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Enhancing the hepatitis B care cascade in Australia: a cost-effectiveness model

Cost effectiveness of enhancing the hepatitis B care cascade in Australia (running title)

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ABSTRACT AND KEYWORDS

If Australia is to successfully eliminate hepatitis B as a public health threat it will need to enhance the chronic hepatitis B (CHB) care cascade. This study used a Markov model to assess the impact, cost and cost-effectiveness of scaling up CHB diagnosis, linkage to care and treatment to reach national and international elimination targets for hepatitis B in Australia. Compared to continued current trends, the model calculated the difference in care cascade projection, disability-adjusted life-years (DALYs), costs, and the incremental cost-effectiveness ratio (ICER), of scaling up CHB diagnosis, linkage to care and treatment to reach: (1) Australia's 2022 national targets; and (2) the WHO's 2030 global targets. Achieving the national and WHO targets had ICERs of A$13,435 (A$10,236- A$21,165) and A$14,482 (A$13,031- A$25,641) per DALY averted between 2016 and 2030 in Australia, respectively. However, this excluded implementation and demand generation costs. The ICER for the National Strategy and WHO Strategy remained under A$50,000 per DALY averted if Australia spent up to A$328 or A$538 million, respectively, per annum (for 2016-2030) on implementation and demand generation activities. Sensitivity analysis showed that cost-effectiveness was predominately driven by the cost of CHB treatment and influenced by disease progression rates. Hence for Australia to reach the National Hepatitis B Strategy 2022 targets and WHO Strategy 2030 targets it requires an improvement in the CHB care cascade. We estimated it is cost-effective to spend up to A$328 million or A$538 million per year to reach the National and WHO Strategy targets, respectively.

Keywords

Hepatitis B

Care cascade

Cost-effectiveness analysis

INTRODUCTION

Chronic hepatitis B (CHB) continues to be a major global health threat: approximately 292 million people were infected with hepatitis B virus (HBV) in 2016 [1] and an estimated 887,000 deaths were attributed to HBV-associated liver disease in 2015 [2]. Decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC) are the most severe outcomes of CHB [2]. Around 20%

of people living with CHB will develop cirrhosis if untreated [3], and CHB increases the risk of developing HCC between 5 and 100-times compared to unaffected individuals [4]. Although there is no current curative therapy for CHB, treatment with nucleos(t)ide analogues can significantly attenuate disease progression, and reduce HCC risk by between 30% and 80% [5]. Timely diagnosis, monitoring and treatment of eligible individuals [6-8] living with CHB can substantially reduce HBV-induced liver related morbidity and mortality.

In 2017, the estimated prevalence of CHB was 1% in Australia (approximately 233,947 people) [9]. Australia has a mature healthcare system that provides fully subsidised diagnostic testing and CHB care, and partially subsidised medication for all Australian citizens. Despite this, modelled estimates suggest that amongst people living with CHB in Australia in 2017: approximately 36% were undiagnosed, 80% were not in care [9], and only 26% of patients eligible for treatment based on Australian national guidelines, were receiving antiviral therapy; this was 8% of the total number of people living with CHB [9-11].

To eliminate viral hepatitis as a major public health threat by 2030, the WHO released its first-ever Global Health Sector Strategy on Viral Hepatitis (hereafter referred to as the WHO Strategy) [12] in 2016. The WHO Strategy set the targets of diagnosing 90% of people living with CHB, treating 80% of those eligible and reducing HBV-related deaths by 65% by 2030. In 2018, the Australian government's 3rd National Hepatitis B strategy (hereafter referred to as the National Strategy) [13] set shorter term targets, aiming to achieve 80% of people living with CHB diagnosed, 50% of people living with CHB linked in care, 20% of people living with CHB treated and HBV-attributable mortality to be reduced by 30% by 2022.

Despite proportional increases in diagnoses, care engagement and treatment among people living with CHB since 2011[10], modelling data [10 14] suggested that current diagnosis rates remain insufficient for Australia to reach the National Strategy or WHO Strategy targets. This suggests further scale up of testing, linkage to care and treatment is required, but such activities come at a cost. To date, the cost and cost-effectiveness of such a scale-up is unknown as no evaluation has been undertaken to measure these costs in Australia.

This study uses a Markov model to assess the cost-effectiveness of enhanced hepatitis B care strategies in Australia. Clinical and economic outcomes were measured under three different HBV strategies: 1) continued current practice; 2) testing, linkage to care and treatment scale-up to reach the National Strategy targets and 3) the WHO Strategy targets. In particular, we estimated the cost of testing, care and treatment associated with reaching both sets of targets,

and determined a threshold annual budget that, if invested by Australia in auxiliary interventions to improve the HBV care cascade, would keep the overall strategies under a cost-effectiveness threshold.

MATERIAL AND METHODS

The model

We simulated the CHB disease and care cascade progression among all people living with CHB in Australia between 2016 and 2030 using a Markov model (*Figure 1*). The model included four exclusive health states (CHB, compensated cirrhosis (CC), DC, and HCC) and three exclusive care cascade states ('undiagnosed', 'diagnosed with CHB but not in care', and 'in care'). People with CHB in care could be on treatment or not on treatment depending on their eligibility.

