

**INCIDENCE AND PREDICTORS OF NONRESPONSE TO
HEPATITIS B VACCINATION AMONG DIALYSIS PATIENTS
AT CHRIS HANI BARAGWANATH HOSPITAL**

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INCIDENCE AND PREDICTORS OF NONRESPONSE TO HEPATITIS B VACCINATION AMONG DIALYSIS PATIENTS AT CHRIS HANI BARAGWANATH HOSPITAL

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A research report submitted to the Faculty of Health Sciences,
University of Witwatersrand, Johannesburg, in partial fulfillment of
the requirements for the degree of Master of Medicine in the branch
of Internal Medicine
Johannesburg, 2020

DECLARATION

I, Leigh Johannes do hereby declare that this research report is my unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine. This research report is submitted in the submissible format (with my protocol and an extended literature review) as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

L Johannes
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The ...24..... day of January 2021.

ABSTRACT

Background: In South Africa the prevalence of Hepatitis B virus (HBV) is relatively high with studies showing HBV prevalence rates of 4.8% for males and 3.2% for females (1). Patients on dialysis have an increased risk of contracting HBV due to hematogenous and sexual spread. HBV vaccination series efficacy is known to be reduced in patients on dialysis (2). The Chris Hani Baragwanath Academic Hospital (CHBAH) renal unit uses the HBV vaccination, but no studies have been done to determine the incidence of HBV in this renal unit or the vaccine's efficacy.

Objectives: The incidence of non-response to the Hepatitis B vaccination of patients dialysing in CHBAH renal unit and predictors of non-response.

Methods: Demographics and hepatitis serology of patients dialysing in September 2018 was captured and analysed.

Results: The study sample consisted of 129 patients, with the mean age 43.01 and 52.7% were male. The most common cause of chronic kidney disease (CKD) was 'unknown aetiology' (39.5%) and 83.7% of the population was HIV negative. CHBAH renal unit has a younger population, less confirmed diabetic nephropathy patients (2.3%) and low levels of Hepatitis C infection (2.3%). Patients on haemodialysis (55%) and peritoneal dialysis (45%) were included. This study concluded that - no variable could predict seroconversion.

Conclusion: CHBAH renal unit has a population which is very different to the patients in international studies, but the seroconversion rates are similar. The researcher hopes this study will create awareness to ensure that patients have appropriate protection with regard to HBV infection.

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NOMENCLATURE

AV	Arterio-venous
BMI	Body Mass Index (Kg/m ²)
CKD	Chronic Kidney Disease
CHBAH	Chris Hani Baragwanath Academic Hospital
DNA	Deoxyribose Nucleic Acid
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESRD	End stage renal disease
GM-CSF	Granulocyte macrophage colony stimulating factor
GN	Glomerulonephritis
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core Antibody
HBcAb IgM	Hepatitis B core Antibody immunoglobulin M
HBcAB IgG	Hepatitis B core Antibody immunoglobulin G
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B surface Antigen
HBsAb	Hepatitis B surface Antibody
HD	Haemodialysis
HIV-HBV	Human Immunodeficiency virus – Hepatitis B virus co-infection
HIV	Human immunodeficiency
I.E.	id Est
IU	International Units
MMF	Mycophenolate Mofetil
PD	Peritoneal dialysis
RVD	Retroviral disease
SARS	South African Renal Society
SLE	Systemic lupus erythematosus
µg	Micrograms

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. INTRODUCTION

1.1 Background

The Hepatitis B Virus (HBV) belongs to the Hepadnaviridae genus (1). It has seven genotypes – A-G (2). The HBV has a lipid bilayer outer coat made from human host derived lipids. Hepatitis B Surface Antigen (HBsAg) protein is presented outwardly. The viral particles of HBV attach to the host cells with this HBsAg protein and this allows the inner coat with Hepatitis B core antigen (HBcAg) to enter the host cell. After endocytosis the viral DNA assimilates with the host DNA and replicates primarily in the hepatocytes (1) resulting in HBV infection.

Transmission occurs through blood and mucous membrane contact (2). Patients on haemodialysis have an increased risk of infection due to hematogenous and sexual spread (2). Secondly, they share dialysis machines. Thirdly, patients with AV fistula's or grafts require regular needling, increasing potential HBV exposure. Lastly, patients with HBV, acute infection or chronic carriers, increases the risk of all patients in unit of contracting HBV by increasing transmission through the three previously mentioned methods (3). The risk of patients on peritoneal dialysis is thought to be about the same as the general population since it has been changed to home therapy (4). HBV spread has therefore been a challenge since the start of chronic dialysis programs (2).

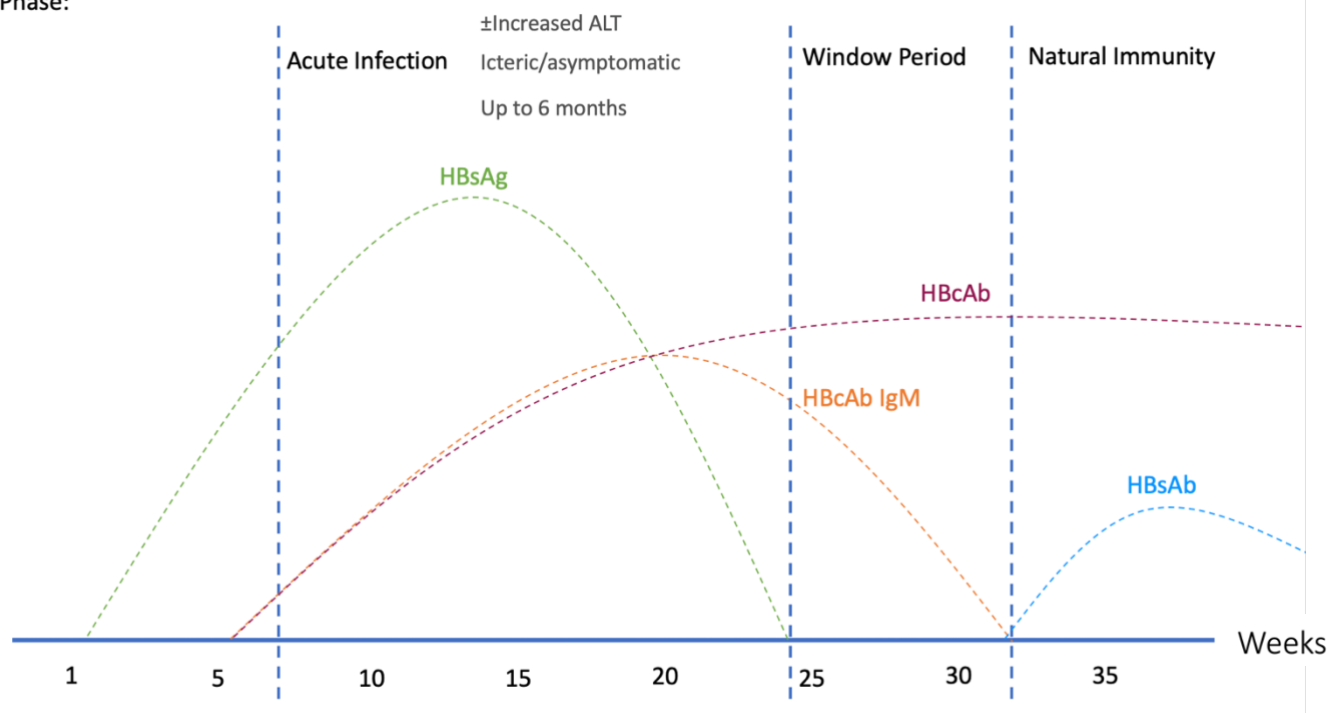
Two billion people worldwide have evidence of past or present infection (1). Approximately 360 million people have chronic HBV infection. 600 000 die each year from HBV related acute hepatitis, liver cirrhosis or hepatocellular carcinoma (2). The prevalence in North America, Western Europe and Japan is 2% and the prevalence fluctuates to more than 8% in endemic areas (5).

