Table of Contents

Additional Results

Here, we present the results of the HBV status determination and cascade of care of different demographic groups from within the study populations. Sex is separated into the binary male and female. The age cohort is separated between people born before and after universal HBV vaccination was available on the NT immunisation schedule. People born before January 1st, 1990, are pre-vaccine, and those born on or after January 1st, 1990, are post-vaccine.

Prevalence

CHB prevalence in people with unknown serostatus was assumed to be equivalent to CHB prevalence in the population with known serostatus. To estimate the number of people infected, the total number of people living with CHB at completion of Hep B PAST was calculated as the sum of people diagnosed plus the estimated number with undiagnosed infection. The percentage prevalence of HBV infection (diagnosed and undiagnosed) at the commencement of Hep B PAST (2018) was assumed to be the same as that estimated at the completion of Hep B PAST (2023). This process assumes all HBV infections found during Hep B PAST were among people with previously unknown serostatus and that the true prevalence of HBV infection in our study cohort did not change substantially over time.

Figures by sex

Fig 1: Male HBV status of population, comparing timepoints – at commencement, post-foundation step and at completion of Hep B PAST (2018-2023).
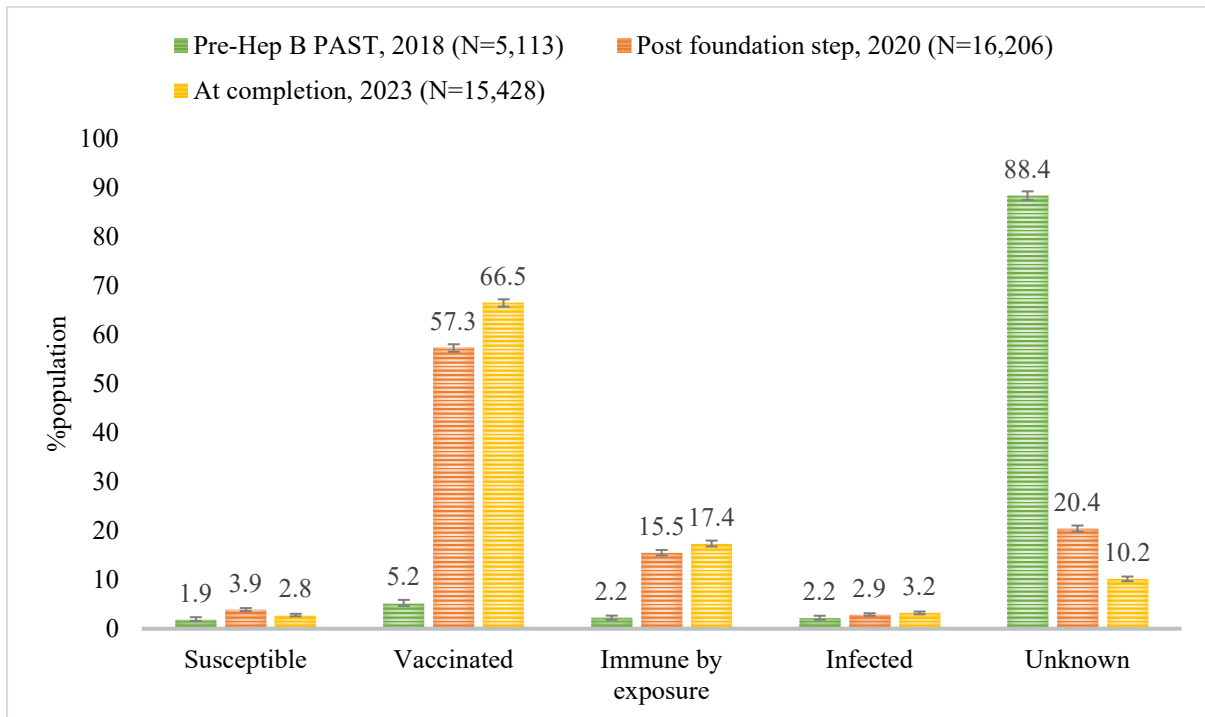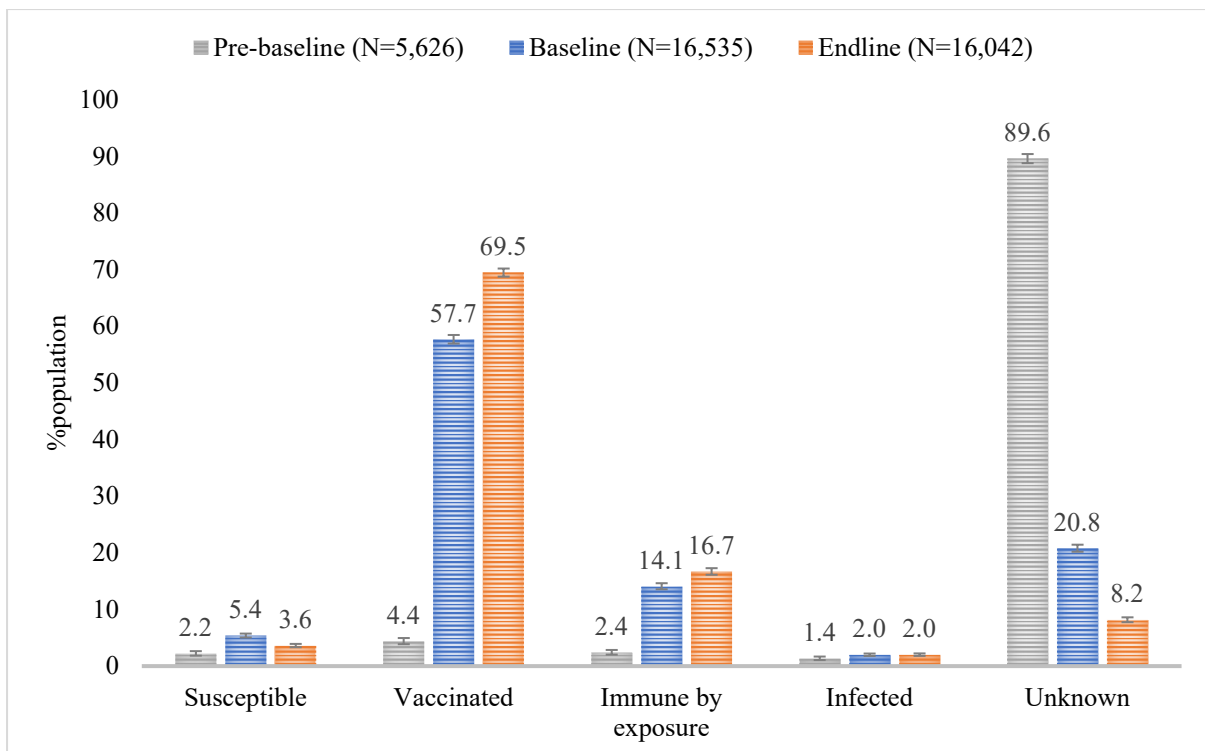

Fig 2: Female HBV status of population, comparing timepoints – at commencement, post-foundation step and at completion of Hep B PAST (2018-2023).

Figures by age cohort

Fig 3: Born pre-vaccine (before 1 Jan 1990) HBV status of the population, comparing timepoints – at commencement, post-foundation step and at completion of Hep B PAST (2018-2023).
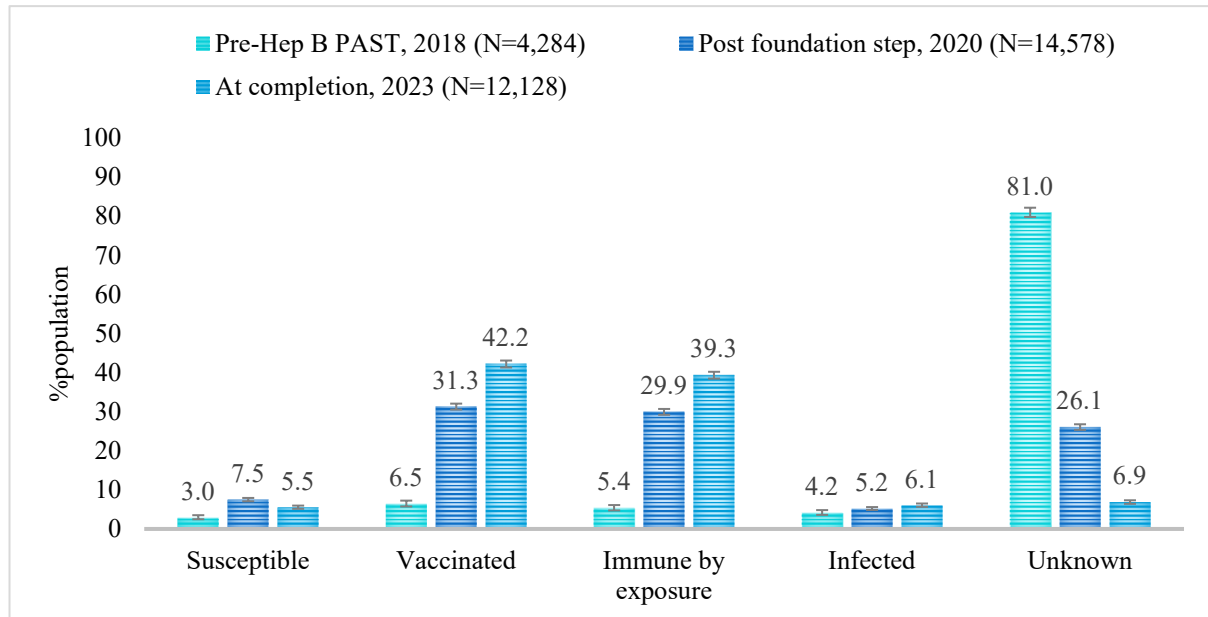

Fig 4: Born post-vaccine (after 1 Jan 1990) HBV status of the population, comparing timepoints – at commencement, post-foundation step and at completion of Hep B PAST (2018-2023).
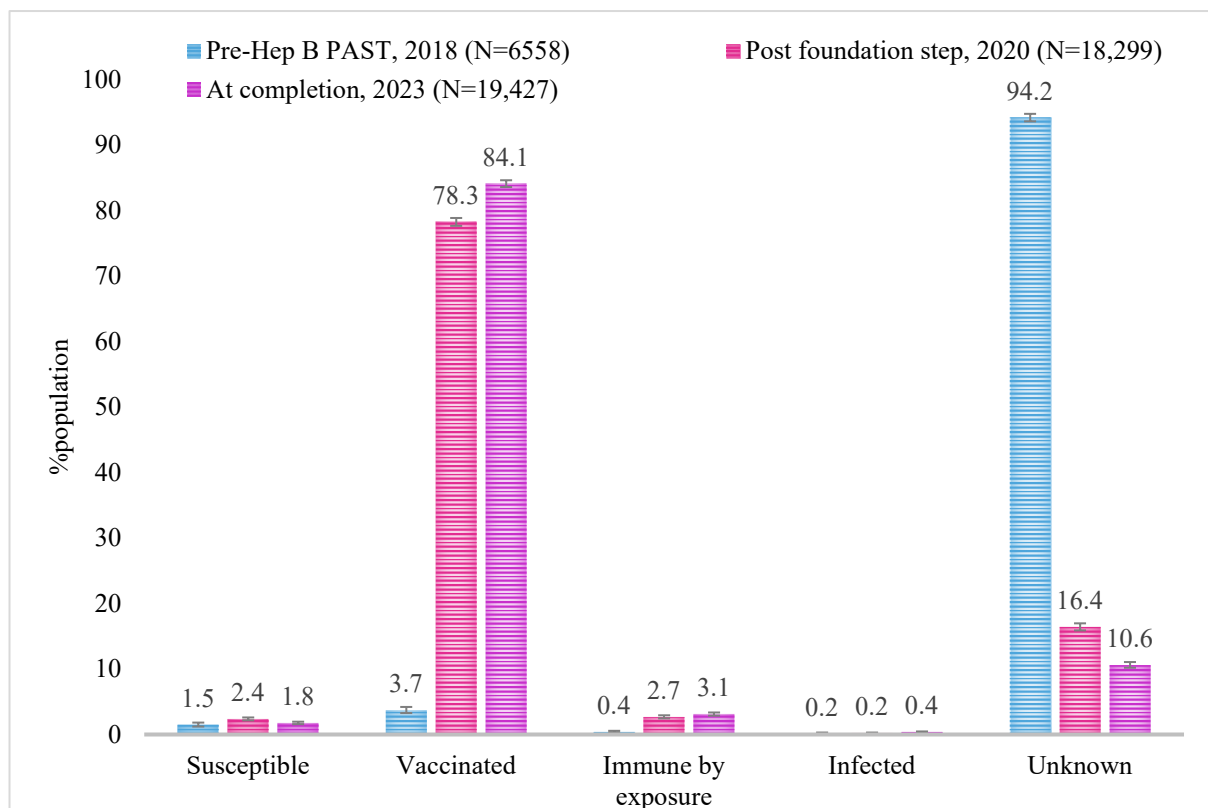
Table 1: Overall population, with known and documented HBV status, per status code, across three time points – Pre-Hep B PAST (2018) Foundation step (2020), at completion of Hep B PAST (2023)

Overall	Pre-Hep B PAST, 2018 (N=10,853)							Foundation step, 2020 (N=32,915)							At completion, 2023 (N=31,588)						
	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff
Non-immune	225	10628	2.1	1.8	0.3	2.4	0.3	1,526	31,389	4.6	4.4	0.2	4.9	0.2	1,015	30,573	3.2	3.0	0.2	3.4	0.2
Fully vaccinated	521	10332	4.8	4.4	0.4	5.2	0.4	18,891	14,024	57.4	56.9	0.5	57.9	0.5	21,466	10,122	68.0	67.4	0.5	68.5	0.5
Immune by exposure	256	10597	2.4	2.1	0.3	2.7	0.3	4,857	28,058	14.8	14.4	0.4	15.1	0.4	5,373	26,215	17.0	16.6	0.4	17.4	0.4
Infected	190	10663	1.8	1.5	0.2	2.0	0.3	801	32,114	2.4	2.3	0.2	2.6	0.2	821	30,767	2.6	2.4	0.2	2.8	0.2
Unknown	9661	1192	89.0	88.4	0.6	89.6	0.6	6,840	26,075	20.8	20.3	0.4	21.2	0.4	2,913	28,675	9.2	8.9	0.3	9.5	0.3

Table 2: Male population, with known and documented HBV status, per status code, across three time points – Pre-Hep B PAST (2018) Foundation step (2020), at completion of Hep B PAST (2023)

Male	Pre-Hep B PAST (N=5,113)							Foundation step (N=16,206)							Completion (N=15,428)						
	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff
Non-immune	99	5014	1.9	1.6	0.4	2.4	0.4	632	15,574	3.9	3.6	0.3	4.2	0.3	428	15,000	2.8	2.5	0.3	3.0	0.3
Fully vaccinated	268	4845	5.2	4.6	0.6	5.9	0.6	9,283	6,923	57.3	56.5	0.8	58.0	0.8	10,255	5,173	66.5	65.7	0.8	67.2	0.7
Immune by exposure	114	4999	2.2	1.8	0.4	2.7	0.4	2,512	13,694	15.5	14.9	0.6	16.1	0.6	2,681	12,747	17.4	16.8	0.6	18.0	0.6
Infected	113	5000	2.2	1.8	0.4	2.7	0.4	468	15,738	2.9	2.6	0.3	3.2	0.3	496	14,932	3.2	2.9	0.3	3.5	0.3
Unknown	4519	594	88.4	87.5	0.9	89.2	0.9	3,311	12,895	20.4	19.8	0.6	21.1	0.6	1,568	13,860	10.2	9.7	0.5	10.7	0.5

