UNIVERSITY OF BIRMINGHAM

Identifying and capturing intersectoral costs and benefits relating to sexual health

by

LENA SCHNITZLER

ORCID ID: 0000-0003-4624-6252

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Health Economics Unit, Institute of Applied Health Research,
University of Birmingham

Department of Health Services Research, Faculty of Health, Medicine and Life Sciences, Maastricht University

Supervisors at the University of Birmingham

Dr Louise J. Jackson

Professor Tracy E. Roberts

Supervisors at Maastricht University

Professor Silvia M. A. A. Evers

Professor Aggie T. G. Paulus

Declaration

This is to certify that:

i. This thesis comprises only my original work towards the Degree of Doctor of Philosophy;

ii. Due acknowledgement has been made in the text to all other material used;

iii. The thesis is fewer than 80,000 words in length, exclusive of tables, figures, references and appendices.

Lena Schnitzler

30.03.2023

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Abstract

Sexual health is a complex but comprehensive concept and is defined by the World Health Organization (WHO) as 'a state of physical, emotional, mental and social well-being in relation to sexuality'. Sexual health problems and interventions can generate wide-ranging health, social and economic implications (i.e. in form of costs and benefits), both within and beyond the health sector. Those costs and benefits that spill over to other sectors outside health are referred to as intersectoral costs and benefits (ICBs). There has been increasing recognition of the importance of capturing ICBs relating to public health interventions (including those in sexual health) in economic studies, and the importance of adopting a societal perspective to capture all relevant costs and benefits including ICBs. Despite international literature highlighting the need to assess economic studies from a broader perspective, most studies around sexual health still adopt a healthcare perspective for analysis, and hence ICBs have remained relatively unexplored. The primary aim of this thesis was to identify and capture relevant ICBs relating to sexual health and to develop a sector-specific (cost) classification scheme that would categorise these ICBs into different (policy) sectors. An additional aim was to develop a consensus-based checklist for the critical appraisal of cost-of-illness (COI) studies to review and assess these studies (including the assessment of the choice of study perspective and the costs included in the analysis). Two systematic literature reviews, one of COI studies and one of economic evaluations, assessed the intersectoral costs relating to sexually transmitted infections (STIs) and HIV considered in these studies. The reviews revealed that the intersectoral costs captured are mostly limited to a few cost sectors, predominantly to patient/family costs and paid productivity losses. Interviews with experts in sexual health, however, revealed there are relevant ICBs for other areas of health (including reproductive health and mental health) and other sectors of society (including education and criminal justice). A sector-specific (cost) classification scheme was developed based on these findings that can assist in guiding future comprehensive research and policy/decision-making. The review of COI studies revealed there was lack of and important need for a standard critical appraisal tool to review and assess COI studies. Hence, a consensus-based checklist for the critical appraisal of COI studies was developed, using a six-step approach that involved a scoping review and key expert interviews. The checklist can be used as a minimum standard to appraise COI studies in terms of their comprehensiveness, transparency and consistency (i.e. as part of a systematic review).

Publications and conferences

Thesis chapters published in peer-reviewed journals

- **Schnitzler, L**., Roberts, T., Jackson, L., Paulus, A. T., & Evers, S. M. (2023). A consensus-based checklist for the quality appraisal of cost-of-illness (COI) studies [COI-checklist]. International Journal of Technology Assessment in Health Care.
- **Schnitzler, L.**, Paulus, A. T., Evers, S. M., Roberts, T. E., & Jackson, L. J. (2023). Expert opinion on a consensus-based checklist for the critical appraisal of cost-of-illness (COI) studies: qualitative interviews. International Journal of Technology Assessment in Health Care, 39(1), e33.
- **Schnitzler, L.**, Paulus, A. T., Roberts, T. E., Evers, S. M., & Jackson, L. J. (2023). Exploring the wider societal impacts of sexual health issues and interventions to build a framework for research and policy: a qualitative study based on in-depth semi-structured interviews with experts in OECD member countries. BMJ open, 13(1), e066663. [Chapter 7]
- **Schnitzler, L.**, Evers, S. M., Jackson, L. J., Paulus, A. T., & Roberts, T. E. (2022). Are intersectoral costs considered in economic evaluations of interventions relating to sexually transmitted infections (STIs)? A systematic review. BMC Public Health, 22(1), 2180. [Chapter 6]
- **Schnitzler, L.**, Janssen, L. M., Evers, S. M., Jackson, L. J., Paulus, A. T., Roberts, T. E., & Pokhilenko, I. (2021). The broader societal impacts of COVID-19 and the growing importance of capturing these in health economic analyses. International Journal of Technology Assessment in Health Care, 37. [Included in Chapter 4]
- **Schnitzler, L.**, Jackson, L.J., Paulus, A.T.G. et al. Intersectoral costs of sexually transmitted infections (STIs) and HIV: a systematic review of cost-of-illness (COI) studies. BMC Health Services Research 21, 1179 (2021). [Chapter 5]

Other topic-related publications

- Pokhilenko, I., Janssen, L. M., Evers, S. M., Drost, R. M., **Schnitzler, L**., & Paulus, A. T. (2021). Do Costs in the Education Sector Matter? A Systematic Literature Review of the Economic Impact of Psychosocial Problems on the Education Sector. PharmacoEconomics, 1-12.

Conference presentations relating to this thesis

- 2021 iHEA (International Health Economics Association) World Congress, July 2021 Oral presentation: Developing a checklist for the critical appraisal of cost-of-Illness studies; Recorded presentation: Developing a checklist for the critical appraisal of cost-of-Illness studies
- 2021 LOLA HESG, May 2021 Oral presentation: Developing a checklist for the critical appraisal of cost-of-Illness studies
- 2020 LOLA HESG, May 2020 Oral presentation: Intersectoral costs of sexually transmitted infections (STIs) and HIV: a systematic review of cost-of-illness studies

Poster presentations relating to this thesis

- 2021 STI & HIV Congress, July 2021. Abstract: Are intersectoral costs of STIs and HIV considered in cost-of-illness studies? A systematic literature review
- 2020 Universitas 21 Health Sciences Group Doctoral Student Forum, University College Dublin, August 2020. Abstract: Intersectoral costs of sexually transmitted infections (STIs) and HIV: a systematic review of cost-of-illness studies
- 2020 Joint Australasian HIV&AIDS and Sexual Health Conferences, November 2020. Abstract: Intersectoral costs of sexually transmitted infections (STIs) and HIV: a systematic review of cost-of-illness studies

Other presentations

- Schnitzler, L. & Bloch SCM. Institute of Applied Health Research PGR Discussion Forum, University of Birmingham; 2021, Birmingham. Engaging in the research community as a postgraduate researcher

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CHAPTER 1 INTRODUCTION, AIMS AND STRUCTURE OF THE THESIS

This thesis aims to explore the intersectoral costs and benefits (ICBs) relating to sexual health. This introductory chapter briefly defines sexual health, introduces and explains the importance of these ICBs, justifies the aims and objectives of the thesis and outlines the structure of the thesis. In addition, this thesis intends to develop a consensus-based checklist for COI studies, for which the consideration of intersectoral costs can be relevant.

1.1 Introduction

Sexual health is a complex but comprehensive concept and is defined by the World Health Organization (WHO) as 'a state of physical, emotional, mental and social well-being in relation to sexuality' (1). It is relevant throughout an individual's lifespan and is fundamental to the health and well-being of individuals as well as their partners, peers, families, communities and wider society. At best, good sexual health requires an approach to sexuality and sexual relationship that is positive, respectful, safe, and free of coercion, discrimination, violence, and stigma (1).

Sexual health problems relating to, for instance, sexually transmitted infections (STIs), human immunodeficiency virus (HIV), sexual dysfunction, sexual discrimination, violence, and/or coercion can have physical, psychological and social impacts, compromising the quality of life of those infected and potentially impacting on those around them (2). In contrast, optimal sexual health, sexual functioning, sexual pleasure and intimacy can have a positive impact on an individual's physical and mental well-being and their relationships (3).

It is evident that sexual health problems can have an impact on the health and social care sectors. For example, the increasing number of STI and HIV cases is putting increased pressure on health services and is leading to significant healthcare costs. Estimates from the Centers of Disease Control and Prevention (CDC) presented that one in five people in the United States have an STI. The estimated lifetime healthcare (direct medical) costs relating to STIs in the United States in 2018 accounted for almost US$16.0 billion, of which HIV consumed US$13.7 billion (4). [Please refer to Chapter 2.3.2 for more information on the economic burden of STIs.]

However, like other public health concerns, sexual health problems can also generate wide-ranging health, social and economic implications that go far beyond the health and social care sector (5). For example, sexual health problems can be associated with shame, (self)stigma and psychological

distress, which can have a ripple effect on an individual's relationships (6). Living with an STI or HIV or subsequent long-term complication can also affect an individual's productivity and participation in the labour market (7-9). Even though evidence is scarce in this area, paid productivity losses relating to non-viral STIs are projected to potentially exceed healthcare costs when accounting for an individual's sick leave (8). Further, living with the (long-term) complications of an STI or HIV can require (unpaid) family or non-family caregiver support, generating substantial costs in the informal care sector (10-12). Similarly, interventions in sexual health such as those to prevent, treat and/or manage sexual health problems can result in better sexual health outcomes and improve overall wellbeing and, at the same time, create spillover effects on other sectors of society (i.e. productivity, informal care). These impacts affecting various non-health sectors such as productivity and informal care are also referred to as intersectoral costs and benefits (ICBs) (5, 13). More information on ICBs is provided in Chapter 4.

There has been increasing recognition of the importance of capturing such ICBs relating to public health and sexual health interventions in economic studies, such as cost-of-illness (COI) studies and economic evaluations (14, 15). The intent behind capturing ICBs in economic studies is to achieve a comprehensive assessment of the wider implications of health-related problems and interventions. This is, above all, true for economic studies that adopt a societal perspective for their analysis. This perspective encompasses all relevant health and non-health costs and benefits (outcomes, effects), irrespective of who incurs them. A societal perspective has always been advocated for but more recently it has increasingly been re-emphasised because of the perceived need to capture all relevant costs and benefits including ICBs (16-18).

Despite international literature highlighting the need to assess economic studies from a broader perspective (i.e. societal perspective), most studies around sexual health still adopt a healthcare perspective for analysis (19). For those studies that do adopt a societal perspective, the types of costs and benefits considered in analysis are often limited in scope (19). Failure to capture relevant ICBs in economic studies can potentially underestimate the true societal impact of a public health and sexual health problem or intervention, and can lead to sub-optimal policy/decision-making (15). This thesis addresses the paucity of evidence on ICBs relating to sexual health problems and interventions.

1.2 Aims and objectives of the thesis

The primary aim of this thesis was to explore and identify relevant ICBs relating to sexual health and to develop a sector-specific (cost) classification scheme that would categorise these ICBs into different (policy) sectors. The motivation behind this aim was to create comprehensive and transparent evidence to provide a stronger foundation for future research and (societal) policy/decision-making processes. In working towards this aim and as part of the systematic review of COI studies that would explore such intersectoral costs, it became apparent that a validated critical appraisal tool for these studies would be beneficial in order to explore the methodological approaches of the identified studies. This is, in part, because COI studies estimate the costs (or resources) associated with an illness or disease but also can include *intersectoral* costs. Thus an additional aim emerged, which was to develop a consensus-based checklist for the critical appraisal of COI studies that can be used as a minimum standard to review and assess existing studies.

