = level\ of\ statistical\ significance\ (1.96)$

$d = margin\ of\ error$

$\hat{p} = expected\ population\ proportion$

In their study, Le Roux and Dramowski (10) reported a 90% prevalence of HBV vaccination among health science students at another South African university. Assuming a 95% confidence level (CL) and a 5% margin of error, the sample size needed for this study will therefore be 139.

(Objective 3) Since we do not know what proportion of the population will have protective levels of anti-HBs we assume a proportion of 50%. Using a 95% CL and 5% margin of error the required sample size is 385.

4.5 Variables, Definition and Data Sources

4.5.1 Definition of Variables

4.5.1.1 Outcome variable

The outcome variables will be measured as:

- Vaccination status: a categorical variable with three levels; '0'= complete (three or more doses), '1'= partial (1 or 2 doses), '2'= unvaccinated
- Seroconversion status (anti-HBs >10mIU/mL): a binary variable defined as '0'= yes, '1'= no

4.5.1.2 Explanatory Variables

The explanatory variables will include the socio-demographic characteristics and clinical information. Please see REDCap questionnaire "Hepatitis B Vaccination Survey" and "Hepatitis B Serology Survey" – attached separately for full list of variables.

4.5.2 Data Source

All socio-demographic as well as clinical information variables will be obtained from self-administered questionnaires.

4.6 Recruitment and Data Collection

(Objective 1 and 2) A semi-structured questionnaire will be created and managed using an Electronic Data Capture (EDC) system (e.g. REDCap). The questionnaire will be piloted on 10-15 undergraduate students to assess for unambiguity and clarity of questions. The final questionnaire will consist of various sections related to socio-demographic data, clinical history, risk behaviour and knowledge and practices of students regarding HBV vaccination. A link to the questionnaire will be made available and emailed to all undergraduate students within the Faculty of Health Science during

March 2021, using their University email addresses. Attached to the email will be the Questionnaire: Participant Information Sheet (PIS) (Appendix 2). Data collection will take place over 6 weeks with reminder emails sent every second week if required. A list of student email addresses will be obtained from the Faculty Registrar after all approvals have been received. The data will then be captured using the REDCap database. All completed questionnaires will be void of any and all personal identifiers. (Objective 3) For the sero-prevalence component of the study, all first-year undergraduate FHS students will be invited to participate via email through the Faculty Registrar office and printed Information sheets available at Campus Health. An outline of the study design, objectives and procedures as indicated in Serology: PIS will be attached to the email (Appendix 3). If the student wishes to participate or find out more they will select a date and time via email suitable for them to meet the researcher or qualified elected proxy. At this meeting, the researcher (or elected proxy) will ensure the participant understands all the aspects of the study, implications of different test results, potential risks involved, and answers any and all questions the participant may have. Serology: ICF will be issued to the participant emphasizing all aspects of the study, the entirely voluntary nature of participating or withdrawing from the study at any time, as well as the said benefits and potential risks to the participant (Appendix 4). The participant is then given another opportunity to clarify any queries or concerns he or she may have. If they decide to participate then both the participant and researcher will sign and date the consent form. A copy of the Serology: ICF will be provided to the participant to take with them while the original Serology: ICF remains at HVDRU.

After informed consent is obtained, the participant will be issued a unique identity number for all data collected for that participant thereafter. A short paper questionnaire

will be issued to the participant for completion (Hepatitis B Serology Survey). The participant will then be issued a blood form and accompanied to the Day Ward at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) where trained nurses will assist with drawing of venous blood samples (2mL-3mL) in accordance with the National Infection Prevention and Control standards. Nurses within the CMJAH Day Ward are qualified to draw blood samples (registered with the Health Professions Council of South Africa). Blood samples will be collected in EDTA tubes, labelled with the unique participant identity number. All samples will then be tested for anti-HBs and quantified by means of laboratory-based immunoassay e.g. chemoluminescence immunoassays (CLIAs) Roche Elecsys® Anti-HBs II (Roche Diagnostics, Germany) . All routine tests will be performed by the NHLS using standard operating procedures and according to the manufacturer's instructions to minimize errors. Each participants short-questionnaire and serology results will be captured directly onto the REDCap database using the unique identity number only.

A similar procedure of events will take place after students have received their vaccination. Email invites will be sent to first-year students inviting them to participate in the serological study in the 1-2 month period after vaccination. Campus Health Vaccination Dates (Appendix 5) will guide this process, however, monthly email invites will be sent to accommodate students who receive their vaccines off-campus at various dates. Students born after 1998 receive one dose of booster vaccine regardless of their proof of prior vaccine receipt.