4.8% of males and 3.2% of females in South Africa are HBsAg positive, with rates increasing in the HIV-HBV co-infected communities (6). With the Human Immunodeficiency Virus (HIV) pandemic HIV-HBV co-infection has gathered attention due to the shared mode of transmission. In the Eastern Cape, HIV-HBV co-infection rates are estimated at 7.1% with a preponderance for the male sex (7). In Gauteng, the HIV-HBV co-infection rate is 5% (8). In Kwazulu-Natal, the HIV-HBV co-infection rate is 6.4% (6). These studies illustrate a high prevalence of HBV in both urban and rural settings in South Africa.

It is estimated that 4% of haemodialysis patients are chronically infected with HBV in low prevalence settings like North America, Western Europe and Japan (5). The only local information we have, is from Kwazulu-Natal – 10.6% of the 85 samples from HBsAg negative patients had detectable HBV DNA (9). Emphasizing the need for adequate vaccination.

1.2 Spectrum of Hepatitis B virus disease

Acute Phase:



Chronic Phase:

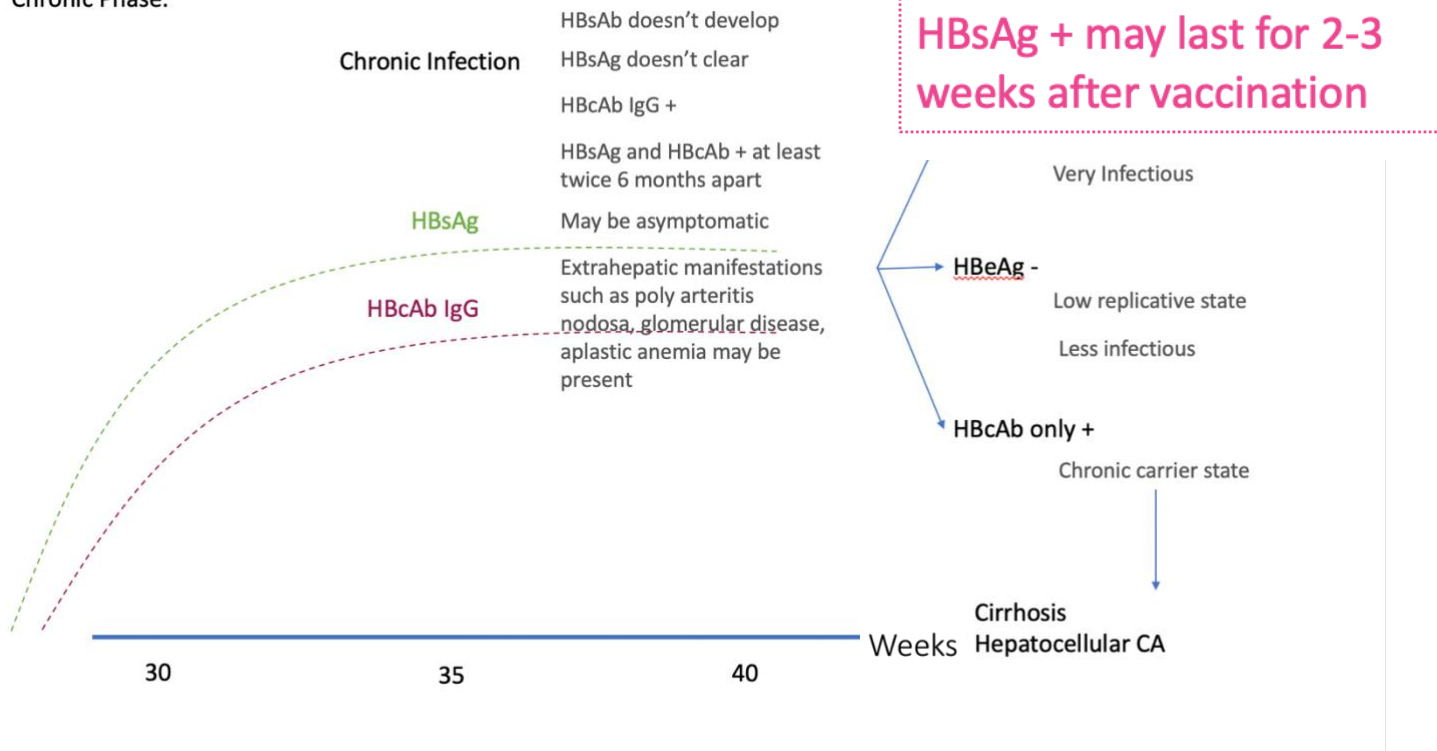


Figure 1.1: Spectrum of Hepatitis B Disease (10, 11)

The diagram above demonstrates the spectrum of HBV disease in humans. Initially acute infection occurs which lasts up to 6 months. At this point the patient who develops natural immunity will clear the HBsAg and develop antibodies - HBcAb. These patients may be asymptomatic, have a serum sickness-like

syndrome or fulminant hepatitis. The remainder of patients progress to chronic disease and the sequela thereof. Patients with chronic disease will either remain infectious and replicating or become chronic carriers, who may progress to hepatic cirrhosis or hepatocellular cancer. Patients in this stage may be clinically asymptomatic, have features of chronic hepatitis or have any of the extra-hepatic manifestations of the disease.

Following acute infection, the virus can persist in the blood and reactivation can occur due to immunosuppression or drugs, namely; anti-CD20 antibodies, antineoplastic agents, glucocorticoids and tumor necrosis factor inhibitors.

Therefore, control of this virus is important in the management of patients with chronic kidney disease as it influences life expectancy and may require adjustment in the chronic medication of the patient. Chronic kidney disease in itself is also a “state of immunosuppression” so these patients need to receive adequate vaccination schedules early in their disease to prevent HBV infections in units and the consequences thereof (10).

1.3 Vaccination

HBV can be eradicated through global vaccination. The implementation of effective vaccination programs in many countries have resulted in a significant decrease in the incidence of HBV infections and its sequela (12). The HBV vaccination was developed in 1984. It was initially HBsAg extracted via plasmapheresis from HBV carriers and then deactivated (3).

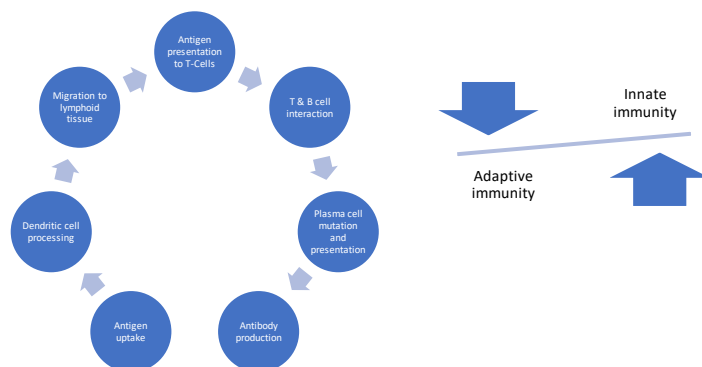


Figure 1.2: How the vaccine works (13)

There are 2 variations of the vaccine currently available.

1.3.1 “Single-antigen vaccines”:

- a. Yeast-derived: HBV S-gene is cloned in the yeast cells
 - Recombivax; Engerix-B
 - They use an aluminum adjuvant and require 3 doses over 6 months in healthy individuals.
- b. Mammalian cell-derived: these contain in addition to the S-Antigen, either the pre-S1 and pre-S2 regions

- Gen Hevac B; Bio-hep-B; Hepacare
 - These are as effective as the yeast-derived vaccines in a two-dose regimen.
- c. Plasma-derived: original vaccine – extracted HBsAg from plasmapheresis and deactivated

1.3.2 “Combination vaccines”

- d. Hepatitis b vaccine combined with other vaccines for example Hepatitis A, Diphtheria, Tetanus, Pertussis, Polio (12).

The “single-antigen vaccines” are safe. Seroconversion rate is more than 90% in healthy adults. Non-response is seen in patients with immunosuppressed states, healthy individuals with immunogenetics known with poor response to vaccination and failure due to technical errors (4).

