



Supporting Information

Supplementary methods and results

**This appendix was part of the submitted manuscript and has been peer reviewed.
It is posted as supplied by the authors.**

Appendix to: Xiao Y, Hellard ME, Thompson AJ, et al. The cost-effectiveness of universal hepatitis B screening for reaching WHO diagnosis targets in Australia by 2030. *Med J Aust* 2023; doi: 10.5694/mja2.51825.

Supplementary methods: model and model inputs

The model schematic is shown in *Figure 1*. In brief, the model considered four disease states (chronic hepatitis B (CHB), compensated cirrhosis (CC), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC)) and three care cascade states (undiagnosed, diagnosed but not in care, and in care). The model was initialised with 222,559 people, simulating all people living with chronic hepatitis B in Australia in 2020. The distribution of age, sex, and ethnicity of the cohort at initialisation was estimated using latest data when available and summarised in *Table 1*. This characteristics distribution was used to get weighted average age of the cohort and weighted average values of disease progression parameters. *Table 2* summarises the estimated distribution of disease states among the cohort. It was assumed 2,000 people enter the model each year due to migration or infection, with a range of 0 to 6,000 tested in sensitivity analysis. This assumption was made given the dynamic change of the estimated number of people with chronic hepatitis B from 2015 to 2020¹ (*Table 3*), and the potential ongoing impacts on international migration flows from the coronavirus disease 2019 (COVID-19) pandemic, on which data have been limited.

Current rates of transition between care cascade states were calculated from national estimates of hepatitis B care cascade from 2015 to 2020 (*Table 3*)¹, in status quo, r1 was estimated to be 7.0% (5-11%), and r2 was estimated to be 2.9% (2.3-5%) (*Figure 1*). For scenario 2 (universal screening to reach diagnosis coverage target), r1 was calculated by having diagnosis coverage to be 90% in 2030, with r2 assumed to be the same as status quo scenario; under base estimates, r1 for scenario 2 was 13.8% (11-20%). For scenario 3 (universal screening + improved linkage to care), r1 was assumed to be the same as scenario 2, while r2 was calculated to reach 50% in care coverage by 2030; r2 for scenario 3 was 6.19% (4.95-7.42%).

Annual probabilities of disease progression were derived from literature and calibrated against most recent hepatitis B-related deaths estimates and hepatitis B attributable HCC incidence. Weighted averages of key parameters over age, sex and ethnicity were summarised in *Table 4*.

Cost inputs were described in *Table 5*. As opportunistic HBsAg testing was assumed in universal screening, unit cost was estimated to be A\$15.65 per test as per Medicare Benefit Schedule (MBS) data². Services provided in and out of hospital setting attracts 75% and 85% of Medicare benefit, respectively, with services provided by a general practitioner attracts 100% Medicare benefit³. We assumed 80% of HBsAg testing would be provided at by GPs, and 10% in hospitals, another 10% out of hospital but not in GP setting, which generates an estimated cost of HBsAg testing being 15.02 (\$11.74-15.65) per test to the healthcare funder. Same mixed level of Medicare benefit was applied to estimate the average cost of a three marker HBV test, which was estimated to be \$38.93 per test

to the healthcare funder. For people who were diagnosed and linked to care, costs of disease management and treatment in relevant disease states were calculated using an ingredients-based approach; people in care were assumed to receive guideline-based care^{4,5}. Details of medical services and antiviral drugs in each model compartment were detailed in explanatory notes in *Table 5* with the main source being MBS and Pharmaceutical Benefit Scheme (PBS) data^{2,6}.

Testing positivity rate is an important input in the scenarios with universal screening approach. It was estimated using number of people with undiagnosed hepatitis B infection divided by the total population without a hepatitis B diagnosis, the population born since 2000 were further deducted from the denominator as we were interested to offer testing only to people born prior to 2000 (see *Equation 1*).

