BMJ Open

Healthcare resource utilisation pattern and costs associated with herpes simplex virus diagnosis and management: a systematic review

Shaun Wen Huey Lee [1,2,3] Sami L Gottlieb,[4] Nathorn Chaiyakunapruk[1,5,6]

To cite: Lee SWH, Gottlieb SL, Chaiyakunapruk N. Healthcare resource utilisation pattern and costs associated with herpes simplex virus diagnosis and management: a systematic review. *BMJ Open* 2022;**12**:e049618. doi:10.1136/bmjopen-2021-049618

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-049618).

Received 28 January 2021
Accepted 28 October 2021

[1]School of Pharmacy, Monash University Malaysia, Bandar Sunway, Selangor, Malaysia
[2]School of Pharmacy, Taylor's University Lakeside Campus, Subang Jaya, Malaysia
[3]Center of Global Health, University of Pennsylvania, Philadelphia, Pennsylvania, USA
[4]Department of Reproductive Health and Research, World Health Organization, Geneve, Switzerland
[5]Department of Pharmacotherapy, University of Utah, Salt Lake City, Utah, USA
[6]School of Pharmacy, University of Wisconsin, Madison, WI, USA

Correspondence to
Dr Nathorn Chaiyakunapruk; nathorn.chaiyakunapruk@utah.edu

ABSTRACT

Objectives Little is known about the economic burden of herpes simplex virus (HSV) across countries. This article aims to summarise existing evidence on estimates of costs and healthcare resource utilisation associated with genital and neonatal HSV infection.

Design Systematic literature review.

Data sources Seven databases were searched from inception to 31 August 2020. A focused search was performed to supplement the results.

Eligibility criteria Studies which reported either healthcare resource utilisation or costs associated with HSV-related healthcare, including screening, diagnosis and treatment of genital HSV infection and neonatal herpes prevention and treatment.

Data extraction and synthesis Two independent reviewers extracted data and assessed the risk of bias using the Larg and Moss's checklist. All data were summarised narratively.

Results Out of 11 443 articles, 38 were included. Most studies (35/38, 94.6%) were conducted in high-income countries, primarily the United States, and were more often related to the prevention or management of neonatal herpes (n=21) than HSV genital ulcer disease (n=17). Most analyses were conducted before 2010. There was substantial heterogeneity in the reporting of HSV-related healthcare resource utilisation, with 74%–93% individuals who sought care for HSV, 11.6%–68.4% individuals who received care, while neonates with herpes required a median of 6–34 hospitalisation days. The costs reported were similarly heterogeneous, with wide variation in methodology, assumptions and outcome measures between studies. Cost for screening ranged from US$7–100, treatment ranged from US$0.53–35 for an episodic therapy, US$240–2580 yearly for suppressive therapy, while hospitalisation for neonatal care ranged from US$5321–32 683.

Conclusions A paucity of evidence exists on healthcare resource utilisation and costs associated with HSV infection, especially among low-income and middle-income countries. Future research is needed on costs and healthcare utilisation patterns to improve overall understanding of the global economic burden of HSV.

Strengths and limitations of this study

- ► This is the first systematic review to assess the healthcare resource utilisation and costs associated with herpes simplex virus (HSV) infections.
- ► Comprehensive literature searches were conducted, which were supplemented by a focused search.
- ► Heterogeneity of study designs and outcome measures limited the meta-analysis of study results.
- ► Relatively few studies described the healthcare resource utilisation patterns and cost of HSV, especially from low–middle income countries.

INTRODUCTION

Herpes simplex virus (HSV)-1 and HSV-2 are DNA viruses that belong to Alphaherpesviridae, a subfamily of the Herpesviridae family.[1] Both viruses can cause genital infection, which can have a profound impact on sexual and reproductive health. HSV-2 is almost entirely transmitted during sexual activity and is the most common cause of genital herpes, affecting more than one in every 8 individuals, or 491.5 million people, aged 15–49 years in 2016.[2] HSV-1 is the main cause of oral herpes but can also be transmitted to the genital area through oral sex. HSV-1 affects an estimated 3.7 billion people under age 50 globally, of which over 120 million may have genital infection.[2] While the prevalence of HSV infection is high globally, it varies widely by region. The highest prevalence of both HSV-1 (88% in women and men) and HSV-2 (44% in women; 25% in men) is in the African region, which is primarily comprised of low-income and middle-income countries (LMICs).[1 2]

Genital HSV infection is lifelong and characterised by periodic reactivation. Many infections are asymptomatic or unrecognised, but up to a third of people may develop painful, recurrent genital sores known collectively as genital ulcer disease (GUD).[3] Antiviral medications can be taken episodically to shorten GUD outbreaks or taken daily (suppressive therapy) to reduce the number of outbreaks, but they are not curative. Pregnant women with genital HSV infection can also transmit the virus to their infants in the peripartum

period, resulting in neonatal herpes.[4] Although this occurs only rarely, neonatal herpes has a high fatality and disability rate among surviving infants. As such, particularly in high-income countries (HICs), prevention measures such as caesarean section are often undertaken if a mother has active HSV lesions at delivery. Genital HSV-2 infection has also been linked to an increased risk of acquisition and transmission of human immunodeficiency virus (HIV) infection.[5]

The World Health Organisation (WHO) has highlighted the need for a vaccine against HSV-2, due to large numbers of infections globally and the resulting disease consequences including GUD, neonatal herpes, and increased risk of HIV acquisition.[6–8] Multiple vaccine candidates have been studied to date with modelling studies showing that prevention of HSV-2 infection with a vaccine could potentially also reduce the incidence of HIV infection.[9] Vaccines targeting HSV-2 might also have benefits against HSV-1.[10] Understanding the potential value of HSV vaccines requires not only predicting the impact of the vaccines on HSV-related disease burden, but also on its economic burden. However, little is known about the economic burden of HSV globally. As a first step in estimating HSV-related economic burden, we conducted a broad systematic review with the aim of summarising all available evidence on costs and resource utilisation associated with diagnosing, treating and managing genital and neonatal HSV infection.

METHODS

The current study followed the guidelines of the *Cochrane Handbook for Systematic Reviews of Intervention*.[11] The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[12]

Data sources and search strategy

We electronically searched for relevant articles published from database inception to 31 August 2020 in seven databases: PubMed, PsychINFO, Embase, Centre for Review and Dissemination, EconLit, CEA registry and WHO Library Database. The search strategy was based on a broad combined search string "Herpes Simplex Virus" AND "cost" OR "resource utilization" OR "econ*", with no language restriction. A complete search strategy is detailed in online supplemental appendix text 1. In addition, bibliographies of relevant articles were examined to identify potential studies not indexed in the aforementioned databases. A focused supplemental search on Google Scholar was performed using the keywords listed in online supplemental appendix text 2 based on the inclusion above.

Study selection

Studies were included if they were original articles that investigated resource utilisation patterns and costs related to HSV infection including the cost of any diagnostic tools, consultation time, treatment and hospital cost related to detecting and managing all types of HSV-1 or HSV-2 related neonatal and genital infections and associated disease outcomes. We included articles which were published in English languages.

Data extraction and quality assessment

The study followed a 2-stage process, where two independent reviewers screened the titles and abstracts for relevant studies, before the full texts were screened by another two independent reviewers for eligibility. Relevant information from the identified studies was extracted independently by two reviewers using a standardised data extraction sheet. At all stages, any disagreement was resolved by discussion between reviewers through consensus. Information collected from the data extraction sheet included: (1) general study information including country of the study, (2) HSV subtype and disease, (3) study design, (4) healthcare resource utilisation, (5) costs of relevant tests, clinical care, hospitalisation and medications and (6) summary estimates of HSV-related economic burden. Methodological quality of all included economic studies was assessed using the Consensus Health Economic Criteria list. This checklist has been recommended for critically appraising published economic evaluations. The checklist has 19 domains and includes reporting standards for economic model characteristics (population, time horizon, perspective and discount rate), identification and valuation of costs and outcomes, discussion points, conclusions as well as funding and conflicts of interest. All cost of illness studies were evaluated for risk of bias using the Larg and Moss's checklist. No quality appraisal was performed on studies reporting healthcare resource utilisation.

Data analysis

A component-based analysis was used to describe and synthesise the overall findings from all included studies. Specifically, tabulation methods were used to report on study characteristics, outcomes and costs. Tables for resource utilisation and disaggregated costs were presented and summarised. All costs were presented according to the recommendations of Turner *et al*.[13] For studies that did not provide the year of cost data, the year of publication was used. Adjustment for inflation was done using the Gross Domestic Product deflator (GDP deflator) of the studied country. Cost estimates were then converted and reported in 2017 United States Dollars (USD). GDP deflator and exchange rates were obtained from the World Bank.[14]

Patient and public involvement

Patients were not involved in this systematic review. Their input was not sought in the design, interpretation or writing of the document.

RESULTS

Study selection

Our search yielded a total of 11 443 articles of which 8779 articles were excluded as they were not relevant for this review based on title screening. The remaining 2664 articles were further screened by title and abstract and 299