Table 3: Female population, with known and document HBV status, per status code, across three timepoints – Pre-Hep B PAST (2018) Foundation step (2020), at completion of Hep B PAST (2023)

Female	Pre-Hep B PAST (N=5,626)							Foundation (N=16,535)							Completion (N=16,042)						
	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff
Non-immune	125	5501	2.2	1.9	0.4	2.6	0.4	891	15,644	5.4	5.0	0.3	5.7	0.4	581	15,461	3.6	3.3	0.3	3.9	0.3
Fully vaccinated	247	5379	4.4	3.9	0.5	5.0	0.6	9,542	6,993	57.7	57.0	0.8	58.5	0.8	11,146	4,896	69.5	68.8	0.7	70.2	0.7
Immune by exposure	136	5490	2.4	2.0	0.4	2.9	0.4	2,331	14,204	14.1	13.6	0.5	14.6	0.5	2,680	13,362	16.7	16.1	0.6	17.3	0.6
Infected	76	5550	1.4	1.1	0.3	1.7	0.3	330	16,205	2.0	1.8	0.2	2.2	0.2	323	15,719	2.0	1.8	0.2	2.2	0.2
Unknown	5042	584	89.6	88.8	0.8	90.4	0.8	3,441	13,094	20.8	20.2	0.6	21.4	0.6	1,312	14,730	8.2	7.8	0.4	8.6	0.4

Table 4: Population born before Jan 1, 1990 (pre-vaccine), with known and documented HBV status, per status code, across three time points – Pre-Hep B PAST (2018) Foundation step (2020), at completion of Hep B PAST (2023)

Born pre-1/Jan/1990	Pre-Hep B PAST (N=4,284)							Foundation (N=14,578)							Completion (N=12,128)						
	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff
Non-immune	127	4157	3.0	2.5	0.5	3.5	0.6	1,092	13,486	7.5	7.1	0.4	7.9	0.4	673	11,455	5.5	5.1	0.4	6.0	0.4
Fully vaccinated	277	4007	6.5	5.7	0.7	7.2	0.8	4,562	10,016	31.3	30.5	0.8	32.1	0.8	5,117	7,011	42.2	41.3	0.9	43.1	0.9
Immune by exposure	231	4053	5.4	4.7	0.7	6.1	0.7	4,365	10,213	29.9	29.2	0.7	30.7	0.8	4,769	7,359	39.3	38.5	0.9	40.2	0.9
Infected	179	4105	4.2	3.6	0.6	4.8	0.6	761	13,817	5.2	4.9	0.4	5.6	0.4	736	11,392	6.1	5.7	0.4	6.5	0.4
Unknown	3470	814	81.0	79.8	1.2	82.2	1.2	3,798	10,780	26.1	25.3	0.7	26.8	0.7	833	11,295	6.9	6.4	0.4	7.3	0.5

Table 5: Population born after Jan 1, 1990 (post-vaccine), with known and document HBV status, per status code, across three timepoints – Pre-Hep B PAST (2018) Foundation step (2020), at completion of Hep B PAST (2023)

| Born on or after 1/Jan/1990	Pre-Hep B PAST (N=6,558)							Foundation (N=18,299)							Completion (N=19,427)						
	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff	n	N-n	%	95%CI min	95%CI min diff	95%CI max	95%CI max diff
Non-immune	98	6460	1.5	1.2	0.3	1.8	0.3	434	17,865	2.4	2.2	0.2	2.6	0.2	342	19,085	1.8	1.6	0.2	2.0	0.2
Fully vaccinated	244	6314	3.7	3.3	0.4	4.2	0.5	14,326	3,973	78.3	77.7	0.6	78.9	0.6	16,345	3,082	84.1	83.6	0.5	84.6	0.5
Immune by exposure	25	6533	0.4	0.2	0.1	0.6	0.2	492	17,807	2.7	2.5	0.2	2.9	0.2	604	18,823	3.1	2.9	0.2	3.4	0.3
Infected	11	6547	0.2	0.1	0.1	0.3	0.1	40	18,259	0.2	0.2	0.1	0.3	0.1	72	19,355	0.4	0.3	0.1	0.5	0.1
Unknown	6180	378	94.2	93.6	0.6	94.8	0.6	3,007	15,292	16.4	15.9	0.5	17.0	0.5	2,064	17,363	10.6	10.2	0.4	11.1	0.4

Cascade of care

CHB prevalence in people with unknown serostatus was assumed to be equivalent to HBV prevalence in the population with known serostatus. The total number of people infected post-Hep B PAST was calculated as the sum of people diagnosed plus the estimated number with undiagnosed infection. The percentage prevalence of HBV infection (diagnosed and undiagnosed) pre-Hep B PAST (2018) was assumed to be the same as that post-Hep B PAST (2023). This process assumes all HBV infections discovered during Hep B PAST were among people with previously unknown serostatus and that the true prevalence of HBV infection in our study cohort did not change substantially over time.

The definition of engaged in care is based on the number of people living with CHB who had HBV viral load monitoring within 15 months. The definition of receiving treatment is the number of people living with CHB prescribed antiviral medication. Current guidelines set eligibility criteria for treatment and are based on an assessment of the phase of the disease and whether liver damage is occurring. Current estimates assume that only 20% of people living with CHB require treatment (1).
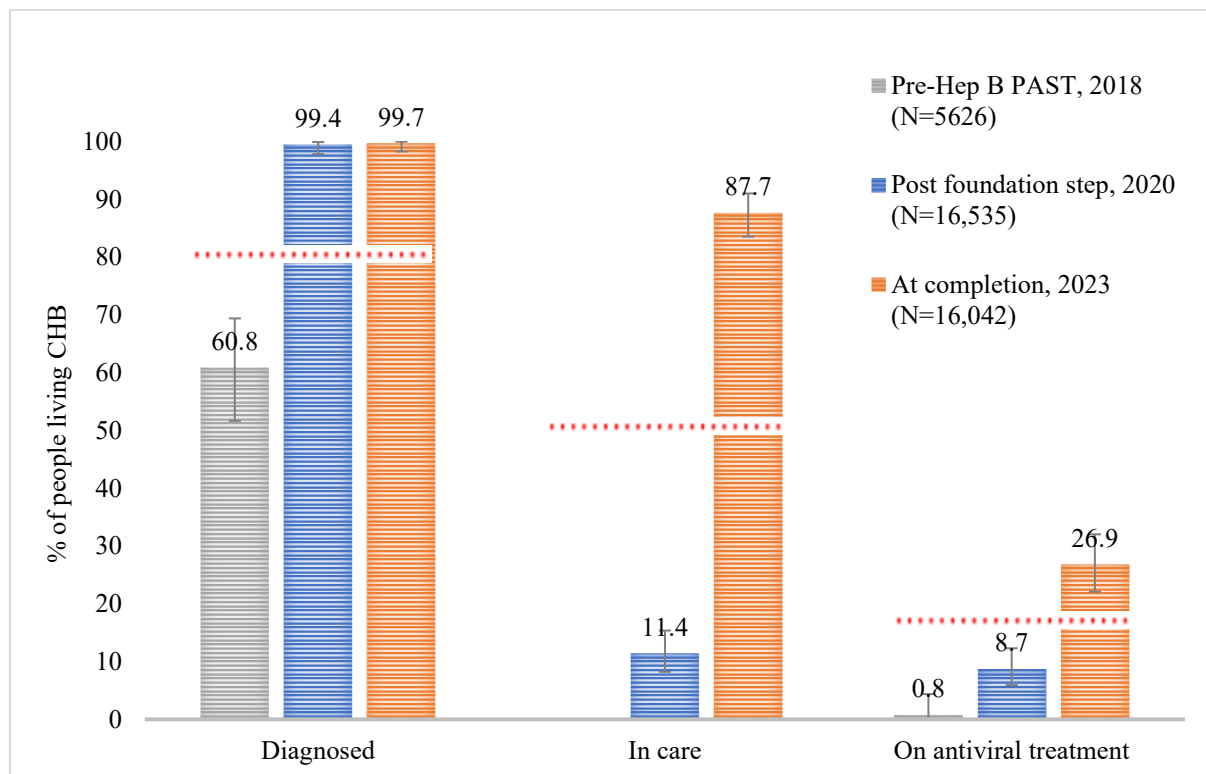
Figures by Sex

Fig 5: Males cascade of care in the study population at commencement, post-foundation step and at the completion of Hep B PAST (2018, 2020, 2023).
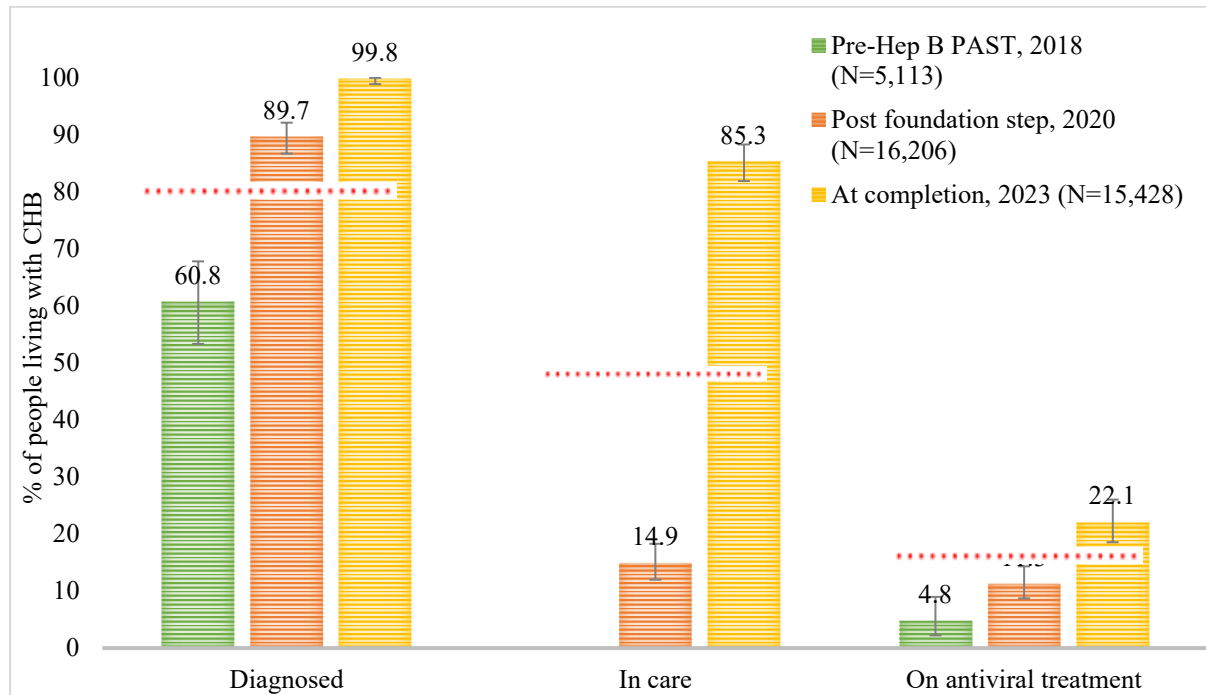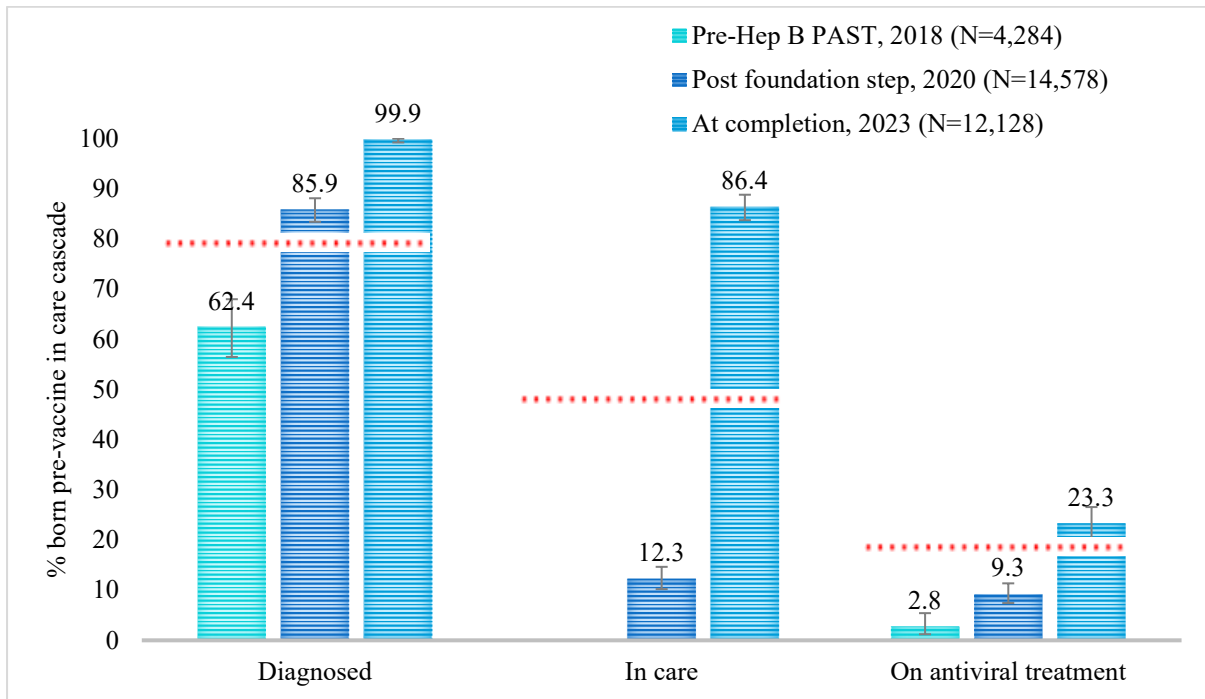

I - error bars represent 95% confidence interval.

.... - red dotted lines represent Third Hepatitis B National Strategy Targets

Fig 6: Females cascade of care in the study population at commencement, post-foundation step and at the completion of Hep B PAST (2018, 2020, 2023).

Figures by age cohort

Fig 6: Born pre-vaccine (before 1 Jan 1990) care cascade, in the study population at commencement, post-foundation step and at the completion of Hep B PAST (2018, 2020, 2023).

