Are Published Health Economic Models for Chronic Hepatitis B Appropriately Capturing the Benefits of HBsAg Loss? A Systematic Literature Review

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Published online: 19 August 2019
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Abstract

Objectives Sustained hepatitis B surface antigen (HBsAg) loss or ‘functional cure’ (FC) is considered an optimal treatment endpoint by international clinical guidelines for chronic hepatitis B (CHB), yet rarely is this achieved with current standard of care (SoC). This leads to an under-reporting of FC in clinical trials, observational studies and health economic (HE) models. This paper systematically identifies and assesses how FC is incorporated in published HE models of CHB.

Methods A systematic literature review was conducted in PubMed and Embase (conducted February 2019) to review how HBsAg loss is captured in HE models. The following items were extracted: rate of (and transition probabilities to) HBsAg loss, HBsAg loss health state costs, and HBsAg loss health state utilities.

Results Sixty-five economics evaluations were identified, and < 50% of these (27/65) incorporated HBsAg loss in their models. Only 15/27 stated HBsAg loss health state costs, 15/27 stated HBsAg loss health state utilities, and 11/27 mentioned treatment-specific transition probabilities to HBsAg loss. The majority of sources these inputs were derived from are not transparent.

Conclusions The benefits of FC in current HE models are not well captured, as FC is often not reported or not directly related to modelled treatments. This has the potential for novel agents with higher efficacy compared with SoC to be overlooked and undervalued if their worth is not appropriately communicated. In order to ensure optimal access for patients to new and effective therapies, it is important that the benefits of FC are better assessed and captured within HE models.

Peter Wigfield and Urbano Sbarigia contributed equally to the work.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s41669-019-00175-w>) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

The benefits of functional cure in current health economic models are not well captured, as functional cure is often not reported or not directly related to modelled treatments.

In order to ensure optimal access for patients to new and effective therapies, it is important that the benefits of functional cure are better assessed and captured within health economic models.

1 Background

Although a prophylactic vaccine for hepatitis B virus (HBV) has been available since 1982, HBV still severely threatens the lives of an estimated 257 million people worldwide [1, 2]. In 2015, complications related to the

disease (including cirrhosis and liver cancer) were responsible for approximately 887,000 deaths globally [1]. The reasons for this may be due to various factors, including availability and reimbursement issues (especially in middle-income countries that experience high prevalence levels), suboptimal coverage due to a lack of treatment and screening services, and a lack of education and awareness promotions to prevent viral transmission.

Current standard of care (SoC) for chronic hepatitis B (CHB) aims to keep viral replication under control and reduce the risk of liver damage and any other further complications in order to improve long-term survival. There are currently two main treatment options for CHB: treatment with a nucleoside analogue (e.g., adefovir [ADV], entecavir [ETV], lamivudine [LAM], telbivudine [LdT], tenofovir disoproxil fumarate [TDF], and tenofovir alafenamide [TAF]), or treatment with pegylated interferon- α -2 (PEG IFN) [3].

The World Health Organization (WHO) recommends the use of oral antiviral agents, with a particular preference for TDF/TAF or ETV since these are regarded as the most potent, rarely lead to drug resistance (relative to antivirals that have lower barriers to resistance, such as LAM, LdT or ADV) and have relatively few side effects [4]. Nucleosides are usually administered for long periods of time in order to keep the virus under control. Despite the efficacy in reducing viral load, in most cases treatment does not cure HBV and is the reason why patients are maintained on these agents.

PEG IFN is an option for those patients with a well functioning liver [5] (its use in decompensated cirrhosis is often avoided due to life-threatening flare-ups and infections [6]). It is usually administered by injection for finite periods of time (usually 48 weeks [7]) and can be an effective alternative; however, its severe side effects often make it an unfavourable choice amongst many patients. Either discontinuation of therapy or suboptimal exposure to treatments can also result in a rebound of the viral load, which can lead to disease progression and an increased risk of viral transmission [1].

According to the American Association for the Study of Liver Diseases (AASLD 2018 [7]), Asian Pacific Association for the Study of the Liver (APASL 2016 [8]), European Association for the Study of the Liver (EASL 2017 [9]), and National Institute for Health and Care Excellence (NICE 2013 [updated 2017] [10]) guidelines on the management of HBV, hepatitis B surface antigen (HBsAg) loss is a key endpoint of interest that is strongly recommended [2]. Other recommended endpoints include long-term suppression of HBV deoxyribonucleic acid (DNA) levels, hepatitis B envelope antigen (HBeAg) loss with/without seroconversion of the antibodies produced against HBeAg

(i.e., anti-HBe seroconversion), and alanine aminotransferase (ALT) normalisation.

Sustained HBsAg loss (or seroconversion [HBsAg SC]) is regarded as an optimal endpoint for patients with CHB. It indicates profound viral suppression and is associated with a sustained reduction in viral and other disease markers in the blood even after treatment has been withdrawn [3, 11]. HBsAg loss is commonly termed ‘functional cure’ (FC), but rarely is this ever achieved using currently available antivirals [2]. This may lead to an under-reporting of FC in clinical trials, observational studies and health economic (HE) models. Most published randomised controlled trials (RCTs) record annual HBsAg loss rates that rarely reach >4% for nucleoside therapies [12–17], and usually around 4–10% for PEG IFN [18–21] (though 20% [22] and 21% [23] have been seen in some cases, with low sample sizes appearing to have an influence, i.e., two and three patients experiencing HBsAg loss, respectively).