The objectives of the thesis were:

(1) to gain insight into whether and to what extent existing COI studies of STIs and HIV consider intersectoral costs in their analyses by conducting a systematic literature review and to categorise these costs by sector;
(2) to undertake a second systematic literature review of economic evaluations relating to STIs to assess whether they consider intersectoral costs in their analyses and to categorise these costs by sector;
(3) to explore potentially relevant ICBs associated with sexual health problems and interventions through expert interviews and to develop a sector-specific (cost) classification scheme that categorises these ICBs into different cost sectors;
(4) to develop a consensus-based checklist for the critical appraisal of COI studies that can be used as a minimum standard to review and assess these studies; and
(5) to explore expert perspectives on the development process of the checklist for COI studies and on the use of COI studies and of critical appraisal tools for COI studies, using semi-structured interviews.

1.3 Structure of the thesis

The thesis presents ten chapters. This chapter outlined the rationale for the thesis as well as its overall aims and objectives. The subsequent chapters are structured as follows (see Figure 1 for an overview of the thesis structure):

Chapter 2 introduces the concept of sexual health in more depth, describing the wider remit and key elements relating to sexual health including STIs and HIV, sexuality and sexual rights. The epidemiological and economic burden of STIs and HIV is briefly outlined. This chapter also describes the role of and increasing demand for sexual health services, the impact of COVID-19 on sexual health service provision, and examines processes of sexual health policy/decision-making, including how sexual health services are commissioned and funded, with a focus on England and The Netherlands.

Chapter 3 provides a brief overview of the key concepts relating to health economic studies and the importance of economic evidence for policy/decision-making in public health and sexual health. It defines COI studies and the four main types of full economic evaluations. It then explains that the choice of perspective in economic analysis (i.e. healthcare, societal) determines the costs (or resources) and benefits (or outcomes) to be included in analysis. The theoretical foundations of the different methodological choices for analysis are briefly described.

Chapter 4 introduces the concept of ICBs in health economic studies assessing public health interventions and explains why the consideration of ICBs under a societal perspective is important. It also outlines methodological challenges associated with capturing ICBs in economic evaluations and refers to a study that identified the consideration of ICBs as one of the four key challenges associated with undertaking an economic evaluation of public health interventions. The final part of this chapter illustrates the importance of ICBs, looking at the example of COVID-19. It identifies and lists the broader societal impacts of COVID-19 on various sectors of society and demonstrates the growing importance of capturing these in health economic analyses.

Chapter 5 summarises the findings from a systematic literature review that explored the intersectoral costs associated with STIs and HIV considered in COI studies and categorised these costs according to (policy) sectors. This chapter also illustrates the impact intersectoral costs related to STIs and HIV can have on the total cost burden.

Chapter 6 summarises the findings from a systematic literature review of economic evaluations of interventions relating to STIs. It presents the relevant intersectoral costs identified in the systematic review, categorising them by (policy) sector and illustrating them in a sector-specific (cost) classification scheme. Further findings presented in this chapter reveal that the inclusion of intersectoral costs as presented in this scheme can have an impact on cost estimates.

Chapter 7 reveals the findings from in-depth semi-structured qualitative interviews with experts in sexual health exploring the different ICBs that can be attributed to sexual health problems and interventions. It reflects on the complex nature of sexual health and presents a sector-specific (cost) classification scheme that can assist in identifying and understanding the intersectoral impact when evaluating interventions in sexual health and when faced with policy decisions in this area.

Chapter 8 presents a consensus-based checklist for the critical appraisal of COI studies in English that can be used as a minimum standard to appraise the quality, comprehensiveness, and transparency of COI studies. The six-step development process of the checklist is outlined in this chapter.

Chapter 9 reveals the findings from in-depth semi-structured qualitative interviews with experts exploring their views on the development of a proposed checklist for COI studies. It further explores expert perspectives on both the use and relevance of COI studies and of critical appraisal tools used for COI studies as well as their experience with existing critical appraisal tools. The same chapter discusses the controversy around COI studies to date.

Chapter 10 synthesises the evidence generated through the systematic literature reviews of STIs and HIV and the qualitative interviews with experts in sexual health. It discusses the implications of the thesis findings for research and policy/decision-makers. Further, it reflects on the development and publication of the checklist for the critical appraisal of COI studies and its implications for users and (future) health economic research.

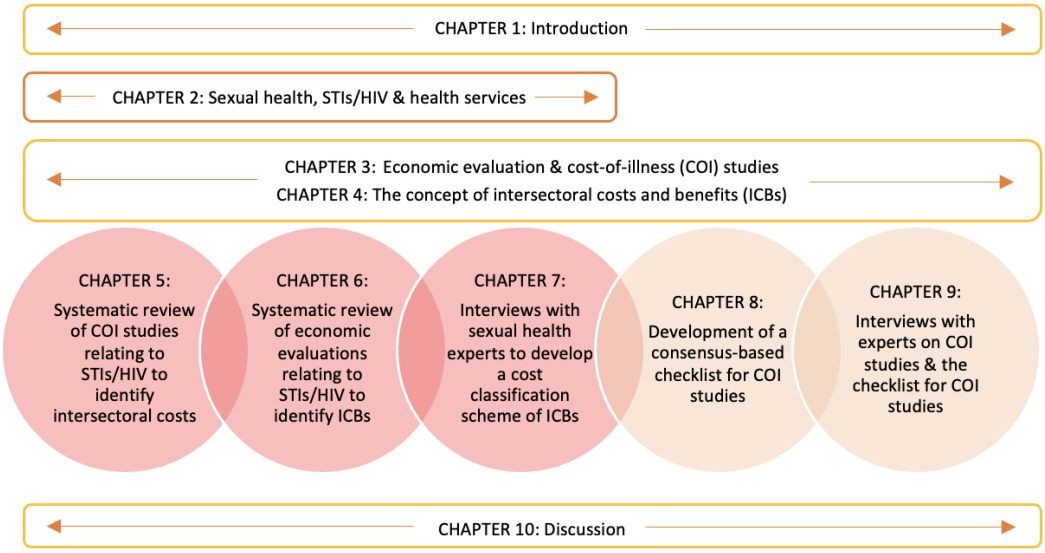

Figure 1 Thesis chapter overview

CHAPTER 2 SEXUAL HEALTH, SEXUALLY TRANSMITTED INFECTIONS/HIV, & HEALTH SERVICES

2.1 Chapter overview

This chapter gives a brief overview of the concept of sexual health, describing the wider remit and key elements relating to sexual health including sexually transmitted infections (STIs) and the epidemiological and economic burden associated with STIs, as well as sexuality and sexual rights. It describes the role of and increasing demand for sexual health services, the impact COVID-19 had on sexual health service provision, and sexual health policy/decision-making. The latter includes information on how sexual health services are commissioned and funded, using the examples of England and The Netherlands. By introducing these elements this chapter lays the foundation for the following chapters. The aspects of sexual health, in particular, STIs and the economic burden associated with STIs will come back in Chapter 5, the systematic review of cost-of-illness (COI) studies of STIs and HIV, as well as in Chapter 6, the systematic review of economic evaluations of interventions relating to STIs and HIV. This chapter also provides relevant background information for Chapter 7, which explores the intersectoral costs and benefits (ICBs) relating to the wider remit of sexual health, using expert interviews.

2.2 Defining sexual health

As introduced in Chapter 1, the World Health Organization (WHO) defines sexual health holistically and emphasises that it "requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled" (WHO, 2006a) (1).

This definition recognises that sexual health is a broad, integrated concept that encompasses key conceptual elements beyond the physical attributes of sexual health. It is about sexual well-being and functioning as much as about the absence of disease. It widens the scope of sexual health to include sexuality, for individuals to express diverse sexualities and to engage in all forms of sexual expression as well as safe and pleasurable sexual relationships. It embraces positive sexual experiences that are based on respect, safety, and freedom from discrimination and violence, as well as the respect, protection and fulfilment of an individual's sexual rights (20). In addition, the key conceptual elements of sexual health as defined by the WHO highlight that "sexual health is relevant throughout the

individual's lifespan, not only to those in the reproductive years, but also to both the young and the elderly".

Sexual health is also intertwined with reproductive health (21). Reproductive health can be considered "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes. Reproductive health implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so." (22).

These definitions acknowledge that sexual health and reproductive health are by nature inextricably linked (21). It can be understood that the promotion of good sexual health and, in particular the prevention of STIs such as chlamydia or gonorrhoea, can help prevent subsequent reproductive health problems such as pelvic inflammatory disease (PID) or infertility. Conversely, efforts to promote reproductive health can also help promote good sexual health. This thesis will focus on sexual health, but the close link to reproductive health is acknowledged.

2.3 Sexually transmitted infections

Sexually transmitted infections (STIs) are infections predominantly spread by unprotected sexual intercourse with an infected individual. They can be spread through vaginal, anal, and oral sex (23). Some STIs can also be transmitted by non-sexual means including mother-to-child transmission during pregnancy or childbirth, blood-to-blood contact or sharing syringes to inject drugs (24).

More than 30 different bacteria, viruses and parasites exist that are known to cause STIs through sexual contact (23). Four of these are currently curable including chlamydia (caused by the *Chlamydia trachomatis* bacteria), gonorrhoea (caused by the *Neisseria gonorrhoeae* bacteria), syphilis (caused by the *Treponema pallidum* bacteria) and trichomoniasis (caused by the *Trichomonas vaginalis* parasite). Incurable viral infections include hepatitis B (caused by the *hepatitis B* virus (*HBV)*), herpes simplex virus (HSV), human immunodeficiency virus (HIV) and human papillomavirus (HPV); though these infections can be managed through treatment (24).

These eight curable and incurable STIs have been associated with a high burden of morbidity, imposing some serious complications and (long-term) sequelae, if not detected and treated (25). In fact, STIs are often asymptomatic, increasing the risk of being undiagnosed and left untreated. Asymptomatic and undiagnosed STIs can also increase the risk of transmission, resulting in higher rates of STIs (26).

Furthermore, living with an STI increases the susceptibility of acquiring HIV and vice versa, in particular when not treated in a timely and effective fashion (27). Some of the most common long-term complications and sequelae of STIs are listed in Appendix 1.

2.3.1 Epidemiological burden of STIs

Worldwide, more than one million STIs are estimated to be acquired every day (24). An estimated 374 million new curable infections were reported in 2020 globally, with chlamydia accounting for 129 million new cases, gonorrhoea for 82 million new cases, trichomoniasis for 156 million new cases and syphilis for 7 million new cases (24). In 2016, there were an estimated 490 million individuals living with genital herpes, an estimated 300 million women living with HPV, and an estimated 296 million people living with chronic hepatitis B globally (23). The number of individuals living with HIV reached 38 million in 2021 (28).

Overall, the prevalence of STIs continues to rise and poses a major public health issue internationally including in many Organisation for Economic Co-operation and Development (OECD) member countries (29-31). For example, in England, the number of STI cases increased by over 10% between 2016 and 2019 (32). The number of sexual health service consultations rose by around 19% over the same period of time. In 2019, STI diagnosis accounted for 468,342 in England (33). In 2021, the number of new STI diagnosis accounted for 311,604 cases (34). This is a decrease of around 33% compared to 2019 that can be explained by the limited access to sexual health services during the start of the COVID-19 pandemic. In the Netherlands, the number of STI diagnoses also rose again after it had dropped during the start of the pandemic, for comparable reasons. In 2021, the number of STI cases increased by 30% from 2020, which is still 8% less than in 2019, before the pandemic (35).