Quality-adjusted life years (QALYs) was calculated to measure health utility impacts. Due to insufficient local data regarding utility value of each disease state of chronic hepatitis B, studies have been reviewed in different countries assessing health utilities across CHB-related health states using non-preference-based or preference-based methods, from people living with CHB, uninfected people, or experts. Utility values of CHB, CC, DC and HCC varied across studies, and no consensus has been reached regarding the most favourable methods or strand of opinion for utility value used in health economics. Therefore, the utilities used in presenting study are derived from a combination of studies that assessed utilities used cardinal preference measures, conducted in similar settings (such as high income countries), or for diseases with similar natural courses (such as chronic liver disease attributable to other aetiologies), or that were used in other economic evaluation studies⁷⁻¹². The utility value and ranges for each health state is summarised in *Table 6*. Critical is that although clinical utility of CHB treatment has been well established, limited data is available comparing health utility value between people on and not on treatment. One Canadian study¹¹ found no difference of health-related quality of life between people with CHB receiving and not receiving treatment, however, the study included small number of people on treatment, and majority of whom were on lamivudine which is no longer first line antivirals for CHB due to its relative low potency and high resistant rate profile. More recent studies^{13,14} have suggested health-related quality of life among people with hepatitis C infection improved significantly post treatment compared with baseline. Considering the potential improvement in physical functioning, vitality, social functioning, and emotional wellbeing following CHB treatment, it was assumed when on treatment, utility value would increase by 1.1-fold in each state, with a range of 1 to 1.2 tested in sensitivity analysis.

Equation 1. Testing positivity rate of universal screening strategy calculation.

Testing positivity rate=

$$\frac{(1 - P_{dx}) * (Prevalence * Population)}{Population - Pr_{age<20} * Population - P_{dx} * Prevalence * Population - P_{tested} * Pr_{age\geq 20} * Population}$$

P_{dx} : percentage of people with chronic hepatitis B that are diagnosed, base estimate was 73% in 2020.

Prevalence: national prevalence of hepatitis B, base estimate was 0.87% in 2020.

Population: total population in Australia

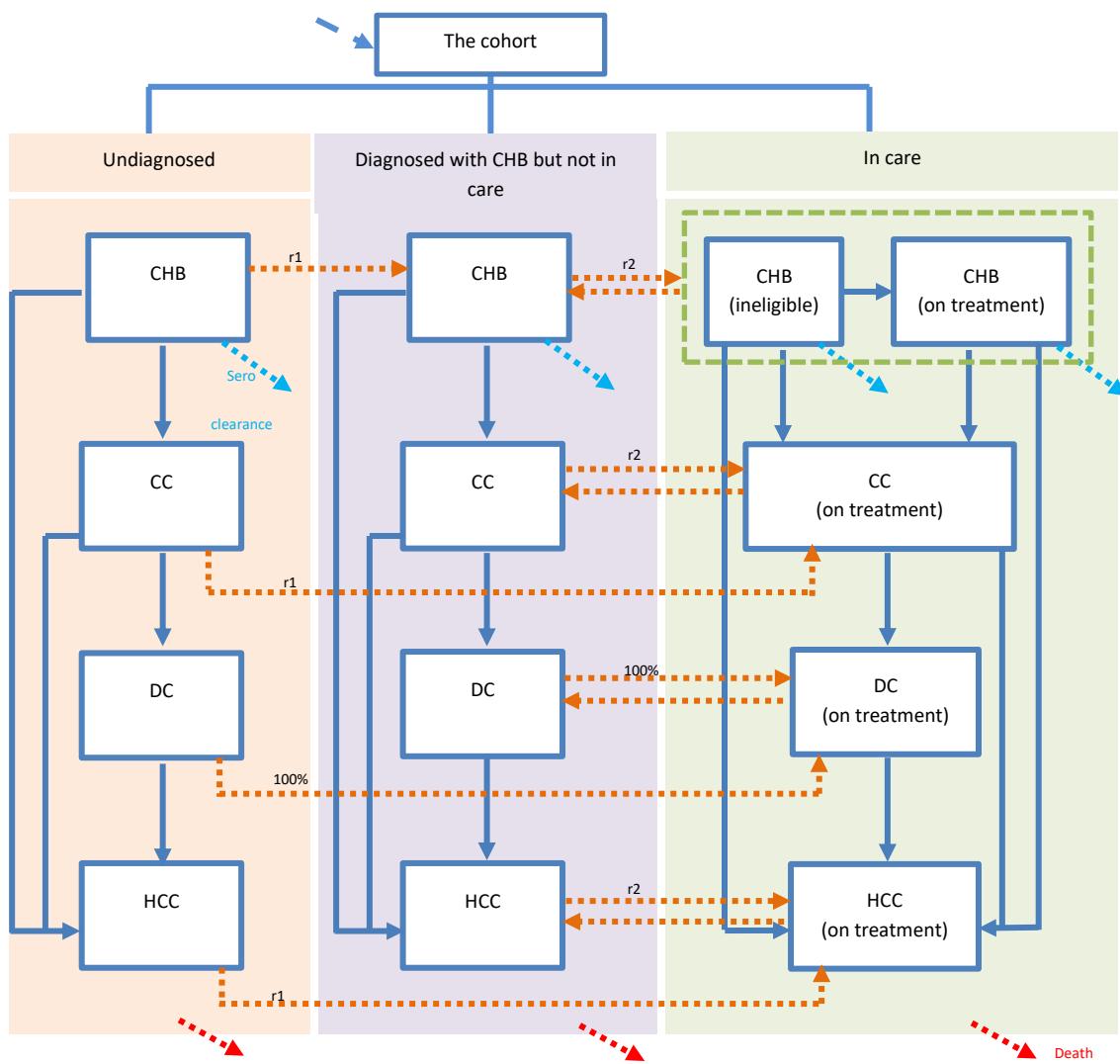
$Pr_{age<20}$: proportion of population that are under 20 years in 2020 (i.e. born since 2000), base estimate was 23.98% using 2021 census data¹⁷ as surrogate.