Economic evaluation (EE) is an important part of health economics that provides a framework to make best use of clinical evidence through an organised consideration of the effects of all available alternatives on health, healthcare costs and other outcomes that are regarded as valuable [24]. Taking this into account, although sustained off-therapy HBsAg loss is a favourable endpoint for CHB patients, it is unclear the extent to which this health state is taken into consideration in current HE models of the disease.

Low reported loss rates in SoC therapies may mean FC as an outcome of interest is often overlooked in current HE models of CHB. This has the potential to undervalue novel treatments that succeed in achieving higher levels of HBsAg loss and, consequently, may hinder their availability to patients in the future.

Therefore, our objective is to systematically identify and assess how FC is incorporated in currently published HE models of CHB. This will involve investigating the extent to which the following components are included:

- HBsAg loss health state costs
- HBsAg loss health state utilities
- Treatment-specific HBsAg loss rates/transition probabilities

2 Methods

A systematic literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement to review how HBsAg loss is captured in HE models (see Supplemental Fig. 1 in the Electronic Supplementary Material [ESM]) [25]. In February 2019, two bibliographic databases (PubMed and Embase) were searched to identify published cost-effectiveness studies in CHB,

restricted to English language publications and with no limitation on publication date (search syntaxes are available in Supplemental Table 1 and Supplemental Table 2, see ESM). Though EE databases could also have been included, the results obtained from PubMed and Embase were determined to be extensive enough for a pragmatic review to be undertaken.

Two investigators (PW, MH) independently reviewed the titles, abstracts and full texts of retrieved articles sequentially using the predefined eligibility criteria. At the full-text stage, references in publications were also reviewed to identify any further relevant studies. Upon agreement of the final list of included articles, data were extracted into a predefined Microsoft Excel template and were subsequently independently validated. Any inconsistencies between either the retrieved articles or subsequent data extracted by the two investigators were individually discussed with an experienced third party member (US) until the disparity was resolved.

The following data items were extracted: study identification items (e.g., PubMed ID, first author, study year, etc.), study characteristics (type of economic analysis, model structure, study population, health states, time horizon, country perspective, funding sources), disease characteristics (baseline HBeAg status, baseline cirrhosis status), interventions compared, and HBsAg health state inputs (both natural history and treatment-specific inputs).

2.1 Inclusion/Exclusion Criteria

Only cost-effectiveness studies comparing two or more interventions to treat CHB that were written in English were included for data extraction (budget impact analyses, economic burden of disease studies, cost of illness studies, cost analyses, cost impact analyses, dose-response studies, duration-response studies, literature reviews or network meta-analyses were excluded). All inclusion and exclusion criteria adhered to during the systematic literature review are outlined in Supplemental Table 3 (see ESM).

EEs considered for full-text screening included all those with study populations that had a diagnosis of CHB infection and were ≥ 2 years of age. EEs that included special patient populations, that is, pregnant women at baseline, patients with any type of cancer or receiving treatment for cancer at the beginning of the study, or coinfecting patients, were excluded. A total of 1926/2182 studies were excluded after screening as outlined in Supplemental Fig. 1 (ESM). The reason for excluding special patient populations was so that a sizeable number of models could be reviewed. EEs comparing either nucleosides and/or interferons used to treat patients with CHB were included, whilst

interventions involving either screening/prevention strategies or HBV prophylaxis were not. This was because interventions in other settings are either finite or have different therapeutic goals (i.e., not related to HBsAg loss, which was the aim of this review). We assumed that the current indication is the main indication in CHB for which key economic models of the disease are developed by industry.

EEs were screened for the HBsAg health state. For studies that contained this state, the following items were extracted: rate of HBsAg loss or seroconversion, transition probabilities to HBsAg loss, HBsAg health state costs and HBsAg health state utilities. Studies reporting health-related quality of life (HRQoL) or health state utility measures as their sole outcome were excluded.

3 Results

3.1 Overview of Included Studies

Of the 2182 papers screened, 65 were identified as EEs that met the inclusion criteria and were used as part of the subsequent review (see Supplemental Table 4 [ESM] for an overview of all included studies).

In terms of type of economic analyses, the vast majority were cost utility analyses (50/65), with cost-effectiveness analyses making up only 12 of the total included studies [26, 31, 52–61]. One study employed a perceived value assessment (PVA) method that is described by the authors as a novel health economics methodology developed by Monitor Deloitte (formerly Monitor Group) [27, 62].

Markov modelling was the most commonly seen modelling approach (53/65), followed by decision-tree modelling, which was utilised in 12 of the 65 studies [53, 55, 60, 61, 63–70] (note that two studies used a combination of Markov modelling and decision-tree modelling in their EEs in order to separate their analysis according to either a short-term or long-term time horizon [55, 63]).

Regarding country perspective, nearly 20 different countries conducted these published HE models. China undertook the largest share (reported in 13 of the 65 studies [27, 31, 32, 34, 56, 69, 71–77]), closely followed by the US (10/65 [46–48, 51, 52, 64, 70, 78–80]) and the UK (7/65 [33, 43–45, 49, 54, 81]).

Of the 65 EEs included, <50% of these (27/65) incorporated HBsAg loss/seroclearance in their models (see Table 1). Furthermore, only 15/27 stated HBsAg loss health state costs (see Table 2), only 15/27 stated HBsAg loss health state utilities (see Table 4) and only 11 of these 27 studies explicitly mentioned treatment-specific transition probabilities to the HBsAg loss health state from other health states (see Supplementary Table 5 [ESM]).