A worrying increase in bacterial STIs has been reported. In England, chlamydia and gonorrhoea were reported as the most commonly diagnosed STIs in 2021, with 159,448 cases of chlamydia (51.2% of all new STI diagnoses) and 51,074 cases of gonorrhoea (16.4% of all new STI diagnoses) (36). In the Netherlands, the number of diagnosis for chlamydia in 2021 accounted for more than 20,000 and 8,000 for gonorrhoea, which is both comparable to pre-pandemic numbers in 2019 (35).

A re-emergence of syphilis has generally been posing a challenge in various high-income countries including Western Europe, North America, and Australia, primarily amongst men who are highly sexually active (29). Data from Public Health England report that syphilis diagnoses increased by 162% (2,874 to 7,541) between 2008 and 2018 (37). An estimated 75% of these diagnoses were found in

men who have sex with men (MSM) in 2018. In 2021, there were 7,506 diagnoses of infectious syphilis in England, rising up to pre-COVID-19 pandemic levels (with 8,010 diagnoses in 2019) (38). In the Netherlands, there were 1,378 diagnoses of syphilis at sexual health clinics in 2021 (35).

Looking at viral STIs, human papillomaviruses (HPV) can pose a high risk on developing precancerous lesions. HPV 16 and 18 are associated with almost 50 % of cervical pre-cancers (39). Estimates from 2020 revealed there were about 604,127 new cases of cervical cancer worldwide and 342,000 associated deaths (39). Human immunodeficiency virus (HIV) affects more than 38 million people worldwide, with 2 million people in the WHO European Region (560,000 in the EU/EEA) (40). The UK reported there were about 106,890 people living with HIV in in the UK in 2020, of which more than 90 % live in England (41). The Netherlands reported an estimated 24,000 cases of HIV in 2021 (42). Herpes simplex virus 2 (HSV-2) is a highly infectious disease almost exclusively sexually transmitted and known to be the main cause for genital herpes, a common incurable and lifelong infection. Worldwide, about 417 million people carry HSV-2 (43). Another highly infectious virus is hepatitis B (HBV) with an estimated 257 million living with chronic hepatitis B worldwide, which can result in cirrhosis, hepatocellular carcinoma and death (44).

2.3.2 Economic burden of STIs

STIs are a public health concern with implications for the individual, their families, and wider society (45). The economic burden of STIs, like other public health problems, manifests itself in healthcare costs (traditionally referred to as *direct costs*) and costs in other sectors. The latter can include patient and family costs, informal care, and productivity (traditionally referred to as *indirect costs*) (45, 46).

The economic burden of STIs is substantial. As briefly mentioned in the introduction of this thesis (Chapter 1.1), the estimated lifetime healthcare (direct medical) costs relating to STIs in the United States in 2018 accounted for almost US$16.0 billion, of which HIV consumed US$13.7 billion (4). Of those US$16.0 billion, chlamydia, gonorrhoea and syphilis combined contributed to $1.1 billion in direct medical costs. HPV infections accounted for $755 million in lifetime medical costs. In England, the number of STIs between 2002 and 2011 increased by 49%, costing the National Health System (NHS) nearly £620 million in 2011 in treatment costs, excluding costs relating to the treatment of HIV (47). The national HIV treatment costs in England between 2016-2017 reached £540 million (48). There is currently little to no data available on the economic burden of STIs in the Netherlands.

Very few studies to date have assessed the costs relating to sexual health problems such as STIs in other non-health sectors. Those studies that did capture non-health costs have predominantly focused on capturing productivity costs in terms of work absence. A study by Owusu-Edusei et al. found that the average productivity loss per case in the United States was estimated at $262 for chlamydia, $197 for gonorrhoea, $419 for syphilis and $289 for trichomoniasis in 2011 (8).

2.3.3 Sexuality

Sexuality has been recognised as a key element of sexual health. The WHO defines sexuality as "a central aspect of being human throughout life, encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious and spiritual factors." (1).

2.4 Sexual rights

The element of sexual rights has been defined as "the fulfilment of sexual health is tied to the extent to which human rights are respected, protected and fulfilled. Sexual rights embrace certain human rights that are already recognised in international and regional human rights documents and other consensus documents and in national laws. The application of existing human rights to sexuality and sexual health constitutes sexual rights. Sexual rights protect all people's rights to fulfil and express their sexuality and enjoy sexual health, with due regard for the rights of others and within a framework of protection against discrimination." (1). Both the 1994 International Conference for Population and Development (ICPD) Programme of Action and the Sustainable Development Goals (SDGs) link sexual health and reproductive health to an individual's human rights.

2.5 Sexual health services

Sexual health services are fundamental to promoting good sexual health, sexual functioning and sexual well-being across an individual's life course, to detect and to treat STIs in a timely manner and effectively, to prevent onward transmission, and to eventually achieve and maintain a healthy society (49). Sexual health services and interventions can be delivered in multiple ways, within a range of settings (i.e. sexual health, reproductive health, primary care) and across a variety of (policy) sectors (i.e. health, education) (49). The WHO Framework for Action recommends a holistic, multisectoral and interdisciplinary approach to the delivery of sexual health services that addresses not only individual

aspects (i.e. sexuality, behaviour) but also societal determinants (i.e. education, economic growth) (49).

As mentioned earlier, sexual health services and interventions can be administered in a variety of settings and can involve different types of programmes. Interventions in the health domain often involve (traditional) biomedical programmes relating to prevention (i.e. vaccination), diagnosis (i.e. testing, screening), treatment (i.e. medication) and control and/or management of disease (i.e. surveillance). Behavioural interventions can, for instance, involve comprehensive sex education, sexual health education and prevention information (for those not in school), and counselling. Structural interventions can involve policies, practices, programmes, and (societal or community) norms that address relevant social, economic, and political factors associated with sexual health (50). There are also a range of interventions, which combine biomedical, behavioural and/or structural interventions at different levels of society including at individual, relationship, community and societal levels (51).

2.5.1 Increasing demand for sexual health services

There is an increasing demand for sexual health services primarily due to the consistent rise of STIs (29, 52). For example, attendances at sexual health clinics in England rose from 2.9 million in 2013 to 3.5 million in 2018 (53). This is challenging at a time of limited resources available for public health and sexual health. The imbalance between an increasing demand for these services and available resources can be challenging for any health system (54).

The rapid increase in monkeypox cases, a viral zoonosis resembling the symptoms of smallpox, in 2022 further exposed the overwhelming demand for and pressure on sexual health service delivery and the fragility of funding for these services (55, 56). Primarily men who have sex with men (MSM) presented with symptoms relating to monkeypox at sexual health clinics in the UK, and other services such as testing for STIs, HIV, and access to contraception were displaced (56).

2.5.2 The impact of COVID-19 on sexual health service provision

Worldwide, the COVID-19 pandemic resulted in excess mortality and morbidity, long-lasting (chronic) health consequences, straining healthcare facilities and entire health systems and leading to rapidly increasing healthcare costs. Even though the healthcare sector appeared to be the most obvious sector affected by the pandemic, it became evident that COVID-19 also led to additional strains and spillover effects on other sectors outside of health including labour, education, criminal justice,

housing, consumption, environment, among others (57, 58). This is, in part, due to the complex nature of the coronavirus itself. But also because the control of the rapid spread of the virus not only required (pharmacological) health interventions but involved a whole society approach including public health interventions across all sectors of society. This included social restrictive measures including isolation, quarantine, physical distancing, country lockdowns, and business and school closures (57) (please refer to Chapter 4 for more information on the wider societal impacts of COVID-19 across a range of different (policy) sectors).

While these measures assisted in the response to the COVID-19 pandemic and enabled resources for and access to services to COVID-19, they also had an impact on the provision of sexual health services (59). In many countries, national and regional lockdowns as well as social and physical distancing led to a decline in sexual health clinic attendance, a reduction in testing and diagnoses for STIs, a decrease in face-to-face consultations, and a limited opportunity for disease surveillance (60-63). To only give one example, in England STI diagnoses dropped by 32% between 2019 and 2020 (32), illustrating the extent to which sexual health services were impacted.

Resources had to be reallocated during the pandemic, which disrupted sexual health and contraceptive services. Some sexual health clinics had to close or divert their services and staff to support COVID-19 related work (64). In order to provide access to sexual health services alternative delivery methods quickly arose including telephone consultations, online/internet and video consultations, online postal self-sampling STI services, and other (63). This represented a rapid intensification of (digitalisation) processes that were already underway and illustrated the high flexibility of sexual health service providers and patients that had to rapidly adapt to the digitalisation of sexual health services. It is important to note that online STI testing in England had already been increasingly seen as a new means to meet the increasing sexual health service demand given the funding cuts for sexual health, to reduce costs and to increase efficiency (65).

2.6 Sexual health policy/decision-making

Many OECD countries face challenges relating to sexual health. This includes the increasing rates of STIs, the spread of antibiotic-resistant infections as well as other infections such as Monkeypox, and the growing demand for STI services, at a time of limited healthcare budgets. Health systems have different approaches in organising and financing sexual health services in order to promote good sexual health, to identify and respond to such challenges, and to promote a sustainable health system. Although the focus of this thesis is generally on OECD countries, this chapter will use England and The

Netherlands as an example to describe two different systems in terms of sexual health commissioning and funding.

2.6.1 Commissioning of sexual health services in England

There are three main groups responsible for the commissioning of sexual health services in England: local authorities, statutory integrated care systems (ICSs) (formerly clinical commissioning groups) and National Health Service (NHS) England. The Health and Social Care Act 2012 in the UK led to a restructuring of the responsibilities of services in the health and social care system, including sexual health services (66). From 2013, the local authorities took on most of the responsibility for the commissioning of sexual health services. This included the provision of information, support, advice and open access to services such as the prevention, testing and treatment of STIs or HIV, and partner notification; advice on and access to the provision of contraceptives; and advice on (unplanned) pregnancy or (sexual) relationships (67). However, commissioning remained fragmented with ICSs being responsible for certain specialised sexual health services. [As of the Health and Care Act 2022, ICSs have absorbed these duties in connection with the abolition of clinical commissioning groups.] These specialist services include for instance abortion services, vasectomy, and sterilisation (68). NHS England has certain responsibilities relating to the commissioning of sexual health services. Sexual health services provided by NHS England include for instance HIV treatment and care (i.e. drug costs), the promotion of opportunistic testing and treatment for STIs, sexual health services in prisons, cervical screening, among other aspects.

2.6.2 Funding for sexual health services in England

With the implementation of the Health and Social Care Act 2012, the Department of Health and Social Care allocated a yearly ring-fenced public health grant to the local authorities, meaning this grant should exclusively be spent on public health services (66). This budget is intended to be spent on the preventative health services such as sexual health services, drug and alcohol services, smoking cessation, and other areas (69). The public health grant that local authorities receive for the year 2022 to 2023 is set to be £3.417 billion (70).

Between 2015/16 and 2020/21, there was a reduction in public health funding by over £1bn (24%), with severe cuts to spending on sexual health services. In England, spending on testing and treating STIs as well as on contraception was reduced by almost 17% between 2015/16 and 2020/21. The Local Government Association (LGA) representing England and Wales reported in 2022 that sexual health services were at a “breaking point” due to these funding cuts (52, 71), and that reduced budgets have

had implications for accessing highly demanded sexual health services (66). In other words, local authorities have faced difficulties meeting the increasing demand for sexual health services.

2.6.3 Commissioning of sexual health services in The Netherlands

There are three main groups responsible for the commissioning of health services under the Dutch healthcare system: government, insurers and providers. Public health services and medical care, including sexual health services, are covered by an individual's public health insurance provider. The Ministry of Health, Welfare and Sport works together with health insurances, health services providers and patient organisations to guarantee choice and accessibility of health insurers.