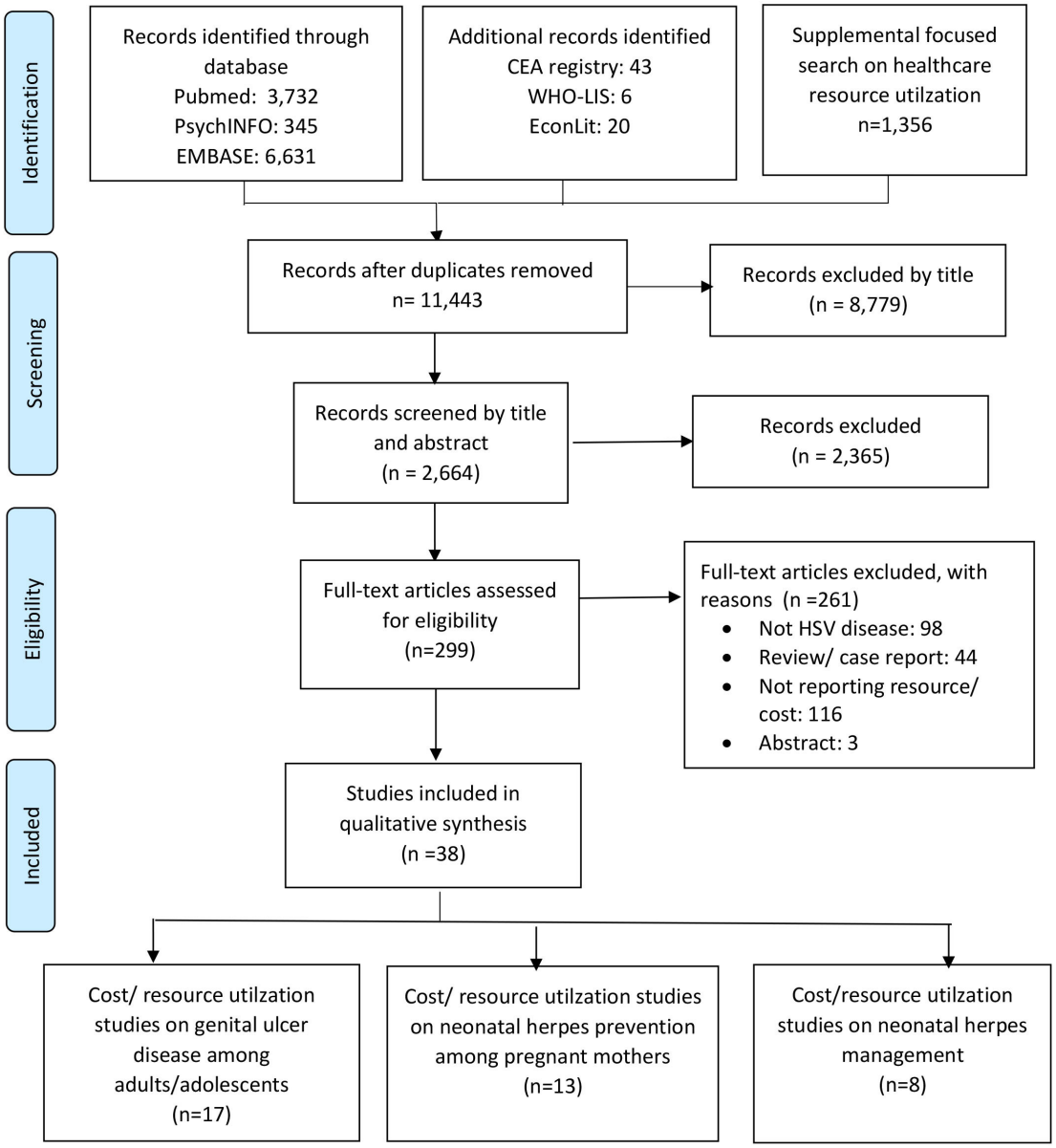

Figure 1 Flow diagram of study selection process. HSV, herpes simplex virus.

articles were assessed for inclusion. We excluded 261 articles (n=98 for not related to HSV, n=44 review articles/case report, n=116 not reporting resource utilisation or cost, n=3 available only in abstract), leaving a total of 38 studies included in this review, as shown in figure 1.

Overview of study characteristics

Of the 38 included articles, 14 studies[15–28] described resource utilisation only, 12 studies[29–40] reported on costs and 12 studies[41–52] reported both resource utilisation and costs of HSV diagnosis/management. These studies, published from 1989 to 2020, reported resource utilisation or costs related to the diagnosis and management of HSV-related GUD among adults/adolescents[18–22 28 30–34 37–40 44 52] (n=17), neonatal herpes prevention in pregnant mothers (n=13)[23–25 27 29 35 36 42 43 46–49] and neonatal herpes management[15–17 26 41 45 50 51] (n=8). The majority of studies were conducted in high income countries (HIC) (35/38, 94.6%) including the United States (USA)[15 17 20 22 25 27 29 30 34 35 38–52] (n=26), Canada[18 19 26 36] (n=4), United Kingdom (UK)[23 33] (n=2), France[16 28] (n=2) and Ireland[24] (n=1)), while only one study (1/38, 2.6%) was conducted in a middle-income country, in particular South Africa.[32] A global survey focusing on the experiences of patients receiving care for genital herpes in 78 countries included some data on healthcare utilisation.[21] In addition, a modelling study estimated the costs of implementing the Global Health Sector Strategy on Sexually Transmitted Infections (STIs), 2016–2021, in 117 LMICs, including costs related to syndromic management of GUD, the vast majority of which is caused by HSV-2.[37] The quality of included studies is summarised in online supplemental appendix figures 1 and 2.

Methodological heterogeneity

There was substantial heterogeneity in the reporting of the included studies. Most studies were cost or resource utilisation studies (n=23), while the remaining were cost-effectiveness studies (n=15). Among cost or resource utilisation studies, data were collected retrospectively (n=13), prospectively (n=7) or not reported (n=7). The number of participants in each study varied, which could be as few as 39 participants to as large as 42 million in studies that analysed claims datasets. Twenty-one studies (21/38, 55.3%) included participants who had either HSV-1 or 2, 10 studies (10/37, 27.0%) specifically included participants with HSV-2, while the remaining eight studies (8/38, 21.1%) did not specify which type of HSV they examined. A summary of the characteristics of these studies is presented in online supplemental appendix table 1, and study findings are presented in online supplemental appendix tables 1 and 2 (see appendix for detailed unit cost tables and accompanying references).

Cost and healthcare resource utilisation pattern of genital herpes infection

Among all 17 studies[18–22 28 30–34 37–40 44 52] investigating cost and healthcare resource utilisation pattern of genital herpes, 11 studies reported some cost components of care for genital herpes infection[30–34 37–40 44 52] (online supplemental appendix tables 1, 2 and 4). All but one of these studies were conducted in HIC and only one LMIC study (from South Africa) was found. The cost components of the included studies were variably reported. Three studies[31 34 52] reported laboratory testing costs associated with diagnosing HSV. Eight studies[30 31 33 34 37 40 44 52] described costs associated with syndromic management of GUD. In four studies,[32 33 37 52] the authors describe the drug charges associated with treatment or prevention of HSV using oral acyclovir (doses of 200–400 mg). The cost reported varied considerably, ranging between US$0.53 and US$16 for a 5–7 day treatment course for episodic GUD and US$40 for a month of suppressive therapy with acyclovir. Two studies[31 44] provided the total drug charges associated with overall management of GUD, but no details related to the treatment regimen, duration or HSV of HSV being treated (online supplemental appendix table 2). Seven studies[31–33 37 47 48 52] described labour and service delivery costs such as cost of physician visits, drug procurement cost, counselling cost and clinical examination associated with HSV. Similarly, there was variation in terms of reported labour and service delivery cost, which could be as low as US$0.28 for 10-min counselling[33] to as high as US$120 for consultation and lost wages of patient time.[52] Indirect costs were considered only by Szucs *et al* who estimated HSV-related productivity losses, which was estimated at a US$60 visit.[31]

Considering the cost components together, Owusu-Edusei *et al* estimated that the lifetime direct medical cost per case of genital HSV infection in the USA (considering only GUD-related costs and adjusted to 2017 USD) was US$855 among men (range: US$428–$1284) and US$698 among women (range: US$350–1047).[30] This translated to a total cost of US$607.3 million (range: US$303.59–910.89 million in 2017 USD) for lifetime management of new or newly diagnosed cases of HSV-2 in the USA occurring in 2008. Szucs *et al* meanwhile estimated that the annual direct and indirect medical costs in the USA would amount to US$983 million, based on an estimated 3.1 million symptomatic genital HSV episodes (both new and recurrent) a year.[31]

The only middle-income country study, from South Africa,[32] reported the diagnostic/operational costs associated with medication, staff and laboratory costs for daily HSV-2 suppressive therapy among people living with HIV.[32] The median cost for HSV-2 suppressive therapy per life-year gained ranged between US$685 and US$951 (adjusted to 2017 dollar) among HIV-1 infected antiretroviral naïve women. The authors estimated that this could be a cost-effective method for delaying HIV disease progression, especially when the price of acyclovir was lower than the price of US$0.026 per day for a two times per day 400 mg dose. However, this study was conducted when antiretroviral therapy (ART) use was recommended only when CD4 count fell below a threshold of <200 cells/µL or <350 cell/µL (online supplemental appendix table 5). On a more global level, in Korenromp *et al*'s cost estimates for implementing the Global STI Strategy in 117 LMIC over 2016–2021, the authors reported that it would cost approximately US$109 million to diagnose and treat HSV-related GUD episodes seen in clinical care, not including service delivery costs.[37] These costs were estimated despite assuming that only about 4% of all HSV-2 infected people would seek care for GUD (15% recognising symptoms and 28% of those seeking care).

A total of eight studies described healthcare resource utilisation patterns for genital herpes infection,[18–22 31 40 44] and all were from high-income countries (online supplemental appendix tables 1 and 3). Five of these studies[18 20–22 40] reported the population rate of seeking medical care for HSV, based on retrospective analyses of databases of patients from health surveys.[20–22] In the study by Di Xia *et al*, the authors found that the total genital herpes associated emergency department (ED) use increased from 24 747 visits in 2006 to 36 518 in 2013.[40] It is important to note that none of the studies reported the proportion of those seeking medical care among HSV-infected individuals. Most of these consultations were relatively short in nature, and were less than 15 min (79%).[21] Two studies described the diagnostic methods used to determine HSV among their population. In the first study conducted in 2004, Patrick *et al* surveyed physicians in 78 countries and reported that the most commonly used test was viral culture, which was performed in 49% of the individuals[21] (online supplemental appendix table 3). A recent study in France by Heggarty *et al* in 2020 found that 43.3% of respondents in their survey stated that they would conduct polymerase chain reaction (PCR) test plus HSV serology and another

39.9% would conduct PCR test only to confirm a HSV diagnosis.[28]

Treatment patterns of individuals with genital herpes were also reported in four studies.[19 21 28 44] The study by DesHarnais *et al* in 1996 reported on antiviral use only among hospitalised patients with herpes infections, which is unlikely to be representative of the vast majority of people with HSV infection. Patrick *et al* in their survey found that 65% of people with genital herpes had ever been treated with antivirals, while 18% used topical prescription medication and 13% used over the counter topical cream. Among these individuals, 67% had received episodic therapy while 31% received chronic suppressive therapy (online supplemental appendix table 2). Another study on herpes-related quality of life reported that 76.9% of respondents had ever been treated with antivirals, and 33.3% of the respondents with HSV were on suppressive antiviral therapy when the survey was administered.[19]

Cost and healthcare resource utilisation pattern of prevention of neonatal herpes among pregnant mothers