I - error bars represent 95% confidence interval.
.... - red dotted lines represent Third Hepatitis B National Strategy Targets

Fig 7: Born post-vaccine (on or after 1 Jan 1990) care cascade, in the study population at commencement, post-foundation step and at the completion of Hep B PAST (2018, 2020, 2023).
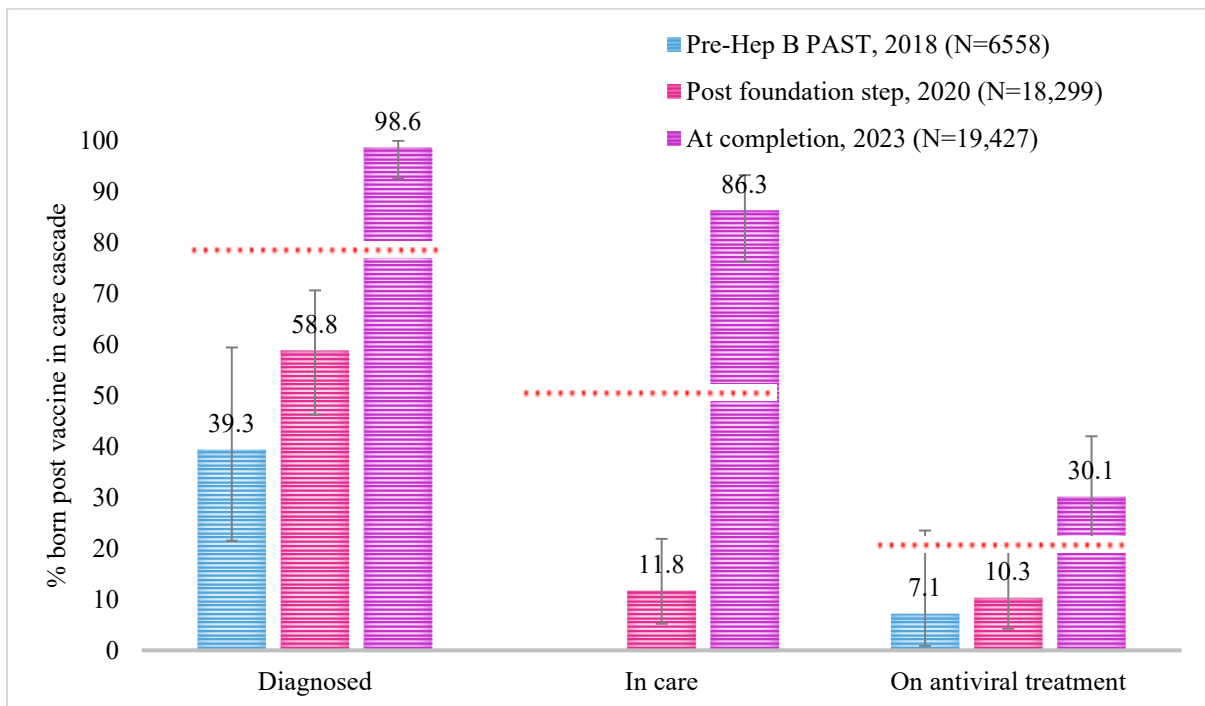
I - error bars represent 95% confidence interval.
.... - red dotted lines represent Third Hepatitis B National Strategy Targets

Table 6: Cascade of care for overall population

	Pre-Hep B PAST, 2018 (10,853)								Foundation step, 2020 (N=32,915)								At completion, 2023 (N=31,588)							
	Infected	n	Infected-n	%infected	95%CI min	95%CI min diff	95%CI max	95%CI max dif	Infected	n	Infected-n	%infected	95%CI min	95%CI min diff	95%CI max	95%CI max dif	Infected	n	Infected-n	%infected	95%CI min	95%CI min diff	95%CI max	95%CI max dif
Diagnosed	313	190	123	60.7	55.1	5.7	66.1	5.4	859	801	58	93.2	91.4	1.9	94.8	1.6	822	821	1	99.9	99.3	0.6	100.0	0.1
In care	313								859	117	742	13.6	11.4	2.2	16.1	2.5	822	709	113	86.3	83.7	2.5	88.5	2.3
On treatment	313	10	303	3.2	1.5	1.7	5.8	2.6	859	89	770	10.4	8.4	2.0	12.6	2.2	822	198	624	24.1	21.2	2.9	27.2	3.1

Table 6: People who were positive at baseline who were not in endline data (n=185), reason.

		Endline				Deceased	Incarcerated	Moved
		Infected not on Tx	Infected on Tx	Cleared HBsAg	Unknown			
Baseline	Infected not on Tx	451	92	30	3	70	22	48
	Infected on Tx	9	64	0	0	7	1	4
	Unknown	163	42	0	0	0	0	0

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Hep B PAST: Partnership Approach to Sustainably Eliminating Chronic Hepatitis B in the Northern Territory

STUDY PROTOCOL

Version 2.1, 2nd February 2024

Study Title:	Hep B PAST: Partnership Approach to Sustainably eliminating Chronic Hepatitis B in the Northern Territory
Principal Investigator:	Assoc/Prof Jane Davies[1,2]
Chief Investigators:	Dr Christine Connors[1,2]
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	Professor Steven Tong[1,4]
	Professor Robert Batey[2]
	Professor Anna Ralph[1,2]
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	Ms Kelly Hosking[1,2]
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	2. Northern Territory Health
	3. Miwatj Health Aboriginal Corporation
	4. Doherty Institute for Infection and Immunity

Administering Institution: Menzies School of Health Research

Coordinating author: Ms Kelly Hosking

Contributing authors: Assoc/Prof Jane Davies

                                                    Ms Paula Binks

1   INVESTIGATOR AGREEMENT

Study Title:

Hep B PAST: Partnership Approach to Sustainably eliminating Chronic Hepatitis B in the Northern Territory

I agree:

- To assume responsibility for the proper conduct of the study;
- To conduct the study in compliance with this protocol, with any future protocol amendments and with any study conduct procedures;
- To ensure that all persons involved with this study are adequately informed about the study-related duties and functions as described in the protocol;
- Not to implement any changes to the protocol without prior review and approval from the Human Research mmittee/s approving the protocol, except where necessary to eliminate an immediate hazard to the subjects, or where permitted by all applicable regulatory requirements (for example, administrative aspects of the study);
- That I am aware of, and will comply with "Good Epidemiological Practice" (GEP) and all applicable NHMRC requirements;
- That I, and any persons employed on this project, will provide up to date curriculum vitaes and any declaration of financial and ownership interests in this project.

Investigator name: Assoc/Prof Jane Davies

Date: 02/10/2018

2 STUDY SYNOPSIS

TITLE:	Hep B PAST: Partnership Approach to Sustainably eliminating Chronic Hepatitis B in the Northern Territory
AIMS:	The **overall goal is** the elimination* of Chronic Hepatitis B (CHB) from Aboriginal and Torres Strait Islander Australians in the Northern Territory (NT).
	Aim: To improve the cascade of care for people living with CHB in the NT. This project will improve health outcomes and decrease morbidity and mortality associated with CHB.
	STEP 1: Document everyone's hepatitis B sero-status and create a Hep B Hub
	Allocate a hepatitis B sero-status code to the electronic health record (EHR) of all Aboriginal and Torres Strait Islander people and follow up accordingly.
	Establish an NT Hepatitis B Virus (HBV) clinical care facilitation tool – "Hep B Hub" to facilitate timely, gold-standard clinical care for people living with CHB.
	STEP 2: Educate Health Staff
	To enable and maintain a core clinical care group for the management of CHB.
	STEP 3: Implement and evaluate
	To implement and evaluate the transition of gold standard care for CHB into Primary Health Care using a hub and spoke care co-ordination model. We envisage the central hub to be the overarching NT HBV clinical care facilitation tool – "Hep B Hub".
	Overarching evaluation against jurisdictional and national benchmarks at population and individual service provider levels, proportion of: 1) Population tested for HBV – target >80% 2) CHB individuals engaged in guideline-based care – target >80% 3) CHB individuals receiving treatment – target 15%
	*Elimination is defined as the absence of newly acquired cases of HBV and minimised morbidity and mortality from existing cases.
FUNDING:	Supported by NHMRC partnership grant APP1151837
ADMINISTERING INSTITUTION:	Menzies School of Health Research
BACKGROUND:	Chronic hepatitis B virus infection (CHB) is endemic in the Aboriginal and Torres Strait Islander communities of the Northern Territory (NT) with a prevalence of 3-12%, meaning the NT has the highest CHB prevalence in Australia at 1.77% (including non-Indigenous people)[1]. Of those living with CHB, 25% will die from decompensated cirrhosis (liver failure) or hepatocellular carcinoma (HCC), hereafter referred to as liver cancer.
	Liver disease is the third most important contributor to the gap in life expectancy between Aboriginal and Torres Strait Islander people and non-Indigenous Australians[2] and we have shown that NT Aboriginal and Torres Strait Islander Australians have an incidence of liver cancer that is 5.9 times higher than non-Indigenous Australians[3].
	These deaths could be prevented with currently available treatment. Therefore, it is the right of everyone to know their hepatitis B sero-status so they can get the care, monitoring, and treatment they require – to decrease morbidity and mortality and improve the health outcomes of people living with CHB.

The Second National Hepatitis B strategy identified Aboriginal and Torres Strait Islander people as a key priority group. In 2014, in response to this strategy, the NT Hepatitis B Action Plan was developed with an emphasis on; [4]

- Determining the hepatitis B sero-status of all Aboriginal and Torres Strait Islander Territorians
- Building the capacity of Primary Health Care to manage CHB.
- Raising awareness of hepatitis B and it's management and treatment.

RATIONALE:	There are currently gaps in the cascade of care in the NT setting.

Table 1: The Cascade of care for CHB, National Targets vs NT estimates vs Pilot

	NT overall	Pilot	National Target
Aware of Infection	61%	96%	80%
Engaged in Care	15%	83%	No specific (but >80%)
On Treatment	3.1%	20%	15%

Documenting people's sero-status.

There are approximately 3500 Aboriginal and Torres Strait Islander Australians in the NT living with HBV. Chronically HBV-infected patients have a 25% chance of developing either liver failure or liver cancer. However, approximately 40% (~1400) of people living with CHB are unaware they are infected.

In the NT, the majority of HBV infection was acquired at birth and is chronic, requiring lifelong follow-up however, HBV has traditionally been managed with other blood borne viruses under a communicable disease or sexual health model. Although we know that 54% of the NT Aboriginal and Torres Strait Islander population have had HBV serology testing[5], a major gap in our public health response to HBV is establishing in an organised way who is infected, who is immune and who has not been tested, especially as CHB can be asymptomatic for decades. Any downstream response relies on accurate diagnosis and an ability to keep track of these diagnoses (that can change over time).

Creating the Hep B Hub for people living with CHB.

A Hep B Hub will be established for all individuals identified as living with chronic hepatitis B. The primary purpose of this clinical care facilitation tool is to improve timely access to gold-standard clinical care. This will improve the health outcomes of people living with CHB and reduce the incidence of liver cancer and preventable death.

Providing care to those with CHB.

We have access to effective antiviral therapies through the Pharmaceutical Benefits Scheme, however prescribers must either be a hospital-based specialist or a GP who has undergone s100 prescriber training. At least until recently, most CHB care has been provided by tertiary specialists either at the Royal Darwin or Alice Springs Hospital or through specialist outreach services.

In our setting, the care needs of people living with CHB both from a virological and liver cancer screening perspective better fit within a chronic disease model of care[6]. A key component of our proposed project, already endorsed but not implemented, by all the project partners in the NT Hepatitis B Action Plan (2014 Table 2), is to shift CHB into the primary care chronic disease model.

Table 2 Summary of key aspirations of Northern Territory Hepatitis B Action Plan (2014)

Priority action area	Focus areas
Prevent new cases	Prevention of mother to child transmission
	Early follow up of potentially exposed babies
	Increase immunisation coverage amongst adults
Increase testing	Increase detection of undiagnosed cases of CHB
Provide treatment care and support	Increase the number of people accessing and remaining on treatment through reorientation towards chronic care model and follow up in primary care
Capacity building	Increase capacity of health systems to HBV through skill development
	Increase the capacity of health systems to HBV through system strengthening

The geography, available human resources and capacity, and existing models of care for other chronic diseases, make a so called "hub and spoke model" of care for CHB attractive. Rather than the traditional hierarchical movement from simple care at the spoke service to complex care at the centre or hub, our model encourages movement in both directions between the hubs and the spokes. This bidirectional movement also fits well with local, culturally appropriate delivery of care, especially when incorporating co-ordination through the Hep B Hub, IT systems and the availability of telehealth. Over the last 7 years we (CI Davies, Bukulatjpi, Tong, Davis) have partnered with one specific clinic and iteratively developed the "liver health one stop shop". This outreach service delivered in the community (2 hour flight from Darwin) includes specialist review (CI Davies), portable ultrasound scan and Fibroscan®, education using the Hep B story app and is co-ordinated by a community based AHP (CI Bukulatjpi).The improved cascade of care for this service from a recent audit has shown that of the 103 people diagnosed and living with CHB 84% are engaged in regular care and 11% are receiving and maintained on antiviral treatment (all with an undetectable viral load) this is compared to 17% and 3.1% respectively for the remainder of the NT.

STUDY DURATION:	November 2018 – June 2023
NUMBER OF PARTICIPANTS:	Step 1: ~ 60,000 Step 2: ~ 3,500
NUMBER OF CENTRES:	NT-wide
INCLUSION CRITERIA:	Step 1: All Aboriginal and Torres Strait Islander people living in the Northern Territory Step 2: All people living with Chronic Hepatitis B in the NT
EXCLUSION CRITERIA:	Nil
WITHDRAWAL:	This project is practical and applied, and its main aim is to have people engaged in gold standard clinical care (which should be a routine part of their Primary Health care). The research component of this project is the evaluation of the different interventions. We are planning a hybrid model of consent for those with HBV to enter the Hep B Hub. For communities who agree to this process (all partners) we will be using an opt-out approach. Each other non-partner service will be approached individually for service level consent. If a service does not choose the opt out process and chooses to obtain individual consent from all CHB infected individuals to enter the Hep B Hub, this will be done using the attached consent forms and patient information sheets. Participants are free to withdraw from the Hep B Hub at any time. If this occurs, their care will continue through the health provider, as desired.