4.7 Data Management

All data captured within REDCap will be de-identified and access to the database will be restricted to the study team with the use of a personal username and password.

Participants who agree to blood collection will have their personal identifying details (and matched unique study identity number) kept in a separate password-protected electronic log file for the sole purpose of contacting the participant with their anti-HBs results. This log will only be accessible to the principal researcher, study supervisor and collaborating nurse in charge of the Vaccination program at Campus Health.

Data checks and validations will be encoded into the REDCap database to ensure data quality during entry. When all data has been collected and captured on the REDCap database, it will then be exported into an Excel spreadsheet for data cleaning. All missing data and duplicate entries will sought and excluded. Data will then be exported for analysis.

Data Analysis Plan

OBJECTIVE	VARIABLES AND STATISTICAL ANALYSIS
1	• Descriptive analysis will be performed • Continuous variables will be reported as means ± standard deviation for normally distributed data and median /Interquartile range (IQR) for non- normality. • Categorical variables will be expressed as frequencies and proportions. • Student awareness of policies and practices of HBV vaccination at Wits will be reported at frequencies and proportions and compared between year of study within and between registered programs through chi-squared analysis
2	• HBV vaccination status will be categorised as 'complete' (3 or more HBV vaccine doses), 'partial' (1 or 2 HBV vaccine doses) or 'unvaccinated' (never received any doses). The proportion of students in each category will be calculated by dividing the number of students in each vaccine status category by the total number of students recruited and multiplying by 100. • Further stratification according to exploratory variables such as sex, race, registered health science programme, year of study etc. will allow for further statistical tests such

	as a chi-squared to determine if vaccine coverage was statistically different among various groups. • Multiple logistic regression analysis will be performed to identify factors influencing vaccine coverage among students
3	• Titres of anti-HBs ≥10 mIU/ml will be considered positive and protective against HBV infection, while titres <10 mIU/ml will be considered non-protective. • Pre-vaccination serology: The proportion of participants in each category will be calculated and further stratified according to the duration of time since their last vaccine dose and number of doses received. • Post-vaccination serology: The proportion of participants in each category will be calculated 4 weeks after vaccination. Further regression analysis will be performed to identify risk factors in those who remain unprotected post- HBV vaccination. • The correlation between pre- and post-vaccination antibody levels will be determined by the Spearman's Rank correlation test

All statistical analysis will be done using Stata/IC 15.1 statistical software for Mac (Stata Corp 800-STATAPC, USA), at 0.05 level of significance.

Data Storage

Data will be maintained and stored in the REDCap database for a period of 6 years according to regulatory and institutional requirements. Blood samples will be discarded by the NHLS according to their standard operating procedures (approximate time of one week) after specimens have been analysed and results obtained.

Ethical Considerations

7.1 Ethics and Approvals

Any student identifiers will be coded to maintain anonymity and confidentiality. All electronic databases will be password-protected and accessible to the immediate

study team only. Any students found to have low immunity to HBV despite vaccination will be contacted and referred to CH for further HBV testing, revaccination and serology testing, and/or referral to a specialist hepatologist at CMJAH.

Ethics approval will be sought from the Human Research Ethics Committee (Medical), University of the Witwatersrand before the commencement of this study. Further approval to carry out the study will be requested from the University Registrar and individual programme Heads of Department within the Faculty of Health Science, University of Witwatersrand.

7.2 Declaration of Personal Conflict of Interest

I, Nisha Makan, am currently employed by the University of Witwatersrand in the Unit for Undergraduate Medical Education within the Faculty of Health Science. As the Head of Assessment, I have unrestricted access to the third and fourth year medical student results as well as demographic information. All invitations to students will go via Faculty registrar office or CH to avoid me personally sending emails. Questionnaires will be anonymous. Third and Fourth year medical students will not be invited to participate in the seroconversion study.

7.3 Risks and Benefits

7.3.1 Potential Risks for participants

Contact numbers are provided in Serology: PIS if such adverse events occur.

7.3.1.1 Venipuncture

Localised pain, discomfort or bruising can occur at the site of venipuncture. Infrequently fainting may occur.

7.3.1.2 Psychological Stressor

Study participants may experience anxiety or distress when contacted about their HBV immune status. All arrangements and referral systems will be streamlined for participants to ensure swift and appropriate management effects.