Nine studies reported costs for neonatal herpes prevention among pregnant mothers[29 35 36 42 43 46–49] (online supplemental appendix tables 1, 2 and 6). Seven studies[35 36 42 43 46 47 49] provided estimates on the cost for treatment and childbirth delivery options, including caesarean and vaginal delivery in addition to inpatient costs. The cost of hospitalisation ranged considerably, and could be as low as US$300 to as high as US$32 483, while the cost of delivery ranged between US$2300 and US$9490. The costs associated with different laboratory tests used, such as ELISA screening or viral cultures[36 43] were reported, while detailed listing of the cost component of different delivery methods and hospital care were included in some studies (online supplemental appendix table 6). The cost-effectiveness studies examined the impact of either acyclovir suppressive therapy[29 35 46 47] or routine antenatal screening[36 42 43 48 49] for prevention of neonatal herpes. In a study by Randolph *et al*,[47] the authors found that prophylaxis with acyclovir during late pregnancy could be a cost-effective strategy to reduce the need for caesarean delivery due to genital herpes outbreaks during labour. Baker *et al* further expanded this work and estimated that adding serological testing to antiviral suppressive therapy had an incremental cost per quality-adjusted life year gained of US$18 680, compared with no screening or suppressive therapy.[42] A modelling study by Tuite *et al* had similar findings related to screening for HSV in pregnancy.[36]

Our focused search found a total of 10 studies which reported resource utilisation among pregnant mothers to prevent neonatal herpes.[23–28 42 43 46 48] Among these, four were cost-effectiveness studies which had provided some information regarding resource utilisation based on estimates from literature or assumptions.[42 43 46 48] In one of the earliest studies by Brocklehurst in 1995, a survey of British obstetrician–gynaecologists revealed that most would recommend some form of antenatal screening for HSV using viral cultures usually by week 34 of gestation.[23] However, such screening is no longer recommended in the UK. Studies within HICs that have national obstetrics guidelines recommending caesarean delivery when HSV lesions are present at delivery have shown that most clinicians follow this guidance.[24–27] For example, in a Canadian study, caesarean section was offered 'most of the time' to women with HSV lesions at delivery by 92% of obstetricians and 82% of family physicians.[26] In addition, in these settings women with genital herpes are often offered antiviral suppressive therapy in the third trimester.[24 26] Both valacyclovir and acyclovir have been used, with difference in preference by country. In the most recent survey of clinicians managing pregnant women with HSV by Heggarty *et al* in 2020, the authors noted that 68.4% 'always' prescribe suppressive antiviral therapy during the third trimester and an additional 11.6% 'often' prescribe it for women with symptomatic primary HSV infection during pregnancy.[25] For women with recurrent symptoms during pregnancy, 55.1% of providers always prescribe and 12.9% often prescribe antiviral prophylaxis in the third trimester.[28]

Cost and healthcare resource utilisation pattern of neonatal herpes management

Four studies[41 45 50 51] reported cost of neonatal herpes management and reported only direct medical costs (online supplemental appendix tables 1 and 2). One study reported direct non-medical cost for long-term care of individuals with neurological disability due to sequelae of HSV.[43] All studies were in HIC. The reported cost of hospitalisation of neonatal HSV ranged considerably, from US$27 843 to US$92 664. One study reported the cost associated with hospital readmission, which was reportedly similar to the first hospitalisation episode.[50] Six studies[36 46–49 52] accounted for the costs of informal care in their calculation. Informal caregiving was defined as care provided by caregivers for infants who had neurological sequelae following neonatal herpes. In total, seven studies[36 43 46–49 52] estimated long-term care costs of neonatal herpes patients. One of these, by Thung and Grobman,[49] provided the estimated cost for long-term care of neonates with mild neurological deficit due to HSV, which cost US$17 304.61 after adjusting for inflation to 2017 values. Six studies[43 46–49 52] provided estimates for the lifetime cost of caring for a child with moderate and severe disability, and fall within the range US$68 894–US$432 263 and US$232 698–US$ 1 296 792, respectively. It is important to note that all studies relied on estimation of long-term costs calculated by Weitzman *et al*[53] with some different assumptions, while one study[43] used other sources of data.

A total of seven studies[15–17 41 45 50 51] described resource utilisation among individuals with neonatal herpes (online supplemental appendix tables 1 and 3). These studies described the length of stay for hospitalisation which varied considerably, with median hospital stays ranging from 6 to 34 days[15 16] Ahmad *et al* noted that

nearly 9.4%–9.8% of neonates who had HSV required ICU stay.[15] None of the studies reported the number of days for intensive care unit (ICU) hospitalisation.

DISCUSSION

Our review revealed a heterogeneous body of evidence on the healthcare resource utilisation and costs associated with genital and neonatal HSV infection, as well as some summary economic estimates and cost-effectiveness studies of HSV intervention strategies, such as use of antivirals or screening, which included unit cost data. While the evidence base provides a starting point for understanding, several gaps remain. Despite the broad search strategy and inclusion criteria, we identified only 38 papers, which shows the paucity of data on HSV-related healthcare resource utilisation as well as economic costs, especially from LMIC settings. The lack of data from LMIC is particularly concerning, as these countries bear the greatest burden of HSV infection and disease.[2 3 54] The current review only identified one cost-effectiveness analysis from a middle-income country[32] focused on people living with HIV only, and one high-level modelling study predicting costs of implementing care for HSV GUD across 117 LMIC globally.[37] In addition, many of the studies we found were relatively old and may not reflect current practices such as the use of newer diagnostics (eg, PCR test) and newer care recommendations. For example, the global study by Patrick *et al* reported that viral culture was the most common test used to diagnose HSV but this is likely because the use of PCR test was not yet common in clinical practice at the time of the study. The 2020 study in France by Heggarty *et al* reveals that PCR test is now the most commonly used test, at least in this HIC setting, with and without HSV serology.[28]

While data on resource utilisation and costing were most comprehensive from the USA, large gaps remain in many areas. For example, Gilbert *et al*[20] described the proportions of individuals seeking care for genital herpes among adults aged 18–24 from 2000 to 2006, but since then there have been no new updates. In terms of costing, we noticed similar trends, as studies[30] mostly referenced cost data collected in 2001 by Szucs *et al*.[31] This lack of data is similarly noted related to HSV infection during pregnancy. While some information from health surveys exists, healthcare resource utilisation information is rarely tracked or reported. Our search demonstrated that for most of the world, data on HSV related resource utilisation are sparse. As such, new data sources and better data collection efforts are needed to collect these standardised non-fatal data from diverse healthcare settings. One major need is an understanding of how closely clinicians follow national guidelines on HSV care and treatment, such as the studies by Kenny *et al*[26] and Heggarty *et al*[28] from Canada and France, respectively. For example, while there are structured guidelines for the workup of neonatal herpes and its related management, our review did not identify any studies that described the compliance to these guidelines. Such information can provide us with vital clues into the economic burden of neonatal HSV as there is substantial cost due to the high mortality rates neonatal HSV was not treated.

Our review was also constrained in summarising findings across studies or countries and in conducting across-study comparisons, due to the limited data and differing methodologies, healthcare settings, and practices, particularly for healthcare resource utilisation. Another concern was the heterogeneity in data presentation in many studies identified. For example, the length of hospital stay reported in studies varied considerably, with different assumptions used by authors, and as a result, the cost of hospitalisation varied significantly even within the USA, which limits the potential generalisability of these findings across different settings.[16 41 45 51] Healthcare practices also differ between LMIC and HIC with respect to how HSV is managed, for example, most HSV cases in LMICs are treated as part of syndromic management for GUD, without diagnostic testing. This may mean that additional testing costs might need to be considered for HICs, whereas additional treatment, for example, for syphilis and chancroid, which can also cause GUD syndromes, might need to be considered for LMICs. The focus on GUD more generally in LMICs may have made it more challenging to identify potentially relevant HSV-specific studies for LMIC settings.

In order to estimate the global economic burden of HSV to contribute to the understanding of the potential value of HSV interventions, research on HSV-related costs and healthcare utilisation patterns is urgently needed, especially from LMIC settings. Standardisation of methods for the measurement and reporting of economic costs would enhance across-study comparisons and inform prioritisation strategies of global funders. Only one study broadly attempted to quantify the economic burden of HSV, which the authors estimated would require a projected investment of around US$109 million from 2016 to 2021, just for the management of HSV-associated GUD, not considering service delivery costs.[37] However, this analysis only modelled treatment of HSV GUD for a small proportion of people with HSV-2 infection (approximately 4%; assuming 15% would recognise symptoms and 28% of those would seek care) and did not account for HSV recurrences within a given year. New global estimates of HSV GUD suggest this is likely an underestimate.[3] In addition, as this model lacked country-level estimates of baseline disease and did not take into account the full spectrum of disease outcomes related to HSV nor the burden on health systems, the costing estimates remain imprecise and incomplete, suggesting the need for a more comprehensive model.

This is the first systematic review of scientific literature on the healthcare resource utilisation for HSV. We conducted a comprehensive literature search and included grey literature through our focused search. Nevertheless, most studies were only conducted in HIC especially from the USA. As the practice and thus utilisation of resources

will vary between settings and countries due to epidemiological and health systems differences, this will limit the generalisability of findings. Nevertheless, results of this study will serve as a future repository for studies that wish to examine the economic evaluations of any public health interventions for HSV. This review also highlights the importance and need for more studies to describe on the healthcare resource utilisation and associated cost of HSV, especially from LMIC. We assessed study quality of all included studies, which allows readers to assess the internal validity of these studies. The literature search was also limited to studies published in English language. As data on healthcare resource utilisation may be published in government reports, or book chapters, these may not have been retrieved and included in this review, which may partly explain the lack of studies describing healthcare resource utilisation from LMIC.

CONCLUSION

This review is the first attempt and a key step towards providing data needed to understand the global economic burden of HSV infection, for both HICs and LMICs. Available economic estimates, primarily from HICs, suggest the economic burden of HSV infection could be substantial. However, the global picture remains incomplete. Nevertheless, results obtained from this study will form a repository which can inform future economic evaluations of interventions for HSV infection, including HSV vaccines, microbicides or new antiviral medications.[55] These types of economic data are crucial not only to improve the planning and development of any future HSV-related healthcare interventions, but also to optimise the allocation of healthcare expenditures and medical resources.