The vaccines we have available in South Africa is Engerix – B and Recombivax. They are both recombinant “single-gene vaccines”. Both vaccines are equally efficient and safe with no reported side effects when doubling the dosage according to international research (4).

Seroconversion is defined as more than 10 IU/l. Seroprotection is defined as more than 100 IU/l (14). Dialysis patients drop their antibody titers more rapidly in comparison to healthy individuals. The exact mechanism for this rapid drop is unknown, but it is postulated that it is linked to the relative immunodeficient state of patients with chronic kidney disease. In patients with an initial titer more than 100 IU/l, repeat antibody levels drop rapidly to less than 10 IU/l after one year in 60% of patients and 90% of patients in two years (13).

For this reason it is recommended that patients on dialysis and immune compromised hosts require an increased dose (40µg), or extending the courses (4 instead of 3 vaccine dosages) and recurrent courses of the vaccine series (12).

Is there evidence for this premise of doubling the dose to improve efficacy? Yes a few smaller studies have shown this to improve the seroconversion rate - Turkey(15), Saudi Arabia(16) and Brazil(17). However, the only systematic review available does not show a statistical difference between the two doses. This review done in Australia containing 501 patients showed 54% seroconversion in the 40µg x 4 dose group in comparison to 46% in the 20µg x 4 dose group(18).

Can we predict non-response to the HBV vaccine series? It is well known that there are traditional risk factors for non-response such as older age (>58); body mass index (BMI) (BMI>25 is linked to an accelerated decline in immunity); late vaccination (>143 days since initiation of dialysis) and chronic illness (4).

Why does chronic kidney disease affect the HBV vaccine efficacy? Pre-dialysis and dialysis patients are expected to have higher levels of urea. This uremic environment has been linked to immune dysfunction

reducing antibody production post vaccination (19). This said, the exact mechanism for the reduced response is unknown.

Recent research has brought about variables that are more contentious for the reduced efficacy of the HBV vaccine series up as topics for investigation. Hepatitis C is one of these variables, a Brazilian study showed this to be the only factor affecting non-response. 7 out of their 10 patients infected with Hepatitis C did not seroconvert (17). We cannot extrapolate from their outcome in a subset of 10 patients to a population level as the sample size is extremely small. Currently we do not have any local research to establish if this variable affects seroconversion in our population.

Another variable which has received recent attention is the use of immunosuppressant's. Research from Patel et al. in New York reports they have not had any significant change in efficacy linked to use of immunosuppressant's. The immunosuppressant's used by patients included in their study was tacrolimus, sirolimus, cyclosporine, mycophenolate, azathioprine or corticosteroids (19).

The last variable I have taken into account is the HIV status of our population. South Africa has been significantly affected by this pandemic. Does the immunosuppression linked to HIV affect the efficacy of the HBV vaccination schedule? Currently there is no research on the HBV vaccine efficacy in patients with HIV on dialysis.

1.4 Vaccination Schedules

The current vaccination recommendation for the healthy population is any variant of the recombinant yeast-derived vaccines in a three-dose schedule, with 4 weeks between dose 1 and dose 2; 8 weeks between dose 2 and dose 3 (12).

The South African Renal Society (SARS) guidelines of 2015 recommends that all patients should be vaccinated prior to haemodialysis. Screening is suggested 1-2 months after the vaccine schedule completion. Followed by screening every 6 months. If Hepatitis B surface antibody (HBsAb) levels are less than 10mIU/ml a booster dose is recommended. The guidelines suggest the use of a different dialysis machine for HBsAg positive patients and it is common practice that the patients are dialyzed in a separate room (20).

International guidelines for HBV vaccinations in patients on dialysis provide us with more detail regarding schedules:

1. Recombivax HB 40µg/1ml at 0,1, 2 and 6 months or Engerix B 40µg/2ml at 0,1,2 and 6 months.
2. Measure Anti-HBs 1-2 months after last dose.
3. If Antibody titre <10 mIU/ml repeat complete vaccine series.
4. If Antibody titre >10 mIU/ml, i.e. once achieved seroconversion monitor antibody titres annually and reimmunize with a single booster dose if drops <10mIU/ml (4).

Current practice at the Chris Hani Baragwanath Academic Hospital (CHBAH) is that on initiation of care full hepatitis serology is done. All patients with negative HBsAg serology are vaccinated irrespective of mode of dialysis. For follow-up care patient's serology are repeated and HBsAg and HBsAb are checked every 6 months. Patients identified as HBsAg positive are dialyzed with a different machine and currently in a different room (21). The vaccines available at Chris Hani Baragwanath Academic Hospital are all "single-antigen" yeast-derived variants – Engerix B, Euvac and Hepebiovac Hb.

The current vaccine schedule used at Chris Hani Baragwanath Academic Hospital - Adult renal Unit can be seen below:

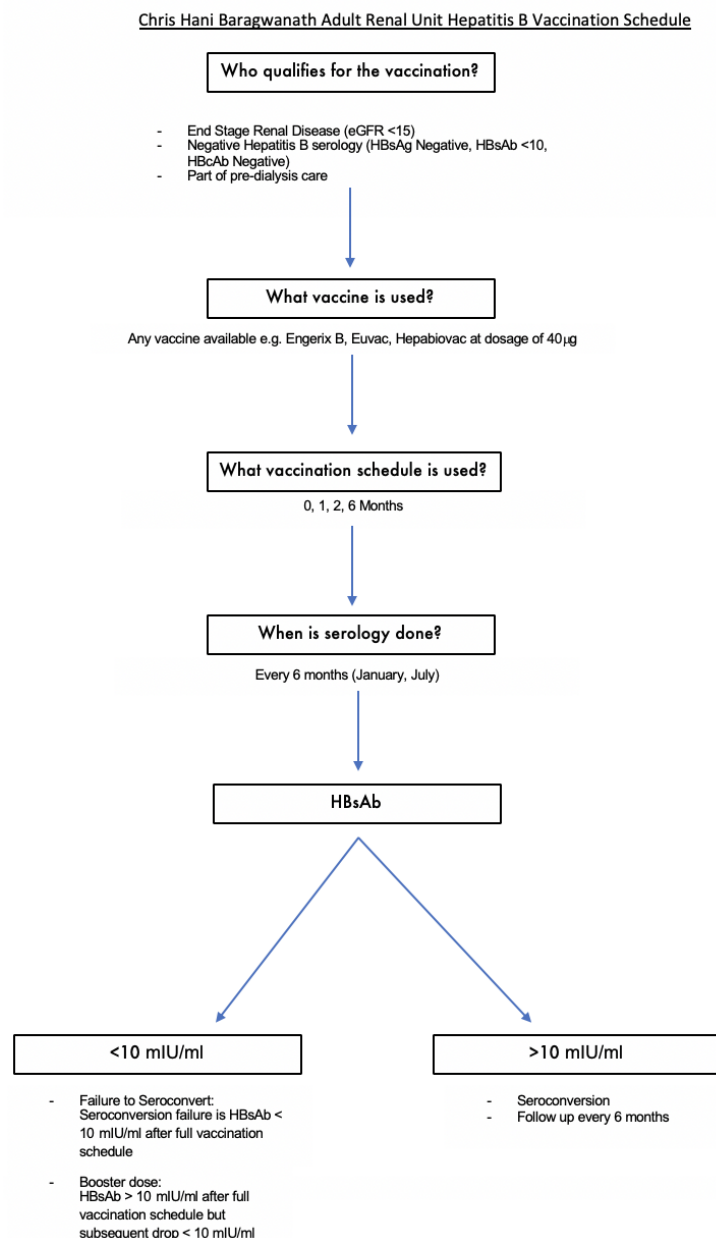


Figure 1.3: Vaccine Schedule at Chris Hani Baragwanath Academic Hospital – Adult Renal Unit (21)

1.5 Other measures to prevent infection

- Separate rooms;
- Separate trolleys;
- Dedicated machines for HBsAg positive patients;
- Reduced numbers of infected patients in dialysis units through improved vaccination i.e. herd immunity;
- Regular screening of hepatitis statuses of patients (2).