7.3.2 Known Potential Benefits

Participants in this study do not have any guaranteed direct benefit. Those who participate and learn of their anti-HBs status may be reassured if levels are indicative of protection or seek further management, if found to be non-responsive to vaccination. For the majority of the study participants, who take part in the online questionnaire, their contribution to the study will lead to further understanding of HBV vaccination practices among high-risk university students, potential factors associated with vaccine uptake, and the possible revision of policies and recommendations made by the university for the prevention of HBV infection among health science students.

Strengths and Limitations

The large sample size allows sufficient power to determine the HBV vaccine coverage and prevalence of anti-HBs antibody and the potential risk factors associated with non-seroconversion. A significant limitation of this research is the possibility of missing data during data capture by the participants and a particularly high non-response rate expected with electronic self-administered questionnaires. However, to overcome this, all participants with missing data will be dropped from further analysis and bi-weekly reminders through email will be sent to maximise the sample size. Recall bias may be a further challenge. Another limitation is the cost of laboratory tests to be conducted and consumables required.

Project Management

9.1 Timelines

This study will run from January 2021 to December 2021. The milestones and time frame are shown below:

	2020					2021									
	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct
Literature review															
Preparing protocol															
Protocol assessment															
Ethics application															
Amendments / Approval															
Data collection - Serology															
Data collection - Questionnaire															
Data analysis															
Writing up - dissertation															

9.2 Funding

Objectives 1 and 2 are not expected to incur any costs.

Objective 3 will cost an estimate R510 000, assuming all students registered in first-year wish to take part in both pre- and post- vaccination testing. The cost takes into account fees for labour, consumables, testing and printing of results. Funding is available through the HVDRU grant and Alive consortium (if necessary).

OBJECTIVE 3 - Seroprevalence study		
	Cost/ item	Cost for 924 students x 2 (pre- and post-vaccination)
Printing (ICF & PIS)	R 1.50	R 2 772
anti-HBs tests (NHLS) incl. VAT	R 275	R 508 200
TOTAL		**R 510 972**

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Appendices

11.1 Appendix 1

Table 1: The number of students enrolled in the various undergraduate academic programmes in the Faculty of Health Science at the University of Witwatersrand in 2020.

PROGRAMME	# of students enrolled
Bachelor of Clinical Medical Practice (BCMP)	171
Bachelor of Oral Health Sciences (BOHSc)	46
Bachelor of Health Sciences (BHSc)	508
Bachelor of Medicine and Bachelor of Surgery (MBBCh)	1828
Bachelor of Nursing	171
Bachelor of Science in Physiotherapy	273
Bachelor of Science in Occupational Therapy	268
Bachelor of Pharmacy	355
Bachelor of Dental Science (BDS)	165
TOTAL	**3785**

11.2 Appendix 2

QUESTIONNAIRE: PARTICIPANT INFORMATION SHEET

HEPATITIS B VIRUS VACCINE COVERAGE AND PREVALENCE OF SEROCONVERSION IN HEALTH SCIENCE STUDENTS AT THE UNIVERSITY OF THE WITWATERSRAND, 2021

Good day,

My name is Nisha Makan and I am a medical doctor and MSc of Vaccinology student at the University of Witwatersrand. I would like to invite you to be a part of my research study which looks to determine the vaccine coverage rates of Hepatitis B among all Health Science students at the university.

Why participate?
I am kindly requesting you to take part in this research study, as your opinions and suggestions may help the university to create better vaccination policies and programs that may benefit future students. The benefits of vaccination extend beyond just protecting the individual who receives them. As future health care workers, vaccines reduce the risk of transmission to your families, fellow colleagues and patients.

What does this study involve?
1) If you agree to participate in this study, you will be asked to complete an online questionnaire. It will be completely anonymous and is divided into multiple sections addressing socio-demographic factors, clinical history, your thoughts and opinions on Hepatitis B vaccinations, and your practices regarding vaccine uptake within Wits. Some questions may be of a sensitive nature but you can skip any questions you do not feel comfortable answering

The questionnaire should take between 5-8 minutes.

What are the possible disadvantages, risks or side effects of taking part?
There are no foreseen risks to you participating in this online questionnaire.
You are under NO obligation to answer any questions you do not wish to.

What do I do If I experience any negative effects from participating in this study?
Please do not hesitate to contact me immediately and personally, if any negative consequences, mentioned above or otherwise, are experienced by you due to your participation in this study.

What are the possible benefits of taking part?
1) There are no direct benefits to you taking part in the questionnaire component. However, your input is invaluable to the outcomes of this study and may assist in developing comprehensive vaccination policies at the university.

Do I have to take part?