Twitter Shaun Wen Huey Lee @nuahSeelL

Contributors SWHL served as the lead author, conducted the research, conducted the analyses, integrated the input from all team members and drafted the initial manuscript. SLG directed the initial research and contributed to the initial draft, integrated her view points and served as an expert in this work. NC conducted the research, mediated the discussion and helped refine the draft. All authors approved the final manuscript. NC is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish

Funding This work was funded by the WHO Department of Sexual and Reproductive Health and Research, via support from the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) and the U.S. National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (U01 AI108543).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iD

Shaun Wen Huey Lee http://orcid.org/0000-0001-7361-6576

REFERENCES

1 Gupta R, Warren T, Wald A. Genital herpes. *Lancet* 2007;370:2127–37.
2 James C, Harfouche M, Welton NJ, *et al*. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. *Bull World Health Organ* 2020;98:315–29.
3 Looker KJ, Johnston C, Welton NJ, *et al*. The global and regional burden of genital ulcer disease due to herpes simplex virus: a natural history modelling study. *BMJ Glob Health* 2020;5:e001875.
4 Pinninti SG, Kimberlin DW. Maternal and neonatal herpes simplex virus infections. *Am J Perinatol* 2013;30:113–20.
5 Looker KJ, Welton NJ, Sabin KM, *et al*. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. *Lancet Infect Dis* 2020;20:240–9.
6 Gottlieb SL, Low N, Newman LM, *et al*. Toward global prevention of sexually transmitted infections (STIs): the need for STI vaccines. *Vaccine* 2014;32:1527–35.
7 Gottlieb SL, Giersing BK, Hickling J, *et al*. Meeting report: initial World Health Organization consultation on herpes simplex virus (HSV) vaccine preferred product characteristics, March 2017. *Vaccine* 2019;37:7408–18.
8 Gottlieb SL, Deal CD, Giersing B. The global roadmap for advancing development of vaccines against sexually transmitted infections: update and next steps. *Vaccine* 2016;34:2939–47.
9 Freeman EE, White RG, Bakker R, *et al*. Population-level effect of potential HSV2 prophylactic vaccines on HIV incidence in sub-Saharan Africa. *Vaccine* 2009;27:940–6.
10 Belshe RB, Heineman TC, Bernstein DI, *et al*. Correlate of immune protection against HSV-1 genital disease in vaccinated women. *J Infect Dis* 2014;209:828–36.
11 Cochrane handbook of systematic review of interventions. 6.2 ed 2021.
12 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
13 Turner HC, Lauer JA, Tran BX, *et al*. Adjusting for inflation and currency changes within health economic studies. *Value Health* 2019;22:1026–32.
14 The World Bank. GDP deflator: linked series (annual %) 2019, 2019. Available: https://data.worldbank.org/indicator/NY.GDP.DEFL.KD.ZG.AD [Accessed 25 Nov 2019].
15 Ahmad FA, Storch GA, Miller AS. Impact of an institutional guideline on the care of neonates at risk for herpes simplex virus in the emergency department. *Pediatr Emerg Care* 2017;33:396–401.
16 Bernard S, Mailles A, Stahl JP, *et al*. Epidemiology of infectious encephalitis, differences between a prospective study and hospital discharge data. *Epidemiol Infect* 2013;141:2256–68.
17 Owusu-Edusei K, Flagg EW, Gift TL. Hospitalization cost per case of neonatal herpes simplex virus infection from claims data. *J Pediatr Nurs* 2015;30:346–52.
18 Aslam M, Kropp RY, Jayaraman G, *et al*. Genital herpes in Canada: deciphering the hidden epidemic. *Can J Infect Dis Med Microbiol* 2012;23:e6–9.
19 Fisman DN. Health related quality of life in genital herpes: a pilot comparison of measures. *Sex Transm Infect* 2005;81:267–70.
20 Gilbert LK, Levandowski BA, Roberts CM. Characteristics associated with genital herpes testing among young adults: assessing factors from two national data sets. *J Am Coll Health* 2010;59:143–50.
21 Patrick DM, Rosenthal SL, Stanberry LR, *et al*. Patient satisfaction with care for genital herpes: insights from a global survey. *Sex Transm Infect* 2004;80:192–7.

22 Tao G, Kassler WJ, Rein DB. Medical care expenditures for genital herpes in the United States. *Sex Transm Dis* 2000;27:32–8.
23 Brocklehurst P, Carney O, Ross E, *et al*. The management of recurrent genital herpes infection in pregnancy: a postal survey of obstetric practice. *Br J Obstet Gynaecol* 1995;102:791–7.
24 Lynn N, Murphy S, Cunningham O. HSV management in pregnancy at a joint antenatal-genitourinary clinic in a large maternity hospital in Dublin, Ireland-a model of care. *Sexual Transmit Infect* 2017;93:A91.
25 Stankiewicz Karita HC, Moss NJ, Laschansky E, *et al*. Invasive obstetric procedures and cesarean sections in women with known herpes simplex virus status during pregnancy. *Open Forum Infect Dis* 2017;4:ofx248.
26 Kenny K, Leung W, Stephanson K, *et al*. Clinical practice in prevention of neonatal HSV infection: a survey of obstetrical care providers in Alberta. *J Obstet Gynaecol Can* 2013;35:131–7.
27 Brown ZA, Wald A, Morrow RA, *et al*. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003;289:203–9.
28 Heggarty E, Sibiude J, Mandelbrot L, *et al*. Genital herpes and pregnancy: evaluating practices and knowledge of French health care providers. *Eur J Obstet Gynecol Reprod Biol* 2020;249:84–91.
29 Barnabas RV, Carabin H, Garnett GP. The potential role of suppressive therapy for sex partners in the prevention of neonatal herpes: a health economic analysis. *Sex Transm Infect* 2002;78:425–9.
30 Owusu-Edusei K, Chesson HW, Gift TL, *et al*. The estimated direct medical cost of selected sexually transmitted infections in the United States, 2008. *Sex Transm Dis* 2013b;40:197–201.
31 Szucs TD, Berger K, Fisman DN, *et al*. The estimated economic burden of genital herpes in the United States. An analysis using two costing approaches. *BMC Infect Dis* 2001;1:5.
32 Vickerman P, Devine A, Foss AM, *et al*. The cost-effectiveness of herpes simplex virus-2 suppressive therapy with daily aciclovir for delaying HIV disease progression among HIV-1-infected women in South Africa. *Sex Transm Dis* 2011;38:401–9.
33 Vickerman P, Ndowa F, Mayaud P. Cost-effectiveness of incorporating episodic treatment for herpes simplex virus type-2 (HSV-2) into the syndromic algorithm for genital ulcer disease. *Sex Transmitt Infect* 2008;84:243–8.
34 Owusu-Edusei K, Nguyen HT, Gift TL. Utilization and cost of diagnostic methods for sexually transmitted infection screening among insured American youth, 2008. *Sex Transm Dis* 2013a;40:354–61.
35 Scott LL, Alexander J. Cost-effectiveness of acyclovir suppression to prevent recurrent genital herpes in term pregnancy. *Am J Perinatol* 1998;15:57–62.
36 Tuite AR, McCabe CJ, Ku J, *et al*. Projected cost-savings with herpes simplex virus screening in pregnancy: towards a new screening paradigm. *Sex Transm Infect* 2011;87:141–8.
37 Korenromp EL, Wi T, Resch S, *et al*. Costing of national STI program implementation for the global STI control strategy for the health sector, 2016-2021. *PLoS One* 2017;12:e0170773.
38 Fisman DN, Lipsitch M, Hook EW, *et al*. Projection of the future dimensions and costs of the genital herpes simplex type 2 epidemic in the United States. *Sex Transm Dis* 2002;29:608–22.
39 Almonte-Vega L, Colón-Vargas M, Luna-Jarrín L, *et al*. Cost analysis of treatment strategies for the control of HSV-2 infection in the U.S.: a mathematical modeling-based case study. *Math Biosci* 2020;324:108347.
40 Di Xia F, Fuhlbrigge M, Dommasch E, *et al*. Cost of routine herpes simplex virus infection visits to U.S. emergency departments 2006-2013. *West J Emerg Med* 2018;19:689–92.
41 Ambroggio L, Lorch SA, Mohamad Z, *et al*. Congenital anomalies and resource utilization in neonates infected with herpes simplex virus. *Sex Transm Dis* 2009;36:680.
42 Baker D, Brown Z, Hollier LM, *et al*. Cost-effectiveness of herpes simplex virus type 2 serologic testing and antiviral therapy in pregnancy. *Am J Obstet Gynecol* 2004;191:2074–84.
43 Binkin NJ, Koplan JP. The high cost and low efficacy of weekly viral cultures for pregnant women with recurrent genital herpes: a reappraisal. *Med Decis Making* 1989;9:225–30.
44 DesHarnais S, Simpson KN, Paul JE. Variations in practice patterns: antiviral drug use in hospitalized patients with herpes infections. *Am J Med Qual* 1996;11:33–42.
45 Donda K, Sharma M, Amponsah JK, *et al*. Trends in the incidence, mortality, and cost of neonatal herpes simplex virus hospitalizations in the United States from 2003 to 2014. *J Perinatol* 2019;39:697–707.
46 Little SE, Caughey AB. Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: a cost-effectiveness analysis. *Am J Obstet Gynecol* 2005;193:1274–9.
47 Randolph AG, Hartshorn RM, Washington AE. Acyclovir prophylaxis in late pregnancy to prevent neonatal herpes: a cost-effectiveness analysis. *Obstet Gynecol* 1996;88:603–10.
48 Rouse DJ, Stringer JS. An appraisal of screening for maternal type-specific herpes simplex virus antibodies to prevent neonatal herpes. *Am J Obstet Gynecol* 2000;183:400–6.
49 Thung SF, Grobman WA. The cost-effectiveness of routine antenatal screening for maternal herpes simplex virus-1 and -2 antibodies. *Am J Obstet Gynecol* 2005;192:483–8.
50 Mahant S, Hall M, Schondelmeyer AC, *et al*. Neonatal herpes simplex virus infection among Medicaid-enrolled children: 2009-2015. *Pediatrics* 2019;143:e20183233.
51 Flagg EW, Weinstock H. Incidence of neonatal herpes simplex virus infections in the United States, 2006. *Pediatrics* 2011;127:e1–8.
52 Fisman DN, Hook EW, Goldie SJ. Estimating the costs and benefits of screening monogamous, heterosexual couples for unrecognised infection with herpes simplex virus type 2. *Sex Transm Infect* 2003;79:45–52.
53 Waitzman NJ, Romano PS, Scheffler RM. Estimates of the economic costs of birth defects. *Inquiry* 1994;31:188–205.
54 Looker KJ, Elmes JAR, Gottlieb SL, *et al*. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. *Lancet Infect Dis* 2017;17:1303–16.
55 Gottlieb SL, Deal CD, Giersing B, *et al*. The global roadmap for advancing development of vaccines against sexually transmitted infections: update and next steps. *Vaccine* 2016;34:2939–47.