Table 1 Studies that incorporated HBsAg loss/seroclearance in their models (27/65)

Study	Title	Country	Economic analysis type	Model structure
Kockaya et al. 2015 [26]	Cost-effectiveness analysis of oral anti-viral drugs used for treatment of chronic hepatitis B in Turkey	TUR	CEA	Markov
Wei et al. 2013 [27]	A novel estimation of the impact of treatment with entecavir on long-term mortality, morbidity and healthcare costs of chronic hepatitis B in China	CHN	PVA method	Markov
Ruggeri et al. 2017 [28]	Economic analysis and budget impact of tenofovir and entecavir in the first-line treatment of hepatitis B virus in Italy	ITA	CUA	Markov
Chinnaratha et al. 2017 [29]	Assessing the clinical and economic impact of increasing treatment uptake in chronic hepatitis B infection using a Markov model	AUS	CUA	Markov
Keshavarz et al. 2016 [30]	A cost-utility and cost-effectiveness analysis of different oral antiviral medications in patients with HBeAg-negative chronic hepatitis B in Iran: an economic microsimulation decision model	IRN	CUA	Markov
Banerjee et al. 2016 [31]	Telbivudine for the treatment of chronic hepatitis B in HBeAg-positive patients in China: a health economic analysis	CHN	CEA	Markov
Toy et al. 2015 [32]	Cost-effectiveness and cost thresholds of generic and brand drugs in a national chronic hepatitis B treatment program in China	CHN	CUA	Markov
Bermingham et al. 2015 [33]	Cost-effectiveness analysis of alternative antiviral strategies for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B in the United Kingdom	UK	CUA	Markov
Zhang et al. 2015 [34]	Cost-effectiveness analysis of antiviral therapies for hepatitis B e antigen-positive chronic hepatitis B patients in China	CHN	CUA	Markov
Lo et al. 2015 [35]	Cost effectiveness of response-guided therapy with peginterferon in the treatment of chronic hepatitis B	HKG	CUA	Markov
Iannazzo et al. 2013 [36]	Individualized treatment of HBeAg-negative chronic hepatitis B using pegylated interferon- α 2a as first-line and week-12 HBV DNA/HBsAg stopping rule: a cost-effectiveness analysis	ITA	CUA	Markov
Hulstaert et al. 2013 [37]	Should chronic hepatitis B be treated as early as possible?	BEL	CUA	Markov
He et al. 2012 [38]	Cost-effectiveness analysis of antiviral treatments for HBeAg-positive chronic hepatitis B in Canada	CAN	CUA	Markov
Toy et al. 2012 [39]	The cost-effectiveness of treating chronic hepatitis B patients in a median endemic and middle income country	TUR	CUA	Markov
Dakin et al. 2011 [40]	Cost effectiveness of tenofovir disoproxil fumarate for the treatment of chronic hepatitis B from a Canadian public payer perspective	CAN	CUA	Markov
Colombo et al. 2011 [41]	A cost-effectiveness analysis of different therapies in patients with chronic hepatitis B in Italy	ITA	CUA	Markov
Wiens et al. 2011 [42]	Cost-effectiveness of telbivudine versus lamivudine for chronic hepatitis B	BRA	CUA	Markov
Dakin et al. 2010 [43]	Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B	UK	CUA	Markov
Shepherd et al. 2009 [44]	Entecavir for the treatment of chronic hepatitis B infection	UK	CUA	Markov
Jones et al. 2009 [45]	Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation	UK	CUA	Markov
Spackman and Veenstra 2008 [46]	A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B	US	CUA	Markov

Table 1 (continued)

Study	Title	Country	Economic analysis type	Model structure
Veenstra et al. 2008 [47]	Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: a cost-effectiveness analysis	US	CUA	Markov
Veenstra et al. 2007 [48]	Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B	US	CUA	Markov
Takeda et al. 2007 [49]	A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B	UK	CUA	Markov
Pwu and Chan 2002 [50]	Cost-effectiveness analysis of interferon-alpha therapy in the treatment of chronic hepatitis B in Taiwan	TAI	CUA	Markov
Louis-Jacques and Olson 1997 [51]	Cost-benefit analysis of interferon therapy in children with chronic active hepatitis B	US	CBA	NA
Wong et al. 1995 [52]	Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B	US	CEA	Markov

AUS Australia, BEL Belgium, BRA Brazil, CAN Canada, CBA cost-benefit analysis, CEA cost-effectiveness analysis, CHN China, CUA cost-utility analysis, HBeAg hepatitis B envelope antigen, HBsAg hepatitis B surface antigen, HKG Hong Kong, IRN Iran, ITA Italy, NA not applicable, PMID PubMed ID, PVA perceived value assessment, TAI Taiwan, TUR Turkey, UK United Kingdom, US United States

3.2 HBsAg Loss Health State Costs

Table 2 provides an overview of the 15 studies that explicitly mentioned HBsAg loss health state costs. Four studies were conducted using a US country perspective [46–48, 52], four were conducted using a UK perspective [45, 49, 87, 88], three were conducted using China as their country perspective [27, 31, 34], one was conducted using an Australian country perspective [29] and one used a Taiwan perspective [50]. Note that the studies by Wong et al. 1995 [52] and Pwu and Chan 2002 [50] are mentioned twice in the table since two relevant health state costs have been recorded (i.e., HBsAg loss in combination with compensated cirrhosis [CC], and HBsAg loss alone).

For all studies outlined in Table 2, the specific health state has been described along with the health state cost per year as recorded in the accompanying study. All studies describe cost per year of the health state.

The health state cost per year reported from the studies has then been converted to 2019 US dollars (US\$). This enables comparison of reported costs across studies and shows that the values cited in the articles range widely from US\$0.00 [29, 45, 49, 87] to US\$1377.45 [31] per year when investigating HBsAg loss health state costs alone (this increases to US\$2472.77 if HBsAg loss in combination with CC is included, i.e. CC is a large cost driver in this instance). There is also a large disparity seen when the HBsAg loss health state is included: five studies [27, 31, 34, 50, 52] state costs between US\$814.83 [40] and US\$1377.45 [31], whilst 11 studies [29, 38, 43, 45–50, 52, 87] state costs between US\$0.00 [29, 45, 49, 87] and US\$224.62 [50].