No, your participation in this study is **completely voluntary** and refusal to participate will not involve any penalty or loss of benefits. You may discontinue/ withdraw from the study at any stage without giving a reason and without incurring any costs.

How will my taking part in this study be kept anonymous and confidential?
No personal identifiable information will be requested in the questionnaire component of the study thereby maintaining anonymity. We will **not** be able to link any answer or submitted questionnaire to you at any stage.
All submissions will be captured on to the Wits REDCap database which is encrypted and password protected and accessible only to the study investigators.

Any submission of a completed questionnaire will be taken to mean consent for participating in the research.

Contact details
If you would like any information about this study or would like to receive feedback once it is complete please feel free to contact me:

Dr. Nisha Makan
Associate Lecturer
Unit for Undergraduate Medical Education
Faculty of Health Science - University of Witwatersrand
E: nisha.makan@wits.ac.za
T: 079 391 6985 / 011 717 2390

Supervisor of the study:
Professor Anna Kramvis
Director Hepatitis Virus Diversity Research Unit
Department of Internal Medicine - University of the Witwatersrand
E: Anna.Kramvis@wits.ac.za
T: 082 802 9292 / 011 717 2654

If you have any complaints about ethical aspects of the research or feel that you have been harmed in any way by participating in this study, please contact the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg:

Zanele Ndlovu
Administrative Officer
Research Office – HREC (Medical)
E: zanele.ndlovu@wits.ac.za
T: 011 717 2700/1252/2656/1234

Dr Clement Penny
Chairperson of HREC
Research Office – HREC (Medical)
E: clement.penny@wits.ac.za
T: 011 717 2301

I would like to sincerely express my gratitude for your support, time and consideration in assisting me with my research and reading through this Information Sheet.

Dr Nisha Makan
Date: January 2021

11.3 Appendix 3

SEROLOGY: PARTICIPANT INFORMATION SHEET

HEPATITIS B VIRUS VACCINE COVERAGE AND PREVALENCE OF SEROCONVERSION IN HEALTH SCIENCE STUDENTS AT THE UNIVERSITY OF THE WITWATERSRAND, 2021

Dear First-year student,

My name is Nisha Makan and I am a medical doctor and MSc of Vaccinology student at the University of Witwatersrand. I would like to invite you to be a part of my research study which looks to determine what proportion of students have protective levels of antibody against Hepatitis B virus (HBV) infection before and after they receive the vaccine. This is known as a seroprevalence study.

What does this seroprevalence study involve?
This requires 2-3ml of blood to be drawn from individuals for laboratory testing to determine the level of antibodies against the Hepatitis B surface antigen (anti-HBs). If this value is above a certain threshold (>10mIU/mL), the individual is assumed to be protected against HBV infection. If the antibody levels are lower than the protection limit, you will continue with the Wits recommended vaccination schedule and follow up for a repeat blood test to see if you mounted the protective antibodies.

Why do these tests?
According to the World Health Organization (WHO) and the Centre for Disease Control (CDC), all health care workers, including Health Science Students who are at risk of exposure to infectious blood and bodily fluids during their training, should receive a complete course of Hepatitis B vaccination (ie. three-doses if you've never been vaccinated, or 1 booster dose if you've received the infant three-dose schedule). Thereafter, post-vaccination antibody tests (anti-HBs) is recommended 1-2 months after the last vaccine dose to ensure protection.

5-10% of people do **NOT** mount the protective antibody levels (anti-HBs >10mIU/mL) following a complete vaccine series therefore it is important for high risk groups such as ourselves to receive this test.

The South African Department of Health and University policies recommend vaccination but do not provide post-vaccination testing and as a result students may not be aware of their immune status and some students may in fact be unprotected even after a complete vaccine series.

What tests will be done?
The Hepatitis B surface antibody (anti-HBs) only
Once results have been obtained, any residual blood will then be discarded.

What do I do after I receive my results?

You will receive post-test counselling and appropriate referrals and management based on your test results.
A rough guide to further management:

Anti-HBs level	Management
<10mIU/mL	Pre-vaccination - Referred to campus health for complete vaccine series / booster (Wits policy) and re-testing 1-2 months later (if desired) OR Post-vaccination - refer to Campus Health for additional HBV tests, revaccination, and specialist hepatologist at CMJAH for follow up of results
>10mIU/mL	Pre-vaccination - immune to HBV infection but to comply with university policy regarding booster vaccine dose Post-vaccination – immune to HBV infection

What is the procedure?