APPENDIX

TABLE OF CONTENTS

Search methodology 2

Text 1: Keyword terms used in the search..... 3

Text 2: Keywords used in focused search using exploding terms..... 4

Table 1: Summary of included studies reporting healthcare costs and/or resource utilization related to HSV infection..... 5

Table 2: Detailed description of studies reporting cost (unit cost) 13

Table 3: Detailed description of studies reporting resource utilization 19

Table 4: Detailed cost incurred in genito-ulcer diseases due to HSV 22

Table 5: Detailed cost associated with genitoulcer disease prevention in people living with HIV 25

Table 6: Detailed cost associated with neonatal herpes prevention/management..... 26

Figure 1: Methodological quality of included economic studies using CHEC Checklist..... 30

Figure 2: Methodological quality of included costing studies using Larg and Moss Checklist ... 31

Search methodology

1. Search strategy

- The current search strategy was developed based upon keywords which have been used in previous existing HSV reviews commissioned by WHO. All search keywords used were subsequently cross-checked with the following articles to ensure comprehensiveness

    - Looker, 2017. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis
    - Khard, 2019. The Epidemiology of Herpes Simplex Virus Type 1 in Asia: Systematic Review, Meta-analyses, and Meta-regressions
    - Looker,2012. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One 2015;10(1) : e114989-e89. Doi: 10.1371/journal.pone. 0114989

- The following databases were identified for the search including: PubMed, PsychINFO, EMBASE, Centre for Review and Dissemination, EconLit, CEA registry and WHO Library Database (WHOLIS)

2. **Keywords search** was revised to compare between a) search including exploding terms and b) search including title and abstract. A total of 10,113 articles was found for search when terms were exploded versus 5,966 when these terms were not exploded. As such, the methods will only use search including exploding terms to minimize the risk of missing relevant study despite its low specificity. The initial search was performed in April 2019, with an updated search in October 2019.

3. Neonate search

- We also conducted search over again using all relevant HSV terms with neonate as keyword. All articles identified in the search overlapped with existing broader search, thereby there is no need to add neonate as key words

Text 1: Keyword terms used in the search

No.	Keyword
#1	Genital ulcer disease.mp.
#2	Herpes labialis.mp.
#3	Herpes genitalis.mp.
#4	Genital herpes.mp.
#5	Herpesvirus.mp.
#6	Herpes virus.mp.
#7	HSV.mp.
#8	Herpes simplex.mp.
#9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
#10	Healthcare util*ation.mp.
#11	Util*ation.mp.
#12	Physician visit.mp.
#13	General practitioner visit.mp.
#14	Hospital visit.mp.
#15	Clinic visit.mp.
#16	Hospital stay.mp.
#17	Hospitali*ation.mp.
#18	Hospital readmission.mp.
#19	Cost.mp.
#20	Cost-effectiveness.mp.
#21	Cost-utility.mp.
#22	Cost-benefit.mp.
#23	Cost-minimi*ation.mp.
#24	Counselling.mp.
#25	Seek care.mp.
#26	Behavio*r.mp.
#27	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
#28	9 and 27

Text 2: Keywords used in focused search using exploding terms.

No.	Keyword
#1	Genital ulcer disease.mp.
#2	Herpes labialis.mp.
#3	Herpes genitalis.mp.
#4	Genital herpes.mp.
#5	Herpesvirus.mp.
#6	Herpes virus.mp.
#7	HSV.mp.
#8	Herpes simplex.mp.
#9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
#10	pregnancy.mp.
#11	pregnant.mp.
#12	c*esarean.mp.
#13	delivery.mp.
#14	10 or 11
#15	12 or 13
#16	9 AND 14 AND 15

Table 1: Summary of included studies reporting healthcare costs and/or resource utilization related to HSV infection

Author, year Country	Population and setting	Study design	Study objective	Sample size	HSV-subtype		Cost data		Healthcare resource utilization	
					1	2	Healthcare delivery process	Treatment	Healthcare delivery process	Treatment
HSV genital ulcer disease among adults/adolescents										
Almonte-Vega, 2020 USA[39]	General population aged 15-49 years old	Cost-analysis	To study the dynamics of HSV–2 transmission, control and impact of treatment policies	-		x		x		
Aslam, 2012 Canada[18]	Records of individuals in the Canadian Disease and Therapeutic Index (CDTI)	Retrospective study	To investigate the rates of diagnosed cases of GH in Canada from 2002 to 2007	652					x	
Desharnais, 1996 USA[44]	Adults with herpes diagnosis from the HCIA Clinical Pathways Data Base	Retrospective study	To describe patterns of antiviral drug use for patients hospitalized with chickenpox, herpes simplex, and herpes zoster infections, and also for a subgroup of herpes patients with severe infections (systemic infections, eye infections, encephalitis, hemorrhagic pneumonitis, and other severe conditions)	3011	x	x		x		x
Fisman, 2002 USA[38]	Individuals aged 15 to 39 years	Cost-effectiveness	To project the future burden of HSV-2 infection in the United States, using a	-		x	x	x		

			mathematical model that incorporated epidemiologic trends documented between 1976 and 1994							
Fisman, 2003 USA[52]	Heterosexual couples	Modelling study	To evaluate the projected cost effectiveness of strategies to prevent HSV-2 transmission in couples with no history of HSV-2 infection	-		x		x		
Fisman, 2005 Canada[19]	Individuals with recurrent genital ulcer	Prospective study	To estimate the impact on health-related quality of life associated with both symptomatic and asymptomatic GH	39	x	x				x
Gilbert, 2010 USA[20]	Young adults	Retrospective study	To investigate characteristics associated with GH screening and diagnosis in sexually active young adults aged 18 to 24	Add Health Data: 11,570 NCHA: 222,740	x	x			x	
Korenromp, 2017[37]	People 15-49 year old living with HSV-2	Modelling study	To estimate the costs of reaching the 2020 STI strategy milestones for the period 2016–2021, to support policy, planning, implementation, and future cost-benefit evaluation of the global STI strategy 2016–2021.	-		x	x	x		
Owusu-Edusei, 2013a USA[34]	People aged 15-25 years	Retrospective study	To examine the utilization and cost of the diagnostic methods used for STI screening among	-		x	x			

			privately insured adolescent and young adult population							
Owusu-Edusei, 2013b USA[30]	-	Cost of illness analysis	To update the estimates of lifetime direct medical cost for 8 major STI	-				x		
Patrick, 2004 Worldwide survey from 78 countries[21]	Subjects with genital herpes	Survey	To describe patient experiences and views regarding genital herpes management	2075	x	x			x	x
Szucs, 2001 USA[31]	General population	Economic analysis	To estimate the economic burden of GH in the USA, using two different costing approaches	465,075			x	x		
Tao, 2000 USA[22]	General population	Cost-of-illness analysis	To assess the US direct medical expenditures for genital herpes and its complications to assist policy makers in allocating limited STD resources efficiently	-		x			x	
Vickerman, 2008 UK[33]	-	Cost-effectiveness	To compare the cost per ulcer treated of using the 1994 and 2003 algorithms amongst individuals presenting with GUD	-		x		x		
Vickerman, 2011 South Africa[32]	HIV+ women	Cost-effectiveness	To estimate the cost-effectiveness of daily acyclovir for delaying HIV-1 disease progression in women not eligible for antiretroviral therapy (ART)	300		x		x		

Xia, 2018 United States[40]	General population	Retrospective study	To determine the utilization and cost burden associated with HSV infection visits to U.S. EDs in recent years from 2006-2013	704,728			x		x	
Neonatal herpes prevention among pregnant women										
Baker, 2004 USA[42]	-	Cost-effectiveness	To determine whether serologic testing for herpes simplex virus type 2 (HSV-2) in pregnant women and their partners is cost-effective	100,000		x		x	x	x
Barnabas, 2002[29] USA	-	Cost-effectiveness	To assess the potential effectiveness, cost effectiveness, and benefit of suppressive therapy among herpes simplex virus serodiscordant sex partners during pregnancy		x	x	x	x		
Binkin, 1989 USA[43]	Pregnant women with HSV	Cost-effectiveness	To present a reanalysis of the cost effectiveness of maternal herpes screening and a review of the changes that have occurred in the screening recommendations since 1980	3,600,000	x	x	x	x	x	
Brocklehurst, 1995 UK[23]	All members and Fellows of the Royal College of Obstetricians and Gynaecologist resident	Survey	To determine the clinical practice among obstetricians in the antepartum and intrapartum management of women with recurrent genital herpes infection	2252	x	x			x	x
Brown, 2003 USA[27]	Pregnant women from university,	Cohort study	To determine the effects of viral shedding, maternal HSV	58362	x	x				x

	army and community hospitals		serological status and delivery route on risk of transmission of HSV from mother to infant							
Heggarty, 2020 France[28]	Healthcare providers for pregnant women	Survey	To evaluate health care provider knowledge, and collect information on management of genital herpes during pregnancy and infants born to mothers with herpes	354	x	x			x	x
Kenny, 2013 Canada[26]	Obstetrician, gynaecologist and family physicians offering maternity care practicing in Alberta	Survey	To identify the practice patterns of physicians providing prenatal care in Alberta with respect to prevention of neonatal HSV infection, including their prescribing of antiviral therapy to pregnant women in the third trimester.	183	x	x			x	x
Little, 2005 USA[46]	Women with a history of diagnosed genital HSV	Cost-effectiveness	To determine the clinical benefits and cost-effectiveness of prophylactic acyclovir in women with a history of HSV but no recurrence during pregnancy	-	x	x		x		x
Lynn, 2017 Ireland[24]	Pregnant women with genital HSV from a university hospital	Antenatal chart review	To describe the HSV management in pregnancy at a joint antenatal genital maternity hospital	107	x	x			x	x
Randolph, 1996 USA[47]	Antenatal women with recurrent genital HSV	Cost-effectiveness	To compare the cost-effectiveness of oral acyclovir prophylaxis in late pregnancy compared to caesarean delivery for genital herpes	10,000			x	x		

			lesions in the prevention of neonatal herpes transmission from mothers with recurrent genital infections							
Rouse, 2000 USA[48]	Antenatal women	Cost-effectiveness	To evaluate the potential cost effectiveness of herpes simplex virus antibody screening	8,538	x	x	x	x	x	
Scott, 1998 USA[35]	-	Cost-effectiveness	To determine whether acyclovir suppression provides a greater cost savings over no medical therapy in the management of recurrent genital herpes (HSV) in pregnancy	-	x	x	x	x		
Stankiewicz Karita, 2017 USA[25]	Pregnant women from a hospital	Retrospective study	To investigate the frequency of invasive obstetric procedures and caesarean deliveries for women with known HSV infection	449		x			x	
Thung, 2005 USA[49]	Married women	Cost-effectiveness	To determine the cost-effectiveness of routine antenatal screening for HSV-1 and HSV-2 in women without a known history of genital herpes.	100,000	x	x		x		
Tuite, 2010 Canada[36]	Pregnant women	Cost-effectiveness	To assess the effectiveness and cost effectiveness of identifying pregnant women at risk of de novo HSV acquisition to prevent vertical HSV transmission	100,000	x	x	x	x		