1.6 Adjuncts to the vaccination

As indicated by the global studies below the HBV vaccination appears to have a low efficacy rate. This has led to the exploration of various adjuncts to supplement the vaccination. A solution to improving seroconversion rates remains unknown, but the following adjuncts are being reviewed with some improvement in seroconversion levels:

- GM-CSF;
- HBV-AS04;
- Erythropoietin;
- Hepatitis A and B combined vaccination (3).

In my study I, looked at the current HBsAg, HBsAb and HBcAb status of our patients in retrospective cohort study and determined the incidence and predictors of non-response to Hepatitis B vaccination among dialysis patients at Chris Hani Baragwanath Academic Hospital - Adult renal Unit.

This study aims to review the rates of seroconversion and to improve the awareness around HBV vaccination in dialysis centres in South Africa. By improving awareness, we hope that more patients will complete the vaccine series, regular screening of hepatitis statuses will take place with complete serology testing, and appropriate action upon these results. If this occurs, we should be able to reduce the numbers of HBV infected patients in our dialysis units and reduce HBV infection through dialysis practices.

Table 1.1: Table depicting international studies and their efficacy to the HBV vaccine series

Country	Year	Author	Population Size	Vaccine Schedule	Seroconversion Rate	Mean Age	Gender		Cause of Renal Failure	Type of Renal Replacement Therapy			Comment
							M	F		HD	PD	Post-transplant	
UK	1996	Bel'eed K (14)	406	Engerix 40µg at 0,1,2,3 months	64%	52	67%	33%		x	x	x	Seroconversion rates in haemodialysis and peritoneal dialysis was similar. Patients who seroconverted where younger (54±18).
India	2010	Siddiqui S (22)	130	Recombinant vaccine either 4x40µg or 3x20µg	87,5% in 40µg group 57,6% in 20µg group	42	65,40%	34,60%		x	x	x	Seroconversion rates were better in the 40µg group. Worsening renal function at vaccination was linked with decreased seroconversion rates. 14% seroconversion in the ESRD group on the 40µg vs none in the ESRD group on 20µg.
Saudi Arabia	2014	Al Saran K (16)	144	Engerix 40µg at 0,1,2,6 months	89,60%	51	54%	46%	Diabetes Mellitus	x			Seroconversion rates were not affected by gender, age, Diabetes Mellitus, anaemia and antibody status. Good nutritional status which was based on a score looking at weight gain, functional status, amount of subcutaneous fat, muscle wasting, and oedema was linked to good seroconversion rates.

Table 1.2: Table depicting international studies and their efficacy to the HBV vaccine series

Country	Year	Author	Population Size	Vaccine Schedule	Seroconversion Rate	Mean Age	Gender		Cause of Renal Failure	Type of Renal Replacement Therapy			Comment
							M	F		HD	PD	Post-transplant	
New York	2015	Patel N (19)	119	Recombinant vaccine 40µg, >3, 3 or <3 doses	42%	62,3	84%	16%	Diabetes Mellitus	x			Seroconversion rates are low among patients on haemodialysis. The 3 variables predicting non-response were advanced age, time of vaccination and high BMI. (>30)
Austria	2016	Zitt E (13)	426	Recombinant vaccine either 3x20µg or 4x20µg	51,40%	63	61%	39%	Diabetes Mellitus	x	x		Mortality was significantly lower in patients with seroconversion (49.3%) and seroprotection (39.8%). Seroprotection inferred a significant reduction in all-cause mortality.
Turkey	2016	Asan A (15)	584	Recombinant vaccine 40µg at 0,1,2, 6 months	83,50%	60	52,50%	47,50%	Diabetes Mellitus	x	x		This study found that seroconversion rates where decreased with hepatitis c infection, BMI > 30, age > 65 and if dialysed > 5 years.
Australia	2016	Mulley WR (18)	501	Recombinant vaccine either 4x40µg or 4x20µg	54% in 40µg group 46% in 20µg group					x	x		The double dose regimen increases the rate of seroconversion but doesn't increase rate of seroprotection significantly.
Italy	2017	Cordova E (5)	60	Engerix 40µg at 0,1,6 months	77%	64	66%	34%		x			Lower serum albumin (<35) levels were linked to non-response. Older age was linked to non-response.

2. OBJECTIVES

- 2.1 The incidence of non-response to the Hepatitis B vaccination of patients in our unit on dialysis;
- 2.2 The factors affecting non-response to the Hepatitis B vaccination – age, gender, BMI, eGFR at inception into programme, comorbid disease, mode of dialysis;
- 2.3 The prevalence of HBsAg and HBcAb positivity in this population.

3. METHODOLOGY

Study Design

A retrospective cohort analysis of the HBsAg, HBsAb and HBcAb results of the patients in the Adult renal Unit of Chris Hani Baragwanath Hospital. Firstly, I compiled a list of all patients who received dialysis for the month of September 2018 – Haemodialysis and Peritoneal dialysis. Then I reviewed the results of their hepatitis serology for July 2018. Lastly, the Then I will patient files were checked to determine which patients were dialyzed for more than 6 months and have completed the 6-month vaccination schedule to include them in the study. The following data was collected from the patient files:

- Age;
- Gender;
- BMI;
- Smoking status;
- Diabetes;
- Cause of CKD;
- HIV status;
- Hepatitis C Status;
- HBsAg, HBsAb, HBcAb.

All data was captured by the researcher, see attached data sheet. (Appendix A)

3.1 INCLUSION CRITERIA

- CKD patients on dialysis at Adult renal Outpatient Department of Chris Hani Baragwanath Academic hospital

3.2 EXCLUSION CRITERIA

- Patients less than 18 years of age;
- Patients who haven't completed the Hepatitis B vaccination series;
- Less than 2 months from final Hepatitis B vaccination.

3.3 LIMITATIONS OF THE STUDY

- Data not captured in the patient's files;
- Loss of patient records;
- Inability to accurately assess the adequacy of dialysis continuously for patients.

4. TIME SCHEDULE

Task	Time Required	Deadline Date
Submit Protocol to Post Graduate Committee		12 October 2018
Post Graduate Committee Meeting	30 Min	31 October 2018
Submit to Ethics for clearance		08 October 2018
Corrections and final preparations for data collection with supervisor	2 Months	January 2019
Data Collection		February 2019
Writing of first draft	3 Months	
Submit first draft to supervisor		May 2019
Prepare report for submission		August 2019

5. FUNDING

The costs include stationery and printing costs will be covered by the principal investigator.

Stationery	300
Photocopies, printing	500
Total	800

6. DATA ANALYSIS AND STATISTICS

Excel spread sheets will be used to store data. The patient names will not be entered in the data collection sheets instead patient numbers will be used. Due to the small size of the population a sample size could not be calculated. I will include all patients meeting criteria on haemodialysis and peritoneal dialysis – it is estimated to about 150 patients in total will be part of the cross-sectional analysis. HBsAg, HBsAb and HBcAb was checked of all patients in the Adult renal unit dialyzing in September 2018, and their files reviewed for further data. Descriptive statistics will be used to describe the findings.

7. ETHICAL CONSIDERATIONS

All information will be collected anonymously in the data collection sheets (Appendix A), therefore patient confidentiality will be respected. The research proposal was submitted to the WITS HREC for approval. Approval has been granted by the Head of Division, renal unit. Approval for the study has been granted by the hospital.

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CHAPTER 2: SUBMISSIBLE ARTICLE

TITLE: INCIDENCE AND PREDICTORS OF NONRESPONSE TO HEPATITIS B VACCINATION AMONG DIALYSIS PATIENTS AT CHRIS HANI BARAGWANATH HOSPITAL ACADEMIC HOSPITAL

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Conflict of Interest:

Nil

Keywords:

Hepatitis B Vaccination; Chronic Kidney Disease Vaccinations; Vaccine Nonresponse

Word count:

2215

Abstract word count:

246

1. ABSTRACT

Background: In South Africa the prevalence of Hepatitis B virus (HBV) is relatively high with studies showing HBV prevalence rates of 4.8% for males and 3.2% for females (1). Patients on dialysis have an increased risk of contracting HBV due to hematogenous and sexual spread. HBV vaccination series efficacy is known to be reduced in patients on dialysis (2). The Chris Hani Baragwanath Academic Hospital (CHBAH) renal unit uses the HBV vaccination, but no studies have been done to determine the incidence of HBV in this renal unit or the vaccine's efficacy.