1) Read through the participant information sheet and decide if you would like to participate in this component of the study or wish to receive more information before you decide
2) Determine a date and time suitable for you to meet with the study investigators to go through the informed consent form (ICF) and address any questions or concerns you may have
3) If you are satisfied and wish to continue with the study, you will sign and date the ICF (2 copies; 1 to remain at the study site and 1 for you to take)
4) Your name and contact details will be recorded in a separate encrypted online file in order to contact you with your test results. You will then be assigned a unique ID number for all other documentation purposes. Only you, the Head Vaccination Nurse at Campus Health and two study investigators will be able to link your personal details with the given ID number.
5) You will be given a short survey to fill out regarding sociodemographic factors, academic program and previous Hepatitis B vaccine status.
6) A trained health worker will then draw 2-3ml of venous blood from your non-dominant arm following strict infection prevention and control processes
7) You will then be contacted within 2-3 days to receive your official anti-HBs results and advised accordingly.

What are the possible disadvantages, risks or side effects of taking part?

- Time taken to complete the consent, discussion, counselling and blood tests ≈ 1 hour
- Side effects to drawing blood – feeling faint, discomfort/pain from venipuncture, slight bruising at the site of injection
- Other potential risks - emotional distress or despair when awaiting results

What do I do If I experience any negative effects from participating in this study?

Please do not hesitate to contact me immediately and personally, if any negative consequences, mentioned above or otherwise, are experienced by you due to your participation in this study.

A list of student health facility contact details have also been included at the end of this document.

What are the possible benefits of taking part?

- you will have access to counselling and education on HBV.
- you will determine your immune status against HBV infection
- If your antibody test shows that you are unprotected, you will be referred to Campus Health for further HBV testing, revaccination and serology and/or referral to a specialist hepatologist at CMJAH based on your results.

Do I have to take part?

No, your participation in this study is **completely voluntary** and refusal to participate will not involve any penalty or loss of benefits. You may discontinue/ withdraw from the study at any stage without giving a reason and without incurring any costs.

Will my test results be kept confidential?

Yes, the document containing your personal information will be an electronic, password-protected document accessible to only the study investigators and Head Vaccination Nurse at Campus Health in order to contact you for your test results.
All other data in the study will be linked to the study ID and therefore no personal data of yours will be printed or published.
You are not required to disclose your results to anyone.

Contact details

If you would like any information about this study / experience any negative outcomes due to the conduct of this study / simply wish to receive feedback once it is complete please feel free to contact:

Dr. Nisha Makan
Associate Lecturer
Unit for Undergraduate Medical Education
Faculty of Health Science - University of Witwatersrand
E: nisha.makan@wits.ac.za
T: 079 391 6985 / 011 717 2390

Supervisor of the study:
Professor Anna Kramvis
Director
Hepatitis Virus Diversity Research Unit
Department of Internal Medicine - University of the Witwatersrand
E: Anna.Kramvis@wits.ac.za
T: 082 802 9292 / 011 717 2654

The Wits Student Crisis Line is available to all Wits students for counselling 24/7/365 on 0800 111 331.

The Campus Health and Wellness Centre is available to assist with primary healthcare and mental health enquires:

- Primary healthcare enquiries – Call 0743077259 or 0824832251
- Mental health enquiries – Call 0766093924

If you have any complaints about ethical aspects of the research or feel that you have been harmed in any way by participating in this study, please contact the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, Johannesburg:

Zanele Ndlovu
Administrative Officer
Research Office – HREC (Medical)
E: zanele.ndlovu@wits.ac.za
T: 011 717 2700/1252/2656/1234

Dr Clement Penny
Chairperson of HREC
Research Office – HREC (Medical)
E: clement.penny@wits.ac.za
T: 011 717 2301

11.4 Appendix 4

SEROLOGY: INFORMED CONSENT FORM

HEPATITIS B VIRUS VACCINE COVERAGE AND PREVALENCE OF SEROCONVERSION IN HEALTH SCIENCE STUDENTS AT THE UNIVERSITY OF THE WITWATERSRAND, 2021

1. I have been given a Participant Information Sheet which explains the features and processes involved in this study; I was given sufficient time to read it.
2. I have been informed by the study investigator about the nature, conduct, and potential benefits and risks of hepatitis B testing.
3. I have had the opportunity to ask questions and feel that they have been adequately answered.
4. I understand that I will be informed of the results of the test in confidence.
5. I understand that any personal identifying information will be used for contact purposes regarding test results only and this information will be kept secure and accessible to only the Head Vaccination Nurse at Campus Health and two study investigators.
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons;
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study, I am free to speak to any of these contacts.