$Pr_{age\geq 20}$: proportion of population that are 20 years or over in 2020 (i.e. born before 2000), base estimate was 76.02% using 2021 census data¹⁷ as surrogate.

P_{tested} : percentage of people born after 2000 that ever-had hepatitis B tested with records, base estimate was assumed to be 30% (10%- 50%).

This assumes that undiagnosed infections are concentrated among the population born prior to the year 2000.

Figure 1. Model schematic



CHB = chronic hepatitis B. CC = compensated cirrhosis. DC = decompensated cirrhosis. HCC = hepatocellular carcinoma.

Table 1. Baseline characteristics (distribution by age, sex, ethnic background), 2020

Sex	Ethnic background (by at-risk ethnic group)	Age group (years)					Total
		0-19	20-39	40-59	60-84	>85	
Men	Aboriginal and Torres Strait Islander people	0.27%	1.94%	1.73%	0.79%	0.07%	4.80%
	African	0.21%	1.54%	1.37%	0.62%	0.06%	3.80%
	Asian	1.58%	11.44%	10.18%	4.65%	0.41%	28.27%
	Other	1.67%	12.06%	10.73%	4.90%	0.44%	29.80%
Women	Aboriginal and Torres Strait Islander people	0.13%	0.97%	0.86%	0.39%	0.04%	2.40%
	African	0.11%	0.77%	0.68%	0.31%	0.03%	1.90%
	Asian	0.79%	5.72%	5.09%	2.32%	0.21%	14.13%
	Other	0.84%	6.03%	5.37%	2.45%	0.22%	14.90%
Total		5.60%	40.48%	36.02%	16.43%	1.46%	100.00%

Female proportion was assumed to be 33%, range [25%-50%] was tested in sensitivity analysis.

Ethnic background distribution by risk group was sourced from mapping project report 2020.¹⁸

Age distribution was estimated from chronic hepatitis B prevalence by age in Australia in 2016, as previously described.¹⁹

Table 2. Distribution by disease state at baseline, 2020

Health state at model initialisation	Not in care	In care	Reference
Chronic hepatitis B, no cirrhosis (CHB)	97.6% (95.1%-99.1%)	92.0% (89.0%-95.0%)	20-23
Compensated cirrhosis (CC)	1.9% (0.9%-4%)	6.9% (4.6%-9.2%)	
Decompensated cirrhosis (DC)	0.1% (0-0.2%)	0.8% (0.4%-1.2%)	
Hepatocellular carcinoma (HCC)	0.5% (0-1%)	0.3% (0-0.5%)	

Table 3. Modelled estimates of hepatitis B epidemics in Australia, 2015-2020 (source: hepatitis B mapping project national report series¹), and the distribution by care cascade at baseline, 2020

Year	Estimated number of people with chronic hepatitis B	Diagnosed (%)	Engagement in care (%)	Treatment uptake (%)
2015	239,167	63.2%	18.6%	7.2%
2016	237,894	63.5%	19.6%	7.8%
2017	233,947	63.7%	20.2%	8.3%
2018	226,566	68.1%	22.1%	9.3%
2020	222,559	73.0%	22.6%	10.7%

Proportions of *diagnosed*, *engagement in care*, and *treatment uptake* are for people with chronic hepatitis B (diagnosed or undiagnosed).

Engagement in care includes people receiving regular clinical management but not treatment, as well as people receiving treatment.