The model was initialised according to disease and care cascade distributions for Australia in 2016 [11]. At each time step, representing one year, people could:

1) enter the model (e.g. when migrating to Australia with CHB or when acquiring CHB infection);

2) progress through the different disease stages (according to age, sex and ethnicity-weighted progression rates);

3) move through the care cascade (with rates estimated from a time-series of cross-sectional Australian care cascade estimates);

4) clear their virus (surface antigen loss);

5) leave the model due to death (from either an age-weighted all-cause mortality or HBV-attributable mortality).

Calibration

Calibration was against HBV-related deaths and incidence of HBV-related HCC, which are key indicators of CHB disease burden. Disease progression parameters in our study were scaled to fit the calibration target of HBV-related deaths data, which were estimated to be 419- 504 per year in 2015- 2017 in Australia[10 11], and HBV-related HCC incidence predictions in Australia for 2017- 2021, sourced from Australian Institute of Health and Welfare[15] reports (with 22% assumed to be attributed by HBV infection[16]).

Input parameters for the model

Study population

The study population was all people living with CHB in Australia. Previous modelling estimated that 215,264 to 237,894 people were living with CHB in Australia in 2016[10 14 17]. The model was initialised assuming 63.5% of people living with CHB were diagnosed (45.9% without care and 17.6% with care), sourced from modelled data [9 14 17] which was estimated from Australian census data, hepatitis B surveillance system and national health care/medication subsidy program (*Table s4*). Health state distributions were assumed to be different for those in care and not in care. For people living with CHB not in care, we assumed 97.8% did not have cirrhosis, 1.9% had CC, 0.1% had DC and 0.2% had HCC, mainly based on a Victorian community CHB cohort with non-invasive fibrosis assessment data [18]. For people living with CHB in care, we assumed 91.7% of people living with CHB did not have cirrhosis, 6.9% had CC, 1% had DC and 0.4% had HCC, based on the same study but using the hospital-based CHB cohort data, as well as unpublished hospital-based cohort data of 2,032 CHB patients attending liver clinics from St Vincent's Hospital (Melbourne, Victoria). These inputs are detailed in the supplement, *Table s3*.

People living with CHB in Australia are of mixed age, sex and ethnicity (*Table s2*), and so disease progression and mortality parameters were weighted accordingly. In 2016, an estimated 38.8% of people with CHB were born in Asia, 3.5% were born in Sub-Saharan Africa and 10.6% were Aboriginal and Torres Strait Islanders [17]. We assumed the sex ratio of people with CHB was 1:2 (female to male) based on sex-specific seroprevalence in CHB cohorts and the range of female proportion (25%-50%) was tested in sensitivity analysis [18 19]. The age structure of people with CHB was based on modelled estimates of the age-specific CHB prevalence in Australia in 2016 [14 20], with the weighted average being 43 years. We assumed that the age, gender and ethnicity of the open cohort would stay the same between 2016 and 2030, with this assumption tested in sensitivity analysis.

Disease progression parameter

Parameters of CHB progression and HBV-related mortality (*Table 1*) were sourced from a literature search and mainly generated from three reviews [21-23] and recent studies with reasonable sample size and follow-up time. As older age, male gender and being Asian or African were associated with increased risks of progression to cirrhosis and HCC occurrence [21 22],

relevant disease progression parameters were weighted by age, sex and ethnicity according to the study population characteristics (see supplement, *Table s5*).

Costs

We took the healthcare funders' perspective and assessed direct medical costs, including the average use of medical services, provider time and medicines for people in each model compartment (*Table 2*). For people diagnosed with CHB but not in care, we recorded the once-off costs of diagnosing CHB. We assumed that people in care received standard care based on the Gastroenterological Society of Australia guidelines [8]. For CHB and CC management, when the standard care guidelines included multiple medical procedure options or different pathways, we recorded the cost range for the uncertainty analysis and consulted a study steering group composed of medical professionals to obtain best estimate values. We chose to model with the medication use of Entecavir and Tenofovir disoproxil fumarate based on local prescribing patterns [11], assuming life-long treatment until HBsAg loss, no drug resistance and no adverse effects.

The costs of medicine and medical services were sourced from the Pharmaceutical Benefits Scheme (PBS) [24] and Medicare Benefits Schedule (MBS) [25] respectively. We collected the costs of each item, as reported in December 2018, and used an ingredients-based approach to estimate the total annual costs incurred by a person in each compartment, in addition to a once-off diagnosis cost where appropriate. All costs were reported in 2018 Australian dollars (AUD) and a 5% discounting rate was applied for any past or future costs as per national guidelines on discounting in health economic evaluations [26].

Scenarios

Baseline

Model baseline was a continuation of current practice within Australia. Annual probabilities of being diagnosed and linked to care were estimated by comparing the care continuum from 2015-2017 national surveillance reports [11] (*Table s1*). The annual probabilities of being diagnosed were assumed to be the same in undiagnosed people with CHB/CC/HCC but people with DC were assumed to be diagnosed and linked to care immediately. We assumed that people with CC/DC/HCC were linked to care once being diagnosed. People diagnosed with CHB (without complications) may or may not link to care; we estimated a linkage to care rate from the national surveillance reports that was applied across the CHB/CC/HCC stages, and assumed immediate

linkage to care if progressing to DC. People with CHB in care who were ineligible for treatment were assumed to become eligible and receive treatment at an annual rate of 7%-12% [27 28], which translated to a net rate of 3% (1%-10%) transiting from the ineligible to eligible compartment after accounting for treatment drop-off [29] (*Figure 1*). The status-quo projection assumed that these annual rates of care cascade transition remained constant in the study timeframe. The range of the estimated annual transition rates were tested in sensitivity analysis.