In order to investigate these costs further, the sources these costs have been referenced from have been included in the table alongside a description of the study type. Some short notes detailing how these sources refer to HBsAg health state costs are also provided.

As is seen in Table 2, other than the studies that rely on expert opinion and assumptions to determine HBsAg loss health state costs, the vast majority of sources that were used to collect such costs for the original studies [27, 31, 34, 38, 40, 43, 46–48] do not specifically mention any relevant costs in their articles. The remaining two studies either referred to the Clinical Cost Manager accounting system at the New England Medical Center as their source [52], or Southampton University Hospitals Trust in combination with expert opinion [87]; neither of which were available for this review.

In order to elucidate this further, an overview of the health state cost references recorded in the articles were investigated and are outlined in Table 3. As can be seen, the only source that specifically mentions a value for HBsAg loss (in this case seroconversion) is Dakin et al. 2010 [86], which states a yearly cost of US\$5.32. All other sources fail to mention an explicit cost for HBsAg loss, instead outlining yearly costs for other health states (including CHB, CC, decompensated cirrhosis, hepatocellular carcinoma and liver transplant). From looking at Table 3, it is likely that (when included in the studies) the health state costs for HBsAg loss have been predicted by the authors from other CHB health states.

Table 2 Overview of studies that mentioned HBsAg loss health state costs

Author	Health state	Cost per year	Cost per year (converted to 2019 USD)	Range	Source	Type of study	Notes	Country perspective
Wong et al. 1995 [52]	HBsAg loss + CC	1500 (USD)	2472.77		Clinical Cost Manager (Transition Systems I, Boston, Massachusetts) accounting system at New England Medical Center	NA		US
Banerjee et al. 2016 [31]	HBsAg loss	1315.90 (USD)	1377.45		Zhang et al. 2015 (PMID 25672930) [34]	CUA	Referenced from Hu et al. 2009 [82]; no specific mention	CHN
Zhang et al. 2015 [34]	HBsAg loss	1284.60 [1156.20–1413.10] (USD)	1361.65	1225.55–1497.86	Hu et al. 2009 (PMID 20586991) [82]	Economic Burden of Disease	Not referenced in study	CHN
Wei et al. 2013 [27]	HBsAg loss	7316 (RMB)	1194.78		Assumed about 50% of CHB cost based on EASL guideline (Korean Association for the Study of Liver. The Korean Association for the Study of Liver Treatment guideline 2011) [83] + Hu et al. 2009 [82]	NA + Economic Burden of Disease	Not referenced in study	CHN
Pwu and Chan 2002 [50]	HBsAg loss + CC	19,553 (NT\$)	887.33		Estimated based on the 1996 National Health Insurance reimbursement rate [84]	NA		TAI
Dakin et al. 2011 [40]	HBsAg loss	989 (CAD)	814.83		Gagnon et al. 2004 (PMID 15602168) [85]	CHB costing study	Not referenced in study	CAN
Pwu and Chan 2002 [50]	HBsAg loss	4960 (NT\$)	224.62		Estimated based on the 1996 National Health Insurance reimbursement rate [84]	NA		TAI

Table 2 (continued)

Author	Health state	Cost per year	Cost per year (converted to 2019 USD)	Range	Source	Type of study	Notes	Country perspective
Wong et al. 1995 [52]	HBsAg loss	65 (USD)	107.15		Clinical Cost Manager (Transition Systems I, Boston, Massachusetts) accounting system at New England Medical Center	NA		US
Spackman and Veenstra 2008 [46]	HBsAg loss	64 [48–79] (USD)	74.68	56.01–92.18	Kanwal et al. 2005 (PMID 15897532) [80]	CUA	Not referenced in study	US
Veenstra et al. 2007 [48]	HBsAg loss	59 [44–74] (USD)	71.49	53.31–89.66	Kanwal et al. 2005 (PMID 15897532) [80]	CUA	Not referenced in study	US
He et al. 2012 [38]	HBsAg loss	83.01 [62.25–102.46] (CAD)	69.10	51.82–85.30	Spackman and Veenstra 2008 (PMID 18850763) [46]	CUA	Refer to 'Spackman and Veenstra 2008' row	CAN
Veenstra et al. 2008 [47]	HBsAg loss	59 [44–74] (USD)	68.85	51.34–86.35	Kanwal et al. 2005 (PMID 15897532) [80]	CUA	Not referenced in study	US
Dakin et al. 2010 [43]	HBsAg loss	3.64 (GBP)	5.52		Dakin et al. 2010 (PMID 20825624) [86]	NA	Not referenced in study	UK
Shepherd et al. 2006 [87]	HBsAg loss	0 (GBP)	0.00		Southampton University Hospitals Trust + Expert opinion	NA		UK
Takeda et al. 2007 [49]	HBsAg loss	0 (GBP)	0.00		Expert opinion	NA		UK
Jones et al. 2009 [45]	HBsAg loss	0 (GBP)	0.00		Expert opinion	NA		UK
Chinnaratha et al. 2017 [29]	HBsAg loss	0 (AUD)	0.00		Assumption	NA		AUS

AUD Australian dollars, AUS Australia, CAD Canadian dollars, CAN Canada, CC compensated cirrhosis, CHB chronic hepatitis B, CHN China, CUA cost-utility analysis, EASL European Association for the Study of the Liver, GBP pound sterling, HBsAg hepatitis B surface antigen, NA not applicable, NT\$ New Taiwan dollars, PMID PubMed Identification number, RMB Chinese Yuan, TAI Taiwan, UK United Kingdom, US United States of America, USD US dollars