Table 4. Annual probability of disease progression

Disease progression probabilities		Estimate	PSA parameters (beta distribution)	Reference
Natural history	Annual rate of transition from CHB to CC	1.51% (0.05%- 4.85%)	$\alpha=1.47; \beta=46.80$	24
	Annual rate of transition from CHB to HCC [†]	0.20% (0.13%- 0.58%)	$\alpha=2.93; \beta=721.19$	24-27
	Annual rate of sAg sero-clearance from CHB [†]	0.64% (0.39%-0.92%)	$\alpha=22.10; \beta=1704.41$	28,29
	Annual rate of transition from CC to DC	1.53% (0.75%-2.30%)	$\alpha=14.39; \beta=457.43$	24,30,31
	Annual rate of transition from CC to HCC [†]	1.23% (0.51%- 2.41%)	$\alpha=6.27; \beta=247.21$	24,25,27
	Annual rate of transition from DC to HCC	3.55% (1.15%- 5.95%)	$\alpha=7.74; \beta=101.24$	30,32,33
Under NAs	Annual rate of transition from CHB to CC	0.12% (0.12%- 0.30%)	$\alpha=5.52; \beta=2292.91$	34
	Annual rate of transition from CHB to HCC [†]	0.04% (0.03%- 0.12%)	$\alpha=2.94; \beta=3633.43$	24-27,35
	Annual rate of sAg sero-clearance from CHB	1.87% (0.00%- 2.70%)	$\alpha=7.07; \beta=181.85$	4,34
	Annual rate of transition from CC to DC	0.50% (0.45%- 1.90%)	$\alpha=1.80; \beta=178.09$	36
	Annual rate of transition from CC to HCC [†]	0.68% (0.28%- 1.69%)	$\alpha=3.50; \beta=253.74$	35,36
	Annual rate of transition from DC to HCC	2.17% (1.85%- 2.49%)	$\alpha=6.70; \beta=132.91$	35,33,37
Probability of HBV-related death				
Annual probability of dying in DC		15.7% (2.15%- 28.5%)	$\alpha=3.43; \beta=7.49$	30,32
Annual probability of dying in DC (antiviral therapy)		7.9% (1.1%-14.3%)	$\alpha=4.44; \beta=23.85$	37,38 (Assumed 50% reduction)
Annual probability of dying in HCC		35.0% (20%- 50%)	$\alpha=5.57; \beta=2.39$	22,30,32
Annual probability of dying in HCC (antiviral therapy)		17.5% (10%-25%)	$\alpha=13.25; \beta=24.60$	39 (Assumed 50% reduction)

NA= Nucleos(t)ide analogs. CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HCC= Hepatocellular carcinoma. HBV= Hepatitis B virus. PSA= probabilistic sensitivity analysis (beta distribution for parameters in this table).

[†] Adjusted for age, sex and ethnic background.

^{*} Weighted by age.

Table 5. Costs input

Health and care cascade state	Point estimate and range (2020 Australian dollars)	Reference	Explanatory notes
Hepatitis B testing in universal testing strategy	\$15.02	MBS (Feb 2022) ²	Assumption; cost as per MBS item 69475 (one test for hepatitis antigen/ antibodies to determine immune status or viral carriage to hep A, B, C or D) adjusted by level of Medicare benefit for services provided in and out of hospital setting.
CHB diagnosis	\$114 (\$89-\$142)	MBS (Feb 2022) ²	One-off cost; including GP consultation*1, three markers of hepatitis B test, basic lab test.
CHB in care (not receiving treatment)	\$611 (\$469-\$683)	MBS (Feb 2022) ²	Annual cost; including GP/specialist consultation*2, monitoring lab tests*2, ultrasound*1.
CHB in care and on treatment	\$2,678 (\$1,047-\$3,509)	MBS, PBS (Feb 2022) and hospital pharmacy data ^{2,6}	Annual cost; including GP/specialist consultation*2, monitoring lab tests*2, ultrasound*1, and drug costs. Range of drug costs considered costs as private patient and public patients.
CC in care on treatment	\$2,858 (\$1,227-\$5,119)	MBS, PBS (Feb 2022) ^{2,6}	Annual cost; including all costs of CHB on treatment and optional Fibroscan, imagining tests and liver biopsy.
DC in care on treatment	\$20,061 (\$9,247-\$30,875)	Estimation	Estimated from the costs of chronic liver failure management in South Australia ⁴⁰ .
HCC in care on treatment	\$16,533 (\$8,630-\$31,398)	Estimation	Estimated from unpublished data of a Melbourne HCC cohort consisting of 722 patients.

CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HCC= Hepatocellular carcinoma.

Table 6. Utility value input

Health states and treatment status	Point estimate	Lower bound	Upper bound	References/ explanatory notes
Natural history	CHB	0.85	0.70	1.00
	CC	0.80	0.65	0.95
	DC	0.45	0.30	0.60
	HCC	0.55	0.45	0.65
Under treatment	CHB	0.94	0.77	1.00
	CC	0.88	0.72	1.00
	DC	0.50	0.33	0.66
	HCC	0.61	0.50	0.72
Sero-clearance	1	0.95	1	7-11

CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HCC= Hepatocellular carcinoma. HBV= Hepatitis B virus.

Table 7. ICER of scenario 3 when testing positivity rate and additional cost per person screened (i.e. any cost in addition to testing cost of \$15.02)

ICER of scenario 3 (A\$/QALY gained)		Additional cost per person screened (\$)				
		0	40	80	120	160
Testing positivity rate	0.25%	55,071	102,036	149,000	195,964	242,928
	0.50%	46,251	69,733	93,216	116,698	140,180
	0.75%	43,311	58,966	74,621	90,276	105,930
	1.00%	41,841	53,582	65,324	77,065	88,806
	1.50%	40,371	48,199	56,026	63,854	71,681
	2.00%	39,636	45,507	51,377	57,248	63,119

Table 8. Sensitivity analysis: impacts on ICERs of using population-based testing to reach diagnosis target scenario.

Parameters		Best estimates	Lower bound value (LB)	Upper bound value (UB)	ICER of scenario 2, LB (A\$/QALY gained)	ICER of scenario 2, UB (A\$/QALY gained)	ICER of scenario 3, LB (A\$/QALY gained)	ICER of scenario 3, UB (A\$/QALY gained)
Total Population (when initialising the model)	222,559	215,264	237,894	105,141	104,497	47,393	47,243	
Female proportion	33.3%	25.0%	50.0%	104,626	105,524	47,340	47,344	
Care cascade distribution of the cohort at baseline	Proportion undiagnosed	27.0%	32.6%	21.4%	92,235	124,907	47,166	47,659
	Proportion diagnosed but not in care	50.4%	46.6%	54.2%				
	Proportion receiving care	22.6%	20.8%	24.4%				
Distribution of the cohort by health state, not in care cohort	CHB	97.5%	95.1%	99.1%	90,065	117,319	45,868	48,142
	CC	1.9%	3.7%	0.9%				
	DC	0.1%	0.2%	0.0%				
	HCC	0.5%	1.0%	0.0%				
Distribution of the cohort by health state, in care cohort	CHB	92.0%	89.1%	95.0%	104,719	105,193	47,351	47,329
	CC	6.9%	9.2%	4.6%				
	DC	0.8%	1.2%	0.4%				
	HCC	0.3%	0.5%	0.0%				
Annual probability of ineligible cases becoming eligible for treatment		3.0%	1.0%	10.0%	107,558	97,721	50,095	41,439
Annual new CHB cases joining the cohort		2,000	0	6,000	97,449	117,111	45,485	51,149
Diagnosed proportion of people when entering the model		10.0%	0.0%	30.0%	105,430	103,884	47,165	47,670
Annual transition probabilities, natural history	CHB to CC	1.5%	0.1%	4.9%	149,235	71,747	52,626	40,915
	CHB to HCC	0.2%	0.1%	0.6%	105,614	101,395	47,346	47,315
	CHB to seroclearance	0.6%	0.4%	0.9%	104,122	105,782	46,329	48,474
	CC to DC	1.5%	0.8%	2.3%	111,410	99,224	48,887	45,908
	CC to HCC	1.2%	0.5%	2.4%	110,706	97,121	48,290	45,942
	DC to HCC	3.6%	1.2%	6.0%	104,911	104,929	47,324	47,358
Annual transition probabilities, antiviral therapy	CHB to CC	0.1%	0.1%	0.3%	104,910	105,015	47,325	47,488
	CHB to HCC	0.0%	0.0%	0.1%	104,872	105,198	47,258	47,823
	CHB to seroclearance	1.9%	0.0%	2.7%	111,767	102,284	56,484	44,297
	CC to DC	0.5%	0.5%	1.9%	104,425	119,986	47,228	50,553
	CC to HCC (antiviral therapy)	0.7%	0.3%	1.7%	101,480	114,396	46,599	49,263
	DC to HCC	2.4%	0.6%	4.2%	104,904	104,937	47,337	47,346
Annual probabilities of dying from	DC(natural history)	15.7%	2.2%	28.5%	105,623	104,365	47,443	47,256
	DC (antiviral therapy)	7.9%	1.1%	14.3%	105,286	104,599	47,342	47,341
	HCC (natural history)	35.0%	20.0%	50.0%	115,840	100,490	49,866	45,994
	HCC (antiviral therapy)	17.5%	10.0%	25.0%	99,921	109,177	46,801	47,783
All-cause mortality		0.5%	0.0%	0.9%	106,114	104,059	48,169	46,664
Cost- In care but not on treatment (CHB only) (A\$)		611	469	683	103,960	105,406	45,221	48,413
Cost- On treatment (A\$)	CHB	2,678	1,047	3,509	100,500	107,170	36,860	52,674
	CC	2,858	1,227	5,119	95,183	118,410	43,073	53,254
	DC	20,061	9,247	30,875	105,598	104,244	47,629	47,053
	HCC	16,533	8,630	31,398	100,453	113,325	45,341	51,103