I hereby consent to having a hepatitis B test performed on myself.

_____

Participant's Full name and surname:

_____ _____ _____

Signature / Mark or Thumbprint Date Time

Person providing informed consent information and obtaining consent: Study Investigator:

I, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of HIV and Hepatitis B testing.

_____

Printed Name & Surname

Signature	Date	Time

Dr. Nisha Makan
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Unit for Undergraduate Medical Education
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T: 079 391 6985 / 011 717 2390

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Chairperson of HREC
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E: clement.penny@wits.ac.za
T: 011 717 2301

11.5 Appendix 5

Figure 1: 2020 Campus Health Vaccination Days For Each Program Group at the Faculty of Health Science (Wits)

GROUP	1st DOSE	2nd DOSE	3rd DOSE	NOTES
GEMP 1 (130)				
DATE	FRIDAY 03.01.2020	FRIDAY 07.02.2020	THURSDAY 02/07/2020	Please report major side effects
TIME	11:00 – 14:00	11:00 – 14:00	11:00 – 14:00	
VENUE	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	
MBBCH 1 (230)	1st DOSE	2nd DOSE	3rd DOSE	
DATE	MONDAY 03.02.2020	TUESDAY 02.03.2020	MONDAY 03.08.2020	Please report major side effects
TIME	11:00 – 14:00	11:00 – 14:00	11:00 – 14:00	
VENUE	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	
BOHSc 1 (16) BDS (40) BCMP (55)	1st DOSE	2nd DOSE	3rd DOSE	Please report major side effects
DATE	MONDAY 10.02.2020	MONDAY 09.03.2020	MONDAY 10.08.2020	
TIME	11:00 – 14:00	11:00 – 14:00	11:00- 14:00	
VENUE	CAMPUS HEALTH, EDUCATION CAMPUS	CAMPUS HEALTH, EDUCATION CAMPUS	CAMPUS HEALTH, EDUCATION CAMPUS	
BSc OT 1 (75) BSc PHYSIO (75)	1st DOSE	2nd DOSE	3rd DOSE	Please report major side effects
DATE	THURSDAY 13.02.2020	THURSDAY 13.03.2020	THURSDAY 13.08.2020	
TIME	11:00 – 14:00	11:00 – 14:00	11:00 – 14:00	
VENUE	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	

GROUP	1st DOSE	2nd DOSE	3rd DOSE	NOTES
BHSc 1 (200)				
DATE	MONDAY 17.02.2020	TUESDAY 16. 03.2020	TUESDAY 17.08.2020	Please report major side effects
TIME	11:00 – 14:00	11:00 – 14:00	11:00 – 14:00	
VENUE	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	
B. Pharm 1 (100) B.NURSING (60)	1st DOSE	2nd DOSE	3rd DOSE	
DATE	THURSDAY 20.02.2020	WEDNESDAY 20.03.2020	THURSDAY 22.08.2020	Please report major side effects
TIME	11:00 – 14:00	11:00 – 14:00	11:00 – 14:00	
VENUE	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	CAMPUS HEALTH, MAIN CAMPUS	

Appendix 2: Ethics Clearance Certificate

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

Office of the Deputy Vice-Chancellor (Research and Postgraduate Affairs

TO: Dr N Makan
School of Pathology
Wits ALIVE Consortium
Medical School
University

E-mail: Nisha.Makin@wits.ac.za

CC: Supervisor: Professor A Kramvis
<Anna.Kramvis@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

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

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

DATE: 2021/02/02

REF: R14/49

PROTOCOL NO: **M201157** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Hepatitis B virus vaccine coverage and prevalence of serocoversion in Health Science students at the University of the Witwatersrand, 2021*

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

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr N Makan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M201157

NAME: (Principal Investigator)	Dr N Makan
DEPARTMENT:	School of Pathology Wits ALIVE Consortium Medical School University
PROJECT TITLE:	*Hepatitis B virus vaccine coverage and prevalence of serocoversion in Health Science students at the University of the Witwatersrand, 2021*
DATE CONSIDERED:	2020/11/27
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor A Kramvis
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/02/02

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **«Missing mail merge field»** and therefore reports and re-certification will be due in the month of **«Missing mail merge field»** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

4/2/2020
Date

Appendix 3: Approval from the Office of the Deputy Registrar

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

OFFICE OF THE DEPUTY REGISTRAR

11 February 2021

Nisha Makan
Staff/Student number (A0030278 / 307254)
MSc of Science in Medicine: Vaccinology
School of Pathology

TO WHOM IT MAY CONCERN

"Hepatitis b virus vaccine coverage and prevalence of seroconversion in health science students at the University of the Witwatersrand, 2021"

This letter serves to confirm that the above project has received permission to be conducted on University premises, and/or involving staff and/or students of the University as research participants. In undertaking this research, you agree to abide by all University regulations for conducting research on campus and to respect participants' rights to withdraw from participation at any time.