Objectives: The incidence of non-response to the Hepatitis B vaccination of patients dialysing in CHBAH renal unit and predictors of non-response.

Methods: Demographics and hepatitis serology of patients dialysing in September 2018 was captured and analysed.

Results: The study sample consisted of 129 patients, with the mean age 43.01 and 52.7% were male. The most common cause of chronic kidney disease (CKD) was 'unknown aetiology' (39.5%) and 83.7% of the population was HIV negative. CHBAH renal unit has a younger population, less confirmed diabetic nephropathy patients (2.3%) and low levels of Hepatitis C infection (2.3%). Patients on haemodialysis (55%) and peritoneal dialysis (45%) were included. This study concluded that - no variable could predict seroconversion.

Conclusion: CHBAH renal unit has a population which is very different to the patients in international studies, but the seroconversion rates are similar. The researcher hopes this study will create awareness to ensure that patients have appropriate protection with regard to HBV infection.

2. BACKGROUND

Hepatitis B is a prevalent disease in Johannesburg with recent research showing the HIV-HBV coinfection rates of 5% (3). From South African studies we know that HBV infection is a problem, even in HBsAg negative groups in dialysis centres (4). Transmission of HBV occurs through blood and mucous membrane contact (5). Patients on haemodialysis have an increased risk of infection due to hematogenous spread. Secondly, they share dialysis machines. Thirdly, patients with AV fistula's or grafts require regular needling increasing potential HBV exposure. Lastly, patients with HBV infection increases the risk of all patients in the unit of contracting HBV by increasing transmission through the three previously mentioned methods (2). HBV spread has therefore been a challenge since the start of chronic dialysis programs (5).

Recent international research has shown that seroconversion with HBV vaccination while on dialysis is a contentious issue with various studies showing varied response rates to different schedules with or without the use of adjuncts. It is known that the response rate to the vaccination schedule is reduced, but the exact response and reason for the reduction is unclear (6).

Seroconversion is defined as more than 10 IU/l. Seroprotection is defined as more than 100 IU/l (7). It has also been observed that patients who do achieve seroconversion drop their antibody titres significantly faster than healthy individuals after vaccination (8). With the knowledge of this difference the international studies used for comparison used seroconversion instead of seroprotection as the cut off. Therefore, that was chosen as our target point.

The South African Renal Society (SARS) guidelines of 2015 recommends that all patients should be vaccinated prior to haemodialysis. Screening is suggested 1-2 months after the vaccine schedule completion. Followed by screening every 6 months. If Hepatitis B surface antibody (HBsAb) levels are less than 10mIU/ml a booster dose is recommended. The guidelines suggest the use of a different dialysis machine for HBsAg positive patients and it is common practice that the patients are dialysed in a separate room (9).

International guidelines for HBV vaccinations in patients on dialysis provide us with more detail regarding schedules:

- Recombivax HB 40µg/1ml at 0,1, 2 and 6 months or Engerix B 40µg/2ml at 0,1,2 and 6 months
- Measure Anti-HBs 1-2 months after last dose
- If Antibody titre <10 mIU/ml repeat complete vaccine series
- If Antibody titre >10 mIU/ml, i.e. once achieved seroconversion monitor antibody titres annually and reimmunize with a single booster dose if drops <10mIU/ml (10).

Other measures to prevent HBV infection:

- Separate rooms;
- Separate trolleys;
- Dedicated machines for HBsAg positive patients;
- Reduced numbers of infected patients in dialysis units through improved vaccination i.e. herd immunity;
- Regular screening of hepatitis statuses of patients (5).

Current practice at the Chris Hani Baragwanath Academic Hospital is that on initiation of care, hepatitis serology is done. All patients with negative HBsAg serology are vaccinated irrespective of mode of dialysis. For follow-up care patient's serology are repeated and HBsAg and HBsAb are checked every 6 months. Patients identified as HBsAg positive are dialyzed with a different machine and currently in a different room (11). The vaccines available at Chris Hani Baragwanath Academic Hospital are all "single-antigen" yeast-derived variants – Engerix B, Euvac and Heperbiovac Hb.

At Chris Hani Baragwanath's Adult renal Unit currently uses a vaccination schedule as depicted below (11). See Figure 2.1.

It is known that HBV infection in dialysis units is prevalent but there is no data locally about the efficacy of the vaccine (4). Furthermore, there are no local guidelines available to give clear guidance with regard to hepatitis serology for screening in dialysis centres. As HBcAb serology is not specifically stated in the schedule some infected patients may be missed.

3. METHOD

A retrospective cohort analysis of the Hepatitis B status of all patients dialysing at Chris Hani Baragwanath Academic Hospital's Adult renal Unit during the month of September 2018 - Haemodialysis and Peritoneal dialysis. All the files were collected, and the following patients were excluded:

- Patients less than 18 years of age;
- Patients who haven't completed their Hepatitis B vaccination series;
- Patients less than two months from their final Hepatitis B vaccination.

The remainder of the patient files were then checked for the following data:

- Hepatitis serology results
 - o HBsAg, HBsAb, HBcAb;
- Age;
- Gender;
- Body mass index;
- Smoking status;
- Cause of CKD;
- Diabetic status;
- HIV status;
- Hepatitis C status;
- The use of previous immunosuppressant's.

All the data was first captured on the data sheet and then transcribed to an excel spreadsheet and then interpreted for results.

Statistical Package

The data was captured in Microsoft Excel and later exported into SPSS (originally, Statistical Package for the Social Sciences and now called Statistical Product and Service Solutions) software where the analysis was conducted.

Descriptive Statistics

Descriptive statistics such as mean and standard deviation were conducted to summarise the data. The mean and the standard deviations were used to summarise continuous data such as the age of the patients and the CD4 count of HIV positive patients. Graphs were used to present a pictorial view of the outcomes.

Odds ratio

The odds ratio was calculated for univariate data.

Chi-square test

Chi-square test of association was used to assess whether there was an association between two categorical variables such as whether a patient's outcome was dependent on a patients' gender as well as whether they are a smoker or not.

Independent Samples t- test

Independent samples t-test was used to assess whether the mean value of a continuous variable such as age is significantly related to the outcome.

4. RESULTS

The initial sample was a total of 140 patients, 11 were excluded - of the 11 patients: 1 had Hepatitis B virus exposure, 2 had Chronic Hepatitis B infection and 8 had Acute Hepatitis B infections. The remaining 129 patients were further analysed. See Figure 2.2

Demographic Characteristics

In CHBAH renal unit the sample population's mode of dialysis and cause of CKD can be seen in the diagram below. See Figure 2.3.

The male to female ratio was similar to the other dialysis centres, except the Italian centre which had 40 males and 20 females (12) and the Austrian study with 263 males and 163 females (13).

CHBAH renal unit's population had a mean±standard deviation age of 43±12.64. The male to female ratio was 1:1 with 68 males and 61 females. The calculation of body mass index (BMI) was difficult as most files did not have heights documented.

The population is different to many international studies in that our average age is 43 a lot younger than the average age in similar studies in Austria – 63 (13); Turkey -65(14) and Saudi Arabia – 51(8).

The most common aetiology for CKD in CHBAH renal unit's population is 'unknown aetiology' in contrast to mostly diabetic nephropathy in Turkey (14), New York (15) and Saudi Arabia (8).

The mean eGFR at inception to dialysis programme at CHBAH renal unit was 6.

Currently 83.7% of the population was HIV negative. The HIV positive population had a mean±standard deviation of their CD4 of 457.28±237.68. There were no international studies looking at HIV and its relationship to the efficacy of the HBV vaccination.