Parameters		Best estimates	Lower bound value (LB)	Upper bound value (UB)	ICER of scenario 2, LB (A\$/QALY gained)	ICER of scenario 2, UB (A\$/QALY gained)	ICER of scenario 3, LB (A\$/QALY gained)	ICER of scenario 3, UB (A\$/QALY gained)
Yearly discount rate (cost and outcome)		5.0%	3.0%	10.0%	98,760	122,326	46,304	50,197
Utility value (Natural history)	Sero-clearance	1.00	0.95	1.00	105,478	104,921	48,074	47,341
	CHB	0.85	0.70	1.00	109,685	100,553	52,894	42,844
	CC	0.80	0.65	0.95	118,562	94,094	48,210	46,503
	DC	0.45	0.30	0.60	102,901	107,021	46,935	47,754
	HCC	0.55	0.45	0.65	106,732	103,169	47,601	47,085
Ratio of utility increased if receiving treatment		1.10	1.00	1.20	397,371	60,439	204,039	26,777
Eligible proportion among people with CHB (without complications)		23.7%	11.9%	47.5%	115,398	89,567	56,883	37,672
Status quo	Annual rate of 'undiagnosed' to 'diagnosed with CHB but not in care'(CHB/CC/HCC)	6.8%	5.0%	11.0%	107,220	100,401	50,490	41,159
	Annual rate of 'diagnosed with CHB but not in care' to 'in care (with or without treatment)' (CHB/CC/HCC)	2.9%	2.3%	3.5%	109,467	100,996	46,025	49,116

CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HBV= Hepatitis B virus. HCC= Hepatocellular carcinoma. ICER= Incremental cost-effectiveness ratio. LB= Lower bound. UB= Upper bound. QALY= Quality adjusted life year.

Table 8. Comparison of main study components between our 2020 paper¹⁹ and the present study

Study components	2020 paper ¹⁹	Present study
Main objective	Potential cost-effectiveness of reaching national 2022 and global 2030 targets in Australia	The cost-effectiveness of a universal hepatitis B screening strategy in Australia
Timeframe	2016-2030	2020-2030
Interventions to improve the care cascade evaluated	None	A universal screening strategy
Cost of interventions	Not considered	Included as part of intervention
Effectiveness of intervention considered	No	Yes (testing positivity rate included)
Differences in status quo scenario based on more recent data		
Total number of people living with chronic hepatitis B	Estimated 233,947 in 2017	Estimated 222,559 in 2020
Distribution of people living with chronic hepatitis B in Australia, by ethnicity (year of sourced data represented)	2016	2020
Distribution of the cohort entering the model by care cascade state (year of sourced data represented)	2016	2020
Estimated care cascade progression (year of sourced data represented)	2015-2017	Updated using care cascade estimates 2015-2020
Number of addition of people living with chronic hepatitis B per annum (due to migration)	Estimated 7,024 based on based on the average increase of the total people living with chronic hepatitis B in 2015-2017	Estimated 2,000 per annum as migrant number were significantly affected by COVID-19 pandemic during 2019-2021
Costs inputs from MBS, PBS	Accessed in 2018	Accessed in 2022

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