Scale-up to reach targets

Two scenarios were tested and compared against continued current practice: the National Strategy and the WHO Strategy. In each scenario, annual probabilities of being diagnosed and linked to care were increased until they were sufficient to meet the strategy targets (*Table s1*). This was defined as '80-50-20' by 2022 for the National Strategy. However, the WHO Strategy does not include a target for linkage to care coverage, so this was estimated to be 85% (among all people living with CHB) to be consistent with previous global modelling study [30], which used a target of 95% of the diagnosed population to be linked to care. Thus, the WHO strategy targets were interpreted as '90-85-'80" by 2030, where the final '80' refers to 80% eligible people with CHB on treatment. The parameters used in each scenario are detailed in the supplement (*Table s1*).

Outcomes

We compared the projection of the CHB care continuum, total annual costs and HBV-related disability-adjusted life years (DALYs). Disability weight for disease stages were obtained from the 2017 Global Burden of Disease study [31] (*Table 2*). The average age of people with CHB in Australia in 2016 was used to estimate years of life lost due to HBV-related death. DALYs were discounted at 5% annually [26].

Cost-effectiveness

The incremental cost-effectiveness ratios (ICERs; cost per DALY averted) were calculated for each of the target scenarios compared to continued current trends, with a threshold of A$50,000 per DALY averted used to assess the cost-effectiveness of the strategy.

Each strategy modelled only included the direct medical costs and did not include the costs of the demand generation activities that would be required to achieve the necessary improvements in diagnosis and treatment (as they are unknown). Therefore, a threshold annual budget was

calculated, that if spent on these activities would leave each strategy under the A$50,000 per DALY averted cost-effectiveness threshold (if applicable).

Uncertainty and sensitivity analysis

Confidence intervals (CIs) for projected outcomes were generated using a probabilistic uncertainty analysis. One thousand sets of parameter values were obtained by randomly sampling each parameter from its individual uncertainty range, using either uniform, normal or beta distributions as shown in *Table s10*. CIs were taken as the interquartile range of the corresponding model runs.

One-way deterministic sensitivity analysis was used to test the effects of single parameter variations on the ICER of the two interventional strategies, and the annual budget able to be spent on demand generation/implementation activities while remaining cost-effective. Specifically, we tested when disease progression parameters, costs and disability weights took their lower or upper bound values, and when the average age of people with CHB was 20-60 years old. The different health states distribution of people with/without care was also tested. We further tested a range of annual probabilities of being diagnosed (0-10%) and linked to care (0-10%) under the status-quo to reflect uncertainties in these estimates over time.

RESULTS

Under a base assumption that 5.7% of undiagnosed individuals with CHB/CC/HCC were diagnosed each year and annual net rate of care linkage of 3.3% (*Table s1*), the status-quo scenario projected that by 2030, 69% of people living with CHB were diagnosed, 30% of people living with CHB were in care and 18% were receiving treatment (*Figure 2*). The accumulated direct medical costs of status quo scenario in 2016-2030 was A$1.7 billion, with 1.1 million DALYs incurred (*Table 3*).

To reach the National Strategy targets by 2022, the model estimated that annual rates of diagnosis and linkage to care of 16.5% per year and 16% per year respectively would be required (*Table s1*). Enhancing the hepatitis B care cascade to achieve the National Strategy targets was projected to lead to 86% of people with CHB diagnosed in 2030, slightly short of the WHO 2030 elimination target (*Figure 2*). Under the National Strategy scenario, an estimated 69% of people living with CHB were linked to care and 37% of people living with CHB were receiving treatment by 2030 (*Table 3*). Total medical costs of the National Strategy scenario were estimated

to be A$3 billion (A$1.3 billion more than status-quo); and there were an estimated 1.02 million DALYs between 2016-2030 (97,743 DALYs less than status quo). The ICER of enhancing the hepatitis B care cascade to achieve the National Strategy was A$13,435/DALY averted (2016-2030) (*Table 3*).

The scenario aiming to reach WHO Strategy targets by 2030 led to a care cascade of 85%, 76% and 32% in diagnosis, linkage to care and treatment among people living with CHB by 2022 (*Figure 2*), sufficient to reach the National Strategy targets. To achieve the WHO Strategy target of diagnosing 90% people by 2030, a scale-up of annual diagnosis rate among people with CHB/CC/HCC to 24.5% per year was necessary, i.e. an approximately 4-fold increase of annual diagnosis rate from the status quo (*Table s1*). Total medical costs of WHO Strategy scenario were estimated to be A$4.1 billion (A$2.4 billion more than status quo); and there were an estimated 0.95 million DALYs between 2016-2030 (165,134 DALYs less than status quo). The ICER of enhancing the hepatitis B care cascade to achieve the WHO Strategy was A$14,482/DALY averted (2016-2030) (*Table 3*).