Sexual health services in the Netherlands are mainly provided by general practitioners (GPs) and specialised sexual health clinics (72). The difference between those two providers is that sexual health clinics mainly perform services for high-risk groups such as individuals who had sexual contact with another infected individuals (i.e. identified through partner notification), and men who have sex with men (MSM); whereas services through GPs are more designed for lower risk groups. The majority of STI consultations, testing and care are therefore undertaken at GP practices who generally play the role of a "gatekeeper" to further (secondary) healthcare in the Dutch healthcare system.

2.6.4 Funding for sexual health services in The Netherlands

As mentioned above, public health care including sexual health services in the Netherlands is financed through mandatory health insurance contributions (premiums) paid monthly to an insurance company, supplementary health insurance, tax revenues and government grants. Between 2018 and 2019, the Netherlands spent around 10 % of their gross domestic product (GDP) on healthcare, which is reportedly similar to the health care spending in the UK (73).

The Healthcare Insurance Act in the Netherlands guarantees that regular healthcare is reimbursed. To give an example, costs relating to testing and treating of STIs are usually covered by an individual's health insurance company. This, however, depends on the obligatory deductible excess, which is an out-of-pocket payment that an individual is obliged to pay annually before their insurance company starts to cover the (remaining) expenses above that deductible. GP consultations are exempted from this deductible and are in any case reimbursed by the health insurer (74).

2.7 Chapter summary

This chapter provided a brief overview of the concept of sexual health including STIs, the epidemiological and economic burden associated with STIs, as well as sexuality and sexual rights. It explained the role of and increasing demand for sexual health services, the impact COVID-19 had on the provision of these services, and how sexual health services are commissioned and funded, using the examples of England and The Netherlands. The next chapter (Chapter 3) will introduce the theoretical frameworks and methodological approaches for economic evaluation and the importance of economic evidence for policy/decision-making in public health and sexual health. It will also define the four main types of full economic evaluations as well as cost-of-illness (COI) studies and will describe the different perspectives that can be applied in economic analysis.

CHAPTER 3 THEORETICAL AND METHODOLOGICAL BACKGROUND FOR ECONOMIC EVALUATION AND COST OF ILLNESS (COI) STUDIES

3.1 Chapter overview

This chapter provides a brief overview of the theoretical frameworks and methodological approaches for economic evaluation and the importance of economic evidence for policy/decision-making in public health and sexual health. It defines the four main types of full economic evaluations as well as cost-of-illness (COI) studies. The theoretical foundations of the different methodological choices for analysis are briefly described. It then explains the different perspectives that can be applied in in economic evaluation and COI studies (e.g., healthcare, societal), which determine the costs (or resources) and benefits to be included in analysis. By introducing economic evaluation and COI studies as well as the different perspectives for analysis, this chapter provides relevant background information for Chapter 5, the systematic review of COI studies relating to STIs and HIV, and Chapter 6, the review of economic evaluations of interventions relating to STIs and HIV. Both systematic reviews look at the costs considered in these studies under a societal perspective. Furthermore, introducing COI studies in this chapter is important for Chapter 8 and Chapter 9. These two chapters explain the development process of a consensus-based checklist for the critical appraisal of COI studies.

3.2 The importance of economic evidence for policy/decision-making

Given the increasing demand for healthcare services and rising pressures on health budgets, policy/decision-makers are encouraged to ensure the optimal use of scarce resources. Generating evidence on the burden of illness (i.e. with the use of COI studies) as well as the cost-effectiveness of interventions (i.e. with the use of economic evaluation) is fundamental for addressing resource scarcity and priority setting for interventions. Policy/decision-makers are expected to make evidence-based decisions, using appropriate methods or tools to effectively commission public health services (75).

Economic evaluations play a prominent role in generating such evidence about the value of public health investments and interventions. Evidence on the cost-effectiveness of public health interventions has become more and more important in supporting healthcare choices that would ideally optimise population health (76, 77). It is pertinent for collective decision-making and is increasingly requested by national authorities (78). Findings from economic evaluations are often used

in support of applications for funding and reimbursement (79), supporting decisions around the allocation of (limited) resources and the prioritisation of interventions (76).

Full economic evaluations (i.e. cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, cost-consequence analysis) can help identify, measure and value the input (resources/costs) and output (health and non-health benefits/outcomes) of alternative (potentially competing) interventions (80). These are described in more detail below, see Chapter 3.3.

3.2.1 Theoretical foundations

There are two main theoretical approaches that have shaped health economic evaluations and that are distinct: welfarism and extra-welfarism (81).

Welfarism

Welfarism focuses on individual welfare (comprised of utilities) and states that individual welfare contributes to societal welfare. This is because one of the main underpinning concepts of welfarism is the Pareto principle. A Paretian welfarist point of view in health economics states that 'individuals are the best judges of their own welfare (well-being) and that, if one individual can be made better off without another being made worse off, there is a global improvement in welfare' (82).

With its foundation in welfare economics, it is important to consider and capture the broader societal implications of a health intervention in health economic analyses. Hence, from a welfarist point of view, a societal perspective is preferred for analyses as it is expected to capture all relevant costs and benefits associated with an intervention both within the health sector and across other sectors of society, which could contribute to societal welfare. Byford and Raftery (1998) state that 'adopting a societal or population perspective facilitates policies aimed at maximising the welfare gains to society, or minimising the losses' (83).

Extra-welfarism

Extra-welfarism has been seen as concerned with the maximisation of health exclusively and focussing on health outcomes. As opposed to welfarism that is concerned with overall welfare and for which 'the output of healthcare should be judged according to the extent to which it contributes to overall welfare (i.e. the [weighted] sum of individual utilities)', extra-welfarism defines 'the output of healthcare according to its contribution to health itself' (84).

Culyer (1989) explained the difference between welfarism and extra-welfarism as follows: '*Under Paretianism, for example, the notion of welfare relates to goods and services and is the utility of the individual affected by their consumption. Under extra-welfarism, while this notion of utility may still apply, there is the further idea that uses utility theory in order to derive measures of characteristics of individuals that are not goods, not services, nor necessarily having a value content that corresponds to the Paretian notion that the individual is the best judge of his/her own welfare*' (85).

3.3 Economic evaluation methods

Economic evaluation is a comparative analysis of the costs (resources) and outcomes (benefits, effects) of two or more alternative interventions or alternative courses of action (75). The objective of a health economic evaluation is to provide policy/decision-makers in health care with evidence on the most efficient and cost-effective use of resources, with the goal to maximise population health benefits from a given budget (75, 86). The subsequent sections will briefly outline the different types of economic evaluations which are based on varying theoretical foundations.

How outcomes are expressed in the different types of economic evaluations is linked to the theoretical foundations as outlined in section 3.2. For example, the theoretical foundation of a cost-benefit analysis (CBA) lies in welfarism, whereas the underlying theoretical framework for a cost-utility-analysis (CUA) lies in extra-welfarism. The value of a health intervention from a welfarist point of view is based on how an individual perceives and judges such value or result (e.g., individual utilities). In other words, the individual is considered to be the best judge of their own welfare, according to a welfarist point of view. In a CBA the health outcomes are valued by the contribution to overall societal welfare such as the willingness to pay, which is based on the preferences of individuals (87).

3.3.1 Cost-consequence analysis

Cost-consequence analysis (CCA) is a form of an economic evaluation that lists (a wide range of) the costs (resources) and outcomes (benefits, effects) of two or more alternative interventions, presenting a series of these measures separately (88). In other words, it provides a disaggregated overview of the costs and outcomes, without valuing the outcomes in an incremental-cost-effectiveness ratio (ICER) or cost-benefit ratio (88). Outcomes listed in a CCA can for instance involve health effects, non-health effects, effects on a patient and caregiver, among other. A CCA is often seen as a first step in identifying whether a full economic evaluation (CBA, CEA, CUA) would be helpful. Where a CCA can be useful when evaluating and comparing a broad scope of health and non-health outcomes, it can also have

some limitations. For example, the results might be less generalisable in particular because the choice of costs and benefits can vary by context (89).

3.3.2 Cost-benefit analysis

A Cost-Benefit Analysis (CBA) is a comparative analysis of the costs (resources) and outcomes (benefits, effects) of two or more alternative interventions for which both costs and outcomes are measured in monetary values (90). In other words, all costs and benefits are converted to a common metric and compared. This allows a CBA to compare interventions across different sectors (87). Where a CBA can be useful when evaluating and comparing interventions for which health and non-health outcomes are different and for cross-sectoral comparison, it can also have some limitations. With one being that the value being assigned to a health or non-health outcome in monetary values can differ and be influenced by an individuals' ability to pay, characteristics and socioeconomic status (87).

3.3.3 Cost-effectiveness analysis

A Cost-Effectiveness Analysis (CEA) is a comparative analysis of the costs (resources) and outcomes (benefits, effects) of two or more alternative interventions for which the outcomes are assessed in natural (physical) units (91). These are typically clinical outcomes such as blood pressure, HIV viral load or life years saved. Where a CEA can be useful when evaluating and comparing different interventions for which the outcome measure is similar, such as the HIV viral load, it can also have some limitations. For example, by focusing on health outcomes a CEA can omit non-health outcomes and hence benefits that can fall outside of the healthcare sector (87).

3.3.4 Cost-utility analysis

A Cost-Utility Analysis (CUA) is a comparative analysis of the costs (resources) and outcomes (benefits, effects) of two or more alternative interventions for which outcomes are assessed in health utilities such as quality-adjusted life years (QALYs) (92). QALY is a measure of the quality of life and the survival. Where a CUA can be useful when policy makers are concerned with allocating resources across different areas of health and, for instance, when comparing interventions that fall within one (healthcare) budget, such as in the UK (where UK NICE recommends the use of CUA), this same argument can also be interpreted as a limitation. In other words, relevant (non-health) costs and benefits could be missed (87).

Table 1 Types of economic evaluations

Type of economic evaluation	**Measure of costs**	**Measure of outcome (benefit)**

Cost-consequence analysis (CCA)	Money	Range of health and non-health outcomes
CEA: Cost-Effectiveness Analysis	Money	Natural units i.e. blood pressure, life years
CBA: Cost-Benefit Analysis	Money	Health benefit converted to monetary units
CUA: Cost-Utility Analysis	Money	Health status/ utilities i.e. QALYs

3.4 Cost-of-illness (COI) studies

COI studies are a commonly used framework designed to identify, measure and value the costs incurred by society due to a particular illness (or disease, health condition, risk factor) (93). These studies are distinct from economic evaluations because they do not assess the benefits (outcomes) or utility loss associated with an illness, but merely consider related costs or resources. Due to the lack of comparison of the costs and benefits COI studies do not give an indication of what it would cost to prevent, treat or manage an illness or disease and the value for money of such intervention (94). In other words, the cost burden on its own may not relate to the value for money of interventions to prevent, treat or reduce the cost of an illness or disease. However, an accurate estimation of COI can be essential to inform different stakeholders.

In the context of health policy/decision-making, it can be essential to demonstrate the impact of an illness in order to prioritise certain health interventions or policies and to allocate resources accordingly and under budget constraints (95, 96). In health economics research, assessing the cost of an illness or disease can be relevant in order to provide adequate information on valuable cost estimates, for instance, to inform the conduct of full economic evaluations (75). COI studies can generate relevant information regarding the different cost components and cost categories (or sectors) associated with an illness and can describe healthcare spending within and beyond healthcare (i.e. intersectoral costs) (97). Just to give one example, the annual costs relating to an HIV infection illustrate the severity and spending on the infection. Rather than indicating the effectiveness or cost-effectiveness of the spending on HIV, it provides an indication of the importance of the disease (46).