Table 3 CHB costs outlined from sources referenced (converted to 2019 USD)

Author	CHB (not specified)	CHB (treated)	CHB (untreated)	HBeAg SC	HBsAg SC	CC	DC	HCC	LT
Hu and Chen 2009 [82]	1953					3310	5505	7898	
Gagnon et al. 2004 [85]	2634					3104	11,668	13,874	102,952
Kanwal et al. 2005 [80]						1264		50,776	167,220
Dakin et al. 2010 [86]		552	496	354	5.32	1959	15,701	13,992	88,059

CAN Canada, CC compensated cirrhosis, CHB chronic hepatitis B, DC decompensated cirrhosis, HBeAg SC hepatitis B envelope antigen seroconversion, HBsAg SC hepatitis B surface antigen seroconversion, HCC hepatocellular carcinoma, LT liver transplant, USD US dollars

3.3 HBsAg Loss Health State Utilities

Table 4 presents an overview of the 15 studies that explicitly mentioned HBsAg loss health state utilities. Four were conducted using China as their country perspective [27, 31, 32, 34], three studies were conducted using a US country perspective [46–48], three were conducted using a UK perspective [33, 43, 45], two were conducted using a Canadian perspective [38, 40] and the remaining three studies used an Australian [29], Iranian [30] and Italian [36] country perspective, respectively.

For all studies outlined in Table 4, the health state utility value specific to the HBsAg loss health state is reported. As seen, the utility values used in the studies range fairly substantially from 0.71 (reported in three studies [27, 31, 34]) to 0.99 (reported in four studies [32, 46–48]). As was undertaken for HBsAg health state costs, the sources these utilities were referenced from have been included in the table alongside a description of the study type. Some short notes detailing how these sources refer to HBsAg loss health state utilities are also included.

Other than the study by He et al. 2012 [38], which relied on assumptions to calculate the HBsAg health state utilities, a total of five sources [52, 89–92] were used for the remaining studies.

For three of the four studies that used a utility value of 0.99 (Veenstra et al. [47, 48] and Spackman and Veenstra 2008 [46]), it was assumed that the HBsAg loss health state utility was equal to the HBeAg seroconversion health state utility using Wong et al. [52] as a reference. For the remaining study that reported a value of 0.99 [32], Levy et al. [89] was referenced yet there was no mention of a utility value of HBsAg loss in the study. Levy et al. [89] was also referenced for six other studies [27, 29, 31, 32, 34, 36, 45].

For the majority of the studies, a utility value specific to HBsAg loss was not able to be identified from the sources referenced in the original articles. The remaining studies either used a utility value for non-cirrhotic CHB [33] or used “UK population norms for EQ-5D” [40, 86].

3.4 Treatment-Specific HBsAg Loss Rates/Transition Probabilities

Supplemental Table 5 (see ESM) provides an overview of the 11 studies that explicitly mentioned treatment-specific transition probabilities for the HBsAg loss health state. The transition probabilities used in the models are shown along with the HBeAg status of the population referred to (when HBeAg status has not been specified, this has been recorded as such in the table). Though efficacy values are presented for each treatment, it is important to note that comparisons between regimens must be conducted with caution. This is because of the heterogeneity of the baseline patient populations and study designs between trials, which will undoubtedly affect the outcomes explored.

For TDF, annual HBsAg loss rates between 0.7% (Banerjee et al. [31]) and 10% (Ruggeri et al. [28]) are used in HBeAg-positive patients, with Colombo et al. [41] and Ruggeri et al. [28] presenting increasing annual rates beginning from 3% and 3.2% respectively in year one. In HBeAg negative patients, a 0% annual loss rate is used in Colombo et al. [41] and a 12% lifetime loss rate is used by Lo et al. [35]. For studies that did not differentiate HBsAg loss rates by HBeAg status, Chinnaratha et al. [29] used an annual rate of 0.8%, and Iannazzo et al. [36] used an annual rate of 0.4%.

For LAM, annual HBsAg loss rates between 0% (Colombo et al. [41]) and 14% (Jones et al. [45]) are used in HBeAg-positive patients, with Zhang et al. [34] and Banerjee et al. [31] both reporting annual rates of 0.7%. Colombo et al. [41] is the only study that reported a loss rate for HBeAg-negative patients (0%), and He et al. [38] used a loss rate that was equal to baseline (this was for all patients regardless of HBeAg status).

For ADV, annual HBsAg loss rates ranged more conservatively between 0% (Colombo et al. [41]) and 1.3% (Zhang et al. [34] and Banerjee et al. [31]) in HBeAg-positive patients. Again, Colombo et al. [41] is the only study that reported a loss rate for HBeAg-negative patients (0%), whilst no studies reported a loss rate that was not specific to a particular HBeAg status.