The total costs of each scenario only included medical costs incurred by the cohort; it didn't include costs of programs to have more people diagnosed and linked to care, i.e. the implementation costs of care cascade scale-up, as these costs are unknown. Thus, we used the model to estimate the threshold of willingness to pay for these implementation activities. The model estimated that if an annual amount of less than A$328 million was spent on programs to achieve the National Strategy or A$538 million for WHO Strategy, then the overall ICERs would remain under A$50,000/ DALY averted (*Table 3*).

One-way sensitivity analyses showed that several key parameters affected the estimated ICERs of the National Strategy and WHO strategy (*Figure 3*). The annual probability of progressing from CHB to CC had the largest impact on both ICERs: when this probability was as low as 0.05% per annum (compared to base estimates of 1.5%), the ICER of National Strategy and WHO Strategy were as high as A$27,671/ DALY averted and A$29,505/ DALY averted, respectively. Average age of the cohort also affected both ICERs, with both strategies being more cost-effective for a younger cohort. The cost of CHB treatment was another key parameter affecting the cost-effectiveness of care cascade scale-up strategies: if the overall costs of treating CHB was A$799 per person per annum (compared to base estimates of A$3,985), the ICERs of the National Strategy and WHO Strategy were reduced to A$7,351- 7,484/ DALY averted. All other parameters analysed in sensitivity analysis are detailed in the supplement (*Table s13*).

DISCUSSION

This is the first study to analyse the requirements to reach national and global hepatitis B service coverage targets and the potential cost-effectiveness of reaching these targets in Australia. Our model shows that the current rates of CHB diagnosis, care linkage and treatment would not enable Australia to meet the National strategy or WHO targets. Using A$50,000/ DALY averted as the willingness-to-pay threshold, scaling up the hepatitis B care cascade to reach the National Strategy targets by 2022 or WHO Strategy targets by 2030 was cost-effective. Up to A$328 million or A$538 million per year spent on implementation and demand generation would maintain the overall National and WHO strategies being cost-effective, respectively. The model provides economic evidence to support a greater hepatitis B public heath response in Australia.

A key finding was that Australia will struggle to meet the national and global hepatitis B service coverage targets if the status quo continues. This finding is consistent with a recent modelling report [10] that suggested Australia would not reach the WHO diagnosis and treatment coverage targets until 2059 and 2048, respectively, under current practice.

The model also suggested that the ICERs of the National Strategy scenario and WHO Strategy scenario were both below A$50,000/ DALY averted, the conventional upper limit of cost effectiveness thresholds. The cost-effectiveness of both strategies was significantly affected by the cost of CHB treatment. The first-line treatments for CHB, entecavir and tenofovir, currently cost an average of A$2,000-5,000 per person per annum in Australia which is higher than in most countries. Tenofovir is now off patent in many countries including high-income countries, with reported annual costs ranging from US$400 to US$1,500 [2]. Entecavir came off patent earlier than Tenofovir in most countries with the generic Entecavir price ranging globally from US$430 to US$6,127 [32]. However even these prices are high with the actual production of entecavir estimated to cost as low as US$36 per person-year [32]. Given treatment cost impacted the cost-effectiveness in the model, this suggests that a significant reduction in the cost of treatment would concordantly improve the cost-effectiveness of the scale-up of the CHB care cascade. For Australia, as both Entecavir and Tenofovir are listed in the PBS, which means that because the government subsidises the cost of medicine, the cost-effectiveness of scaling up the hepatitis B care cascade would be markedly improved through government negotiations on drug price.

The model suggested if up to A$328 million of A$538 million per annum was to be spent on the implementation of the National strategy or WHO strategy over a 15-year period, respectively, the

ICERs would remain under A$50,000 per DALY averted. Future studies are needed to identify what demand generation and outreach interventions are required to improve the care cascade and the cost and cost effectiveness of this, in order to assess how this funding, if available, could be spent to achieve the targets.

Even though both strategy scenarios were cost-effective, the costs to achieve the national and international targets were considerable: an additional A$1.3 billion or A$2.4 billion investment over the status quo is required for CHB management over a 15-year period, approximately 0.7-1.3% of Australia's 2016-2017 annual national health expenditure [33]. However, as well as being cost-effective, this additional spending on CHB management will most likely save additional future costs not captured in this model, such as costs from work productivity loss and costs of managing liver disease that were averted over a longer timeframe [34].

It should be noted that our model estimations were conservative, and the strategies are likely to be more cost-effective than we estimated, for several reasons. First, there has been a changing epidemiology of CHB due to the changing ethnicity structure of people living with CHB in Australia over time, for example the proportion of people migrating from Asia and Sub-Saharan Africa has increased between 2011- 2016 [35]. As Asians tend to have a poorer prognosis with untreated CHB [6 16 22], the changing epidemiology pattern will lead to an overall higher disease progression rate in the cohort, thus a smaller ICER of scale-up of the CHB care cascade. Second, the cost of CHB care cascade could be overestimated with the assumption that people in the cohort received an infinite course of antiviral treatment. Growing evidence suggests discontinuation of nucleos(t)ide analogue is possible for some people and future guidelines may consider a finite-course treatment for subgroups of people living with CHB [36]. Additionally, our model does not specifically include the scenario of CHB cure, which would be expected to reduce long-term costs due to finite curative treatment, albeit with greater initial up-front costs whilst the new drugs remain under patent [30 37].