The methodological approaches to conducting COI studies can vary. The epidemiological approach can be a prevalence-based or incidence-based approach. In a prevalence-based approach the economic burden of an illness or disease on society is measured during a period of time, for example, in a given

year. In contrast, in an incidence-based approach the lifetime costs of an illness or disease on society is measured, for instance, from the onset of an illness or disease to the endpoint (e.g., end of treatment, death) (98).

The costing approach can be a top-down or bottom-up approach. Using a top-down approach, cost or resource estimates are typically identified and accessed through aggregate data, published national indicators, published studies or national surveys including for instance hospital admissions, mortality rates, or other. Using a bottom-up approach, the cost or resources estimates are typically measured, quantified and estimated by referring to a patient sample or individual patient record such as through questionnaires (98).

The data collection approach can be a prospective or retrospective approach. In a prospective approach the data is collected at present and with time, for example, collecting patient medical records or data from clinical trials. In a retrospective approach the data is usually past data that is already available and that can be accessed and collected, for example, previously recorded data (98).

More information on COI studies, the controversy around COI studies, and the critical appraisal of COI studies is provided in Chapter 8 and 9.

3.5 Perspectives in economic evaluation and COI studies

The perspective chosen for an economic analysis is the point of view from which an analysis is conducted. The choice of perspective can depend on the study objective, the interests of a stakeholders for the analysis and the guidelines for the conduct of economic evaluations in place. Where guidelines recommend a certain type of perspective for economic evaluations this means that often researchers have no choice but to adopt the respective perspective. The chosen study perspective determines the types of costs and benefits (or consequences) that will be included in the analysis. Commonly used perspectives include the patient/family perspective, healthcare perspective, payer perspective and societal perspective. The societal perspective is considered the broadest and most comprehensive study perspective and is expected to capture all relevant costs and benefits irrespective of who incurs them (99).

Studies that adopt a healthcare or health system perspective assess the healthcare (or direct medical) costs relating to an illness (i.e. in COI studies) or relating to one or more intervention (i.e. in economic evaluations). In COI studies, this includes for instance treatment costs such as pharmaceuticals,

hospitalisation, general practitioner visits, costs relating to administration and monitoring, among others (99). In economic evaluations, this includes for instance the aforementioned healthcare costs as well as health outcomes (benefits, effects).

Studies that adopt a societal perspective are expected to consider all relevant costs and benefits relating to an illness or intervention, irrespective of who incurs them. In addition to the costs and benefits falling on the health sector, a societal perspective is also expected to consider relevant costs and benefits falling on the patient/family (i.e. travel costs, out-of-pocket payments), productivity losses (lost productivity, reduced productivity (presenteeism), absence at work (absenteeism)), and on other sectors of society (75). Costs and benefits in other sectors outside of health can for instance relate to those in the education sectors, the criminal justice, the housing sector, or other (5). These wider costs and benefits spilling over to other non-health sectors are also referred to as *intersectoral costs and benefits* (ICBs). (Please refer to Chapter 4 below for more detailed information on intersectoral costs and benefits.)

To give one example of a reference case, the UK NICE recommends using the 'NHS and personal and social services' perspective. This NHS perspective considers medical costs such as treatment costs and health services costs in their analysis. Personal social care services include services for vulnerable people or groups and people with special needs e.g., residential care homes, social work services, or other (100). Patient and family costs such as transportation costs or out-of-pocket payments are not included in the analysis (99).

3.6 Chapter summary

This chapter provided a brief overview of the theoretical frameworks and methodological approaches for economic evaluation and the importance of economic evidence for policy/decision-making in public health and sexual health. It briefly introduced the four main types of full economic evaluations and COI studies before describing the theoretical foundations of the different methodological choices for analysis. It also explained that the different perspectives that can be applied in economic evaluations and COI studies, which determine the costs (or resources) and benefits to be included in analysis. The following chapter (Chapter 4) will introduce the concept of intersectoral costs and benefits (or ICBs), which can be considered those costs spilling over to other sectors outside the health sector. This is relevant information because both systematic reviews (Chapter 5 and 6) explore the intersectoral costs considered in economic evaluation and COI studies under a societal perspective.

CHAPTER 4 THE CONCEPT OF INTERSECTORAL COSTS AND BENEFITS

4.1 Chapter overview

This chapter first explores the concept of intersectoral costs and benefits (ICBs) in economic studies such as economic evaluations as well as cost-of-illness (COI) studies, particularly focussing on public health interventions. Second, it explains why the consideration of ICBs under a societal perspective is important. Third, this chapter outlines the methodological challenges associated with capturing ICBs in economic evaluations and refers to a study that identified the consideration of ICBs as one of the four key challenges when undertaking an economic evaluation of public health interventions. Last, this chapter illustrates the importance of ICBs, utilising the example of COVID-19. It identifies and lists the broader societal impacts of COVID-19 on various sectors of society and demonstrates the growing importance of capturing these in health economic analyses. By introducing these elements this chapter lays the foundation for Chapter 5, a systematic review of COI studies, and Chapter 6, a systematic review of economic evaluations, exploring the intersectoral costs included in analyses under a societal perspective. The consideration of intersectoral costs will also be reflected in Chapter 8, a consensus-based checklist for the critical appraisal of COI studies. More specifically, the checklist includes a question on the type of perspective applied and whether health and non-health costs (e.g., intersectoral) were included in analysis.

4.2 What are intersectoral costs and benefits?

In health economics, the term ICBs refers to those costs and benefits that spill over to non-health sectors of society, as a result of a health-related intervention (5). Other international literature might also refer to it as *societal* or *multisectoral* costs and benefits (or consequences) (101, 102).

The concept of ICBs can be explained by looking at public health interventions. Public health interventions, including those targeting elements of sexual health, are complex by nature. This is because these types of interventions are often directed at populations or communities rather than at an individual and can be delivered within and across different sectors (i.e. health, education). As a result, they can generate wide-ranging impacts that are broader than health.

Traditionally, these costs have been categorised broadly into *direct costs* and *indirect costs* (86). In this case, direct costs referred to the resource use associated with healthcare (direct medical and non-medical) costs, whereas indirect costs referred to the productivity loss or gain relating to an illness or intervention (86). However, there has been a move away from this broader categorisation of direct

and indirect costs and toward defining cost components and cost sectors more specifically (16, 103). Drummond et al. (2015) more specifically categorises the wide-ranging impacts relating to public health interventions as follows: (i) health sector, (ii) patient and family, (iii) productivity, and (iv) other sectors (75). Sanders et al. (2016) further identified costs and benefits in other non-health care sectors, categorising these as follows: productivity, consumption, social services, legal or criminal justice, education, housing, environment, and other (104) (see Table 2).

Table 2 Impact Inventory Template (based on Sanders et al. 2016)

Sector	**Type of Impact**
Formal health care sector	
Health	Health outcomes (effects): longevity effects; health related quality of life effects; other health effects (i.e. adverse evets, secondary transmissions of infections)
	Medical costs: paid for by third-party payers, paid for by patients out-of-pocket; future related medical costs (payers and patients); future unrelated medical costs (payers and patients)
Informal health care sector	
Health	Patient time costs; unpaid caregiver time costs; transportation costs
Non-health care sectors	
Productivity	Labor market earnings lost; cost of unpaid productivity due to illness; costs of uncompensated household production
Consumption	Future consumption unrelated to health
Social services	Cost of social services as part of intervention
Legal or criminal justice	Number of crimes related to intervention; cost of crimes related to intervention
Education	Impact of intervention on educational achievement of population
Housing	Cost of intervention on home improvements (i.e. removing lead paint)

Environment	Production of toxic waste pollution by intervention
Other	Other impacts

4.3 Why is the consideration of intersectoral costs and benefits important?

Understanding and capturing ICBs in economic studies is important to optimally inform policy/decision-making (15, 75). There has been a growing recognition of the need to capture these wider societal impacts of public health interventions, to ensure that a comprehensive assessment of these impacts of an intervention is achieved (13, 83, 86). For example, following the transfer of public health responsibilities to local authorities in 2013, UK NICE updated their guidelines for economic evaluation to account for the wider societal impacts of public health interventions in appropriate circumstances (105). In other countries, such as The Netherlands and Sweden, a societal perspective has long been recommended in national guidelines when assessing health interventions (79, 106). However, capturing these ICBs in economic studies can be challenging in practice (107).

4.4 Methodological challenges in capturing intersectoral costs and benefits in economic studies

In 2009, Weatherly et al. identified the consideration of intersectoral costs and benefits (ICBs) as one of the four key challenges when undertaking an economic evaluation of public health interventions (15). In fact, standard approaches to economic evaluations of public health interventions have been criticised (13), in part for their limited consideration of costs and benefits outside of health (13, 15, 108). In their study, Weatherly et al. give the example of evaluating an intervention to prevent substance use from a healthcare perspective, which might tend to ignore costs in other sectors such as those falling on the criminal justice sector (15).

One reason for this is that, traditionally, guidelines for (pharmaco)economic evaluations focused on the assessment of clinical interventions such as pharmaceutical drugs and medical devices (107). Hence, these guidelines are well-established, but mainly centre around methodological approaches from a rather narrow perspective, predominantly considering (direct medical) health care costs relating to an intervention (108). This implies that these traditional guidelines represent a challenge when evaluating public health interventions, as it risks not capturing relevant intersectoral impacts in analysis.

Because of the lack of focused guidance on the evaluation of public health interventions, international literature has begun to assess and update existing guidelines (15, 75, 104); such that they would allow

consideration of the complexity of public health interventions. As mentioned above, this includes the work by Drummond et al. (2015) recommending a multi-sectoral perspective when conducting economic evaluations of public health interventions as well as the work by Sanders et al. (2016) recommending a societal and a healthcare system perspective for analysis (75). Both approaches provide a framework that categorises costs and benefits into different sectors of society.

4.5 An example of the importance of intersectoral costs and benefits (COVID-19)

In this section, an Editorial is presented that is based on the work of this thesis and is published in the *International Journal of Technology Assessment in Health Care*. The Editorial is entitled 'The broader societal impacts of COVID-19 and the growing importance of capturing these in health economic analyses'. It demonstrates that the pandemic not only had devastating impacts on the health sector but also other sectors including the labour market and productivity, education, criminal justice, housing, consumption, and environment. It highlights the importance of adopting a societal perspective to consider these broader impacts of public health issues and interventions. Furthermore, it describes how the COVID-19 pandemic exposed and exacerbated existing deep-rooted structural inequalities that contribute to the wider societal impacts of the pandemic.

The main article in this chapter is kept the same as the original publication. A link to the published article is presented in Appendix 2.

4.5.1 Background

The rapid spread of the current coronavirus disease, SARS-CoV2 (COVID-19), has not only left societies with a high number of excess deaths and a wide range of health consequences but it has taken a heavy toll on wider global economies, impacting other sectors outside health (109). Moreover, COVID-19 exposed and exacerbated deep-rooted structural inequalities in our societies that can have an additional weight on the consequences arising from COVID-19.

The sectors most obviously affected by COVID-19 include the healthcare and social care sector, with high numbers of COVID-19 cases and deaths, in particular in the care home sector, straining healthcare facilities and entire health systems and leading to rapidly increasing healthcare costs (110, 111). Various areas of healthcare have suffered from the pandemic including the disruption in the delivery of essential health services, substantial increases in intensive care usage, shortages of medical equipment, disruption of routine immunisation, the increased vulnerability of those with underlying conditions, along with many other aspects.