Neonatal herpes management										
Ahmad, 2015 USA[15]	Neonates who sought care in emergency department	Retrospective study	To evaluate whether guideline implementation affected the ED's decision to test for HSV, ED use of HSV polymerase chain reaction (PCR) and acyclovir	308	x	x				x
Ambroggio, 2009 USA[41]	Neonates with HSV and received intravenous acyclovir and discharge from Paediatric Health Information System	Retrospective study	To quantify the economic burden of neonatal HSV during initial hospitalization while focusing on factors, such as congenital anomalies and HSV-associated complications, which increase hospital charges and length of hospital stay among neonates with HSV	406	x	x		x		x
Bernard, 2013 France[16]	Patients aged 28 days and above from the French national hospital discharge database	Prospective study	To compare the data from the French national hospital discharge database (Programme de Me´ dicalisation des Syste` mes d'Information; PMSI) and from the prospective study conducted in 2007 and evaluate the reliability of PMSI as a tool to assess the trends of encephalitis in France	1,947	x	x				x
Donda, 2019 USA[45]	Neonates with ICD-9 codes for neonatal HSV in the National	Retrospective study	To examine the temporal trends in the incidence and outcomes of neonatal HSV in the United States	42,726, 336				x		x

	Inpatient Sample from 2003-2014									
Flagg, 2011 USA[51]	Inpatient records of infants aged 60 days or younger from the Healthcare Cost and Utilization Project Kids' Inpatient Database	Retrospective study	To estimate the incidence of HSV infections for the United States during 2006, as well as demographic-specific rates, by using nationally and regionally weighted estimates from a population-based sample of inpatient data	4,106,488	x	x		x		x
Mahant, 2019 USA[50]	Records of neonates from the Medicaid claims database from 2009 - 2015	Retrospective study	To examine the incidence, mortality, and health care use related to neonatal herpes HSV infection.	2,107,124				x		x
Owusu-Edusei, 2015 USA[17]	Insurance claim data on inpatient admission from the Truven Health Analytics MarketScan Commercial Claims and Encounters Database	Cost-of-illness analysis	To estimate the average excess inpatient cost of neonatal herpes simplex virus (NHSV) infection from 2005 to 2009 insurance claims data	474,743	x	x				x

Table 2: Detailed description of studies reporting cost (unit cost)

Author, year Country	Population and setting	Diagnostic costs (range)	Treatment costs* in original year of value (range)	Hospitalisation costs (range)	Other healthcare delivery costs (range)	Lifetime management cost (range)
Genital ulcer disease among adults/adolescents						
Almonte-Vega, 2020 USA[39]	General population aged 15-49 years old	Microbiological lab test (unspecified): $80.17	Acyclovir treatment (duration not specified): $86.33	NR	Consultation, clinical examination and diagnostic: $161.85	NR
Desharnais, 1996[44]	Adults with herpes diagnosis identified from the HCIA database	NR	Total drug charges: $1941 Antiviral drug charges (not specified): $1070	Hospital charges: $5637	NR	NR
Fisman, 2002[38]	Individuals aged 15 to 39 years	NR	Cost of treatment for primary syndrome Male: $470 ($370-5$60) Female: $830 ($670-$1000) Antiviral therapy Relapse: $17 ($9-$36) Monthly suppressive therapy: $40 ($20-$220)	NR	Clinic visit: $120 ($90-$150) Obstetrical care: $310 ($130-$800)	Initial cost of caring for neonates with HSV: $42,600 Lifetime medical and long-term care cost for infants with moderate neurological sequalae: $97,000 Lifetime medical and long-term care cost for infants with severe neurological sequalae: $291,000

Fisman, 2003[52]	Heterosexual couples	Western blot: $60 ($45-$90) ELISA: $5 ($3-$35)	Cost of treatment for primary syndrome Male: $450 ($360-5$40) Female: $800 ($640-$960) Acyclovir (per episode): $16 ($9-$35) Acyclovir (monthly suppressive): $40 ($20-$215)	NR	Clinic visit: $120 ($90-$145) Labour: $120 ($90-$145)	Lifetime cost of care of neonatal HSV-2: $110,000 ($85,000-$860,000)
Korenromp, 2017[37]	People 15-49 year old living with HSV-2	NR	Acyclovir 400mg per tab: $0.04	NR	Treatment service delivery (not specified): $10 Procurement cost: $0.21	NR
Owusu-Edusei, 2013a[34]	People aged 15-25 years	Laboratory test (unspecified): $24.30-27.05	NR	NR	NR	NR
Owusu-Edusei, 2013b[30]	-	NR	NR	NR	NR	Lifetime medical cost per case, median(range): Men: $761 (381-1,142) Women: $621(311 - 932) Lifetime cost of new infections acquired in 2008: $435.9 million

Szucs, 2001[31]	General population	Laboratory test: $1.5-76.50	Drug: $64-131	Hospitalisation: $669	Labour: $39.8 -62.6 Clinic visit: $36.20-73 Day off work: $144	NR
Vickerman, 2008[33]	-	NR	Acyclovir 200mg tds for 5 days: $0.53- 5.24	NR	Counselling cost: $0.28	NR
Vickerman, 2011[32]	HIV+ women	NR	Acyclovir 400mg: $0.07 Yearly ART cost: $1700 (1359-2000)	NR	Staff costs/women 3m treatment cycle: $15.60	NR
Xia, 2018[40]	General population	NR	NR	ED: $1,069		
Neonatal herpes prevention among pregnant mothers						
Baker, 2004[42]	-	Laboratory test with labor cost for HSV-2: 15.58 – 60.00	Average antiviral daily cost (assuming 50% on generic acyclovir 400mg tds and 50% on valacylovir qd): $1.70-7.90 Acyclovir 400mg: $0.366- 1.955 Valacyclovir 500mg/tab: $3.95 Valacyclovir 1g/tab: $6.49	Delivery: $4,779-22,838	Labour cost: $15.58 – $60 Counselling cost: $5.98-$6.67	Lifetime cost of care of neonatal HSV: $54,516- $129,576

Barnabas, 2002[29]	-	Diagnostic cost: $16-$100	Drug cost per couple per pregnancy: $37 Acute neonatal herpes treatment $1,500-50,000	C/S cost (personnel, supplies, surgery and ward care): $11,084	Labour cost: $200-1628 Counselling cost: $12-$19	Neonatal care after C/S: $884 Long term care for neonatal herpes: $140,766 - $273,712
Binkin, 1989[43]	Pregnant women with HSV	Viral culture: $30	NR	Hospitalisation for complication: $300-698 Hospital care associated with neonatal herpes: $25,000 Delivery: $2,300-3,600	NR	Long term care for neonatal herpes: $125,000-$250,000
Little, 2005[46]	Women with a history of diagnosed genital HSV	NR	Acyclovir (prophylaxis) from 36 weeks of gestation: $46	Delivery: $4,939-9,490 Hospitalisation: $32,483	NR	Lifetime cost of care of neonatal HSV: $349,7533-$1,049,260
Randolph, 1996[47]	Antenatal women with recurrent genital HSV	Laboratory: $35	Acyclovir 400mg (200caps): $228	Delivery: $3,500	Labour: $74	Lifetime cost of care of neonatal HSV: $85,000- 255,000
Rouse, 2000[48]	Antenatal women	Laboratory: $4 – 13	NR	Hospitalisation for neonatal care: $11,126	Labour: $3.50-10.50	Lifetime cost of care of neonatal HSV: $48,519- 163,879
Scott, 1998[35]	-	HSV culture: $80	Acyclovir 400mg tds for 4 weeks: $180	Hospitalisation for neonatal care: $480-1470 Delivery: $5,321 – 9,039	NR	NR

Thung, 2005[49]	Married women	HSV screening: $37.5-$75	Acyclovir 400mg tds for 4 weeks: $71	Delivery: $4,281 - 9,283	Counselling cost: $13	Lifetime cost of care of neonatal HSV: $13,202 – 325,602
Tuite, 2010[36]	Pregnant women	ELISA test: $7-$14	NR	Delivery: $5680- 8780	NR	Lifetime cost and consequence of neonatal HSV: $164,870
Neonatal herpes management						
Ambroggio, 2009[41]	Neonates with HSV and received intravenous acyclovir and discharge from Paediatric Health Information System	NR	Median pharmaceutical (not specified): $4,231 Median Imaging: $2,010	Median hospital charge: $37,431	NR	NR
Donda, 2019[45]	Patients aged 28 days and above from the French national hospital discharge database	NR	NR	Hospitalisation: $27,843	NR	NR
Flagg, 2011[51]	Neonates with ICD-9 codes for neonatal HSV	NR	NR	Hospitalisation: $92,664	NR	NR

	in the National Inpatient Sample from 2003-2014					
Mahant, 2019[50]	Records of neonates from the Medicaid claims database from 2009 - 2015	NR	NR	Hospitalisation: $32,683 Hospital readmission: $31,531 ED visit: $527	NR	NR

*All costs are mean costs except where explicitly labelled as median costs.