There are several limitations of this study. Our estimation of the change of current rates of testing, linking to care and treatment initiation were based on data from 2015-2017, and the actual trend may be different over time. However, a broad range of rates were considered and tested in sensitivity analysis. Our model was a simplified simulation of the natural history of CHB without considering HBV e antigen or HBV-DNA levels of individuals in the cohort. However, disease progression parameters sourced from clinical studies targeting subgroups of people living with CHB were considered in the range and tested in sensitivity analysis. For disease progression parameters, as most data were from studies involved in Asian population, the

estimated relative risks of progressing to HCC from CHB or CC in African or Aboriginal and Torres Strait Islanders compared to Asians were mainly based on reviews comparing population in different continents[21 22]. However, a broad range of disease progression parameters including studies conducted in different sub-populations were tested in sensitivity analysis. Finally, this study used a simplified linear scale-up approach to care cascade progression rates for different scenarios, while in the real world the actual change is likely to be more complicated. Our approach requires a short-term prioritisation of HBV-related care in the early years of investment, which could potentially pose a challenge for strategy implementation. While this is one approach of care cascade scale-up to achieve the targets, further modelling studies are needed to inform the optimal scale-up method.

CONCLUSION

For Australia to reach the National Hepatitis B Strategy 2022 targets or WHO 2030 targets requires investment to improve all steps in the hepatitis B care cascade. Our results suggest that an immediate and substantial scale-up of the CHB care cascade is required if Australia is to meet the national and international targets of eliminating CHB as a major public health threat. Moreover, we found that it would be cost-effective to spend up to A$328 million or A$538 million per year (up to 2030) on implementation activities beyond direct medical costs to achieve the WHO and National Strategy targets, respectively. The key challenge will be to build community support and political will to fund this investment.

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Tables

Table 1. Inputs of disease progression parameters after calibration

Disease progression probabilities		**Estimate**	**PSA parameters**	**Reference**
Natural history	Annual rate of transition from CHB to CC	1.51% (0.05%- 4.85%)	α=1.44 β=46.36	[21]
	Annual rate of transition from CHB to HCC†	0.20% (0.13%- 0.58%)	α=2.93 β=741.03	[21 22 38 39]
	Annual rate of sAg seroclearnce from CHB‡	0.64% (0.39%-0.92%)	α=22.10 β=1704.41	[40 41]
	Annual rate of transition from CC to DC	1.53% (0.75%-2.30%)	α=14.39 β=457.43	[21 23 42]
	Annual rate of transition from CC to HCC†	1.23% (0.51%- 2.41%)	α=6.27 β=248.04	[21 22 39]
	Annual rate of transition from DC to HCC	3.55% (1.15%- 5.95%)	α=7.74 β=101.24	[23 43 44]
Under NAs	Annual rate of transition from CHB to CC	0.12% (0.12%- 0.30%)	α=6.74 β=2801.25	[45]
	Annual rate of transition from CHB to HCC†	0.04% (0.03%- 0.12%)	α=2.94 β=3732.64	[5 21 22 38 39]
	Annual rate of sAg seroclearance from CHB	1.87% (0.00%- 2.70%)	α=7.07 β=181.85	[6 45]
	Annual rate of transition from CC to DC	0.50% (0.45%- 1.90%)	α=1.80 β=178.09	[46]

	Annual rate of transition from CC to HCC†	0.68% (0.28%- 1.69%)	α=3.50 β=254.58	[5 46]
	Annual rate of transition from DC to HCC	2.17% (1.85%- 2.49%)	α=6.70 β=132.91	[5 44 47]
Probability of HBV-related death				
Annual probability of dying in CC		1.65% (1.45%- 4.00%)	α=6.19 β=131.34	[21 23 42]
Annual probability of dying in CC (antiviral therapy)		0.21% (0.05%- 1.04%)	α=0.72 β=166.15	[45 46]
Annual probability of dying in DC		15.7% (2.15%- 28.5%)	α=3.43 β=7.49	[23 43]
Annual probability of dying in DC (antiviral therapy)		12.56% (2.15%-28.5%)	α=2.36 β=7.04	[47 48]
Annual probability of dying in HCC		35.0% (20%- 50%)	α=5.57 β=2.39	[15 23 43]
Annual probability of dying in HCC (antiviral therapy)		17.5% (3.5%-50%)	α=1.06 β=1.98	[49]

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, gender and ethnicity composition.

‡ Weighted by age.

Table 2. Inputs of direct medical costs and disability weight in CHB related health states and care cascade statuses.