However, the response to this pandemic has not only involved the health sector, but has required a whole society approach that involves a wide range of other sectors (112, 113). The pandemic has clearly exposed the broader societal impacts a public health threat can have on society. In addition to healthcare interventions (i.e. test and tracing, vaccination), multiple social restrictive measures have been employed 'to flatten the curve' and to reduce the pace and the extent of the infection rate including physical distancing, country lockdowns, and business and school closures (58). These measures certainly assisted in controlling the rapid spread of the virus but also led to additional strains and spillover-effects in other sectors including labour, education, criminal justice, housing, consumption, environment, among others (112, 113). In health economics, these broader societal impacts that spill over to other sectors of society outside health are referred to as *intersectoral* costs and benefits (15). Other international literature might also refer to *multi-sectoral* or *non-health(care)* costs and benefits or consequences.

In practice, assessing the economic impact of a disease or a health intervention commonly involves capturing the associated healthcare costs and productivity losses due to an illness, disability and/or premature death. Such narrow approach to conducting an economic analysis is likely to severely underestimate the total cost burden, potentially leading to suboptimal decision-making (i.e. inefficient resource allocation) (113). Although more recent research demonstrates the extent to which broader societal costs and benefits can contribute to the total cost burden of a disease or related intervention (114, 115), relevant spillover-effects are not always fully considered in economic analyses.

The aim of this editorial is to show how COVID-19 has exposed that broader societal costs and benefits are central for public health issues and interventions. In this paper, we acknowledge that the complex interplay between the different sectors can make it challenging to capture all relevant societal impacts in an economic evaluation, but that its estimation is fundamental for optimal decision-making. We also advocate the use of a societal perspective and suggest a way that can help assist in identifying and capturing the broader societal impacts.

To structure this paper and better demonstrate the different sectors affected by COVID-19, we used the impact inventory by The Second Panel on Cost-Effectiveness in Health and Medicine (see Table 2 in Chapter 4), a table outlining the different 'non-health care' sectors that can be impacted by a disease or health intervention more explicitly and transparently (104).

4.5.2 Understanding the broader societal impacts of COVID-19

The different sectors affected by COVID-19 illustrate the importance of considering a societal perspective.

Labour market and productivity

A wide range of measures were implemented to control the outbreak including the closure of non-essential businesses, quarantine, trade and travel restrictions, which have resulted in a slowdown of the global economies. The subsequent economic consequences on the labour market have involved being furloughed or laid off from work, loss of employment, a drop in the overall household income (116), and less employment opportunities being created due to business shutdowns or production cuts. The time spent on unpaid activities such as household work, childcare and supporting children's education at home increased for many (117).

Education

The closure of schools and other educational facilities had a severe impact on the education sector (118). Consequences included for instance interrupted learning and personal development opportunities, a limited social environment for children and teenagers as well as the lack of access to childcare options (119). For many teachers and students, the closures also meant moving to online, digital and distance learning as much as possible, which can be associated with certain challenges (i.e. disparity amongst families without access to technology or the internet, proctorship during online exams) (118). This change reflects a high level of adaptability, reorganisation and innovation.

Criminal justice

The introduction of new regulations to control the virus such as lockdowns and curfews required a reallocation of police time to enforce regulations related to this pandemic response and to ensure that people adhere to these regulations. It also stretched resources for many European criminal justice systems as, for instance, law enforcement agencies and courts needed to deal with proceedings against potential violations of new regulations. Further, crime rates for domestic violence and child abuse increased but simultaneously became less evident during the time of lockdown (120).

Housing

The impact of the current pandemic on the housing sector is wide-ranging, affecting tenants, mortgage-holders, real estate companies, sellers, buyers, builders, and more. At an individual level, decreasing employment opportunities and mass redundancies had an impact on many people's ability

to pay rent or mortgages. Various measures were implemented that aimed at, for instance, supporting tenants by freezing or reducing the monthly rent, halting transactions and introducing a mortgage holiday for lenders (121). In terms of real estate market, the demand for housing dropped, the numbers of property viewings decreased, and sellers and buyers are reconsidering their (mortgage) plans, along with many other aspects. Low mortgage rates can certainly be attractive to people that do want to invest at this particular time.

Consumption

Globally, non-essential businesses such as restaurants, cafes, bars and movie theatres were forced to temporarily close down. Meanwhile, supermarkets, pharmacies and other essential service providers faced an enormous strain to continue operating under the new regulations. Consumer behaviour and purchasing habits changed, with one example being panic-buying that led to a scarcity of essential supplies in supermarkets (122). As the demand for essential goods (i.e. food, medicines) increased during a pandemic, the demand for non-essential goods (i.e. travel, tourism) declined. Consequently, prices of goods with higher demand tend to increase posing a problem to many, but particularly the most vulnerable groups of society.

Environment

Travel restrictions and slowed production, in particular, led to a decrease in air pollution and greenhouse gas emissions (123). Internationally, this led to improvements in the quality of air, cleanliness of water and beaches (124). At the same time, the volumes of unrecyclable waste have risen due to the increase in the use of face masks and single-use packaging of goods (124).

In addition to the broader societal impacts there are structural inequalities that have been ripped open, further exacerbating the societal impacts of COVID-19 on society.

Exposing inequalities

The COVID-19 pandemic exposed and exacerbated existing deep-rooted structural inequalities and disparities in wealth that contribute to the wider societal impacts related to the COVID-19 pandemic. For example, people living under poorer socio-economic circumstances and those with underlying health conditions are at a higher risk of contracting the virus and developing complications compared to others. The current pandemic also exacerbated the domestic and household burden that is predominantly borne by woman. In general, employed women experienced a different and more severe impact as a consequence of the lockdowns, in particular those working in female dominated

professions such as in the hospitality/service industry and social care sector that were halted in many countries during lockdown (125). On average, women work fewer hours, have a lower salary and generally spend a shorter period of time in the labour market, making them more vulnerable to lay-offs, the loss of income and financial insecurities compared to men (125). Another example is the reduction in sexual health and contraception services due to reallocation of resources that have led to women facing difficulties in accessing (in-clinic) contraception services, which may impact their future employment (126). In addition, the lockdown imposed a higher burden on the mental health of people living under difficult socio-economic circumstances and those living in smaller houses and with less space. These are only a few examples that make it evident that these aspects of structural gender, health and socio-economic inequalities can exacerbate the broader societal impacts arising from this pandemic.

4.5.3 Discussion

The broader societal impacts of COVID-19 is indisputable. Alongside severe health impacts, this pandemic has led to wider and severe economic, social and political consequences to societies worldwide. Although the full overview of societal impacts is yet unknown, we have seen that a coordinated whole society response to this outbreak has been a successful driver - if not 'the' successful driver - in slowing the outbreak and mitigating its effects. It has become more than evident that all sectors of society have a role to play in the response and preparedness for an outbreak. We did not aim to provide a complete overview of all the sectors affected by COVID-19, but to demonstrate how we can begin to assess the impact of a public health threat on the different societal sectors.

The experience of the COVID-19 pandemic shows that a broader perspective and approach in health economics research can be essential for certain analyses. This includes for instance prevention, public health, social care, and mental health services. Further, a broader perspective can be particularly significant for chronic illnesses including 'Long COVID' that might result in an individual being off work due to the chronic impacts caused by their illness (127). Economic analyses need to consider the incorporation of broader societal impacts of public health issues and interventions and only omit these where it can be clearly justified as appropriate to do so. For many analyses, and where appropriate, it is the inclusion of wider societal impacts that can increase transparency and best inform decision-makers. Accounting for these wider impacts such as informal care, childcare or household activities in economic analyses can, however, be challenging (15). One aspect that can make this consideration problematic is the complex interplay between the different sectors caused by a public health threat.

As the complexity of capturing and quantifying these wider societal impacts is being recognised for COVID-19, as well as other public health issues, it is the right time to seek the opportunity for change, advocating the adoption of a societal perspective in economic analyses – again, unless its omission can truly be justified.

A narrow perspective applied in economic analyses tends to miss capturing the broader societal impacts of public health issues, ignoring potentially relevant costs and benefits. A broader perspective is expected to estimate all relevant societal costs and benefits, but many economic analyses that apply a societal perspective tend to only focus on the impact on the health and labour sector, particularly paid labour losses (16). A societal perspective also means that it is important to not only focus on paid production such as labour losses but also unpaid production. One approach to help ensure relevant societal impacts are fully captured in economic analyses - from a societal perspective - is the use of a sector-specific (cost) classification scheme, or structured table such as an impact inventory. In fact, the recommendations by the Second Panel on Cost-Effectiveness in Health and Medicine could be a useful tool for assessing which health interventions require a broader perspective in their evaluation (104).

Given the complex, fast-changing and fast-spreading nature of COVID-19, it is important that health economists continue to evaluate and re-evaluate the impact of the current pandemic and related measures. Health economic evidence will continue to be required to assist in further planning to control this virus and should always paint the full 'societal' picture.

4.6 Chapter summary

This chapter first introduced the concept of ICBs in health economic studies assessing public health interventions. Second, it explained why the consideration of ICBs under a societal perspective is important and, third, outlined methodological challenges associated with capturing ICBs in economic evaluations of public health interventions. Last, it illustrated the importance of ICBs for public health problems by looking at the intersectoral impacts of COVID-19. It outlined the broader societal impacts of COVID-19 on various sectors of society and demonstrated the growing importance of capturing these in health economic analyses. The next chapter (Chapter 5) will present a systematic review of COI studies of STIs and HIV, exploring the intersectoral costs included in analyses under a societal perspective.

CHAPTER 5 INTERSECTORAL COSTS OF SEXUALLY TRANSMITTED INFECTIONS (STIS) AND HIV: A SYSTEMATIC REVIEW OF COST-OF-ILLNESS (COI) STUDIES

5.1 Chapter overview

This chapter presents a systematic literature review of cost-of-illness (COI) studies. The review is published in *BMC Health Services Research* and a link to the review is presented in Appendix 3. The aim of the review was i) to explore the intersectoral costs associated with STIs and HIV considered in COI studies, ii) to categorise and analyse these costs according to cost sectors, and iii) to illustrate the impact of intersectoral costs on the total cost burden. This chapter presents those relevant intersectoral costs identified in the review, categorising them by (policy) sector, and illustrates that intersectoral costs associated with STIs and HIV are substantial and largely contribute to the total economic cost burden. As part of the review, a quality assessment of COI studies was undertaken. In doing so, it became evident that there is currently no single standard quality/ critical appraisal tool to review and assess COI studies. This systematic literature review hence presented the opportunity to explore and to address this research gap further in Chapter 8 and 9.

The main article in this chapter is kept the same as the original publication.

5.2 Background

Sexually transmitted infections (STIs) remain a health threat to millions of people (128). Healthcare costs for STIs and human immunodeficiency virus (HIV), particularly direct medical costs (i.e. drugs, hospitalisation), represent a substantial cost burden on society (129, 130). However, STIs and HIV can also have an impact on the wider economy, affecting other sectors of society such as labour, household and education (8, 46). Costs associated with a disease that occur both within and outside the health sector are typically defined as *societal* (131), *multisectoral* (102) or *intersectoral* costs (5).

Cost-of-illness (COI) studies are a commonly used framework designed to identify, measure and value the costs incurred by society due to a particular disease (96, 97). The consideration of intersectoral costs in these studies can generate useful information fundamental for optimal policy/decision-making, including the process of resource allocation to optimise population health and to justify the necessity of an intervention (96, 97).

The majority of existing COI studies, however, primarily consider healthcare costs and, as a consequence, potentially underestimate the total cost burden of a disease to society (132). An

underestimation of the complete cost burden could lead to an inefficient use and distribution of public health resources. A more comprehensive picture of the costs associated with STIs and HIV is crucial to increasing the prioritisation of STIs and HIV on the public health agenda and in the wider political arena, and is important in making the case for more financial support for the area of sexual health.