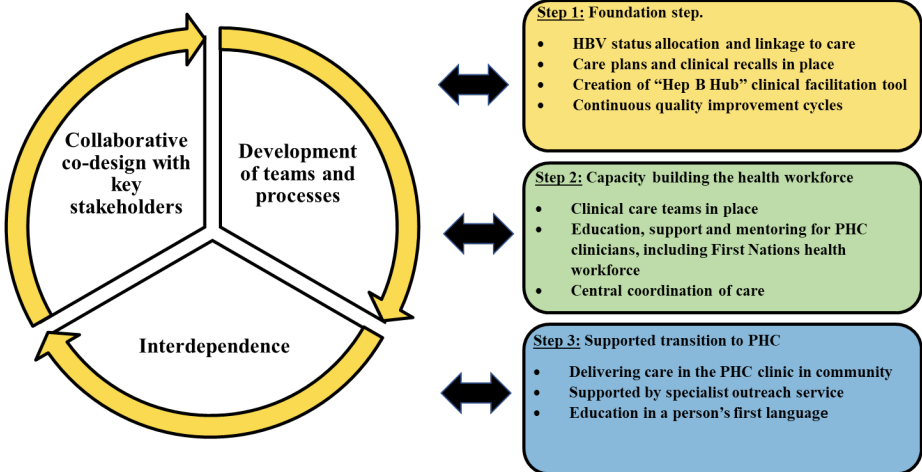|	
STUDY PROCEDURES:	**STEP 1: Document everyone's hepatitis B sero-status and create a Hep B Hub** *Allocating a hepatitis B sero-status to individuals to establish the HBV clinical care facilitation database – Hep B Hub.* We will determine and allocate a hepatitis B sero-status code to each individual in consenting health services which will then triggers an appropriate follow-up response. We will aim for >80% of NT Aboriginal and Torres Strait Islander individuals to have an assigned sero-status, and for those who have not been tested, to have HBV serology performed. The sero-codes: i) HepB: Fully vaccinated; ii) HepB: Immune by exposure; iii) HepB Infected ON treatment; iv) HepB: Infected NOT on treatment; v) HepB: Non-immune; or vi) no data available. We have created a viral hepatitis specific standalone work unit within PCIS and will use this to house the Hep B Hub for the clinical care facilitation of CHB infected people. See Appendix: **Details of processes within the methodology** • *Figure 4. Overview of the process for creation of the NT HBV clinical care database, Hep B Hub.* **STEP 2: Educate Health Staff** *Enabling and maintaining a competent cohort of primary healthcare professionals to provide gold standard CHB care and prescribe HBV antivirals.* Supported by our partnership with ASHM, we will offer the s100 prescriber course twice in 2018 and then annually as well as providing ongoing mentorship of GP prescribers who have previously completed the course. In partnership with ASHM and TEHS we will further develop and adapt the course to focus on the AHP role which is essential to the implementation of our proposed co-ordinated CHB chronic disease model of care described in detail in the methodology below. **STEP 3: Implement and evaluate** *To implement and evaluate the transition of gold standard care for CHB into Primary Health Care using a hub and spoke care co-ordination model. We envisage the central hub to be the overarching NT Hep B Hub* Participants will be individuals identified as living with CHB in consenting health services. Using the Hep B Hub as the central co-ordinating tool a CHB care bundle will be implemented. A 3-step staged approach will enable evaluation of the value added by each incremental step (Figure 1). Depending on service level consent, either opt out or individual written consent will be obtained to enter the study section of the Hep B Hub; each service will spend 18 months in each of steps 1-3 in chronological order. Step 1 is based on CQI –as described above, Step 2 is the addition of a core care group, established in partnership with each service with the following key essential elements: i) an AHP or Aboriginal Community worker with training in viral hepatitis; ii) an s100-trained GP prescriber or specialist; and iii) access to ultrasound and Fibroscan® as needed either in community or a regional hub depending on service/location.

	CHB specific training will be (through Step 2) or has been provided to all members of the care clinical group. Patient HBV education added in Step 3 will focus on the educational app in the 11 Aboriginal languages (part of separate project, with separate ethics application); if the preferred language is not available, an interpreter will be used in conjunction with the English version of the educational app. Translation of the app is part of another project, with a separate ethics application submission.
	Figure 1 - A 3-step staged implementation of a CHB care bundle
	Evaluation indicators for aim 2: NT-wide and within each hub the number of people: i) included in the Hep B Hub; ii) coded as immune/infected/on treatment; iii) successfully completing allocated care plans; iv) receiving key components of guideline-based care (liver function tests, HBV viral loads, ultrasound, Fibroscan®); v) on treatment.
DATA COLLECTION	If a service chooses to use individual consent to enter the Hep B Hub consent forms will be collected in paper format and stored in a locked cabinet and locked office at Menzies.

3   GENERAL INFORMATION

3.1 . Protocol full title

Hep B PAST: Partnership Approach to Sustainably eliminating Chronic Hepatitis B in the Northern Territory

3.2.   Principal investigator

Assoc/Prof Jane Davies
Menzies School of Health Research (MSHR)
John Mathews Building (Bldg. 58)
Royal Darwin Hospital Campus, Casuarina, NT

3.3   Person(s) authorised to sign the protocol amendments

Assoc/Prof Jane Davies, MSHR

3.4   Investigator(s) responsible for conducting study

Assoc/Prof Jane Davies	MSHR, NT Health
Kelly Hosking	MSHR, NT Health
Dr Geoff Stewart	NT Health
Dr Christine Connors	NT Health
Professor Josh Davis	MSHR

Professor Steven Tong	MSHR
Professor Anna Ralph	MSHR, NT Health
Professor Robert Batey	NT Health
AHP Sarah Bukulatjpi	Miwatj Health Aboriginal Corporation
Professor Ben Cowie	Doherty Institute
Dr Belinda Greenwood-Smith	NT Health
Dr Nicole Allard	NT Health
Dr Catherine Marshall	NT Health

3.5 Confidentiality statement

All information found within is the property of Menzies School of Health Research, and therefore provided to you in confidence. Authorised personnel may only access this information and it is understood that its contents shall not be disclosed without written authorisation from the Chief Investigator, **Assoc/Prof Jane Davies.**

3.6 Terminology statement

In consultation with the Aboriginal workforce within the Hep B PAST team and in multiple NT remote communities we established that the preferred terminology is "Aboriginal and Torres Strait Islander Peoples". Throughout this protocol the Aboriginal and Torres Strait Islander health workforce are referred to as "Aboriginal health workforce" in-line with the language used for these professions in the Northern Territory. The study Investigators acknowledge the important role of the Aboriginal health workforce.

Other Instances where we use the terminology "Aboriginal" is when it is in the name of the organisation, for example, "Aboriginal Community Controlled Organisation", "Aboriginal Medical Service".

It will be noticed that when we are referring to the languages translated for the "Hep B Story" app, we refer to only Aboriginal because we have only translated Aboriginal languages and not Torres Strait Islander languages. We have not begun consultations with people from Torres Strait Islander groups.

Also, of note, the Indigenous Reference Group established in 2014 has maintained its original name at the request of the participants, this will continue to be reviewed.

4   AIMS

Aim. Improve the cascade of care for individuals living with CHB in the NT through establishing a hepatitis B clinical care facilitation tool – the "Hep B Hub", healthcare provider training, and transition of CHB into a primary health care based, co-ordinated chronic disease model of care

 Outcomes Substantially improve community health literacy, determine the sero-status of > 80% of Aboriginal and Torres Strait Islander individuals, and by shifting CHB to a chronic disease care model have > 80% of individuals with CHB engaged in guideline-based management with 15% receiving and remaining on treatment.

4.1   Objectives

To eliminate* Chronic Hepatitis B (CHB) from Aboriginal and Torres Strait Islander Australians in the Northern Territory. To decrease Hepatitis B Virus (HBV) related morbidity and mortality in Aboriginal and Torres Strait Islander Australians by implementing NT and national HBV strategies and by filling important knowledge gaps, which currently impede the implementation of these strategies.

*" Elimination" is defined as the absence of newly acquired cases of HBV and minimised morbidity and mortality from existing cases

5   BACKGROUND AND RATIONALE

5.1 Background information:

Chronic hepatitis B virus infection (CHB) is endemic in the Aboriginal and Torres Strait Islander communities of the Northern Territory (NT) with a prevalence of 3-12%, meaning the NT has the highest CHB prevalence in Australia at 1.77% (including non-Indigenous people)[1]. Of those living with CHB, 25% will die from decompensated cirrhosis (liver failure) or hepatocellular carcinoma (HCC), hereafter referred to as liver cancer. Liver disease is the third most important contributor to the gap in life expectancy between Aboriginal and Torres Strait Islander and non-Indigenous Australians[2] and we have shown that NT Aboriginal and Torres Strait Islander Australians have an incidence of liver cancer that is 5.9 times higher than non-Indigenous Australians[3]. We have demonstrated that a shared understanding of Hepatitis B virus (HBV) between patient and care provider is a pre-requisite to sustainable and quality engagement in care[4]

In the Australian context, guidelines state that individuals who are considered high risk for liver cancer include:

- Aboriginal and Torres Strait Islander individuals over the age of 50 years with chronic HBV (1)

In addition to those individuals identified in international guidelines namely:

- All those with cirrhosis of any cause
- Individuals with CHB and a Family history of HCC
- Asian males over the age of 40 with CHB
- Asian females over the age of 50 with CHB
- Africans over the age of 20 with CHB

5.2   Rationale

There is a gap in documenting people's hepatitis B sero-status. The NT has a very sparsely populated diverse population within excess of 20 languages[7] and 641 discrete Aboriginal communities. Within communities, multiple competing priorities including chronic physical and mental illness, coupled with limited staff numbers and high staff turnover means until recently there has sometimes been a nihilistic attitude to HBV[4]. In the NT, the majority of HBV infection was acquired at birth and is chronic, requiring lifelong follow up however HBV has traditionally been grouped with other blood borne viruses under a communicable disease or sexual health model. Although we know that 54% of the NT Aboriginal and Torres Strait Islander population have had HBV serology testing[8], a major gap in our public health response to HBV is establishing in an organised way who is infected, who is immune and who has not been tested, especially as CHB can be asymptomatic for decades. Any downstream response relies on accurate diagnosis and an ability to keep track of these diagnoses (that can change over time). We will establish the Hep B Hub where each individual living with CHB in consenting services will enter and be able to receive best-practice care in a timely manner.

The Second National Hepatitis B Strategy highlights Aboriginal and Torres Strait Islander people as a priority group and defines clear targets for hepatitis B care and management, which currently the NT is not meeting. This project will implement interventions to improve cascade of care and therefore the health and well-being of people living with chronic hepatitis B infection.

With service level consent will review available serology and vaccination data from 3 main data sources.

1. Primary Care information system (PCIS) or Communicare

2. Clinical Work Stations (CWS), hospital pathology data

3. NT and Australian Immunisation Register

This method has been successfully piloted already in a government Health Service. With the systematic review most clinics have achieved >80% of their population knowing their HBV status. See graph, comparing another health service, yet to go through complete clinical audit to the other health service, already complete.

Figure 2 Percentage of Aboriginal and Torres Strait Islander people with a new hepatitis B problem, recorded by clinic.
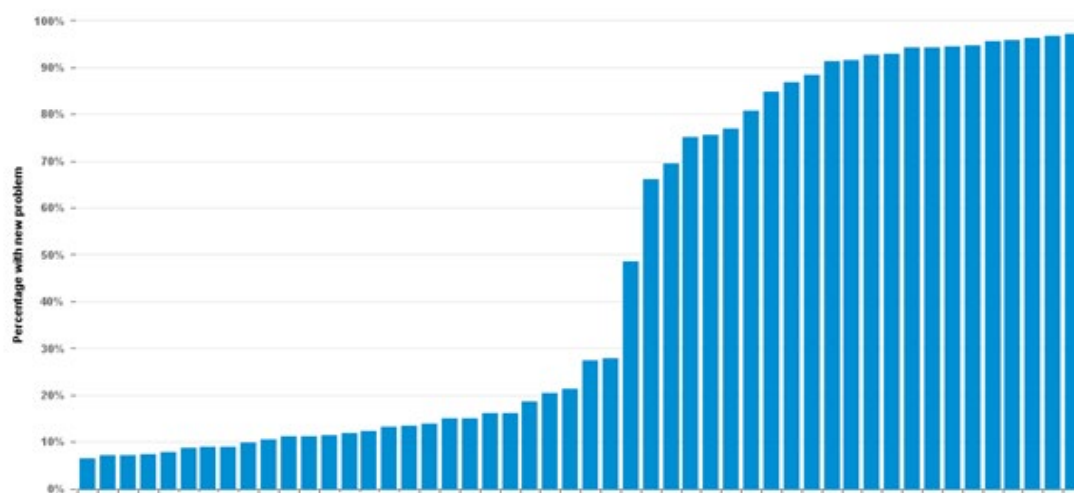
Each bar represents an individual clinic (deidentified).

We have access to effective antiviral therapies through the Pharmaceutical Benefits Scheme, however prescribers must either be a hospital-based specialist or a GP who has undergone s100 prescriber training. At least until recently, most CHB care has been provided by tertiary services. Unfortunately, this model is not sustainable, nor has it provided consistent care for individuals with CHB. For example, in an observational study including 128 remote-dwelling Aboriginal and Torres Strait Islander people with CHB in the NT followed up for a median of 27 months, we have shown clinical follow up did not meet recommended guidelines[9] for any of the parameters measured. Liver function tests, HBV viral load, ultrasound and Fibroscan® were carried out appropriately 55%, 28%, 65% and 25% of the time respectively[8]. Fibroscan® is a non-invasive validated measure of liver fibrosis, enabling individuals to be diagnosed with cirrhosis without a liver biopsy; we currently have just one portable Fibroscan® machine in the NT.

5.3 Rationale for working with Aboriginal and Torres Strait Islander Australians:

In 2010, it was estimated up to 22,000 Aboriginal and Torres Strait Islander people were living with HBV in Australia. In the four years to 2011 the population rate of newly acquired HBV infection, among Aboriginal and Torres Strait Islander Australians, was three times that of non-indigenous Australians[14].

There are approximately 3500 Aboriginal and Torres Strait Islander Australians in the NT living with HBV. Chronically HBV infected patients have a 25% chance of developing either cirrhosis (liver failure) or liver cancer. Liver cancer is the 3rd most significant contributor to the life expectancy gap between Aboriginal and Torres Strait Islander and non-Indigenous Australians.

A 2014 study in the NT showed that NT Aboriginal and Torres Strait Islander patients are generally six times more likely to develop liver cancer than non-Aboriginals in the NT. Recently, a novel genotype of HBV was found to

be the exclusive genotype in Aboriginal Australian populations in the NT [15]. Molecular analysis of the HBV/C4 genome suggests it is more aggressive than other strains and infection may lead to accelerated cirrhosis and increased risk of liver cancer compared to other genotypes[16].

5.4 Benefit of Study to Australian society and Aboriginal and Torres Strait Islander Health

This research will:

- Contribute to the elimination (absence of newly acquired) of HBV from Aboriginal and Torres Strait Islander people in the NT**.**

- Improve health outcomes and well-being of clients with CHB. The long-term consequences of hepatitis B infection and the outcomes that treatment tries to prevent are liver cirrhosis (failure) and liver cancer. Without treatment both these conditions have high mortality and short life expectancy from time of diagnosis. Better care and management of CHB is known to prevent these outcomes and so will contribute to "Closing the Gap" between Aboriginal and Torres Strait Islander and non-Aboriginal Australians' life expectancy.

- Reduce stigma and discrimination around HBV by increasing knowledge amongst Aboriginal Health and Community workers and by using appropriate resources in language

- The establishment of the NT HBV Hep B Hub is important locally and globally.

- The National Strategy for Hepatitis B lists Aboriginal and Torres Strait Islander communities as a priority group.

5.5 Hypothesis

CHB care can be successfully transitioned into the primary care setting in the remote NT context using the chronic disease model.

Central co-ordination through the Hep B Hub and an allocated core clinical care team using a bidirectional hub and spoke model improves the cascade of care for CHB.

5.5.1   Potential Risks

1. A risk is breach of confidentiality or privacy as individual's records will be accessed from identifiable data. However, this is data that is already available in the individual's electronic health records and will only be accessed by project officers who are clinicians so the risk of a third party accessing this information is low. All data will be securely stored, password protected and only available to limited project staff.

    In regard to participating Aboriginal Community Controlled Health Services (ACCHS), as the health care provider of individual clients, will have access to the client's sero-status code on the electronic health records once a client has been sero-coded. This should not present an additional risk for breach of confidentiality. If the client is HBV infected the project team will contact the GP at the ACCHS to inform them and ensure they are aware so the client can be engaged in gold standard care and support.

    No third party will be given access to, or copies of the data. All data will be securely stored, password protected and only available to limited project staff.