Variables affecting serological response

In this study, we had a total of 129 patients which we assessed for non-response. 78.3% of our study population achieved seroconversion. i.e. HBsAb titres of >10 milli-international units/ml. CHBAH renal unit protocol used a single antigen 4 dose vaccination series, at 0, 1, 2, and 6 months which was given to all patients who have negative HBsAg serology.

The 129 patients that were analysed further were either successfully vaccinated or required revaccination (non-responders) as can be seen in the See Figure 2.4.

Interpretation of the results was done with a univariate assessment, as can be seen in Table 2.1. It can be noted that none of the variables were significantly related to the outcome – age, gender, mode of dialysis, HIV status, Hepatitis C status, diagnosis of diabetes, time of vaccine after initiation of dialysis, use of immunosuppressant's or eGFR at inception to programme. All the p-values were greater than 0.05.

The variable that could possibly have influenced seroconversion is the use of immunosuppressant's as the p-value is 0.051.

Logistic regression was also conducted to assess the interaction of the variables assessed in influencing the success of vaccination. The results are shown in Table 2.2 All the factors had a 95% confidence interval containing 1, which means that they were not significant in predicting successful response to the vaccine. The use of immunosuppressant's however had a lower odds ratio of having a successful vaccination.

The major factors which have been internationally identified as influencing efficacy of the vaccination schedule are

- Early vaccination (10) – the patients were vaccinated at mean±standard deviation of eGFR 6.17 ± 4.11 indicating that in this study we could not truly assess early vaccination as a variable as all the patients were vaccinated relatively late in their disease.
- Age (10) – the average of the population was much younger than similar international studies as previously mentioned.
- Diabetes Mellitus and Hepatitis C population numbers in the CHBAH renal unit were too low for us to draw adequate conclusions about them as variables affecting the efficacy of the vaccine.

5. DISCUSSION

HBV can be eradicated through global vaccination. The implementation of effective vaccination programs in many countries has resulted in a significant decrease in the incidence of HBV infections and its sequela (6). By subjecting our patients to chronic renal replacement therapy, we increase their risk of HBV infection, and therefore should prioritize adequate protection in the form of vaccination.

South African local guidelines on the management of patients with chronic kidney disease also emphasise this and encourage regular serological screening of hepatitis studies.

There currently is no guidance for complete HBV serology tests required in dialysis units (9) to reduce the risk of infection in the unit. Less patients with HBV-DNA leads to less exposure. HBsAg and HBsAb serology is only a starting point (4).

None of our variables could predict non-response in the population at CHBAH renal unit. But the study demonstrated high seroconversion rates, albeit not 100%.

The variables selected in the study were ones which were investigated for non-response in international studies. Hepatitis C in the Brazilian study was their main variable affecting non-response (16). Immunosuppressant's did not affect seroconversion rates at all as shown in New York (15). Although our numbers were small 7 of the 11 patients exposed to immunosuppression required repeat vaccination.

The limitations in this study were that it was retrospective in nature so there was data lost due to poor documentation, missing pages from notes and no dates by valuable data (such as the immunosuppressive agents administered to patients). The study sample size was also small.

In spite of the limitations of this study I was able to collect enough data to extrapolate that seroconversion rates to HBV vaccination are not adequate.

So, in conclusion more research is required to attain the solution to having higher seroconversion rates in future. A prospective study is required so we can truly evaluate the effect our variables such as immunosuppressive agents, RVD status and timing of vaccine in relation to dialysis has on the vaccine efficacy.

Research into alternative vaccinations and the use of HBV-ASO4, EPO and GM-CSF to boost vaccine response is needed. However, until a vaccine with better seroconversion rates becomes available in South Africa, education accompanied by regular complete HBV serology (HBsAg, HBsAb, HBcAb IgG and IgM) pre- and post- vaccination is required to prevent HBV infection in dialysis units.

Hopefully this study will create awareness to ensure patients have appropriate protection on dialysis with regard to HBV infection.

Table 2.1: Factors affecting response to Hepatitis B vaccination schedule

Variable		Total	Outcome		Odds Ratio	Analysis Conducted	P-value
			Successfully vaccinated	Revaccination required			
Age	Mean $\pm$ SD	43.01 $\pm$ 12.64	42.62 $\pm$ 12.4	44.39 $\pm$ 13.6		T-test*	.514
Gender	Male	68 (52.7%)	56 (55.4%)	12 (42.9%)	1.659	Chi-square	.287
	Female	61 (47.3%)	45 (44.6%)	16 (57.1%)	0.603		
BMI	< 20	7 (11.3%)	7 (14%)	0 (0%)		Chi-square	.366
	20-25	20 (32.3%)	17 (34%)	3 (25%)	1.545		
	25-30	22 (35.5%)	17 (34%)	5 (41.7%)	.721		
	> 30	13 (21%)	9 (18%)	4 (33.3%)	.439		
Smoker	Yes	21 (29.2%)	15 (26.8%)	6 (37.5%)	.610	Chi-square	.296
	No	51 (70.8%)	41 (73.2%)	10 (62.5%)	1.640		
Cause of Chronic Kidney Disease	Hypertension	40 (31%)	31 (30.7%)	9 (32.1%)	0.935	Chi-square	1.000
	RVD	11 (8.5%)	8 (7.9%)	3 (10.7%)	0.717	Chi-square	.703
	Diabetes	3 (2.3%)	3 (3.0%)	0 (0%)		Chi-square	1.000
	GN (known)	10 (7.8%)	7 (6.9%)	3 (10.7%)	0.621	Chi-square	.452
	Obstructive Uropathy	5 (3.9%)	5 (5.0%)	0 (0%)		Chi-square	.585
	Lupus	9 (7%)	8 (7.9%)	1 (3.6%)	2.323	Chi-square	.683
	Unknown	51 (39.5%)	39 (38.6%)	12 (42.9%)	0.839	Chi-square	.827
eGFR at inception	Mean $\pm$ SD	6.17 $\pm$ 4.11	6.15 $\pm$ 4.20	6.22 $\pm$ 3.85		T-test*	.940
Mode of dialysis	HD	71 (55%)	52 (51.5%)	19 (67.9%)	1.989	Chi-square	.138
	PD	58 (45%)	49 (48.5%)	9 (32.1%)	0.503		
Time between start of dialysis and vaccination	< 6 months	94 (81%)	71 (78%)	23 (92%)	.309	Chi-square	.093
	> 6 months	22 (19%)	20 (22%)	2 (8%)	3.239		
HIV	Positive	18 (14.3%)	14 (14.3%)	4 (14.3%)	1.000	Chi-square	1.000
	Negative	108 (85.7%)	84 (85.7%)	24 (85.7%)	1.000		
CD4 Count	Mean $\pm$ SD	457.28 $\pm$ 237.68	490.71 $\pm$ 250.94	340.25 $\pm$ 154.16		T-test*	.277
Hepatitis C	Positive	3 (2.3%)	1 (1.0%)	2 (7.1%)	0.130	Chi-square	.119
	Negative	126 (97.7%)	100 (99.0%)	26 (92.9%)	7.692		
Diabetes	Yes	4 (3.1%)	3 (3%)	1 (3.6%)	0.835	Chi-square	1.000
	No	124 (96.9%)	97 (97%)	27 (96.4%)	1.198		
Use of immunosuppressant's	Yes	11 (8.5%)	7 (6.9%)	4 (14.3%)	0.447	Chi-square	.252
	No	118 (91.5%)	94 (93.1%)	24 (85.7%)	2.238		
Immunosuppressant Drugs used	Cyclophosphamide	4 (50%)	4 (66.7%)	0 (0%)		Chi-square	.046
	Cyclophosphamide, MMF	1 (12.5%)	0 (0%)	1 (50%)			
	MMF	2 (25%)	2 (33.3%)	0 (0%)			
	Tacrolimus	1 (12.5%)	0 (0%)	1 (50%)			
Completed Vaccine series	Yes	129 (100%)	101 (100%)	28 (100%)		Chi-square	-

*Independent samples t-test

Table 2.2: Logistic regression results on factors affecting response to Hepatitis B vaccination series

Variables in the Equation					
		Odds Ratio	95% Confidence interval for Odds ratio		P-Value
			Lower	Upper	
Step 1 ^a	Age	.980	.943	1.019	.303
	Gender - Male	2.072	.798	5.376	.134
	Hypertension	1.224	.417	3.599	.713
	RVD	.292	.016	5.358	.407
	Lupus	6.911	.543	87.974	.136
	Egfr at inception	1.011	.907	1.127	.840
	Mode of dialysis	.476	.181	1.247	.131
	HIV Positive	2.333	.177	30.769	.520
	Hepatitis C Positive	.137	.006	3.212	.217
	Diabetes (Yes)	.673	.059	7.634	.749
	Use of immunosuppressant's	.181	.033	.999	.0498
	Constant	8.894			.026
a. Variable(s) entered on step 1: Age, Gender_1, Hypertension, RVD, Lupus, Egfr at inception, Mode of dialysis, HIV positive_1, Hepatitis C positive, Diabetes (yes), Use of immunosuppressants.					