If you are conducting research on certain student cohorts, year groups or courses within specific Schools and within the teaching term, permission must be sought from Heads of School or individual academics.

Ethical clearance has been obtained: Protocol number (**M201157**)

Research expiration: (2026/02/02)

Potgieter

Nicoleen Potgieter
University Deputy Registrar

Private Bag 3, WITS, 2050, South Africa | **T** +27 11 717 1204/8 | **E** nicoleen.potgieter@wits.ac.za | www.wits.ac.za
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Appendix 4: Turnitin Report Article 1

Questionnaire Final NM.docx

ORIGINALITY REPORT

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File name:	Questionnaire_Final_NM.docx
File size:	194.61K
Page count:	25
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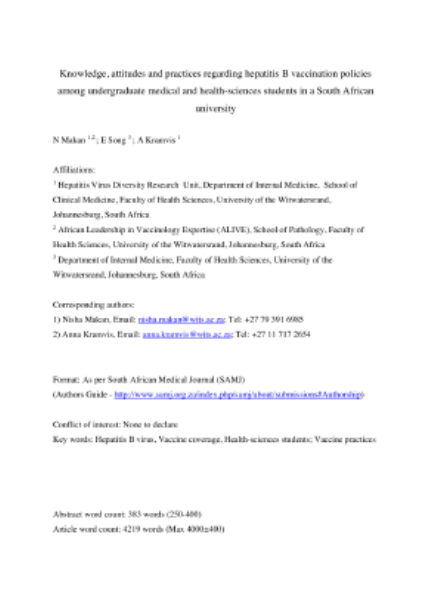
Character count:	41,217
Submission date:	29-Mar-2022 12:05PM (UTC+0200)
Submission ID:	1795931391



Knowledge, attitudes and practices regarding hepatitis B vaccination policies among undergraduate medical and health-sciences students in a South African university

N Makan [1,2]; E Song [3]; A Kramvis [1]

Affiliations:
[1] Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[2] African Leadership in Vaccinology Expertise (ALIVE), School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[3] Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

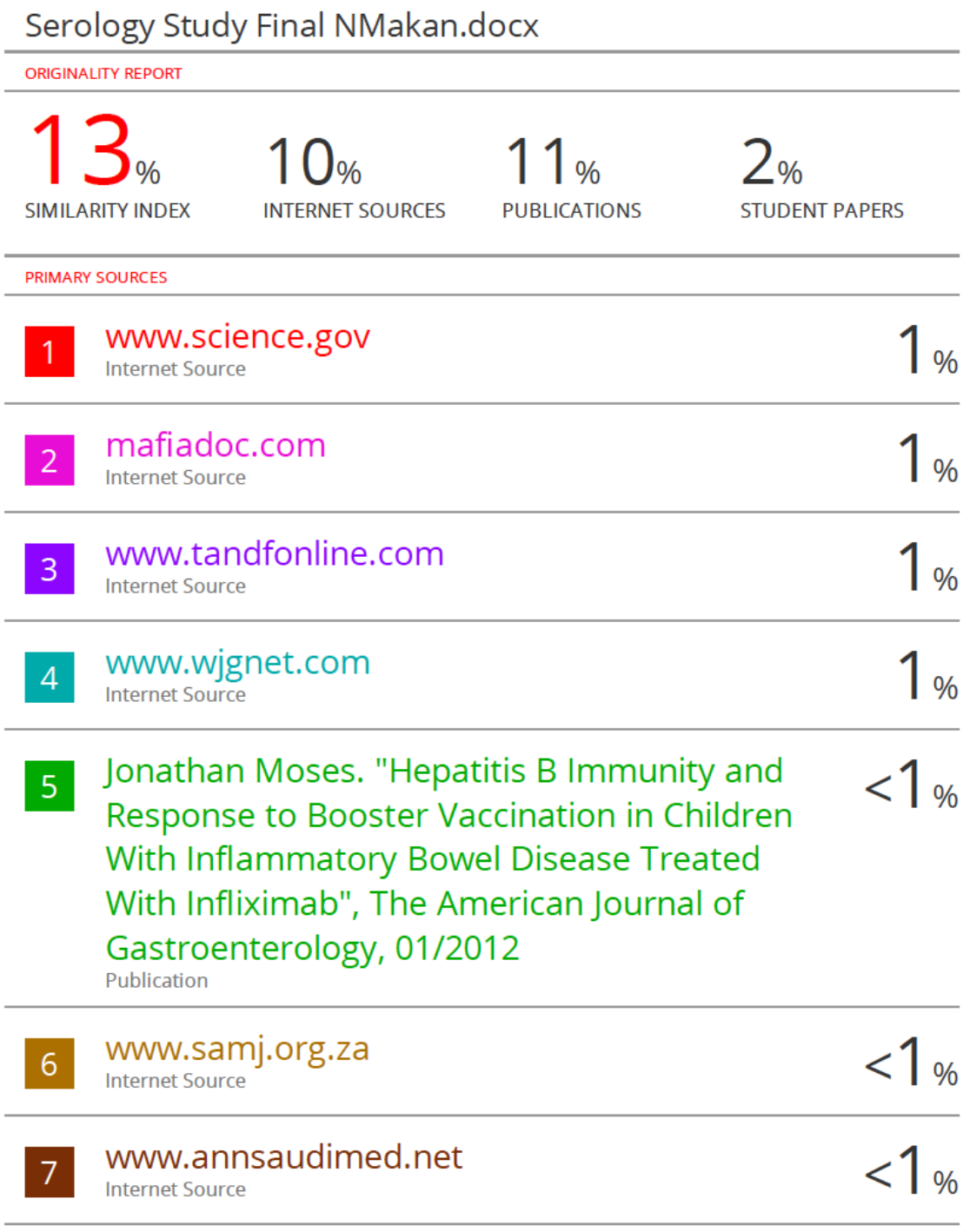
Corresponding authors:
1) Nisha Makan, Email: nisha.makan@wits.ac.za; Tel: +27 79 391 6985
2) Anna Kramvis, Email: anna.kramvis@wits.ac.za; Tel: +27 11 717 2654