Disease management status	Health states	Base case	Lower bound	Upper bound	Reference	Explanatory notes
Direct medical costs						
Diagnosed with CHB but not in care	CHB	$112	$87	$141	MBS (Dec 2018) [25]	Once-off cost
In care (not receiving treatment)	CHB	$557	$441	$887	MBS (Dec 2018) [25]	
In care (on treatment)	CHB	$3,985	$799	$6,198	MBS, PBS (May 2019) [24 25]	Cost range was estimated from MBS, PBS and drug costs in hospitals, online pharmacy stores.
	CC	$4,165	$979	$7,752	MBS, PBS (May 2019) [24 25]	
	DC	$20,061	$9,247	$30,875	Estimation	Estimated from the costs of chronic liver failure management in South Australia [50].
	HCC	$16,533	$8,630	$31,398	Estimation	Estimated from unpublished data of a Melbourne HCC cohort consisting of 722 patients (Hong T, 2018).
Disability weight						
Natural history	CHB	0.051	0.032	0.074	Assumption	DW for 'moderate acute hepatitis B' was used.
	CC	0.123	0.085	0.173	Assumption	DW for 'Decompensated cirrhosis (lower CI)' was used to be in consistent with hep B modelling study [43]
	DC	0.178	0.123	0.25	GBD 2017[31]	DW for 'cirrhosis and other chronic liver diseases due to hepatitis B,

						decompensated' was used.
	HCC	0.44	0.193	0.687	GBD 2017[31]	The range of DW of 'diagnosis phase, metastatic and terminal phase of liver cancer due to hepatitis B' was used. The base case was the average of the range.
Treated	CHB	0.012	0.006	0.023	Assumption	The DW for 'Early HIV without anemia' was used as proxy.
	CC	0.051	0.032	0.074	Assumption	Assumed return to 'natural history CHB'.
	DC	0.133	0.088	0.19	Assumption	Assumed return to 'natural history CC'.
	HCC	0.133	0.088	0.19	Assumption	Assumed return to 'natural history CC'.
Sero-clearance		0	0	0.006	Assumption	The upper bound was assumed to be DW for CHB treated (lower CI used).

CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HCC= Hepatocellular carcinoma. HBV= Hepatitis B virus. DW= Disability weight. GBD=Global Burden of Disease study.

Table 3. Hepatitis B care continuum, clinical and economic outcomes (2016-2030) of people living with chronic hepatitis B in Australia under continued current care, the 3rd National Strategy, and WHO Strategy.

		Status quo	***The 3rd National Strategy***	***WHO Strategy***
Care continuum in 2030	Diagnosed proportion among people living with CHB	69% (64%- 74%)	86% (84%- 88%)	90% (88%- 92%)
	Receiving care among people living with CHB	30% (28%-40%)	69% (66%- 72%)	85% (83%- 87%)
	Receiving treatment among diagnosed people	18% (17%- 25%)	37% (35%- 45%)	46% (44%-56%)
Economic outcomes (2016- 2030)	Costs (million Australian dollars)	A$1,718 (1,425- 2,088)	A$3,031 (2,436- 3,414)	A$4,110 (3,838- 4,463)
	DALYs (million)	1.12 (0.79- 1.20)	1.02 (0.72- 1.11)	0.95 (0.70- 1.04)
	Cost difference † (million Australian dollars)	-	A$1,313 (866- 1,404)	A$2,391 (2,067- 2,738)
	DALYs averted †	-	97,743 (50,300- 108,088)	165,134 (90,568- 183,834)
	ICER (A$/DALY averted) †	-	A$13,435 (10,236- 21,165)	A$14,482 (13,031- 25,641)
Annual value prepared to pay to maintain ICER< A$50,000/DALY averted (million A$)			A$328 (139- 397)	A$538 (220- 639)

† compared to status quo. CHB= Chronic hepatitis B. CC= Compensated cirrhosis. DC= Decompensated cirrhosis. HCC= Hepatocellular carcinoma. HBV= Hepatitis B virus. A$= Australian dollar.

IQR was presented in parentheses if not additionally indicated.

FIGURES LEGEND

Figure 1. Model schematics.

The model included four exclusive health states: *CHB, CC, DC* and *HCC*, and three exclusive care cascade states: *Undiagnosed*, *Diagnosed but not in care* and *In care (with or without treatment)*. The model was initialised according to the disease and care cascade distribution in Australia in 2016. Each time step, representing one year, people could: enter the model (e.g. when migrating to Australia with CHB or becoming chronically infected with HBV); progress their disease stages (rates of disease progression were adjusted for age, sex and race/ethnicity of people living with CHB in Australia); move through the care cascade; clear their virus with surface antigen loss; or leave the model due to death.

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

Figure 2. Projections of 1) diagnosed proportion, 2) linkage in care proportion, and 3) receiving treatment proportion among people living with chronic hepatitis B under status quo, the 3rd National Strategy and WHO Strategy.

Figure 3. Sensitivity analysis: key parameters affect the ICERs of the 1) National Strategy and 2) WHO Strategy.

1) *The impact of key parameters on the of National Strategy ICER.*
2) *The impact of key parameters on the WHO Strategy ICER.*

Figure 1. Model schematics.