Table 4 Overview of studies that mentioned HBsAg health state utilities

Author	Utility value	Range	Source	Type of study	Notes	Country perspective
Veenstra et al. 2008 [47]	0.99	0.94–1.00	Wong et al. 1995 [52]	CEA	Utility assumed same as HBeAg seroconversion	US
Veenstra et al. 2007 [48]	0.99	0.94–1.00	Wong et al. 1995 [52]	CEA	Utility assumed same as HBeAg seroconversion	US
Spackman and Veenstra 2008 [46]	0.99	0.94–1.00	Wong et al. 1995 [52]	CEA	Utility assumed same as HBeAg seroconversion	US
Toy et al. 2015 [32]	0.99	0.90–1.00	Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP) – no mention of HBsAg loss	CHN
Keshavarz et al. 2016 [30]	0.95		EQ-5D questionnaire + Goudarzi 2014 [90]	Interviews	Unpublished sources	IRN
He et al. 2012 [38]	0.9	0.85–0.95	Assumption	NA		CAN
Bermingham et al. 2015 [33]	0.87	0.85–0.88	Woo et al. 2012 [91]	QoL study	Utility for non-cirrhotic CHB	UK
Iannazzo et al. 2013 [36]	0.87	0.7–1	Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	ITA
Dakin et al. 2011 [40]	0.86	SE 0.0039	Kind et al. 1999 [92]	QoL study	“UK population norms for EQ-5D”	CAN
Dakin et al. 2010 [86]	0.86	0.85–0.87	Kind et al. 1999 [92]	QoL study	“UK population norms for EQ-5D”	UK
Chinnaratha et al. 2017 [29]	0.79	0.77–0.80	Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	AUS
Jones et al. 2009 [45]	0.79		Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	UK
Zhang et al. 2015 [34]	0.71	0.64–0.78	Levy et al. 2008 [89]	NA	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	CHN
Banerjee et al. 2016 [31]	0.71		Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	CHN
Wei et al. 2013 [27]	0.71		Levy et al. 2008 [89]	QoL study	Infected and uninfected CHB health state utilities (CHN, HKG, CAN, US, GBR, ESP)—no mention of HBsAg loss	CHN

AUS Australia, CAN Canada, CEA cost-effectiveness analysis, CHB chronic hepatitis B, CHN China, ESP Spain, GBR Great Britain, HBeAg hepatitis B envelope antigen, HBsAg hepatitis B surface antigen, HKG Hong Kong, IRN Iran, ITA Italy, NA not applicable, PMID PubMed identification number, QoL quality of life, SE standard error, UK United Kingdom, US United States of America

For ETV, annual HBsAg loss rates between 1.4% (Ruggeri et al. [28], Zhang et al. [34] and Banerjee et al. [31]) and 2% (Colombo et al. [41], Ruggeri et al. [28]) are used in HBeAg-positive patients, with Ruggeri et al. [28] presenting annual loss rates for the first 5 years in the study. As was seen for TDF, a 0% annual loss rate is used in Colombo et al. [41] and a 12% lifetime loss rate is used by Lo et al. [35] for HBeAg-negative patients. For studies that did not differentiate HBsAg loss rates by HBeAg status, Iannazzo et al. [36] used an annual rate of 0.4% and He et al. [38] again used a much higher annual rate of 8.1%.

For LdT, annual HBsAg loss rates are lower than for any other treatments in HBeAg-positive patients. These annual rates range from 0% (Colombo et al. [41]) to 0.7% (Zhang et al. [34] and Banerjee et al. [31]). In HBeAg-negative patients, a 0% annual loss rate is used in Colombo et al. [41] and a 12% lifetime loss rate is used by Lo et al. [35]. As was seen with LAM, He et al. [38] used a loss rate that was equal to baseline for all patients regardless of HBeAg status.

Banerjee et al. [31] was the only study that mentioned annual HBsAg loss rates for combinations of nucleoside therapies. LDT in combination with ADV was considered to have an annual loss rate of 0.7%, whilst LDT in combination with TDF was considered to have a higher annual loss rate of 4.4% (both in HBeAg-positive patients).

For interferon (IFN), Jones et al. [45] used an annual HBsAg loss of 1.7% in HBeAg-positive patients, which was recorded in a study by Zhao et al. [93], yet it was not clear from the report which values were used in the accompanying model. For HBeAg-negative patients, an annual HBsAg loss rate of 18.8% was recorded in the first year by Wong et al. [52].

For PEG IFN, annual HBsAg loss rates between 0% (Jones et al. [45]) and 8% (Colombo et al. [41]) are used in HBeAg-positive patients. As with IFN, the HBsAg loss rate stated in Jones et al. [45] was recorded in a study by Zhao et al. [93], in which no patients experienced HBsAg loss on PEG IFN, though it is not clear from the report which values were used in the accompanying model. The report by Jones et al. [45] should be interpreted with caution due to its seemingly low loss rates compared with similar studies (also, because PEG IFN performed surprisingly worse than IFN alone). In HBeAg-negative patients, Colombo et al. [41] reported an increasing annual loss rate starting with 3% in year 1 and ending with 8% in year 3. This compares with the Lo et al. study [35], which used a lifetime HBsAg loss rate of 35%. For studies that did not differentiate HBsAg loss rates by HBeAg status, Iannazzo et al. [36] used annual rates starting from 5.3% in year 1–10.6% in year 3.

Jones et al. [45] recorded HBsAg loss rates for PEG IFN in combination with LAM, though it was not clear from the report whether these values were used in the accompanying model. The study reported a loss rate of 10% as was recorded

in a study by Chan et al. [94] (seen in 5 of 50 patients in the study), though it was not clear whether this was a yearly loss rate or overall outcome.

And finally, best supportive care (BSC) was reported by Banerjee et al. [31] to have an annual HBsAg loss rate of 0.7% in HBeAg-positive patients. Whilst in HBeAg-negative patients, Lo et al. [35] reported a lifetime loss rate of 10% and Wong et al. [52] reported an even higher rate of 18.80%. The report by Wong et al. [52], however, stated that the model was purposefully biased against IFN because of significant heterogeneity existing among study results in the meta-analysis that was used.