Chris Hani Baragwanath Adult Renal Unit Hepatitis B Vaccination Schedule

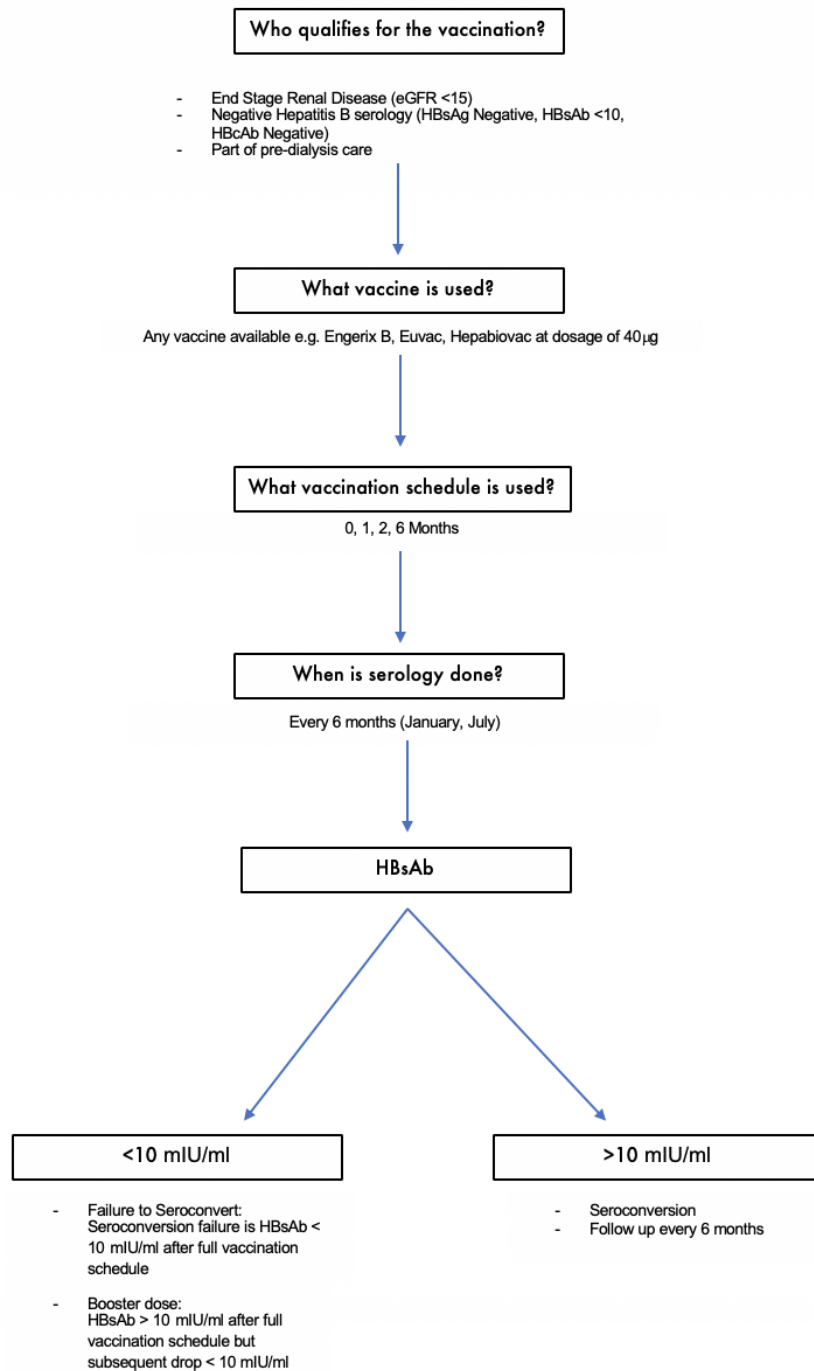


Figure 2. 1: Vaccination schedule at Chris Hani Baragwanath Hospital – Adult renal Unit