C/S – Caesarean section; ED - Emergency department; NR – Not reported

Table 3: Detailed description of studies reporting resource utilization

Author, year	Healthcare seeking and diagnosis	Treatment phase
Genital ulcer disease among adults/adolescents		
Aslam, 2012[18]	• 74.1-93.2% sought care once within 12 months • 6.8-25.9% sought care twice to 8x a year	
Desharnais, 1996[44]		• Oral treatment only: 16.1% • IV treatment: 16.2% • Hospital stay: 5.4 days
Fisman, 2005[19]		• 33.3% used antiviral drugs for HSV • 15.8% had pregnancy complicated by HSV
Gilbert, 2010[20]	• 1.32% of young adults ever tested for genital herpes	
Patrick, 2004[21]	• 49% had viral culture performed • 9% had antibody test • 34% had physical examination	• 65% received oral antiviral therapy • 18% received topical antiviral therapy • 17% obtained alternative therapy
Tao, 2000[22]	• Estimated annual genital herpes visit 499,655 yearly • 2% were inpatient visit • 9% outpatient & ED visit • 20% public STD clinic • 69% private office based visit	
Xia, 2018[40]	From 2006-2013 • 245,484 ED visits with primary diagnosis of genital herpes or 37.3% of total ED visits for HSV • Total charges: $278,335,295 ED visits trend from 2006 – 2013 • 24,747 (33.8%); 26,440 (34.1%); 27,484 (36.1%), 28,440 (36.5%); 33,258 (37.8%); 33,095 (38.3%); 35,501 (40.0%); 36,518 (40.3%)	
Neonatal herpes prevention among pregnant mothers		
Baker, 2004[42]	Estimates used in model • 75% of partners will be willing to undergo HSV screening	Estimates used in model • 1.32% women HSV-2 negative acquiring HSV during last 8 weeks of pregnancy • 57% women or partner offered and accept antiviral therapy with testing

		• 82% women taking antivirals from week 36 compliant
Binkin, 1989[43]	Estimates used in model • Average number of cultures per patient: 8	
Brocklehurst, 1995[23]	• 60% of obstetricians advocated some form of antenatal screening Among those performing screening • 64% perform regular viral cultures • 54% recommend screening ≤34 weeks of gestation	• 92% of providers: visible active lesions at labor are cause for caesarean delivery
Brown, 2003[27]		• All women with HSV genital lesions noted at delivery had caesarean delivery (n=60) unless lesions not noted until too late to proceed with caesarean or lesions noted after delivery (n=14)
Heggarty, 2020[28]	For suspected primary genital HSV: ▪ 43.3% would conduct PCR of lesions plus HSV serology ▪ 39.9% would conduct PCR of lesions alone ▪ 0.4% would conduct HSV serology only	• If primary HSV GUD during pregnancy, 68.4% "always" and 11.6% "often" prescribe antiviral prophylaxis in 3rd trimester • If recurrent HSV GUD during pregnancy, 55.1% "always" and 12.9% "often" prescribe antiviral prophylaxis in 3rd trimester • 83% recommend caesarean delivery if genital HSV lesions suspected during labour
Kenny, 2013[26]	• 30% physicians will perform type-specific serology "most of the time" for patients with no history of herpes but partner with known HSV	• Antiviral suppressive therapy prescribed in third trimester by 90% of doctors (97% of obstetricians and 84% family physicians) ▪ 62% prescribed for any past history of GUD including pre-pregnancy ▪ 28% only after outbreak during pregnancy ▪ More commonly prescribed acyclovir (63%) than valacyclovir (38%) • 65% offer elective caesarean if primary HSV in third trimester • 95% of obstetricians and 84% of family physicians recommend caesarean delivery if HSV lesions during labour
Little, 2005[46]		Estimates used in model • 24% of women will undergo caesarean delivery if no lesion was present

Lynn, 2017[24]	• 89% of patients had type-specific serology sent	• 63% received antiviral prophylaxis ▪ 98.5% received valacyclovir ▪ 1.5% received acyclovir ▪ Mean for initiating: week 36 • 29% of patients underwent caesarean delivery, none for HSV
Rouse, 2000[48]	Estimates used in model • 75% of partners will be willing to undergo HSV screening	
Stankiewicz Karita, 2017[25]		• Antiviral suppressive therapy: ▪ 55% HSV-2 antibody-positive only ▪ 65% history of symptomatic GUD • Similar caesarean section rates for women with/without history of HSV/genital herpes: ▪ 25% without history of HSV-2/GH ▪ 30% on suppressive treatment • 28% without suppressive treatment
Neonatal herpes management		
Ahmad, 2015[15]	• CSF PCR performed in 92.3% • Blood PCR performed in 48.7%	• 9.4 – 9.8% require ICU stay • Hospital stay: 83.1-84.6hr • 71.8% received acyclovir
Ambroggio, 2009[41]		• Median length of stay: 13 days (IQR 4-21)
Bernard, 2013[16]		• Mean hospital admission: 28 -34 days
Donda, 2019[45]		• Median length of stay: 20
Flagg, 2011[51]		• Mean length of stay: 22 days • Median length of stay: 2- days
Mahant, 2019[50]		• Median hospital stay: 18 days • Post discharge, ○ 45.7% required ED visit ○ 16.2% required rehospitalisation
Owusu-Edusei, 2015[17]		• Mean hospital stay: 10.8 (11.5) • Mean hospital stay among those with admission >7 days: 18.5 (12.5)

Table 4: Detailed cost incurred in genito-ulcer diseases due to HSV

Author,year	Outcomes	Unit cost ($) in original year	Unit cost in 2018 ($)
Medication costs			
Vickerman, 2008	One dose of IV benzathine penicillin 2.4MU	0.15 - 0.48	0.19-0.59
Vickerman, 2008	One tab of 500mg ciprofloxacin	0.10 - 0.21	0.12 - 0.26
Vickerman, 2008	One cap of 200mg acyclovir	0.53- 5.24	0.66 – 6.48
Fisman, 2003	Acyclovir therapy for relapse patients	16.00	22.72
Fisman, 2003	Acyclovir cost for suppressive monthly therapy	40.00	56.80
Almonte-Vega, 2020	Acyclovir therapy	86.33	86.33
Fisman, 2003	Condom cost	0.10	0.14
Szucs, 2001	Pharmacological treatment 1st episode (NS)	64.00	94.86
Szucs, 2001	Pharmacological treatment recurrent episode (NS)	131.00	194.18
Vickerman, 2008	Needle and syringe cost	0.15	0.19
Tao, 2000	Pharmacy claim	52.00	73.84
Laboratory test			
Szucs, 2001	Antibiotic testing based on expert opinion	76.50	113.39
Szucs, 2001	Antibiotic testing in first episode based on claims	12.80	18.97
Szucs, 2001	Antibiotic testing in subsequent episode based on claims	6.50	9.63
Szucs, 2001	Complete blood count based on expert opinion	21.29	31.56
Szucs, 2001	Complete blood count in first episode based on claims	4.60	6.82
Szucs, 2001	Complete blood count in subsequent episode based on claims	1.50	2.22
Szucs, 2001	Microbiological test for first GUD episode	17.60	26.09
Szucs, 2001	Microbiological test for subsequent GUD episode	6.70	9.93
Szucs, 2001	Microbiological test based on expert opinion	38.39	56.90
Almonte-Vega, 2020	Microbiological lab test	80.17	80.17

Fisman, 2003	Western blot	60.00	85.20
Szucs, 2001	Urine analysis based on expert opinion	12.59	18.66
Szucs, 2001	Urine analysis in first episode based on claims	4.60	6.82
Szucs, 2001	Urine analysis in subsequent episode based on claims	3.20	4.74
Hospitalisation cost			
Fisman, 2003	Excess obstetrical cost associated with history of symptomatic HSV2 infection	300.00	425.98
Fisman, 2003	Excess obstetrical cost due to symptomatic HSV2 infection	310.00	440.18
Tao, 2000	Inpatient cost	2,530.00	3592.46
Szucs, 2001	Hospital day	669.00	991.63
Clinic visit			
Fisman, 2003	Clinic visit related to GUD (for physician time, test, lost wages due to 2hr patient time)	120.00	170.39
Szucs, 2001	Clinical examination based on expert opinion	40.33	59.78
Szucs, 2001	Clinical examination first episode based on claims	39.80	58.99
Szucs, 2001	Clinical examination on subsequent episode based on claims	36.20	53.66
Szucs, 2001	Physician consultation based on expert opinion	73.00	108.21
Szucs, 2001	Physician consultation in first episode based on claims	62.60	92.79
Szucs, 2001	Physician consultation in subsequent episode based on claims	59.60	88.34
Tao, 2000	Outpatient and ED	59.00	83.78
Fisman, 2003	Outpatient visit	120.00	170.39
Tao, 2000	Office based physician and public clinic	67.00	95.14
Almonte-Vega, 2020	Consultation, clinical examination and diagnostic	161.85	161.85
Vickerman, 2008	Counselling cost	0.28	0.35
Other costs			
Szucs, 2001	Others miscellaneous cost related to first GUD episode(not reported)	33.00	48.91

Szucs, 2001	Others miscellaneous cost related to recurrent GUD episode(not reported)	12.30	18.23
Szucs, 2001	Production losses	60.00	88.94
Szucs, 2001	Total cost of active GUD	355.00	526.20
Szucs, 2001	Total cost of incident GUD	235.00	348.33
Szucs, 2001	Total cost of prevalent GUD	166.00	246.06
Szucs, 2001	Total cost of recurrent GUD	499.00	739.65
Fisman, 2003	Treatment cost for men assuming 2 clinic visit, 7 day course of acyclovir (400mg tds) and 2 days off work	450.00	638.97
Fisman, 2003	Treatment cost for women assuming 2 clinic visit, 7 day course of acyclovir (400mg tds) and 2 days off work	800.00	1135.95

Table 5: Detailed cost associated with genitoulcer disease prevention in people living with HIV

Author, year	Outcomes	Unit cost ($) in original year	Unit cost in 2018 ($)
Vickerman, 2011	Acyclovir 400mg	0.07	0.07
Vickerman, 2011	Staff cost- for default tracer over 3 months	24.00	22.32
Vickerman, 2011	Staff cost for training for STI diagnosis and default tracer	0.46	0.43
Vickerman, 2011	Labour cost for senior nurse	2.52	2.34
Vickerman, 2011	Counselling cost (10 mins)	0.88	0.82
Vickerman, 2011	CD-4 count test	7.90	7.35

NB- Cost reported after adjustment in 2017 were lower than those in the original study due to exchange rates at the time of study.