It is important to note that in the studies that reported increasing annual loss rates (e.g., Iannazzo et al. [36] and Colombo et al. [41]), the last observed response rate was carried forward when further data was not available to the authors. Iannazzo et al. [36] presented HBsAg loss rates after 48 weeks with PEG IFN that seem to suggest that the authors took into account a treatment effect occurring some time after treatment was presumably ended.

4 Discussion

HBsAg loss as a health state in economic models of CHB across multiple country perspectives is not well recorded in terms of costs, health state utilities, and treatment-specific transition probabilities. Of the 65 EEs identified in this review, less than half (27/65) incorporated this health state in their models (see Table 1). And of those studies that did record HBsAg loss inputs, the source of the values used (especially for health state costs and utilities as seen in Tables 2 and 4) were largely unclear.

Of the 27 studies that incorporated HBsAg loss, only 15 explicitly mentioned HBsAg loss health state costs (Table 2). The vast majority of sources that were used to collect such costs for the original studies [27, 31, 34, 38, 40, 43, 46–48] do not specifically mention these values in their articles. The only source that does specifically state a cost (in this case for HBsAg SC) is Dakin et al. [86], which states a yearly cost of US\$5.32. The range of costs recorded between the articles is wide (from US\$0.00 [29, 45, 49, 87] to US\$1377.45 [31] per year) and a large disparity seems to exist: five studies [27, 31, 34, 50, 52] state costs between US\$814.83 [40] and US\$1377.45 [31], compared with 11 studies [29, 38, 43, 45–50, 52, 87] that state costs between US\$0.00 [29, 45, 49, 87] and US\$224.62 [50]. From looking at Table 3, which shows the health state costs recorded by the sources referenced, it is likely that the costs for HBsAg loss have been predicted from other CHB health states. This may explain the disparity between the values used since the studies that contain the higher values may have predicted these from other CHB health states that use higher costs (e.g., the CHB

health state cited in Hu et al. [82], which uses an annual cost of US\$1953). It may not be misguided to suggest that most studies are therefore relying on assumptions rather than explicitly sourcing cost inputs, and referencing other studies that have previously relied on assumptions compounds this problem further.

In terms of health state utilities associated with HBsAg loss, these were explicitly mentioned in only 15 of the 65 EEs identified (see Table 4). Across these studies, the values cited for this health state range from 0.71 (reported in three studies [27, 31, 34]) to 0.99 (reported in four studies [32, 46–48]). All the 0.71 utility values were taken from the same source (Levy et al. [89]), yet there is no mention of utility associated with HBsAg loss in this article. Therefore, the 0.71 value has been assumed to be the same as an alternative health state that is not clearly outlined in the source (likely to be infected patients with CC). When exploring the source of the 0.99 utility values, three of the studies (Veenstra et al. [47, 48], and Spackman and Veenstra [46]) assumed that the HBsAg loss health state utility is equal to the HBeAg seroconversion health state utility using Wong et al. [52] as a reference. And when Wong et al. [52] is explored, the utility values used in this study were derived from an expert panel that assessed their own utilities of being in a particular health state using the standard gamble (SG) and time-trade-off (TTO) techniques. For the remaining study that reported a value of 0.99 [32], Levy et al. [89] was referenced, yet there was no mention of a utility value of HBsAg loss in the study (this has also been used as a source for five other studies [27, 29, 31, 36, 45]). Bermingham et al. [33] used a utility value for non-cirrhotic CHB (0.87) to represent HBsAg loss, and both Dakin et al. [43] as well as Dakin et al. [40] used UK population norms using EQ-5D (0.86). As was seen with HBsAg loss health state costs, suboptimal reporting as well as a clear lack of transparency regarding the source of HBsAg loss health state utilities is evident. When evidence is not available, sources have relied on using other similar health states as a proxy for HBsAg loss.

Treatment-specific HBsAg loss rates/transition probabilities were reported in only 11 of the 65 EEs identified (see Supplementary Table 5 in the ESM). The number of studies is even lower than the 15 that reported HBsAg loss health state costs (Table 2) and the 15 that reported HBsAg loss health state utilities (Table 4). This is probably explained by the likelihood that most studies do not differentiate between SoC treatments in terms of HBsAg loss. This may be because HBsAg loss (and HBsAg SC) are reported in only a small number of patients, so differentiating these loss rates by specific treatments would result in the outcomes becoming heavily underpowered and unreliable when compared with other studies. An example of this problem is outlined in the report by Jones et al. [45], which reported a 10% HBsAg loss rate in a study by Chan et al. [94] whereby a

small sample size (only 50 patients) received PEG IFN in combination with LAM.

For nucleoside analogues (irrespective of HBeAg status), annual HBsAg loss rates vary fairly substantially between studies. TDF varies between 0.4% (Iannazzo et al. [36]) and 11.53% (He et al. [38]), LAM varies between 0% (Colombo et al. [41]) and 14% (Jones et al. [45]), ADV varies between 0% (Colombo et al. [41]) and 1.3% (Zhang et al. [34] and Banerjee et al. [31]), ETV varies between 0% (Colombo et al. [41]) and 8.1% (He et al. [38]), and LdT varies between 0% (Colombo et al. [41]) and 0.7% (Zhang et al. [34] and Banerjee et al. [31]). It is important to note that the higher values for annual HBsAg loss rates (especially by Jones et al. [45] and He et al. [38]) did not seem to be in line with the majority of inputs (which were much lower) reported in the other studies. He et al. [38] cited an RCT (Chang et al. [12]) to obtain its HBsAg loss rate for ETV, yet the rate reported in the study (2%, i.e., 6/354 at 48 weeks) is much lower than the 8.1% figure used in the model. Meanwhile, as stated previously, it was not clear which values Jones et al. [45] used in the accompanying EE. In published RCTs, HBsAg loss recorded at 48 weeks for nucleosides rarely reaches 4% or higher [12–17]; therefore, numerous studies seem to state loss rates that are particularly high in their models.