    Confidentiality agreements are signed as conditions of employment for all partners in the project.

2. Aboriginal and Torres Strait Islander people may be concerned by the high HBV prevalence in their community.

    We will work with our local staff, trainer AHPs and community workers to do community education, using the "Hep B Story" app and other resources

3. The potential risk of distress and shame of a new diagnosis of HBV infection for clients newly identified as part of this process. This will be mitigated with appropriate follow up, education and support. No individual's identity will be made public. Service delivery staff have been / will be educated in the management of people with CHB, including giving diagnosis, counselling support, and offering education and resources in a language that the individual understands. Allowing time for questions at first and subsequent visits.

There is a risk of increased workload initially for clients with no data will require serology to determine a sero-status. There is also a potential for increased workload to manage CHB infected clients. This will be mitigated by having additionally trained people. This includes GPs and NPs being educated through the ASHM S100 prescriber course and the co-designed and delivered Managing hepatitis B training course for the Aboriginal Health workforce. With the trained and supported workforce, we will develop core clinical care groups and a hub and spoke model of care to support transition to primary care. All partners involved understand this issue and are supportive and have already committed their in-kind support. As new services enter the project they will be fully informed of the requirements and anticipated workload before they agree.

4. There is a risk that the new whole of NT Health IT systems currently being updated through the Core Clinical Systems Renewal Program (Acacia) will be delayed and/or that the Hep B Hub may not be able to be housed as we imagine or may be inaccessible to ACCHS. We have an interim solution in the Viral Hepatitis PCIS work unit, which is already operational.

5. Risks to researchers may include.

   o Personal safety – this will be mitigated by appropriate orientation, including pre-travel cultural and security information, strict travel guidelines

   o Vicarious trauma when hearing patient stories or if a patient dies. Researchers will have access to counselling services as required

   o Ethical dilemma of research and the legal obligation mandatory reporting.

5.5.2 *Potential Benefits*

As described above in section 5.4, the benefits of this project will be profound, locally, and globally.

Specifically, the implementation of this project will contribute to the elimination (absence of newly acquired) of HBV from Aboriginal and Torres Strait Islander people in the NT.

Importantly, it will improve health outcomes and well-being of clients with CHB. By systematically identifying everyone who is living with CHB (Step 1) and getting them engaged in best-practice care in a timely manner, facilitated through the Hep B Hub (Step 2,3), this will significantly reduce the incidence of liver cirrhosis (failure) and liver cancer.

Better care and management of CHB is known to prevent will contribute to "Closing the Gap" between Aboriginal and Torres Strait Islander and non-Aboriginal Australians' life expectancy.

6 RESEARCH PLAN

6.1 Study design

STEP 1: Document everyone's hepatitis B sero-status and create a Hep B Hub

Sero-coding

1. Community consultation and service level agreement.
2. Inform District Manager, Primary Health Centre Manager and Rural Medical Practitioner when an audit of their health centre/s is about to take place and to expect recalls and inbox messages for some clients.
3. Review all available data sources (PCIS, NT and Australian Immunisation Register, Territory Pathology) and assign a hepatitis B sero-status code to the client's PCIS problem list where there is sufficient information to determine a hepatitis b status.
4. If a client has no/insufficient data to determine a hepatitis B sero-status add a standardised, detailed PCIS or Communicare recall for serology.
5. If the client is non-immune to hepatitis B add a Hep B vaccination care plan.
6. If there is a client who is HBV infected (HBsAg positive) and is not on a Hepatitis B care plan, send a message to the Medical Officer to add care plan and engage client in care, counsel and review client and contact trace as appropriate.
7. Supersede any old, outdated, or inaccurate hepatitis B sero-codes on PCIS problem list.
8. Clinic staff to action all recalls, manage results and add sero-code to problem list.
9. CQI process to monitor progress and keep the project current and sustainable.

Figure 3: Methodology for determining and allocating sero-status codes

Consultation
1. Service level agreement
2. Consult with key people in community
3. Inform clinicians and managers at the health centre before commencing clinical audit

Review existing pathology and vaccination data to determine and allocate a "Hep B Sero-Code" to patient's EHR (depending on service level agreement)
1. PCIS/Communicare – review hepatitis B serology and vaccinations
2. Clinical workstation (CWS), hospital pathology data – review hepatitis B serology
3. NT immunisation register data – review hepatitis B vaccinations

Infected

Action required:
Add care plan or comprehensive regular recalls
Ensure patient has received counselling, education.
Assess need for contact tracing, ensure offspring of female cases have had appropriate follow up.

Immune

Action required:
Add sero-code. No further action unless becomes immunosuppressed

Non-Immune

Action required:
Add recalls for hepatitis B vaccination/s.

No data

Action required:
Recall patient for hepatitis B serology

Ongoing communication, feedback and consultation throughout

See Appendix: Details of processes within the methodology

- *Table 5: Interpretation of HBV serology sero-status codes and action*
- *Figure 5: How clinicians at health centres can action Hepatitis B sero-coding recalls*

Creation of NT HBV clinical care facilitation tool, the "Hep B Hub"

1. All people with CHB will be incorporated into the Hep B Hub. Potential Hep B Hub participants will be recruited from their Health Care Provider, either at their local Primary Health Care Centre or through Royal Darwin Hospital Liver clinic and associated Liver Clinic Services. Potential participants will be identified during the process of standard clinical care for their liver disease or through interrogation of existing data – in Step 1. We will aim to recruit Aboriginal and Torres Strait Islander people living with CHB; however, non-Indigenous participants will not be excluded.

2. We have already created a viral hepatitis specific standalone work unit within PCIS and will use this to house the Hep B Hub. In 2024 the hep B Hub will transition into the Territory Kidney Care (TKC) integrated care tool. This will allow Hep B care providers and prescribers to access all information reducing manual duplication of data from Communicare into PCIS.

3. There are two consent process options:

   a. Service level consent – every individual who is known to be living with CHB will be part of the Hep B hub as a part of their usual care.

   b. Individual consent - if the patient wishes to be included in the Hep B Hub but does not attend a service which has given service level consent, then a verbal discussion with their health care professional will occur. Individual consent (consent forms included) will be completed.

4. Project staff will add participants to the Hep B Hub to assist with facilitating the client to receive best-practice clinical care, to improve health and well-being.

See Appendix: Details of processes within the methodology

- *Figure 4 Overview of the process for creation of the NT HBV clinical care database, Hep B Hub.*

STEP 2: Educate health staff

1. S100 GP Prescriber Courses held in Darwin (1) and Alice Springs (1) annually.
2. Work with ASHM and AHP coordinators to develop the AHP course.
3. Deliver the course, starting in pilot communities.
4. Evaluate and adapt the AHP course as required.
5. Work with the core clinical group and newly trained AHPs / ACWs on the train the trainer model and support them in the delivery of community/client education.

STEP 3: Implement and evaluate

1. Identify, train, and support the core clinical care group (GP, RN, AHP/ACW) for each district (spoke).
2. Using de-identified data extracted through PCIS query group search and/or Business Intelligence reports evaluate
   a. The number of CHB infected people included on the Hep B Hub
   b. Coded as immune/infected/on treatment
   c. Successfully completing allocated care plans
   d. Receiving key components of guideline-base care
   e. On treatment

Implementation of complex interventions. Evaluations of CQI projects in the NT context have highlighted: stable effective outreach workers; good regional co-ordination and local ownership; creating an interdependence, as important for successful chronic disease care[8]. There are clear evidence-based guidelines for what constitutes gold standard care for people living with CHB [9 11,12]. Therefore, we intend to apply these CQI methodologies to improve the cascade of care from encouraging more complete testing for HBV to maintaining antiviral therapy for those that need it.

7   STUDY ENROLMENT AND WITHDRAWAL

7.1 Inclusion Criteria

- Step 1: All Aboriginal and Torres Strait Islander people living in the Northern Territory

- Step 2: All people living with Chronic Hepatitis B in the NT

7.2 Exclusion Criteria

- Nil

7.3 Withdrawal

7.3.1   Reason for withdrawal

Individual choice

7.3.2   Handling of withdrawal participants including their information

Where individual informed written consent is required, (e.g., participants in the Aboriginal Health Workforce course evaluation), all participants will be advised prior to giving consent and the collection of any data that they are free to withdraw their consent and involvement in the project at any time.

If a Health Service has chosen individual level consent rather than service level consent for inclusion in the Hep B Hub clinical facilitation tool, withdrawal of consent will result in reassurance that participants data will not be included in the project, and this will have no influence on their ongoing care at their relevant clinics. In the event of a participant dying the participant's data will remain in the study unless requested otherwise.

7.4 Study visit schedule

7.4.1   Consenting

- For the Hep B Hub care facilitation tool, an opt-out or informed consent approach will be used – depending on service level agreement and consent and in accordance with Human Research Committee (HREC) approval. Each Hep B PAST participating health service will decide if they will utilise a service level or individual consent process for inclusion into the Hep B Hub.

- If a participating health service chooses individual level consent the following process will apply

- The study will be explained to potential participants utilising a Plain Information Sheet approved by the HREC, an Aboriginal healthcare worker of liaison will be present where applicable to assist with any language barriers.
- Potential participants will be afforded the opportunity to discuss the study with a member of the research team.
- We will arrange for an interpreter to assist with the informed consent process if desired by each participant.

8 STUDY DATA COLLECTION, PROCEDURE AND STUDY TIMELINE

8.1 Data Collection

8.1.1 Data Capture Methods

Using Business Intelligence reports generated by the NT Health Data Warehouse.

8.1.2 Study Records Retention

- The data will be stored indefinitely after study completion and report writing at Menzies School of Health Research on a password protected desktop backed up onto a secure server. This allows for any concerns or enquiries regarding results from the study to be addressed if raised and is in line with NHMRC guidelines.
- No third parties outside of the investigators and institutions named in the proposal will be given access to the data.
- De-identified data will be kept indefinitely. Data to allow re-identification will be permanently destroyed 7 years following completion of the project.

8.1.3 Schedule and Contents of Reports

Report on study progress will be sent annually to HREC.

8.1.4 Data Storage

Source data in paper format will be stored in locked filing cabinets at Menzies School of Health Research

8.1.5 Data Entry

8.1.6 Data Evaluation

Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Data queries will be raised by the study coordinator and Investigators, and missing data or suspected errors will be resolved prior to database lock and analysis.

8.2 Study procedure timeline

1.   Study Timeline

Table 3: Summary of activities included in the complex intervention and proposed timelines

Activities included in complex intervention	2018	2019	2020	2021	2022
S100 prescriber, nurse, and Aboriginal Health Practitioner courses	▓	▓	▓	▓	▓
Creation of clinical Hep B Hub	▓	▓	▓	▓	▓
Care bundle – CQI plus recalls		▓	▓	▓	▓
Care bundle – CQI and recalls plus care co-ordination team			▓	▓	▓
Care bundle – CQI, recalls and care coordination team plus app in first language				▓	▓

Table 4: Timeline for successful completion of the project

Activity	2018	2019	2020	2021	2022	2023	Responsibility key:	
Stakeholder engagement and feedback							Yellow	Health service A
Partnership project launch							Green	Health service B
Ethics							Blue	Health service C
Literature search							Orange	Health service D
Step 1: Allocate a hepatitis B sero-code to individuals to establish the Hep B Hub							Purple	Health service E
Allocate a hepatitis B serocode								
Establish Hep B Hub								
Transfer to Hep B Hub								
Analyse data, evaluate and write up Step 1								

Step 2: Enable and maintain competent cohort of primary healthcare professionals to provide gold standard care and prescribe antivirals																														
Enable and maintain core clinical care group																														
Develop and deliver AHP education program																														
Provide s100 prescriber course to GPs and nurses																														
Analyse data, evaluate and write up Step 2																														
Step 3: Implement and evaluate the transition of gold standard care for CHB into PHC																														
Implement transition to hub and spoke PHC model																														
Evaluation of value added by each incremental step																														
Analyse data, evaluate and publish Step 3																														

9   STATISTICAL CONSIDERATIONS

9.1 Sample size calculation

TOTAL SAMPLE SIZE	60,000/ ~3500
NUMBER OF PARTICIPANTS	60,000/ ~3500
NUMBER OF RECORDS	60,000/ ~3500

The intention is to establish the hepatitis B sero-status of all Aboriginal and Torres Strait Islander people living in the NT, so that "*no one is left behind*". This means that everyone who is HBV infected has a right to know their status and have the opportunity to be engaged in care, monitoring, and treatment. This will prevent morbidity and mortality associated with CHB and improve the health and well-being of people living with CHB. Therefore, the estimated sample size is 60,000 and represents all Aboriginal and Torres Strait Islander people who live in the Northern Territory. These people will be part of **Step 1: Allocating a hepatitis B sero-status to individuals to establish the Hep B Hub.**

We estimate the number of Aboriginal and Torres Strait Islander people in the NT who are HBV infected to be approximately 3500. This is the sample size of those who will benefit from successful implementation of **Step 3 Implementing and evaluating the transition of gold standard care for CHB into primary care using a hub and spoke care co-ordination model**. Participants will be individuals identified as living with CHB in consenting health services. Using the Hep B Hub as the central co-ordinating data repository.

9.2 Primary and secondary analyses

Statistical Data will be extracted from the clinical Hep B Hub and analysed in STATA (Statacorp, College Station, Texas) v15. Proportions within categorical groups will be calculated with the denominator as the total number of individuals with that sero-code, with binomial confidence intervals. Chi squared will be used to assess differences between categorical groups and two-way tests of proportion for differences across categories. Assuming there are 4000 people living with CHB in the NT and we have 3600 (80%) in the Hep B Hub and 15% are receiving treatment we will be able to estimate this with 95% CI of 13.8-16.2.

10   ADMINISTRATIVE ASPECTS

10.1 Committees/panels

The investigators will meet quarterly by teleconference to review study progress reported against a standard agenda.

Project Governance

- Indigenous Reference Group face to face meeting annually (14 members, 8 communities represented)
- Clinical services meeting annually
- Leadership meeting 3 times per year - teleconference (all partners represented)
- Project Management Team face to face meeting weekly
- NT Hepatitis Steering Group meeting 4 times per year (to include all clinical service partners).

10.2 Monitoring

Study monitoring will be the responsibility of Menzies School of Health Research according to standard operating procedures. The institution will have internal quality control guidelines to maintain data quality and safety standards are being adhered to. The Principal Investigator will be responsible for maintaining data quality and safety standards for the study and will be required to report against these as a component of the afore-mentioned investigator meetings. An independent data safety monitor will not be appointed.

The primary responsibility of the Chief Investigator and study coordinator is to oversee progress of the study and to ensure that the study is conducted, and data are handled in accordance with the protocol, HREC and NHMRC requirements. The study coordinator is primarily responsible for controlling adherence to the protocol, ensuring that data are correctly and completely recorded and reported, and confirming that informed consent is being correctly obtained and recorded for all subjects prior to their participation in the study.

10.3 Intellectual Property

Guidelines specific to research in Aboriginal and Torres Strait Islander communities in Australia require acknowledgement and implementation of specific research ownership, knowledge, and transfer protocols. These include recognition of Aboriginal and Torres Strait Islander ownership of the research where appropriate, and any data generated. This also applies to any publication of the research data where information on Aboriginal and/or Torres Strait Islander persons is being reported.