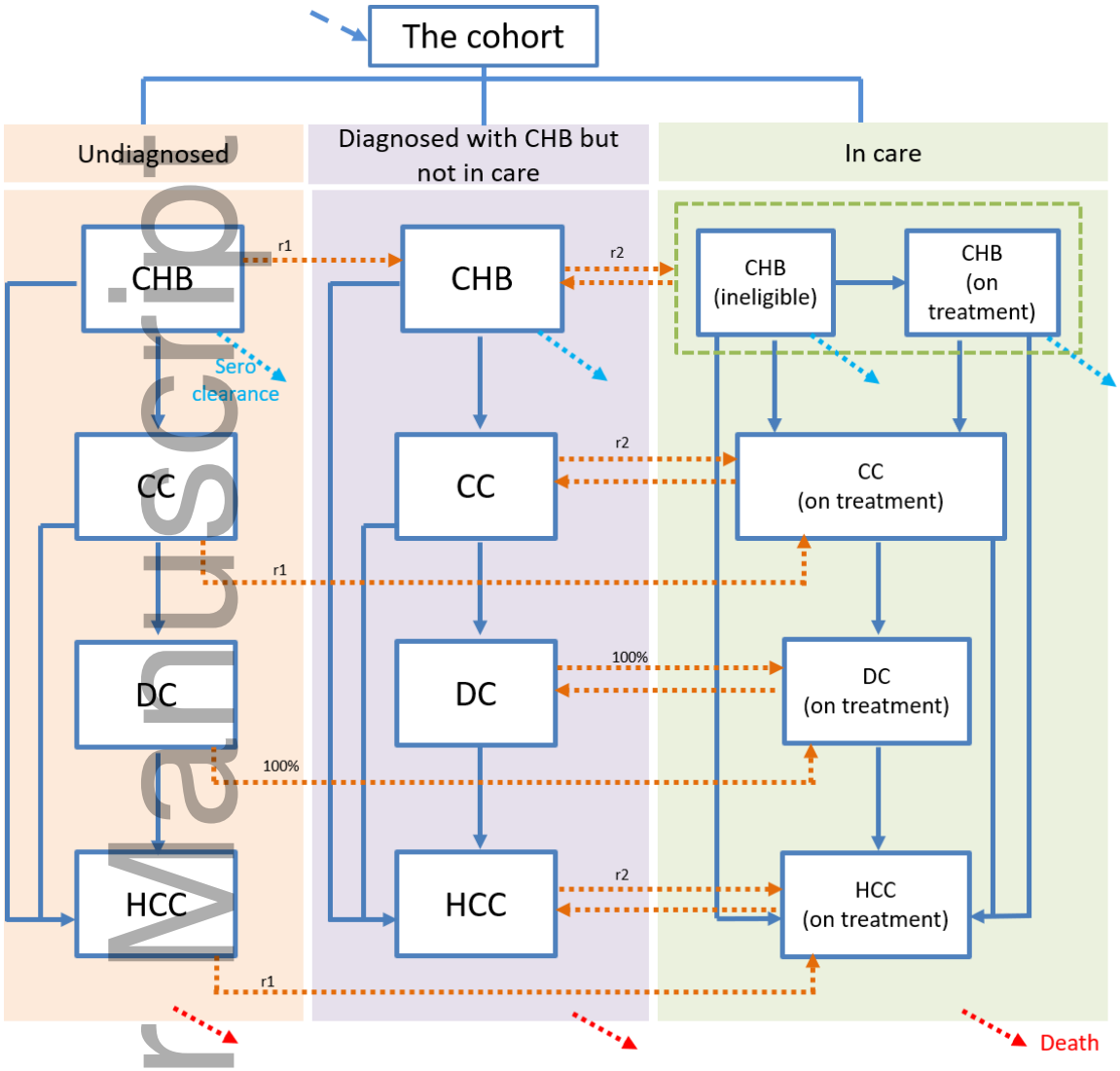


Figure 2. Projections of 1) diagnosed proportion, 2) linkage in care proportion, and 3) receiving treatment proportion among people living with chronic hepatitis B under status quo, the 3rd National Strategy and WHO Strategy.