For IFN, annual HBsAg loss rates (irrespective of HBeAg status) ranged between 1.7% (Jones et al. [45]) and 18.8% (Wong et al. [52]), whilst for PEG IFN, loss rates ranged between 0% (Jones et al. [45]) and 10.6% (Iannazzo et al. [36]). A lifetime HBsAg loss rate of 35% was also recorded for PEG IFN (Lo et al. [35]). However, some of these results need to be interpreted with caution. Jones et al. [45] obtained these values from a study that had a low sample size (Zhao et al. [93]), whilst Wong et al. [52] used assumptions from an expert guidance panel to estimate loss rates. In published RCTs, the loss rate for PEG IFN alone is usually around 4–10% [18–21], but has also been reported in some studies to be above 10% [95, 96] (and these also vary by specific genotype [97]). PEG IFN in combination with a nucleoside analogue has been reported in some cases to be even higher: 20% (2/10 patients) at 60 weeks [22], and 21% (3/14 patients) at 48 weeks [23], although low sample sizes seem to have an influence. Also, an HBsAg loss rate of 18.8% (Wong et al. [52]) seems relatively high compared with a rate of 0% (0/33) at 52 weeks [98], and 10% (7/72) at 48 weeks [6] as seen in two published RCTs.

According to the AASLD 2018 [7], APASL 2016 [8], EASL 2017 [9] and NICE 2013 (updated 2017) [10] guidelines, HBsAg loss is a key endpoint of interest that is strongly recommended in the management of HBV. Often, patients that achieve FC are lost to follow up as they will stop attending physician appointments (especially patients that are non-cirrhotic). As such, it is vital in EEs to model all

important health states (including HBsAg loss in CHB) so that decisions can be made taking into account all available clinical evidence.

From a health economic modelling perspective, the incorporation of HBsAg loss as a health state has the potential to translate into more representative and truer to life health outcomes for the intervention being assessed. This then enables health state-specific utility values and management costs to be incorporated, which can provide credit to interventions that achieve a profound effect on HBsAg loss. The scope of this review was not to provide evidence on how HBsAg loss translates into long-term benefits, but to support future modelling activities so that they do not misrepresent the benefits of curative regimens that are likely to enter the market in the coming years.

Though extensive, this review is not without its limitations. Even though EEs from multiple country perspectives were identified, only studies written in the English language were included for review. This means that the conclusions obtained may be biased towards articles written in English, which may not be seen in studies conducted in other languages.

Studies investigated were not homogenous in terms of baseline patient characteristics. This means that comparisons across studies need to be interpreted with caution due to the fact that these characteristics will undoubtedly influence the outcomes investigated.

The eligibility criteria excluded studies that contained special patient populations. This may have hindered the content of our initial review, and additional searches may be needed to confirm the conclusions in these specific populations. Also, only searches in PubMed and Embase were conducted, which was considered a pragmatic approach with regards to the resources available. Though we do not expect the inclusion of other databases to change our conclusions, this is a limitation of our review.

Overall, there is a clear lack of transparency and reporting surrounding HBsAg loss as a health state in current models of CHB. Future research is required to provide evidence of healthcare resources used for patients that experience HBsAg loss as well as information regarding their HRQoL. With regards to HRQoL, using a disease-specific measure might be better able to capture differences between patients who have HBsAg loss and patients with CHB than conventional questionnaires (e.g. EQ-5D) that may be insensitive to such differences.

5 Conclusions

FC is regarded as an optimal endpoint of interest in multiple clinical guidelines (AASLD [7], APASL [8], EASL [9], NICE [10]). However, the benefits of FC in current HE

models are not well captured, as they are often not directly related to modelled treatments. This has the potential for novel agents that perform well in increasing the rates of FC to be overlooked and undervalued if their worth is not appropriately communicated. In order to ensure optimal access for patients to new and effective therapies, it is important that the benefits of FC are better assessed and captured within HE models. These include, but are not limited to, the impact on clinical and economic outcomes as well as the effect on HRQoL (especially considering that current treatments for CHB can be taken for long periods of time).

After conducting a systematic literature review of all published HE models of CHB, less than half of these seem to incorporate HBsAg loss as a health state. Most of the models do not consider treatment-specific transition probabilities to the HBsAg loss health state and, when the health state was included, heroic assumptions were made with regards to both HBsAg loss health state costs and HBsAg loss health state utilities. More research is required to provide evidence of healthcare resources used and HRQoL measures for patients that experience FC so that this can become a vital component incorporated in HE models of CHB.

Author contributions PW and MH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: US, PW, MH. Acquisition of data: PW, MH, TV. Analysis and interpretation of data: PW, MH, US, BH. Drafting of the manuscript: PW, MH, US. Critical revision of the manuscript for important intellectual content: PW, MH, US, BH, TV. Obtaining funding: BH, MH. Supervision: US.

Data availability statement The data that support the findings of this study are available on request from the corresponding author [PW]. The data are not publicly available due to internal data sharing restrictions within Ingress-health and Janssen Pharmaceutica NV Belgium.

Compliance with Ethical Standards

Funding This study received funding from Janssen Pharmaceutica NV, Belgium.

Conflict of interest Urbano Sbarigia is an employee of Janssen Pharmaceutica NV Belgium and holds stocks at Johnson & Johnson. Peter Wigfield, Mahmoud Hashim, and Talitha Vincken are employees at Ingress-health (a research consultancy specialising in health economics and real-world evidence). Bart Heeg is a partner at Ingress-health.

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