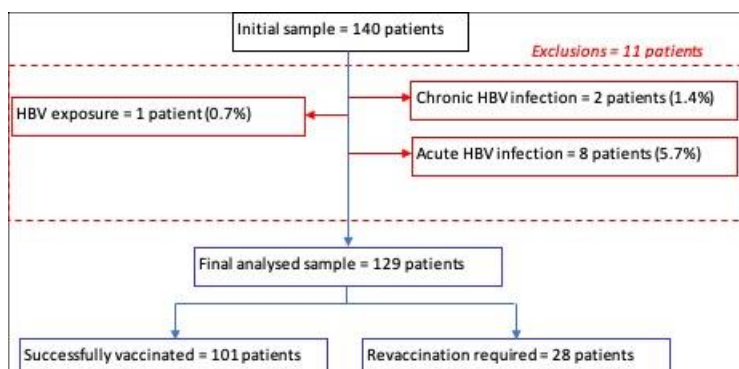


Figure 2.2: The sample population

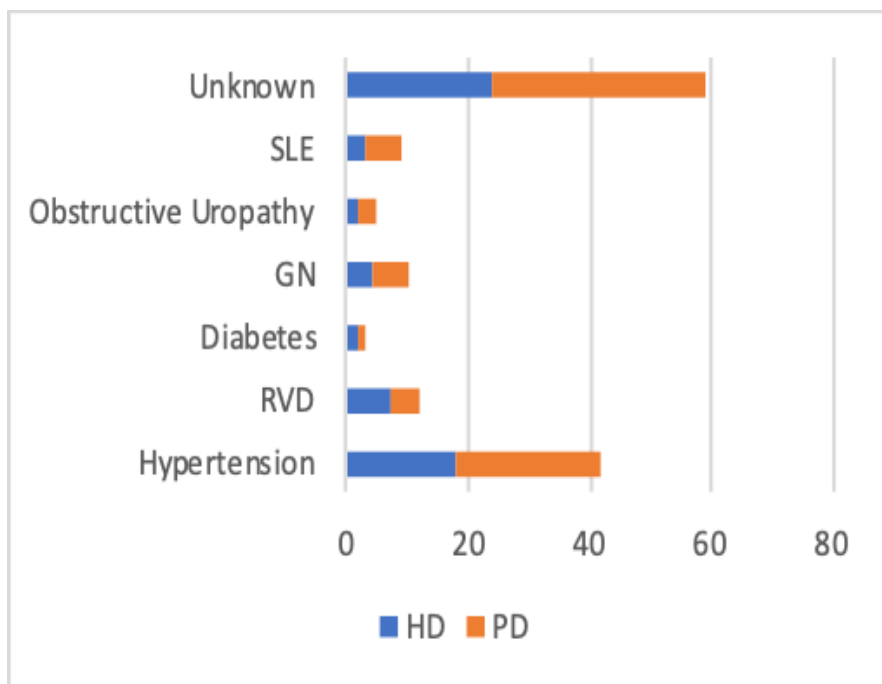


Figure 2.3: Cause of CKD

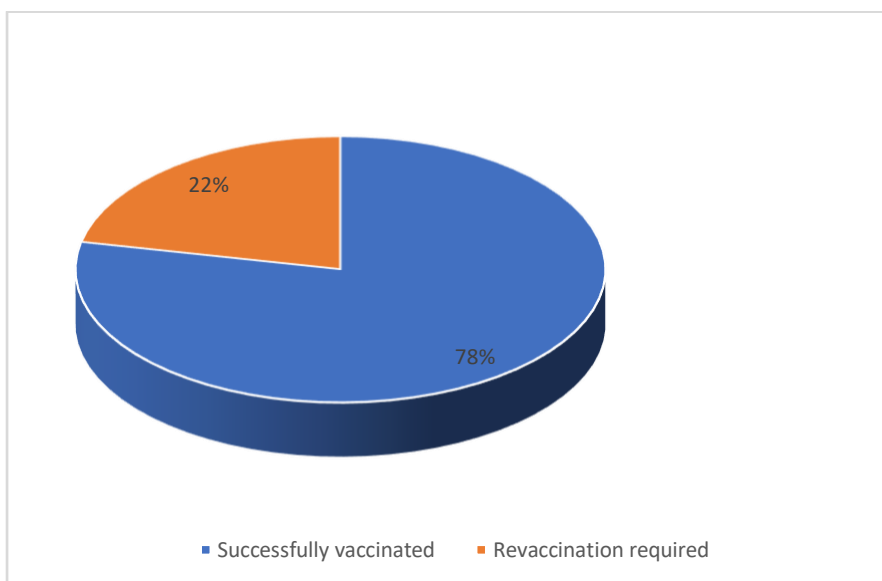


Figure 2.4: Outcomes

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Appendix A- Data Sheet:

Data Sheet:

Study Number: _____

Date of Data Collection: _____

Demographics:

Age: _____

Gender: M • F •

BMI: _____

Level of Education: _____

Smoker: Yes • No •

Cause of Chronic Kidney Disease: _____

Mode of Dialysis: Haemodialysis • Peritoneal dialysis •

Time between start of dialysis and vaccination: < 6 Months • > 6 Months •

eGFR at inception to dialysis: _____

Co-Morbidities:

HIV Status: Positive • Negative •

CD4: _____

Date: _____

Hepatitis C Status: Positive • Negative •

Date: _____

Diabetes Yes • No •

Use of immunosuppressant's: Yes • No •

If yes, which immunosuppressant? _____

Hepatitis B Vaccination

Completed Vaccination: Yes • No •

Last date vaccine received: _____

Hepatitis B Status

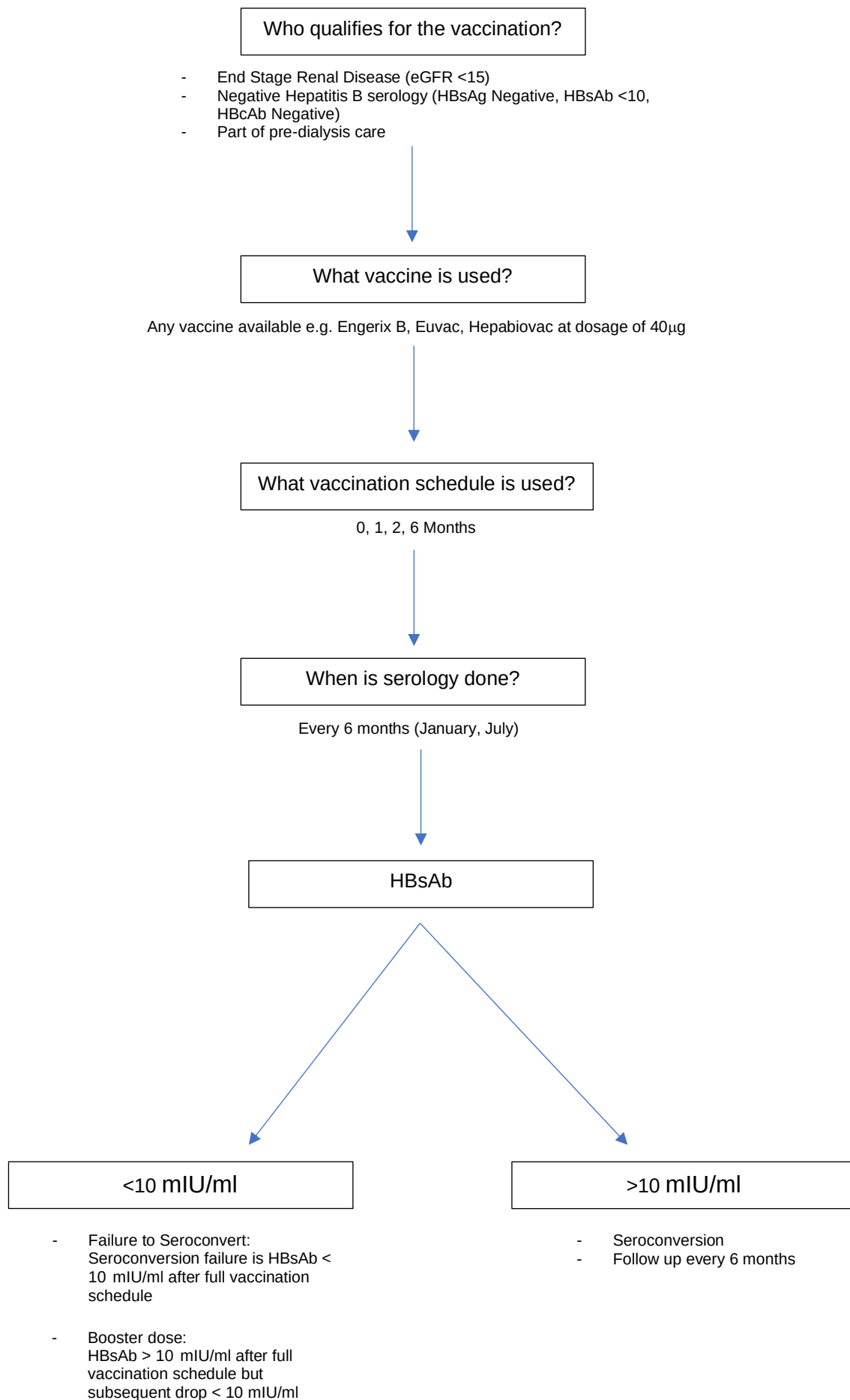
HBsAg: Positive • Negative •

HBsAb: Positive • Negative •

HBcAb: Positive • Negative •

Date of Hepatitis serology: _____

Appendix B – Chris Hani Baragwanath Academic Hospital Adult Renal Unit Vaccination Schedule



Appendix C – Ethics Clearance Certificate



R14/49 Dr Leigh Johannes

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190304

NAME: Dr Leigh Johannes
(Principal Investigator)
DEPARTMENT: Internal Medicine
Chris Hani Baragwanath Academic Hospital

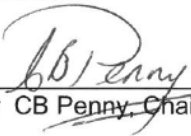
PROJECT TITLE: Incidence and predictors of nonresponse to hepatitis b vaccination among dialysis patients at Chris Hani Baragwanath Hospital

DATE CONSIDERED: 29/03/2019

DECISION: Approved Unconditionally

CONDITIONS:

SUPERVISOR: Dr Mashabane

APPROVED BY: 
Doctor CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 05/04/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **March** and will therefore be due in the month of **March** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

24/03/21
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix D– Site Permission



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 12th April 2019

TITLE OF PROJECT: Incidence and predictors of nonresponse to Hepatitis B vaccination among dialysis patients at Chris Hani Baragwanath Hospital.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr L Johannes

Department: Internal Medicine

Supervisor : Dr M J Mashabane

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.


Recommended
(On behalf of the MAC)
Date: 12/4/2019


Approved/Not Approved
Hospital Management
Date: 18/04/2019

Appendix E: Turnitin Report

1972732:MMED_25_2.pdf

ORIGINALITY REPORT

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SIMILARITY INDEX

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