The data collected will remain within the jurisdiction of the participating site. Menzies School of Health Research will remain responsible for the Hep B Hub dataset and all associated data analyses as the administering institution. Analyses and associated publications will be coordinated by the Investigators.

10.4 Regulatory Issues/Study approvals

Ethics approval for the study must be sought from the Institutional Ethics Committees in the Top End and Central NT.

10.5 Study files

Study files must be kept current and accessible to study monitors as required. Originals of all essential study documents will be retained at Menzies School of Health Research. Corresponding electronic filing systems will be established in a secure, access restricted site on a server network. Back-up of files will be as per Menzies School of Health Research network back-up facilities.

10.6 Data quality control

Following completion of the clinical audit of electronic health records – to determine the sero-status of the Aboriginal and Torres Strait Islander population, the data will be checked for consistency, logic and range, either through the process of the EHR system (i.e., PCIS or Communicare or using reporting system Business Intelligence) or through analyses of the study database. Queries will be generated for spurious data and clarification sought in writing from the PI or delegate. Data query forms will then be forwarded back to the data management centre for database amendment.

10.7 Quality Assurance Audit/Inspection

The study may be subject to an audit by the NHMRC, or at the request of the HREC. In the event of an audit, all relevant documentation must be made available to the auditor(s).

10.8 Study and Site closure

The study may be prematurely terminated or suspended at a particular site, or across all sites, by the HREC. Such termination or suspension is to be documented in writing, including the reasons for the action. The study participants must be informed of premature termination of the study.

However, given this project is core clinical business for CHB care, the aim is that the project's systems will remain current and will be sustained while there are still CHB infected clients in the NT.

Record retention will be in accordance with Menzies School of Health Research archiving policy. In the Northern Territory legislation, all study records, investigator files and source data must be retained and archived. Archiving of files will only occur once all databases have been locked, data analyses have occurred, and the final study report has been completed.

10.9 Study report

Annual summaries of study progress will be made available through publication of study findings. A final study report will be written following completion of the active study phase and data analyses have been finalised. The final study report must be signed by the PI. Progress and final reports will also be forwarded to the HREC and any applicable regulatory and/or funding agencies in accordance with their requirements.

10.10 Confidentiality

All identifiable information on study subjects will be retained in password protected files and locked cabinets at study sites. Access to this information will only be provided to immediate study staff, unless required by legislative or regulatory agencies and the HREC. Consent to participate in the study will include consent for access to data by these agencies. No identifying information will be included in study reports.

11 REFERENCES

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*An author on this paper is an Investigator on this project.

Appendix 1: Details of processes within the methodology

Figure 4: Overview of the process for creation of the NT HBV clinical care database, Hep B Hub.
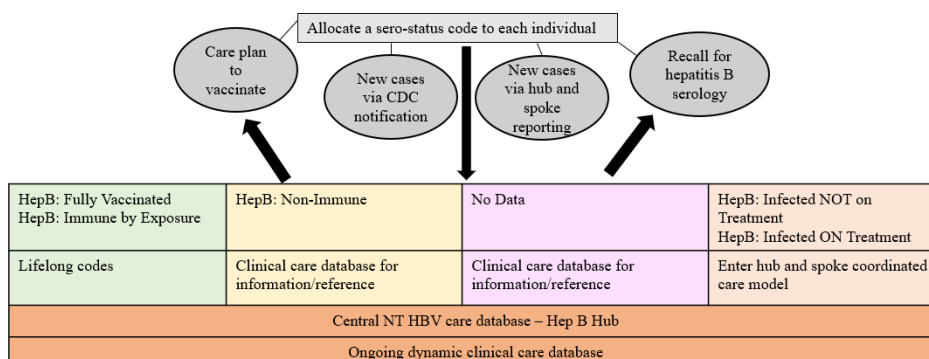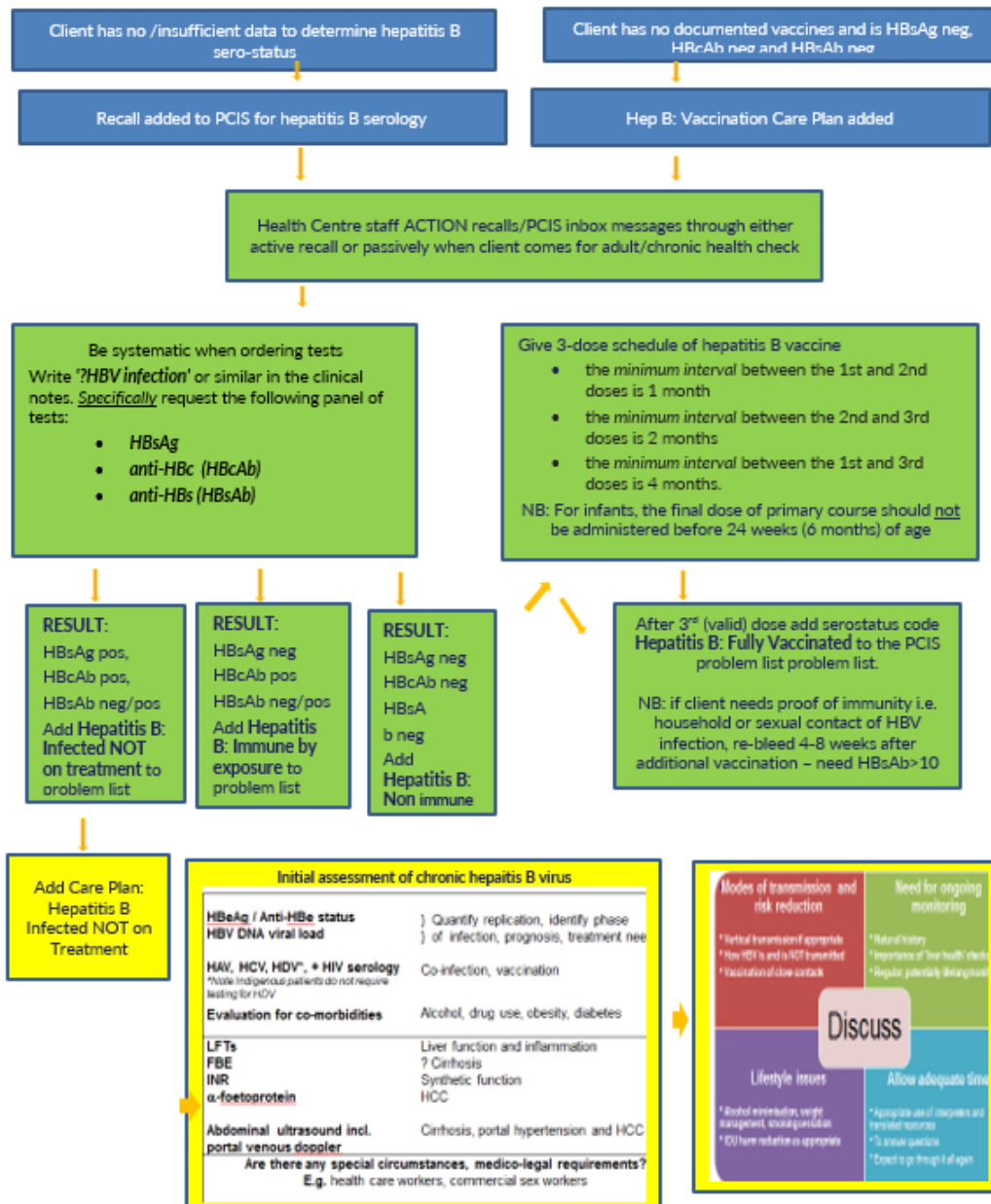

Appendix 2: Details of processes within the methodology

Table 5: Interpretation of HBV serology sero-status codes and action

Tests	Result	Interpretation	Sero-status code	Action
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible	Hepatitis B: non-immune	• Add sero-code to PCIS problem list • Add Hep B vaccination care plan • Once x3 doses, change sero-code on problem list to HepB: fully vaccinated
HBsAg anti-HBc anti-HBs	negative positive positive	Resolved HBV infection	Hepatitis B: Immune by exposure	• Add sero-code to PCIS problem list • No further action – don't test again • NB: if client becomes immunocompromised or they develop unexplained abnormal LFTs they will need to be retested and reassessed
HBsAg anti-HBc anti-HBs	negative negative positive	Vaccinated	Hepatitis B: Fully Vaccinated	• Add sero-code to PCIS problem list • No further action – don't test again
HBsAg anti-HBc anti-HBs IgM anti-HBs	positive positive negative positive	Acute HBV infection	Hepatitis B: acute	• Add sero-code to PCIS problem list • Further tests required • Contact tracing • Counselling and support
HBsAg anti-HBc anti-HBs IgM anti-HBc	positive positive negative negative	Chronic HBV infection	Hepatitis B: Infected	• Add sero-code to PCIS problem list • Add Hep B Infected care plan, testing, monitoring • Contact tracing • Counselling and support

Figure 5. Flowchart: How clinicians at health centres can action Hepatitis B sero-coding recalls

Client has no /insufficient data to determine hepatitis B sero-status

Client has no documented vaccines and is HBsAg neg, HBcAb neg and HBsAb neg

Recall added to PCIS for hepatitis B serology

Hep B: Vaccination Care Plan added

Health Centre staff ACTION recalls/PCIS inbox messages through either active recall or passively when client comes for adult/chronic health check

Be systematic when ordering tests
Write '*?HBV infection*' or similar in the clinical notes. *Specifically* request the following panel of tests:
- HBsAg
- anti-HBc (HBcAb)
- anti-HBs (HBsAb)

Give 3-dose schedule of hepatitis B vaccine
- the *minimum interval* between the 1st and 2nd doses is 1 month
- the *minimum interval* between the 2nd and 3rd doses is 2 months
- the *minimum interval* between the 1st and 3rd doses is 4 months.

NB: For infants, the final dose of primary course should not be administered before 24 weeks (6 months) of age

RESULT:
HBsAg pos,
HBcAb pos,
HBsAb neg/pos
Add **Hepatitis B: Infected NOT on treatment** to problem list

RESULT:
HBsAg neg
HBcAb pos
HBsAb neg/pos
Add **Hepatitis B: Immune by exposure** to problem list

RESULT:
HBsAg neg
HBcAb neg
HBsA
b neg
Add **Hepatitis B: Non immune**

After 3rd (valid) dose add serostatus code **Hepatitis B: Fully Vaccinated** to the PCIS problem list problem list.

NB: if client needs proof of immunity i.e. household or sexual contact of HBV infection, re-bleed 4-8 weeks after additional vaccination – need HBsAb>10

Add Care Plan: **Hepatitis B Infected NOT on Treatment**

Initial assessment of chronic hepatitis B virus

HBeAg / Anti-HBe status HBV DNA viral load	} Quantify replication, identify phase } of infection, prognosis, treatment need
HAV, HCV, HDV*, + HIV serology *Note Indigenous patients do not require testing for HDV	Co-infection, vaccination
Evaluation for co-morbidities	Alcohol, drug use, obesity, diabetes
LFTs	Liver function and inflammation
FBE	? Cirrhosis
INR	Synthetic function
α-foetoprotein	HCC
Abdominal ultrasound incl. portal venous doppler	Cirrhosis, portal hypertension and HCC

Are there any special circumstances, medico-legal requirements?
E.g. health care workers, commercial sex workers

Discuss

Modes of transmission and risk reduction
- Vertical transmission if appropriate
- How HBV is and is NOT transmitted
- Vaccination of close contacts

Need for ongoing monitoring
- Natural history
- Importance of 'liver health' checks
- Regular, potentially lifelong monitoring

Lifestyle issues
- Alcohol minimisation, weight management, smoking cessation
- IDU harm reduction as appropriate

Allow adequate time
- Appropriate use of interpreters and translated resources
- To answer questions
- Expect to go through it all again

37

Data analysis plan

Original version – 11 December 2020

Updated - 2 November 2023

1 Introduction

1.1 Drafts and approval processes

This data analysis plan was written by Dr Ashleigh Qama. Data analysis will be performed by Dr Qama. Responsibility for overall data analysis will be held by Dr Jane Davies, Prof Benjamin Cowie, A/Prof Joshua Davis, Ms Kelly Hosking, and Dr Qama.

This plan will be version controlled. Dr Davies, Prof Cowie, A/Prof Davis, and Ms Hosking will review and approve each iteration of this data analysis plan.

1.2 Changes from previous versions of analysis plan
None to date.

2 Study

2.1 Background

Chronic hepatitis B virus infection (CHB) is endemic in the Aboriginal and Torres Strait Islander communities of the Northern Territory (NT) with an estimated prevalence of 3-12%, meaning the NT has the highest CHB prevalence in Australia at 1.77% (including non-Indigenous people) (1). Of those living with CHB, 25% will die from decompensated cirrhosis or hepatocellular carcinoma (HCC). Liver disease is the third most important contributor to the gap in life expectancy between Indigenous and non-Indigenous Australians, and we have shown that NT Aboriginal and Torres Strait Islander Australians have an incidence of liver cancer that is 5.93 times higher than non-Indigenous Australians (2). However, we know that with currently available and funded treatment these deaths can be prevented. Therefore, it is imperative that people know their hepatitis B status, and if infected, are informed and given the opportunity to be engaged in care monitoring and treatment.

Within Aboriginal and Torres Strait Islander communities, there are multiple competing priorities including chronic physical and mental illness, coupled with limited staff numbers and high staff turnover, which means until recently there has sometimes been a nihilistic attitude (from clinicians) to HBV. In the NT, the majority of HBV infection was acquired at birth and is chronic, requiring lifelong follow up however HBV has traditionally been managed under the sexual health and blood borne virus program framework. We have previously demonstrated that a shared understanding of hepatitis B virus (HBV) between patient and care provider is a pre-requisite to sustainable and quality engagement in care (3).

2.2 Description of the project
This project is a funded NHMRC partnership grant covering the entirety of the NT. All health clinics providing services for Aboriginal communities in Central Australia and the Top End have been approached to be included, so that all people have an equitable opportunity to have their HBV status known and a choice to be engaged in care to improve their health outcomes.

This project will be implemented in three steps, enabling evaluation of the value added by each incremental step. Depending on service level consent, either opt out or individual written consent will be obtained to enter the study section of the Hep B Hub; each service will spend 18 months in each of steps 1-3 in chronological order (Figure 1). Step 1 is based on CQI, whilst step 2 is the addition of a core clinical care group, established in partnership with each service. Patient HBV education added in Step 3 will focus on the educational app in 10 Aboriginal languages.