Table 6: Detailed cost associated with neonatal herpes prevention/management

Author,year	Outcomes	Unit cost (USD$)	Unit cost in 2017 ($)
Medication costs			
Randolph, 1996	One cap of acyclovir 400mg	1.14	1.72
Baker, 2004	Pharmaceutical cost for pregnant women	6.18	8.10
Baker, 2004	Pharmaceutical cost for partner	3.93	5.15
Baker, 2004	Valacyclovir 500mg	3.95	5.18
Baker, 2004	Valacyclovir 1000mg	6.49	8.51
Baker, 2004	Acyclovir 400mg	1.96	2.57
Barnabas, 2002	Acyclovir treatment for a couple for one pregnancy	37.00	51.37
Scott, 1998	Acyclovir 400mg	1.71	2.58
Laboratory test			
Randolph, 1996	Screening using herpes culture	35.00	52.83
Thung, 2005	HSV1 or 2 screening cost	37.50	49.15
Thung, 2005	HSV 1 and 2 screening	75.00	98.31
Rouse, 2000	HSV-2 antibody assay	4.00	5.68
Rouse, 2000	HSV-2 labour and reagent cost, QC etc	9.00	12.78
Tuite, 2010	ELISA screening for HSV	7.00	7.96
Scott, 1998	HSV culture	80.00	120.75
Baker, 2004	Labor and supplies for HSV-2 specific test	15.58	20.42
Baker, 2004	HSV test for partner	40.53	53.12
Barnabas, 2002	Diagnostic kit cost	70.00	97.18
Binkin, 1989	Viral culture	30.00	52.97
Hospitalisation cost			
Scott, 1998	Vaginal delivery with metritis, includes labour, delivery, postpartum and professional	8439.00	12,737.15

Scott, 1998	Vaginal delivery without metritis, includes labour, delivery, postpartum and professional	5,321.00	8,031.09
Ambroggio, 2009	Hospital charges	62,050.90	70,544.69
Tuite, 2010	Vaginal delivery	5,680.00	6,457.50
Little, 2005	Vaginal delivery	4,939.00	6,104.17
Randolph, 1996	Caesarean delivery over vaginal	3,500.00	5,282.62
Tuite, 2010	Caesarean section	8,780.00	9,981.84
Tao, 1999	Caesarean attributable to genital herpes	1,922.00	2729.13
Little, 2005	Caesarean delivery	9,490.00	11,728.80
Little, 2005	Caesarean delivery with lesion	7,608.00	9,402.82
Scott, 1998	Caesarean delivery with metritis, includes labour, delivery, postpartum and professional	9,039.00	13,642.74
Scott, 1998	Caesarean delivery without metritis, includes labour, delivery, postpartum and professional	10,553.00	15,927.85
Thung, 2005	Elective caesarean	7,425.00	9,732.37
Thung, 2005	Labour caesarean	9,283.00	12,167.75
Little, 2005	Hospital care due to neonatal herpes infection	32,483.00	40,146.12
Rouse, 2000	Hospital care due to neonatal herpes infection	11,126.00	15,798.28
Baker, 2004	Caesarean delivery	5,021.00	6,581.31
Binkin, 1989	Hospital stay due to complication	698.00	1,232.38
Binkin, 1989	Hospital care due to neonatal herpes infection	25,000.00	44,139.53
Barnabas, 2002	Caesarean delivery with lesion	11,084.00	15,388.48
Clinic visit			
Scott, 1998	Clinic visit	39.50	59.62
Thung, 2005	Counselling cost	13.00	17.04
Rouse, 2000	Counselling cost (10 mins)	3.50	4.97
Rouse, 2000	Counselling cost for couple (30 mins)	10.50	14.91
Randolph, 1996	Follow-up call and office visit following screening	74.00	111.69
Barnabas, 2002	Pharmacy dispensing and education cost	3.00	4.17
Barnabas, 2002	Obstetrician counselling and testing salary for screening	19.00	26.38

Barnabas, 2002	Obstetrician counselling and testing salary for treatment	12.00	16.66
Long-term care cost			
Scott, 1998	Infant treated for HSV (include drug and culture)	1,470.00	2,218.70
Scott, 1998	Neonatal care if using caesarean delivery	821.00	1,239.15
Scott, 1998	Neonatal care if using vaginal delivery	480.00	724.47
Randolph, 1996	Neonatal herpes acute hospital care	10,160.00	15,334.69
Thung, 2005	Acute and long term care for normal/mild deficit	13,202.00	17,304.61
Randolph, 1996	Long term medical cost for moderate disability (Y1-Y65)	85,000.00	128,292.20
Thung, 2005	Acute and long term care for moderate deficit	134,202.00	175,906.12
Little, 2005	Lifetime cost and care for moderately disabled child	349,753.00	432,263.77
Rouse, 2000	Lifetime cost and care for moderately disabled child 1999	48,519.00	68,894.21
Baker, 2004	Lifetime medical and institutionalised cost for neonatal herpes	92,350.00	121,048.35
Binkin, 1989	Lifetime cost and care for moderately disabled child	125,000.00	220,697.66
Fisman, 2003	Lifetime cost of neonatal HSV with moderate neurological sequel	97,000.00	13,7734.46
Randolph, 1996	Long term medical cost for severe disability (Y1-Y65)	255,000.00	384,876.59
Thung, 2005	Acute and long term care for severe deficit	325,602.00	426,784.88
Little, 2005	Lifetime cost and care for severely disabled child	1,049,260.00	1,296,792.56
Rouse, 2000	Lifetime cost and care for severely disabled child	163,879.00	232,698.82
Binkin, 1989	Lifetime cost and care for severely disabled child	250,000.00	441,395.33
Fisman, 2003	Lifetime cost of neonatal HSV with severe neurological sequel	291,000.00	413,203.38
Tuite, 2010	Lifetime cost of neonatal HSV	164,870.00	187,438.10
Fisman, 2003	Lifetime cost of neonatal HSV	110,000.0	156,193.72
Baker, 2004	Counselling cost nurse (15 mins)	5.98	7.84
Baker, 2004	Counselling cost physician (5 mins)	6.67	8.74
Baker, 2004	Labour cost and supplies	15.58	20.42
Baker, 2004	Total cost without screening program	1,181.35	1,548.46
Baker, 2004	Total cost with screening for women	1,211.95	1,588.57
Baker, 2004	Total cost with screening for women and partner	1,267.24	1,661.04

Barnabas, 2002	Maternal mortality cost	443,858.00	616,230.57
Thung, 2005	Mortality cost	13,202.00	17,304.61
Barnabas, 2002	Neonatal care after caesarean	885.00	1228.69
Barnabas, 2002	Medical services for care of neonatal herpes	273,712.00	380,008.25
Barnabas, 2002	Long term care for neonatal herpes	140,766.00	195,432.58
Barnabas, 2002	Caregiver cost for neonates due to neonatal herpes	149,943.00	208,173.47

Figure 1: Methodological quality of included economic studies using CHEC Checklist

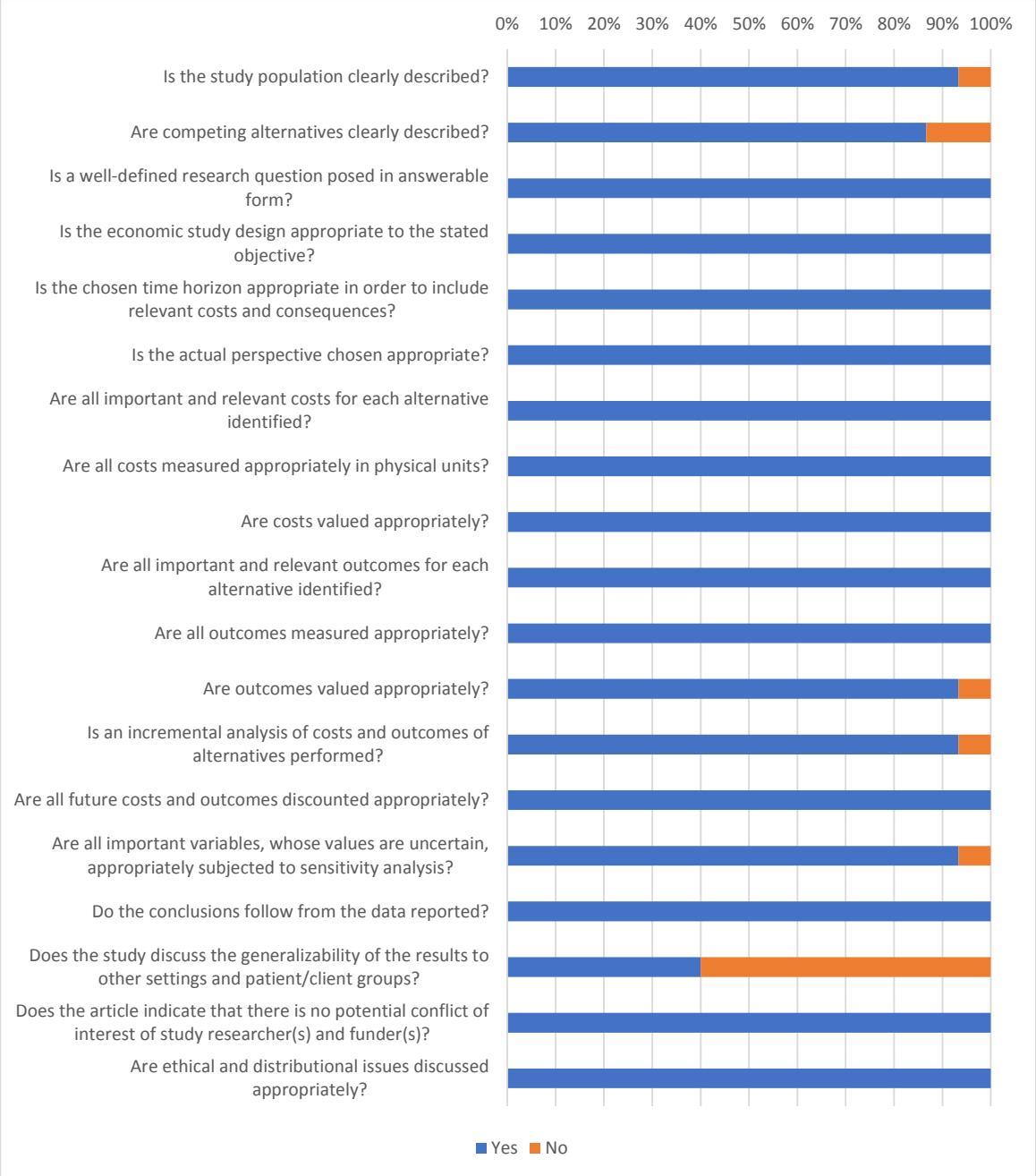

Figure 2: Methodological quality of included costing studies using Larg and Moss Checklist