A societal perspective is often considered appropriate for COI studies, as it allows us to capture all relevant costs in economic analyses (95), but not all studies adopt such a perspective. In some countries where national health economic guidelines require taking a societal perspective, such as in the Netherlands (133), it is vital to consider all relevant costs associated with a disease including healthcare costs and costs spilling over to other sectors (i.e. intersectoral costs). Other countries including the United Kingdom often adopt a healthcare (or National Health Service (NHS)) perspective and predominantly assess costs falling on the healthcare sector (134), but there is acknowledgment of the benefit of considering a wider perspective in the analysis (105). The increasing interest by national authorities in capturing intersectoral costs of public health problems in economic studies reflects the importance of these costs (105). It is notable that the consideration of the intersectoral impacts of a disease has also received more prominence in light of the current COVID-19 pandemic and could potentially shape the way in which economic assessments are done moving forward (113, 135).

Studies exist that identify, measure and value intersectoral costs in areas as, for example, mental health (5) and alcohol prevention programmes (136) but are limited in the field of sexual health. To date, the wider intersectoral impacts of STIs and HIV on society are relatively unexplored but can be significant given the rising STI rates and growing demand for sexual health services (137). The current review aims (i) to explore the intersectoral costs associated with STIs and HIV considered in COI studies, (ii) to categorise and analyse these costs according to cost sectors, and (iii) to illustrate the impact these intersectoral costs can have on the total cost burden of STIs and HIV.

5.3 Methods

Prior to conducting the systematic review, a protocol was registered and published with PROSPERO (Registration Number: CRD42019130940). The PRISMA guidelines were followed for the reporting of this review (Appendix 4) (138).

5.3.1 Search strategy

An extensive search strategy was developed in PubMed as part of a larger systematic literature review including COI and economic evaluation studies (Appendix 5). Relevant key search terms for this present review included terms for cost-of-illness, cost analysis and all terms for STIs including specific infections. Seven databases were searched: Medline (PubMed), EMBASE (Ovid), Web of Science, CINAHL, PsycINFO, EconLit and NHS EED, limiting studies to 1999-2019. Reference lists of selected articles were screened.

5.3.2 Inclusion criteria

Studies were included that assessed costs beyond healthcare costs and were conducted in an Organisation for Economic Co-operation and Development (OECD) member country. The country scope was chosen for better evaluation of comparable health systems and policies. Studies were selected that focused on STIs that were sexually transmitted, and included participants of at least 12 years or older.

5.3.3 Selection of papers

Search results were exported into EndNote X9. Citations were systematically de-duplicated following the guidelines by Bramer and colleagues (139). The study selection was performed by two reviewers (LS, LJ). A three-stage process was adopted to guide the screening of studies for inclusion (140). In stage I, one independent reviewer (LS) screened articles on the basis of titles only, followed by stage II title and abstract screening. The same reviewer categorised included studies into groups as either a A) cost-of-illness study or B) economic evaluation. Studies were further categorised by disease; a) Chlamydia, b) Gonorrhoea, c) Trichomoniasis, d) Herpes/HSV, e) HIV, f) HPV, g) Syphilis, h) Hepatitis B, and i) more than one STI. Studies other than a COI study or economic evaluation were excluded. A second reviewer (LJ) reviewed this process and discrepancies were discussed. This review's analysis focuses on A) COI studies of all diseases (a-i). COI studies were screened for full-text in Stage III. A standardised data extraction form was adopted and modified for the purpose of this review (5, 141).

5.3.4 Analysis

Data were recorded in Microsoft Excel and Word and analysed narratively. A cost component table was established with inspiration from pre-defined sector-specific classification schemes to inform the analysis (5, 75). Cost results for intersectoral costs were listed, categorised and analysed. While assessing the impact of intersectoral costs on the total costs, the reported costs were converted to US

Dollar and the year 2021, adjusting the values by inflation. This was done using an online inflation tool (22) and a currency converter (21).

5.3.5 Quality assessment

No single standard quality assessment tool exists for COI studies. The quality of studies was assessed using a modified version of the Consensus on Health Economic Criteria (CHEC) list (Appendix 6) (142). The guide for critical evaluation of COI studies by Larg & Moss (2011) was also considered (143). The quality assessment was not used to mediate articles for inclusion/exclusion, but to inform the analysis. The results for the quality assessment are presented narratively.

5.4 Results

The search strategy, as part of a larger systematic literature review, identified 21,935 articles after de-duplication. Due to the high number of records identified between 1999-2019, studies were further limited to 2009-2019, which led to the exclusion of 6,426 studies. This time period was selected to reflect the greater attention focused on incorporating intersectoral costs in economic analyses over the past ten years (15, 105, 107). Studies were excluded that did not mention any cost data concerning STIs. Seventy-five COI studies were considered for title/abstract screening. Studies were further excluded that assessed healthcare costs only. Ten studies were eligible for full-text screening of which five were only available in form of an abstract or poster (Appendix 7). Corresponding authors were contacted. One study was found by screening the reference lists of the other five studies selected for analysis (144). Ultimately, six studies were available for full-text analysis and qualified for data extraction and narrative synthesis, having considered intersectoral costs in their analyses, see Figure 2.

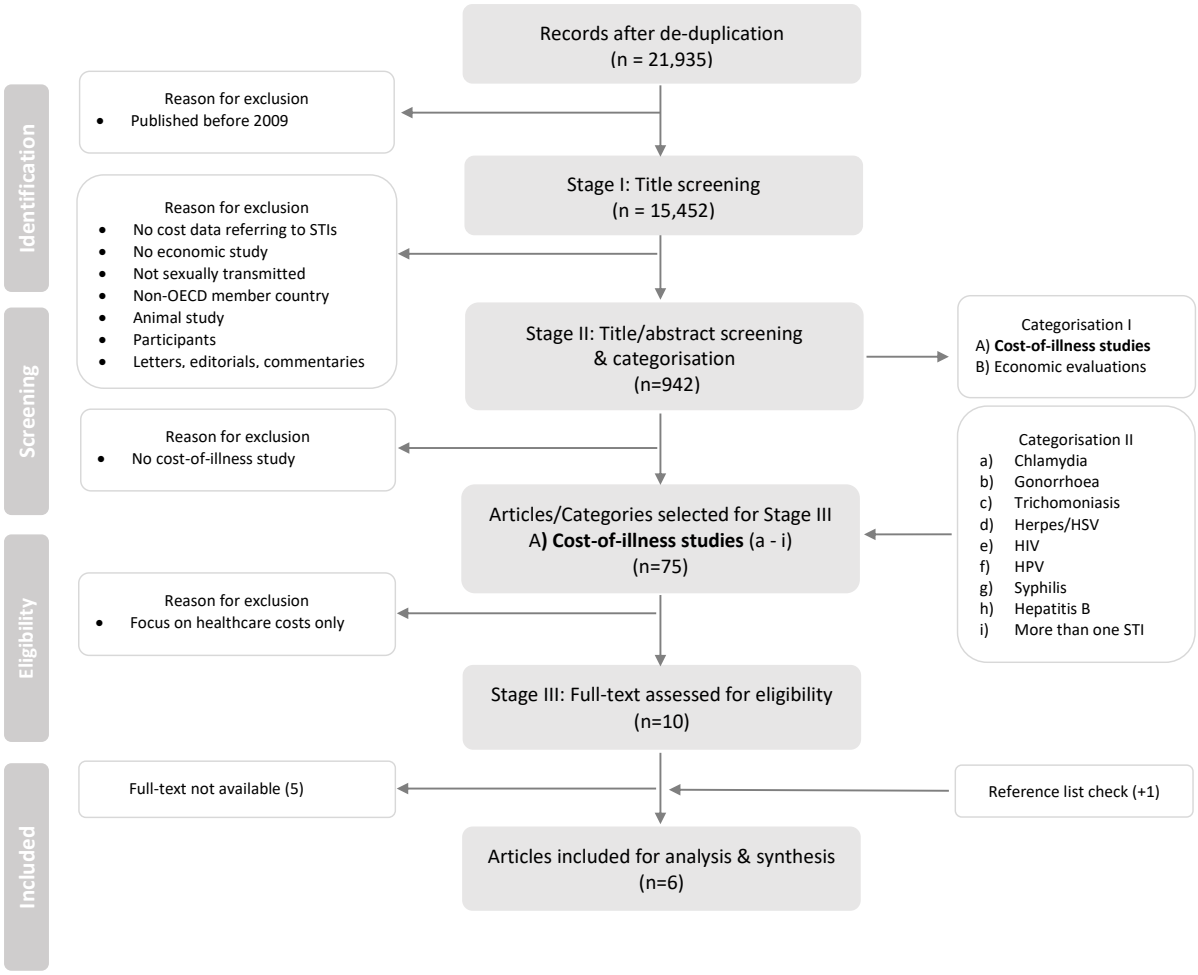

Figure 2 PRISMA flowchart

5.4.1 Study characteristics

Table 3 presents a summary of the study characteristics. Included studies were conducted in Germany, Spain, The United States and South Korea. The societal approach is the recommended approach for ensuring the total cost of a disease is captured and was fully adopted by four studies (8, 144-146). The other two studies used a combination of a societal and payer perspective; both were carried out in Germany (147, 148). A prevalence-based approach is appropriate when assessing the total costs of a disease within a specific timeframe and was followed by three studies (144-146). The remaining studies did not explicitly report the epidemiological approach taken. A bottom-up costing approach can record the quantity of resource use at an individual level ensuring all relevant costs are captured and was followed by the three studies that all focused on HIV (145, 147, 148). The remaining three studies used evidence from claims data or other aggregated data (8, 144, 146), which is typical for a top-down approach. Two studies reported to have used a prospective study design (147, 148), whereas one used a retrospective approach (145).

Table 3 Study characteristics

Authors	Year	Country	Type of STI	Perspective	Epidemiological approach	Resource quantification	Study design	Time horizon	Year of valuation	Currency
Kuhlmann et al.	2015	Germany	HIV	Payer (SHI), Societal	NR	Bottom-up	Pro	2009-2011	2009	EUR
Lopez-Bastida et al.	2009	Spain	HIV	Societal	P	Bottom-up	Re	2013	2003	EUR
Mostardt et al.	2013	Germany	HIV	Payer (SHI), Societal	NR	Bottom-up	Pro	2006-2009	2008	EUR
Owusu-Edusei et al.	2013	USA	Non-viral STIs (Chlamydia, Gonorrhoea, Syphilis, Trichomoniasis)	NR (Societal)	NR	NR	NR	2001-2005	2011	USD
Shon et al.	2015	South Korea	Hepatitis A B C	Societal	P	NR	NR	2008-2011	Average exchange rate during 2008-2011	USD
Yang et al.	2010	South Korea	Hepatitis B	Societal	P	NR	NR	2005	2005	KRW

EUR=Euro
HIV=Human Immunodeficiency Virus
KRW=Korean Won
NR=Not reported
P=Prevalence

Pro=Prospective
Re=Retrospective
SHI=Statutory Health Insurance
USD=United States Dollar

5.4.2 Intersectoral cost components

Table 4 shows which intersectoral costs are included in the selected studies. Five of the six studies estimated healthcare costs and costs in at least one of the following sectors: *patient and family, informal care and productivity (paid labour)* (144-148). One study assessed productivity (labour) costs only (8).