Figure 1: A three-step staged implementation of a CHB care bundle.
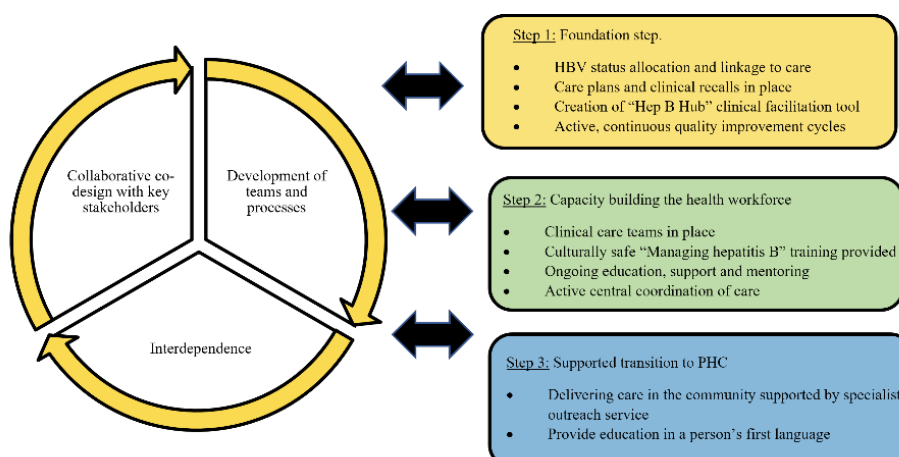
2.2.1 Step 1: Creation of the NT HBV clinical care facilitation tool – the Hep B Hub

In step 1, we will determine and allocate a hepatitis B sero-status code to each individual in consenting health services which will then trigger an appropriate follow-up response. Review of existing pathology and vaccination data will occur using 1 or more of the below electronic records systems, depending on service level agreement:

- Primary Care Information Systems (PCIS), used by the public system
- Communicare, used by Aboriginal Controlled Community Health Services
- NT Pathology Service and hospital data
- NT Immunisation Register

Despite clear guidelines there is often limited adherence to clinical guidelines in a primary health care space (4,5), which can be due to gaps in health provider knowledge and high turnover of staff (4). We propose that by having robust systems in place, including a register we will improve compliance with guidelines. Our register, the Hep B Hub, facilitates clinical care through recalls, reminders and pre-populated care plans that include tests and investigations needed, so patients receive key components of guideline-based care, including liver function tests, viral loads, ultrasounds, and Fibroscans.

2.2.2 Step 2: Education of health staff and the transition of gold standard care for CHB into primary care using a hub and spoke care co-ordination model

Enabling and maintaining a competent cohort of primary healthcare professionals to provide gold standard CHB care and prescribe HBV antivirals is a key step in delivering evidence-based care to people living with CHB in a sustainable way. Supported by our partnership with the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), we will offer the s100 prescriber course twice a year (one in Darwin and one in Alice Springs) providing ongoing mentorship of GP prescribers who have previously completed the course. In partnership with ASHM and NT Health we will further develop and adapt the Aboriginal Health Practitioner (AHP) role which is essential to the implementation of our proposed coordinated CHB chronic disease model of care.

The Hep B Hub is the central coordinating data register (hub) with clusters of communities (spokes) allocated a core clinical care group consisting of a trained Aboriginal Health Practitioner (AHP) or Aboriginal Community Worker (ACW), a doctor who can prescribe, and access to ultrasound and Fibroscan (Figure 2).

Figure 2: Clusters of clinics, core clinical care groups and how communication and care of CHB patients will look transitioning to primary health care.
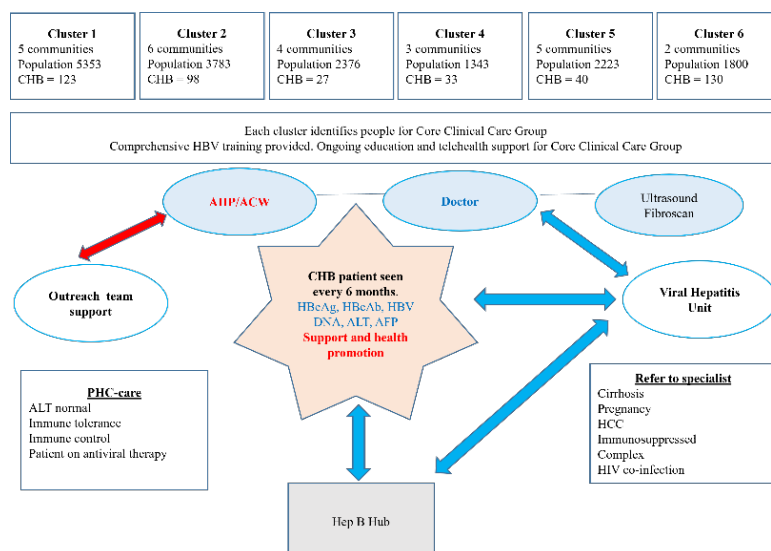
Evaluation of the incremental impact of each of the above steps on the CHB cascade of care will be evaluated against national targets, which is the purpose of this analysis plan.

2.2.3   Step 3: The Hep B Story app

Low levels of health literacy around CHB have been identified in Aboriginal and Torres Strait Islander people from several communities throughout Australia (3–5). Other populations in Australia where English is not their first language have found knowledge gaps and misconceptions around CHB (6). In a study amongst migrant and refugees living with CHB in Melbourne, Dahl et al. found 90% of their study population did not understand the associated risk of cancer and had common misconception around transmission, including believing it is transmitted through mosquitoes and sharing food (7). It is important to dispel myths and clarify routes of transmission to help decrease fear, shame, and stigma, and to prevent ongoing transmission.

English is usually a second, third or fourth language of most Aboriginal people in the NT, and a lack of culturally appropriate resource in-language is consistently documented as a major challenge to improving health literacy (3,8–10). Miscommunications between health staff and Aboriginal people are a major barrier to health literacy (3). We have previously assessed hepatitis B related knowledge in a remote NT community, finding low levels of biomedical knowledge about hepatitis B (3). It is critical to improve health literacy by developing a shared understanding between patients and health staff and that effective communication is the linchpin of this and this should be provided or reiterated in a patient's first language (3). In 2014, we developed the Hep B Story App, a visual, interactive app in English and Yolŋu matha designed for patients living with CHB and their families (11). As part of this project, the app is being translated into ten Aboriginal languages: languages here.

2.2.4   Impact of COVID-19 on care delivery

The COVID-19 pandemic has had a significant impact on the delivery of care by health services, including in the NT. Due to restrictions implemented by the NT Government, a number of interruptions to clinical care occurred, including decreased access to liver ultrasounds and Fibroscans, health services restricting and cancelling face-to-face patient consults, and reduced outreach to remote communities due to the introduction of a biosecurity zone. These measures will have had a significant impact on the care of people living with CHB in the NT.

2.3 Project aims
This project aims to improve the cascade of care for individuals living with CHB in the NT through establishing a NT HBV clinical facilitation tool - the Hep B Hub, healthcare provider training, and transition of CHB into a primary health care based, coordinated chronic disease model of care.

2.4 Study design
A closed cohort, non-randomised stepped wedge trial approach will be taken. This means that the project will be implemented in sequential steps for each health service, at different time points depending on constraints in clinic operations, with all health services progressing through all three steps by the end of the study.

2.4.1 Non-randomisation
Due to the participatory action principles of the project, randomisation of services was not felt to be appropriate. Consequently, each consenting service will enter Step 1 at a different time point and not all services will complete a full 54 months in the study.

2.4.2   Sample size
The intention is to establish the hepatitis B sero-status of all Aboriginal and Torres Strait Islander people living in the NT, so that "no one is left behind". The NT covers a large geographic area, approximately 1.3 million km² but is sparsely populated with 246,205 people, accounting for only 1% of the total Australian population. The NT has the highest proportion of Aboriginal people – 25.5% the majority of whom live in remote communities (12). Therefore, the estimated sample size is 60,000 and represents all Aboriginal and Torres Strait Islander people who live in the Northern Territory. These people will be part of Step 1: Allocating a hepatitis B sero-status to individuals to establish the Hep B Hub. We estimate the number of Aboriginal and Torres Strait Islander people in the NT who are HBV infected to be approximately 3,500. This is the sample size of those who will benefit from successful implementation of Step 3.

2.5 Objectives
The primary goal of the Hep B PAST project is to determine the serostatus of > 80% of Aboriginal and Torres Strait Islander individuals living in the NT, and by shifting CHB to a chronic disease care model have > 80% of individuals with CHB engaged in guideline-based management with 15% receiving and remaining on treatment.

To evaluate the success of this project, this analysis plan will:

1. Establish baseline estimates of hepatitis B immunity, susceptibility, and infection in the Aboriginal and Torres Strait Islander population of the NT
2. Identify the number of Aboriginal and Torres Strait Islander individuals living with hepatitis B in the NT for inclusion in the Hep B Hub
3. Estimate the baseline cascade of care for each health service
4. Assess the impact of CQI cycles upon care delivery at each health service to Aboriginal and Torres Strait Islander people living with hepatitis B
5. Assess the impact of establishing core clinical groups at each health service on the cascade of care
6. Assess the sustainability and impact of training s100 prescribers
7. Evaluate the overall benefit of Hep B PAST as a whole package
8. Estimate the impact of COVID-19 on service delivery
9. Estimate engagement with the Hep B Story app

Essentially, this plan aims to determine the benefit to the cascade of care from each step of the Hep B PAST project, and the benefit of project as a whole.

2.6 Timeline of study implementation

Figure 3: Timeline of study implementation
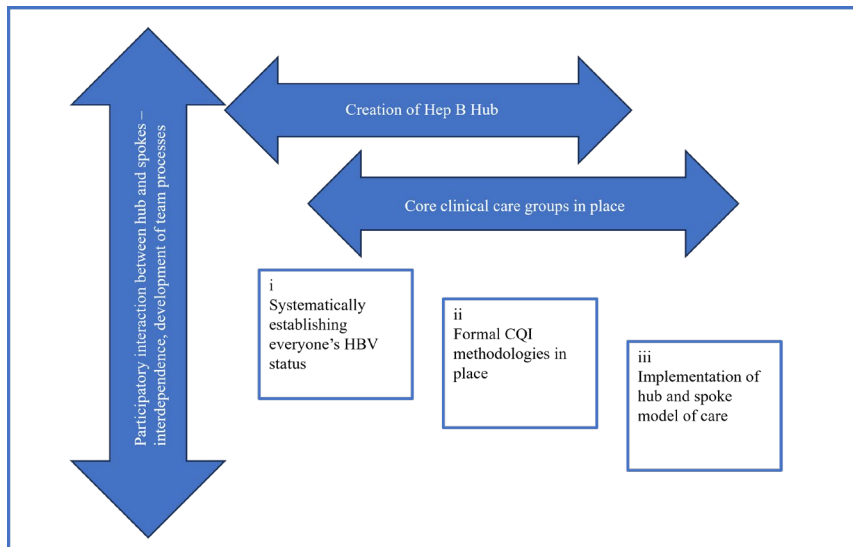
3   Data

3.1 Data sources

The following sources have been used to collect data for the analysis of the Hep B PAST project:
- Primary Care Information System (PCIS): clinical data from NT Government-run health services, and home of the Hep B Hub
- Communicare: clinical data from Aboriginal-Controlled Community Health Organisations
- NT Pathology: clinical data from the Royal Darwin Hospital liver clinic
- NT Immunisation register: vaccination data from 1990 onwards

3.2 Variables collected in provided dataset

A full data dictionary for this dataset will be created once the Hep B Hub has been established. Briefly, the variables collected in the master dataset are:

- Demographic information, including hospital record number (HRN), date of birth, sex, Aboriginal and Torres Strait Islander status, clinic, and region
- Birth data, including individuals born to a HBsAg-positive mother and the administration of hepatitis B immunoglobulin (HBIg)
- HBV testing data, including the dates and results of HBsAg, anti-HBc, HBeAg and anti-HBe testing

- Serocoding data, including an individual's current serocode, if this code is consistent with testing data, and action taken to clarify serocodes
- Vaccination data, including anti-HBs status, historical vaccination records, and dates of booster vaccinations
- Treatment data, including when commenced, indication for treatment, date of commencement, type of treatment, efficacy of treatment (measured by suppression of viral load), LFTs, cirrhosis and HCC screening, and dates of ultrasound and Fibroscans
- Health service data, including number of CQI cycles and access to s100 prescribing

4.   Statistical methods

Analyses will be conducted on the cleaned study data using Stata 15.1.

4.1 General principles
- Statistical significance will be set at 0.05, unless otherwise specified.
- All tests will be two-sided.
- All statistics will include appropriate measures of uncertainty: standard deviations for descriptive statistics, and 95% confidence intervals for inferential statistics.
- Subgroup analyses for all objectives will be conducted for the following parameters: age, sex, residential location, and health service.

4.2 Demographics

Descriptive statistics (frequencies, percentages, medians and standard deviations) will be generated to establish the demographics of participants within this study, including the following parameters:

- Sex
- Age
- Regional, rural or remote residential status
- Health service (see 4.2.1)
- HBV infection or immunity status

4.2.1   Health service and regional sub-analysis
For analysis of and comparisons between health services, a horizontal approach will be taken, meaning data for each health service will be analysed pre- and post-interventions, as per Objectives 3, 4, 5 and 6. These analyses will also be performed to compare progress between health services collectively, by two methods: clustering by Top End and Central, and by ASGC-RA classification.

4.3 Objective 1: Establish baseline estimates of hepatitis B immunity, susceptibility, and infection in the Aboriginal and Torres Strait Islander population of the NT

Individuals in the dataset will be allocated to the following phases, based on their most recent serology and medical record review prior to initiating further follow-up:

HBV status	Vaccinations	HBsAg	Anti-HBc	Anti-HBs
Non-immune	None or missing	Negative	Negative	Negative
Fully vaccinated	3 doses regardless of interval	Missing or negative	Missing or negative	Ignore
Partially vaccinated, needs 1 dose	2 doses regardless of interval	Missing or negative	Missing or negative	Missing or negative
Partially vaccinated, needs 2 doses	1 dose	Missing or negative	Missing or negative	Missing or negative
Immune by exposure	Ignore	Negative	Positive	Any result
Chronic infection	Ignore	**Positive**	Any result	Negative or positive

Discrepant result	Yes, any number	Negative	**Positive**	Negative or positive
No data	Needs interpretation	Missing	Missing	Missing
Insufficient data	Need tests	Missing	Missing	Missing
Presumed fully immunised	Less than 3	Negative	Negative	Positive (i.e. >10)
Discrepant core antibody	Needs interpretation			

Further to this, the following rules will apply when categorising individuals:

- HBsAg is taken from the most recent test
- Anti-HBs and anti-HBc will be considered positive if the individual has ever tested positive

The phasing above has limitations when it comes to vaccination status. Clinically, receiving three vaccinations is not a presumption of immunity. Further, the vaccination schedule will vary depending on an individual's date of birth:

- Prior to 1 May 2000, only 3 HBV vaccinations were given to infants, with no birth dose administered
- Following 1 May 2000, 4 vaccines are administered at the following time intervals:
    - Birth
    - At 42+ days old (2 months)
    - At 70+ days old (4 months)
    - At 126+ days old (6 months)

Mixed-effects logistic regression will be used to assess the associations between HBV phase and subgroups specified in 4.1. This will allow for serological testing and vaccinations being completed at unequal intervals between participants. Additionally, Kruskal-Wallis H tests will be performed to analyse any differences between phases and subgroups.

Prevalence estimates will be compared to existing estimates for Aboriginal and Torres Strait Islander peoples in the NT from the *Viral Hepatitis Mapping Project National Report* for the same time period, with two-sample tests of proportions used to compare the difference between predicted (from the *Mapping Project*) and actual prevalence and vaccination status.