Format: As per South African Medical Journal (SAMJ)
(Authors Guide - http://www.samj.org.za/index.php/samj/about/submissions#Authorship)

Conflict of interest: None to declare
Key words: Hepatitis B virus, Vaccine coverage, Health-sciences students; Vaccine practices

Abstract word count: 383 words (250-400)
Article word count: 4219 words (Max 4000±400)

Appendix 5: Turnitin Report Article 2



Serology Study Final NMakan.docx

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5	Jonathan Moses. "Hepatitis B Immunity and Response to Booster Vaccination in Children With Inflammatory Bowel Disease Treated With Infliximab", The American Journal of Gastroenterology, 01/2012 Publication	<1%
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File size:	290.92K
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Submission date:	30-Mar-2022 06:40PM (UTC+0200)
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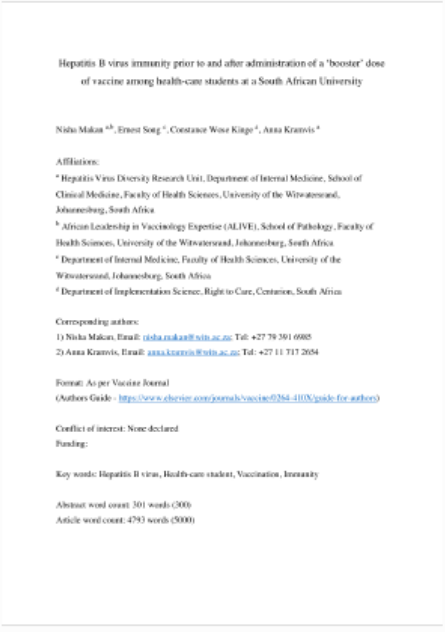

Hepatitis B virus immunity prior to and after administration of a 'booster' dose of vaccine among health-care students at a South African University

Nisha Makan [a,b], Ernest Song [c], Constance Wose Kinge [d], Anna Kramvis [a]

Affiliations:
[a] Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[b] African Leadership in Vaccinology Expertise (ALIVE), School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[c] Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[d] Department of Implementation Science, Right to Care, Centurion, South Africa

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Format: As per Vaccine Journal
(Authors Guide - https://www.elsevier.com/journals/vaccine/0264-410X/guide-for-authors)

Conflict of interest: None declared
Funding:

Key words: Hepatitis B virus, Health-care student, Vaccination, Immunity

Abstract word count: 301 words (300)
Article word count: 4793 words (5000)