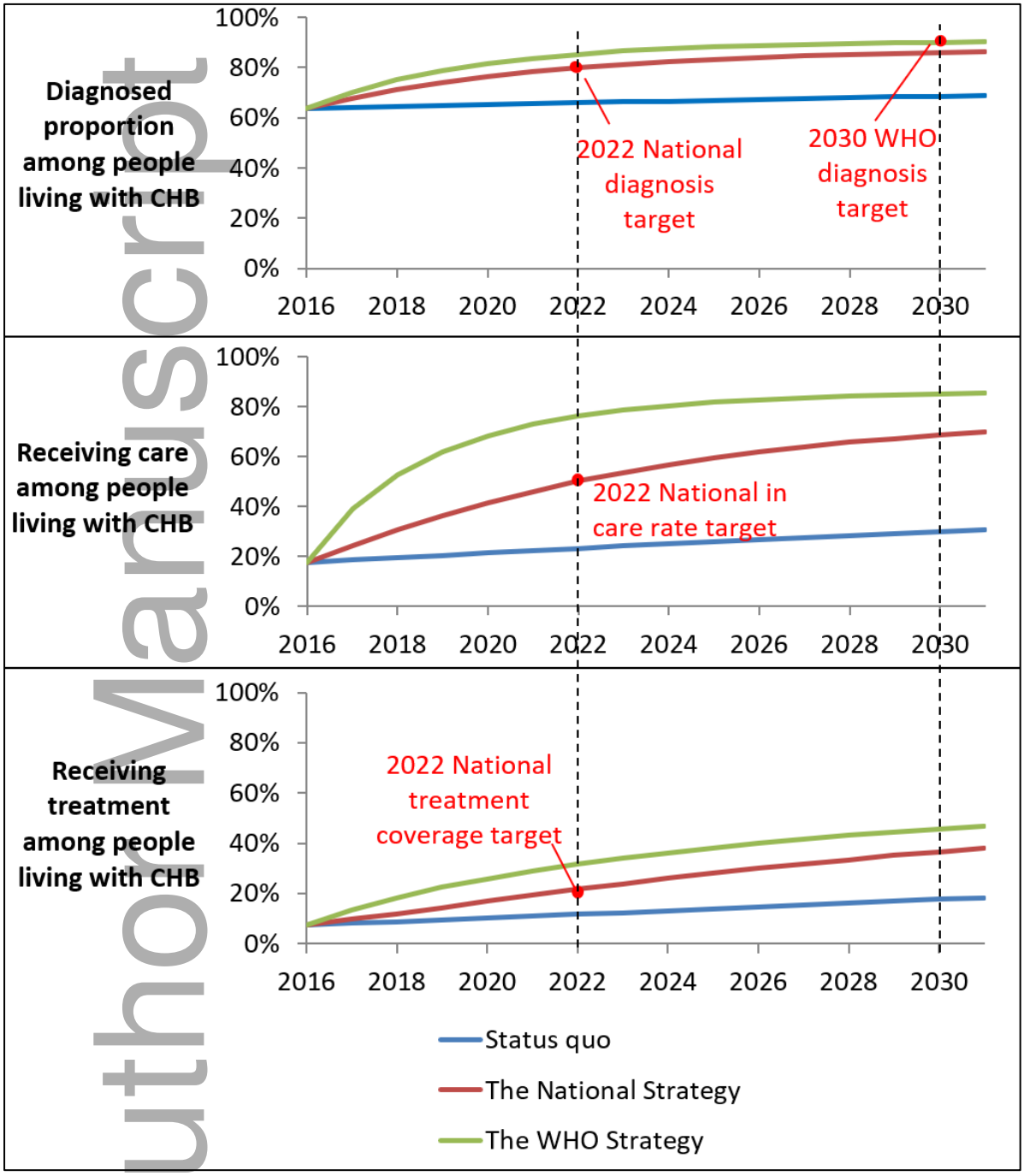
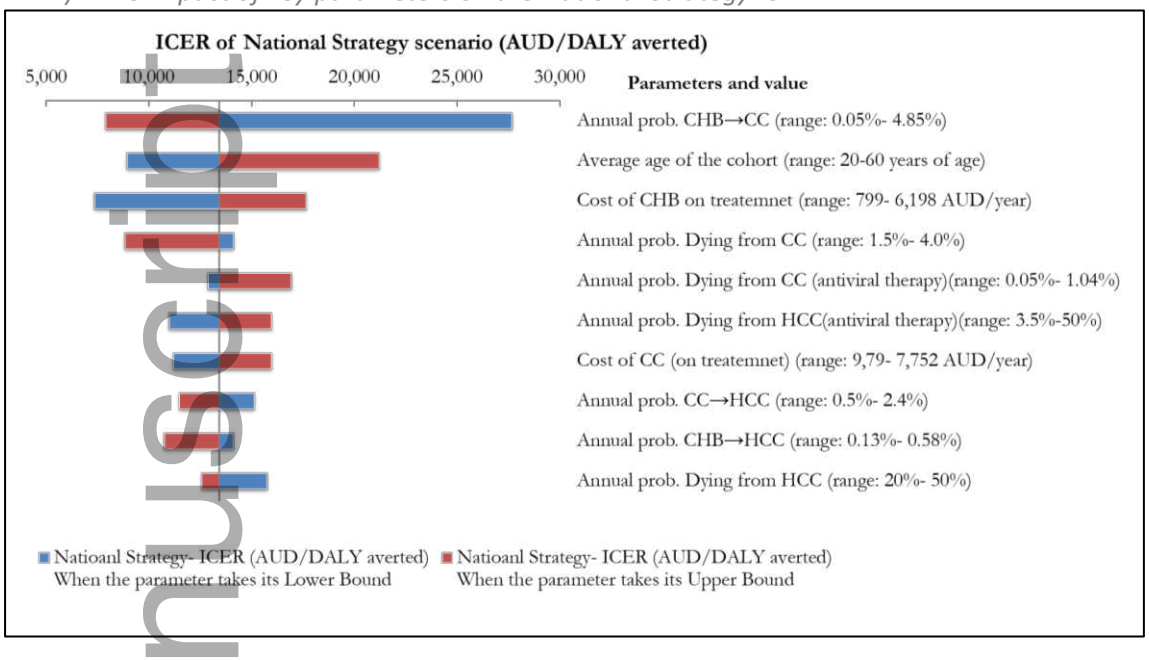


Figure 3. Sensitivity analysis: key parameters affect the ICERs of the 1) National Strategy and 2) WHO Strategy.

1) *The impact of key parameters on the National Strategy ICER.*



2) *The impact of key parameters on the WHO Strategy ICER.*