Sub-analyses will be performed to generate estimates of vaccine efficacy and failure, vaccine coverage in the adult population, and variability in testing by sex. Vaccine efficacy will be estimated by two methods: by the number of individuals who did not mount an anti-HBs response following a full vaccination schedule, and by anti-HBs positivity in individuals who have completed a full vaccination course. Vaccine failure will be evaluated by identifying whether any vaccinated participants developed CHB (ie tested positive for HBsAg in subsequent HBV tests). Vaccine coverage in the adult population will be calculated using those considered fully vaccinated and who were born before 1 January 1982, as they will not have been eligible for infant vaccination or school catch-up vaccination programs. Variability in testing by sex will be calculated by comparing the difference in proportions between men, women and others (if specified) who have insufficient or no testing data at baseline.

Using the prevalence and vaccination data generated in this step, Kaplan-Meier survival analysis will be performed to visualise the relationship between increases in vaccine coverage and subsequent declines in HBV prevalence over time. Sub-analyses will be performed for subgroups in 4.1.

4.4 Objective 2: Identify the number of Aboriginal and Torres Strait Islander individuals living with hepatitis B in the NT for inclusion in the Hep B Hub

Using the phasing data from 4.3, the cascade of care will be mapped for the entirety of the NT, with the following steps:

1. Percentage of the population with valid serology
2. Percentage of the population diagnosed with CHB
3. Percentage of people living with CHB engaged in care at time of enrolment onto the Hep B Hub
4. Percentage of people living with CHB on treatment at time of enrolment onto the Hep B Hub

For step 2 above, descriptive statistics will be generated for the following, at the time of enrolment onto the Hep B Hub: phase distribution, age at time of diagnosis, fibrosis and cirrhosis, with sub-analyses for demographic factors as per 4.2.

Engagement in care in step 3 will be analysed using two definitions of care: the proportion of people living with CHB who received treatment or monitoring in a 12-month period, and the proportion of people who received guideline-based care by annual LFTs and viral load testing. Descriptive statistics will be generated as per step 2 for both definitions of care. Subgroup comparisons using chi-square tests will be performed to establish the difference between groups across the two different definitions of care. Further, the proportion of people at high risk of HCC, including those with cirrhosis and/or a family history of liver cancer at time of inclusion in the Hep B Hub, receiving six-monthly surveillance (either ultrasound or Fibroscan) will be calculated.

For step 4, descriptive statistics will be generated as per step 2 for people living with CHB who have been prescribed antiviral medication in a 12-month period. Additionally, descriptive statistics will be calculated to establish the proportions of people on different treatment regimes, and their adherence (measured by suppression of viral load).

4.5 Objective 3: Estimate the baseline cascade of care for each health service
Using the phasing data from 4.1, the cascade of care prior to CQI cycles being initiated will be mapped for each health service, using the same approach as 4.4. Comparisons between health services for each step will be generated using Kruskal-Wallis H tests.

4.6 Objective 4: Assess the impact of CQI cycles upon care delivery at each health service to Aboriginal and Torres Strait Islander people living with hepatitis B

Following the completion of CQI cycles at each health service, the cascade of care will be re-mapped for each health service and for the NT as a whole, as per the steps in 4.4. Two-way repeated measures ANOVAs will be used to assess the impact of CQI cycles on the cascade of care and estimate the incremental benefit from the baseline, as established in 4.5. Incremental benefit includes the increase in the following over the course of the CQI time period: the percentage of patients with unknown serological status that are subsequently tested, the percentage of unvaccinated patients who are subsequently recalled for vaccination, the percentage of patients living with CHB that were retained in care, and the percentage of patients living with CHB that received guideline-based care. Two-way repeated measures ANOVAs will also be used to assess the impact of CQI cycles on phase distributions, stratified by age, sex, region of residence, pregnancy status, treatment used, adherence to treatment (measured by suppression of viral load).In addition to the effect of CQI cycles on the cascade of care, survival analyses will be performed to measure annual rates of progression of patients living with CHB through the four CHB phases (immune tolerance, immune clearance, immune control, and immune escape), HBeAg seroconversion, progression to cirrhosis, progression to decompensated cirrhosis, and progression to HCC

4.7   Objective 5: Assess the impact of establishing core clinical groups at each health service on the cascade of care
Using the phasing data from 4.6, the cascade of care will be re-mapped for each health service and for the NT following the establishment of core clinical groups (CCGs) at each service, and 18 months post-establishment as per the steps in 4.4. Incremental benefits from the time period following the completion of CQI cycles to 18 months post-CCG establishment will also be analysed as per 4.6, as will rates of progression through CHB and liver disease states.

In addition to subgroup analyses performed outlined in 4.4, the following parameters will be analysed: how many GPs and Aboriginal Health Workers are in each CCG at their formation, and the number of CCG GPs that move between health services or leave the NT following the establishment of the CCGs.

4.8   Objective 6: Assess the sustainability and impact of training s100 prescribers
Data will be sought from ASHM and the Royal Darwin Hospital Pharmacy to evaluate the impact of training s100 prescribers in the NT, their involvement in commencing people living with CHB on treatment, and the retention of these prescribers over time. Descriptive statistics will be generated to explore the following: the number of people who attend each s100 prescriber training course, the number of people who successfully complete each s100 course, the number of active s100 prescribers in the NT each year, and how long each s100 prescriber remains at their health service at the time of training, and in the NT.

4.9 Objective 7: Evaluate the overall benefit of Hep B PAST as a whole package
As this study takes a non-randomised stepped wedge approach with multiple interventions, there is no way to create a model (or models) to analyse the incremental benefits of each intervention, overall benefit of all

interventions combined, as well as which combinations of interventions contributed the most benefit and the confounding effect of time. There are no previously published studies which could serve as a precedent for this type of analysis, and to date the published literature for stepped-wedge models are only useful for the analysis of randomised trials with a single intervention. Further, the Hep B PAST project is designed to be delivered as a whole, rather than a series of individual interventions that might be applied alone. This systemic, purposeful approach is what makes this project unique and ultimately gives the greatest chance of success, as it aims to address structural barriers preventing the delivery of quality care for people living with CHB, health literacy, and long-standing issues with data quality and the siloed, fragmented nature of clinical records. As a result, we expect the overall impact of the Hep B PAST project to be greater than the sum of its parts, and facilitate sustainable, long-term changes for Aboriginal and Torres Strait Islander people living with CHB and decrease the disproportionate levels of HBV-related morbidity and mortality faced by Aboriginal and Torres Strait Islander communities.

To evaluate the total benefit of the Hep B PAST program without a model, using the phasing data from 4.3 through to 4.7, the cascade of care will be re-mapped for each health service and for the NT at the end of the project. Prevalence and vaccination sub-analyses as per 4.3 will also be performed, as will rates of CHB progression and liver disease for patients living with CHB based on 4.6. Comparisons will be made to the data available from the *Viral Hepatitis Mapping Project National Report* for each year of the project. The total impact of the project on the parameters of the *Third National Hepatitis B Strategy* will also be calculated through the re-mapping of the cascade of care.

4.10 Objective 8: Estimate the impact of COVID-19 on service delivery

To account for the impact that COVID-19 had on each health service (as outlined in 2.2.5) and the progress of the project, the cascade of care will be mapped at two time points – 26 March 2020, when the biosecurity zone was imposed, and 5 June 2020, when it was lifted. The percentages of people with unknown serostatus will also be compared at these two time points. This data will be compared to the cascades of care mapped for each health service and the NT as a whole using interrupted time series analyses in order to establish if and how much of an impact COVID-19 had impact on each step of the cascade of care and the progress of this project in its early stages (as measured by clarification of patients' HBV statuses).

4.11 Objective 9: Estimate engagement with the Hep B Story app

Quantifying the incremental benefit of the app being available in many Aboriginal languages is challenging, given that the app was designed to be an educational tool included as a part of a holistic care package, rather than a standalone intervention or research project in itself. Some factors that prevent the impact of the app translations from being analysed as a separate intervention include: many Aboriginal and Torres Strait Islander people speak multiple Aboriginal languages, and there are overlaps between communities that speak the same languages, meaning that the users of each language cannot be traced back to a particular community or geographic region; and each translation in the app has been released at different times due to the translation process with each community, with the Yolŋu matha version available before the commencement of this project. The impact of the app as part of the overall care package will still be evaluated in two ways: through descriptive statistics of app usage and engagement, provided by the app developers, and through qualitative assessment, using community evaluation and questionnaires, following the process that was utilised in evaluating the Yolŋu matha iteration of the app (11). It is also worth noting that an unintended benefit of translating the app into many languages is that this provided an opportunity for Aboriginal and Torres Strait Islander communities to document and preserve their languages.

4.12 Handling of missing values

Missing values will not be imputed unless specified otherwise. Where the number of missing observations is substantial, the number of observations used in the analysis will be reported.

### 4.13 Revised analysis plan as of 20 October 2023

HBV susceptibility, immunity, and infection in the Aboriginal and Torres Strait Islander population of the NT

HBV sero-codes: non-immune, fully vaccinated, immune by exposure, infected on treatment, infected not on treatment, no data/unknown/uncoded

Descriptive analysis comparing pre- and post-Hep B past periods (overall, by sex, by age)

Dummy Figure 1: HBV cascade of care in the Aboriginal and Torres Strait Islander population of the NT

This figure to be generated for all, male, female, age<50y, age>50y
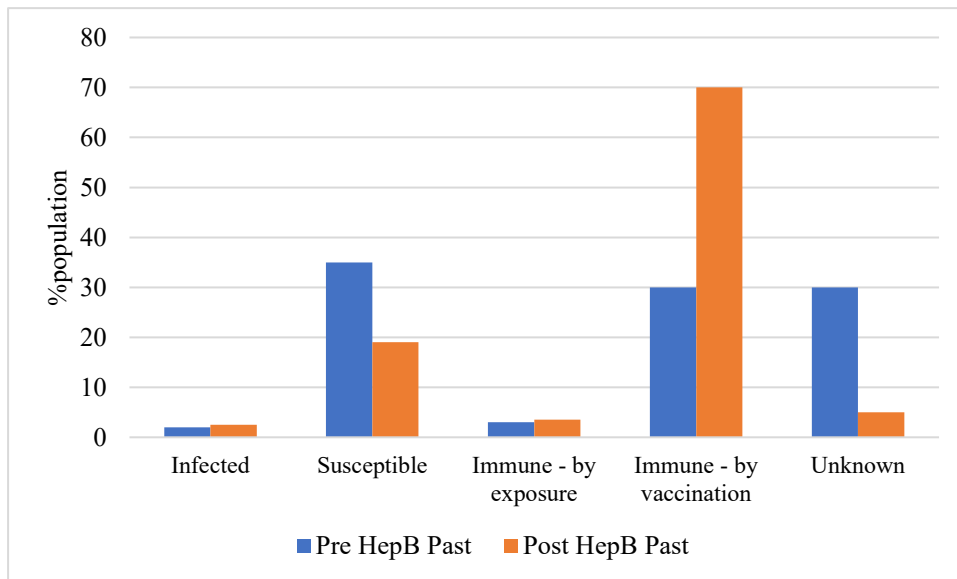
Descriptive analysis comparing pre- and post-Hep B past periods (overall, by sex, by age). Number with chronic HBV to be based on prevalence estimates and total population size.

Dummy Figure 2: HBV serocodes and HBV cascade of care pre-baseline, baseline, and post-Hep B past

This figure to be generated for all, male, female, age<50y, age>50y
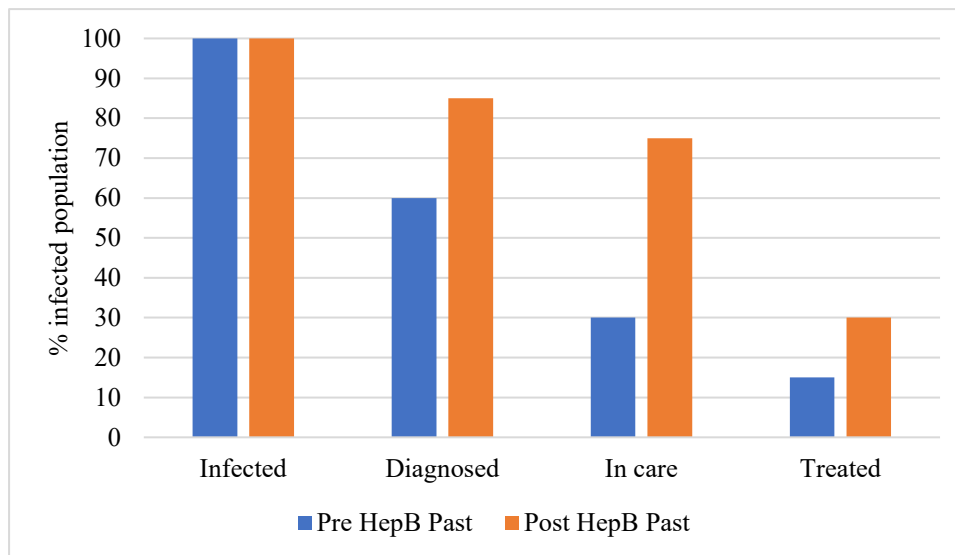
Repeat 1) and 2) with additional pre-baseline bar using only sites that have contributed pre-baseline data.

Dummy Table 1: Age/sex breakdown for HBsAg+ve and HBcAb+ve (but HBsAg-ve)

Describing those diagnosed, in care, and on treatment in post-HBV past era
Diagnosed: Describe sex, age, and fibrosis stage distribution (F0-F4)

Dummy Table 1

Characteristic		n (% HBV diagnosed)
Sex	Male	
Age	<50y	
	>50y	
Fibrosis	F0/1	
	F2	
	F3	
	F4	

In care

Describe sex, age, fibrosis stage distribution (F0-F4), treatment status (yes/no), median AST/ALT, median HBV VL.

Dummy Table 2

Characteristic		Measure	Value
Sex	Male	n (% in care)	
Age	<50y	n (% in care)	
	>50y	n (% in care)	
Fibrosis	F0/1	n (% in care)	
	F2	n (% in care)	
	F3	n (% in care)	
	F4	n (% in care)	
HBV treatment	Currently receiving	n (% in care)	
LFT and viral load	AST, IU/L	Median (IQR)	
	ALT, IU/L	Median (IQR)	
	HBV VL, log copies/mL	Median (IQR)	

Logistic regression to identify factors associated with cirrhosis among those in care

Dummy Table 3

Characteristic		N	Cirrhosis cases (% N)	Univariate OR	p	Multivariate OR	p
Sex	Male						
	Female						
Age	<50y						
	>50y						
Others…							

On treatment

Describe sex, age, regional/rural/remote, fibrosis stage distribution (F0-F4), treatment regimen, median AST/ALT, median HBV VL, eAg status

Dummy Table 4

Characteristic		Measure	Value
Sex	Male	n (% in care)	
Age	<50y	n (% in care)	
	>50y	n (% in care)	
Residence	Regional	n (% in care)	
	Rural	n (% in care)	
	Remote	n (% in care)	
Fibrosis	F0/1	n (% in care)	
	F2	n (% in care)	
	F3	n (% in care)	
	F4	n (% in care)	
Treatment regimen	3TC/TDF	n (% in care)	
	Other?	n (% in care)	
LFT and viral load	AST, IU/L	Median (IQR)	
	ALT, IU/L	Median (IQR)	
	HBV VL, log copies/mL	Median (IQR)	
eAg status	Positive	n (% in care)	

Methodological notes:

Exclude Congress and prison sites for all analyses.

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