Table 4 Intersectoral costs identified in the selected studies

Cost components per sector/ Authors	**Kuhlmann et al.**	**Lopez-Bastida et al.**	**Mostardt et al.**	**Owusu-Edusei et al.**	**Shon et al.**	**Yang et al.**	**Total**
Patient and family	✓		✓		✓	✓	**4**
Out-of-pocket costs as part of health systems/insurance co-pay [a]	✓				✓	✓	
Out-of-pocket costs outside health systems/insurance [b]						✓	
Out-of-pocket costs for hired caregiver						✓	
Travel expenses for patients			✓		✓	✓	
Travel expenses for family/caregiver						✓	
Informal care			✓		✓	✓	**3**
Time invested/productivity lost by non-paid family/friends			✓			✓	
Caregiver support for outpatient care					✓[x]		
Patient productivity - paid labour	✓	✓	✓	✓	✓	✓	**6**
Productivity loss due to absenteeism [c]	✓		✓	✓	✓	✓	
Productivity loss due to morbidity		✓				✓	

Productivity loss due to disability	✓		
short-term	✓		
long-term	✓		
Partial	✓		
Productivity loss stemming from cease-to-work			✓
Productivity loss due to premature death		✓	✓

[a] Categorised and assessed alongside healthcare costs (direct costs) in the original study. It includes patient out-of-pocket co-payments for medical services and drugs not covered by the national health insurance. Kuhlmann et al. referred to it as patient costs (or *Patientenkosten* and *Patientenzuzahlungen)*.
[b] Categorised and assessed alongside healthcare costs (informal direct medical costs) in the original study. It includes over-the-counter drugs, dietary supplements, folk remedies, traditional Korean medicine services and other treatment-related resource utilisations paid for by patients.
[c] Three studies (Owusu-Edusei et al., Shon et al., and Yang et al.) accounted for patient time lost, for instance, for care-seeking. The studies equated these to productivity or income lost.
[*] It was not clear whether caregivers involved paid or unpaid support and whom this involved (i.e. friends, family).

Patient and family costs were addressed in four studies, with some costs being related to healthcare services and treatment within a national insurance system and others to patient-borne expenses outside an insurance system (144, 146-148). Kuhlmann et al. estimated patient out-of-pocket payments or co-payments for their antiretroviral treatment that were not fully covered by their health insurer (147). Healthcare costs that were not covered by the insurer and co-payments for medical services and drugs were also captured by Shon et al. and Yang et al. (144, 146). Other treatment-related costs paid for by the patient included over-the-counter drugs, dietary supplements, folk remedies and other traditional Korean medicine services (144). Yang et al. also captured patient out-of-pocket costs for hired caregivers (144). Expenditures incurred by the patient for traveling to medical visits were estimated in three studies (144, 146, 148). In addition to patient transportation costs, Yang et al. also captured the transportation costs incurred by caregivers (144). All three studies classified travel expenses incurred by the patient or caregiver under healthcare costs (direct non-medical costs).

Two studies explicitly reported to have captured informal care costs, which were concerned with unpaid (home) care support by family or friends (144, 148). Mostardt et al. captured home care provided by family/friends as part of direct costs (healthcare costs) (148), whereas Yang et al. classified and calculated time and productivity costs by caregivers as part of indirect costs (non-health costs) (144). A third study, Shon et al., also captured caregiver costs as part of indirect costs (non-health costs) but did not specify whether caregivers involved paid or unpaid support and whom this involved (i.e. family, friends) (146).

Productivity costs can involve productivity losses for paid and non-paid opportunity costs (i.e. leisure time, domestic work). All six studies estimated patients' productivity costs for paid labour, including costs in terms of absenteeism, short-term/partial/long-term disability, cease-to-work, presenteeism or premature death (8, 144-148). One study assessed productivity (labour) losses for outpatient patients only (8).

5.4.3 The impact of intersectoral costs on the total costs of STIs and HIV

The impact of HIV-related productivity costs per year per patient on the overall costs were presented in three studies and varied between 9% and 41% (145, 147, 148), see Table 5. For non-viral STIs, the average productivity loss per case was estimated at $262 for chlamydia, $197 for gonorrhoea, $419 for syphilis and $289 for trichomoniasis (8). The study did not estimate the healthcare costs involved; therefore, it was not possible to illustrate the additional impact productivity costs have on the total costs. However, the authors argued that productivity losses related to non-viral STIs might be higher

than healthcare costs. For hepatitis A, B and C, opportunity costs lost (as a result of seeking medical care, or premature death and caregiver costs) represented 65%, 53.4% and 42.0% of the total costs, respectively (146). The intersectoral costs for Hepatitis B as estimated by Yang et al. represented around 75,5% of the total costs (144).

Table 5 The impact of intersectoral costs on the total costs

Authors	Healthcare costs	Patient/family costs	Productivity (labour) costs	Total intersectoral costs	Total costs (healthcare and intersectoral)	Proportion of intersectoral costs on the total cost (%)
Kuhlmann et al. (HIV)	Total healthcare costs: 22,457 €/year [2009-2011] per patient	Patient out-of-pocket costs: 216 €/year per patient	1,890 €/year per patient	2,106 €/year per patient	24,563 €/year per patient	9%
	[US$ 2021: 29.437]	[US$ 2021: 283]	[US$ 2021: 2,474]		[US$ 2021:32.200]	[US$ 2021: 2,765]
Lopez-Bastida et al. (HIV)	Total healthcare costs (asymptomatic HIV): 7,148 €/year [2003] per patient	NA	Asymptomatic HIV: 3,383 €/year per patient	3,383 €/year per patient	Asymptomatic HIV: 10,531 €/year per patient	"Productivity losses for people living with HIV to range between 3,383€ (asymptomatic HIV) and 5,981€ (symptomatic HIV), representing a range of 32-41% of the total costs." [as reported in the original study]
	[US$ 2021: 10,611]		[US$ 2021: 5,023]		[US$ 2021: 15,635]	NA
	Total healthcare costs	NA	Symptomatic HIV: 5,981 €/year per patient	5,981 €/year per patient	Symptomatic HIV: 14,489 €/year per patient	NA

	(symptomatic HIV): 8,508 €/year per patient					
	[US$ 2021: 12,632]	NA	[US$ 2021: 8,879]		[US$ 2021: 21,512]	NA
Mostardt et al. (HIV)	Total healthcare costs (SHI): 19,103 €/year [2008] per patient*	NA	Disability-related productivity loss (labour): 489 €/year per patient	489 €/year per patient	23,298 €/year per patient	"Nine percent of total cost from the societal perspective could be attributed to indirect costs [disability, productivity loss]." [as reported in the original study]
	[US$ 2021: 25,865]	NA	[US$ 2021: 662]		[US$ 2021: 31,542]	NA
		NA	Long-term productivity loss (labour): 1,294 €/year per patient	1,294 €/year per patient	NA	NA
			[US$ 2021: 1,752]			
		NA	Partial productivity loss (labour): 337 €/year per patient	337 €/year per patient	NA	NA
			[US$ 2021: 456]			

Owusu-Edusei et al. (non-viral)	NA	NA	Average productivity costs (labour) per case/2001-2005 [2011 values]: US$ 262 for chlamydia [US$ 2021: 312]	US$ 262 for chlamydia per case	NA	NA
			US$ 197 for gonorrhoea [US$ 2021: 234]	US$ 197 for gonorrhoea per case		NA
			US$ 419 for syphilis [US$ 2021: 498]	US$ 419 for syphilis per case		NA
			US$ 289 for trichomoniasis [US$ 2021: 344]	US$ 289 for trichomoniasis per case		NA
Shon et al. (Hepatitis A, B, C)	NA	NA	NA	NA	Hepatitis A: US$ 45.7 million/2008-2011 [US$ 2021: 54,3 million]	"[…] with indirect costs [opportunity costs lost as a result of medical care, or premature death and caregiver costs] accounting for the remaining 65% during the

						observation period [2008-2011].” (Hepatitis A)
	NA	NA	NA	NA	Hepatitis B: US$ 607.8 million/2008-2011 [US$ 2021: 722.8 million]	“Indirect costs were estimated to be approximately 53.4% of this total over the same period [2008-2011]” (Hepatitis B)
	NA	NA	NA	NA	Hepatitis C: US$ 90.7 million/2008-2011 [US$ 2021: 107.8 million]	“[…] with indirect costs accounting for the remaining 42.0% in 2011.” (Hepatitis C) [as reported in the original study]
Yang et al. (Hepatitis B)	Direct costs (direct formal medical costs, informal medical costs, and non-medical costs): 474,642 million KRW/year [2005] [or 0.474,642 trillion]**	NA [refer to the column on the right]	Indirect costs (time costs, caregiver costs, productivity losses): 1.463 trillion KRW/year incurred by HBV-related disease patients	1.463 trillion KRW/year incurred by HBV-related disease patients	1.937 trillion KRW/year	75,5%

	[US$ 2021: 558,639,140]	[US$ 2021: 1,721,832,880]	[US$ 2021: 2,279,692,610]

KRW = Korean Won
NA=Not applicable
SHI=Statutory health insurance
US$ = United States Dollar
*In the original study, patient travel costs and costs for homecare provided by family/friends were included in the calculation of healthcare costs.
**In the original study, patient costs (patient resource consumption outside the health care system: dietary supplements, over the counter drugs, other treatment-related services) and transportation costs were included in the calculation of direct costs (healthcare costs).

5.4.4 Quality assessment

The quality of the COI studies did not vary considerably, but methodological differences were evident (Appendix 6). Five studies mentioned the study perspective adopted for analysis (145-148). The type of epidemiological approach taken was explicitly reported by three studies, in this case a prevalence-based approach (144-146). Three studies explicitly reported they had used a bottom-up approach for resource use quantification (145, 147, 148). The same studies also stated the type of study design, with two assessing data prospectively (147, 148) and one retrospectively (145). One study did not disclose any information regarding the choice of methodological approaches such as perspective, resource quantification, study design or epidemiological approach (8). The time horizon for assessment, year of cost evaluation and currency were reported in all studies. Important costs were identified, measured and valued in five studies in relation to the perspective and the study objectives (144-148). One study limited their analysis to productivity (labour) costs, though, this was also in line with their research objectives (8). None of the studies discounted future costs. Sensitivity analysis was conducted in one study (144). Almost all studies discussed the generalisability of results.

5.5 Discussion

5.5.1 Principal findings

This review is the first to explore whether existing COI studies carried out for STIs and HIV considered intersectoral costs in their analyses, and to categorise these according to specific cost sectors. Further, it clearly demonstrates that intersectoral costs significantly contribute to the total cost burden of STIs and HIV.

Only a small number of COI studies were identified that captured intersectoral costs of STIs and HIV. This small number implies that intersectoral costs are often overlooked in the literature and remain largely excluded from COI studies in this area. Some might argue this finding could indicate that intersectoral costs are not relevant, but this review concludes differently. For example, this review provides evidence that productivity losses for people living with HIV can account for up to 40% of the total costs per year.

There are several reasons that could explain why many studies ignored the wider scope of costs, even though intersectoral costs for STIs and HIV can be substantial (8). One reason could be a more narrow study perspective applied, for instance, to inform decision-makers in the health sector that might only be interested in the costs paid from the health budget. Another reason could be feasibility in terms of the lack of time, resources or data available for the wider analysis. Yet another reason for a narrow

focus on costs might be the lack of realisation of the importance of intersectoral costs, particularly in COI studies. As mentioned earlier such lack of realisation might have changed in light of the current COVID-19 pandemic that has exposed the larger intersectoral impacts of health issues on society (57, 113). The importance of considering these wider costs is evident and fundamental in order to avoid the risk of omitting important costs to inform decision-making, in both health and other sectors.

This review suggests that the COI studies that adopted a societal perspective tend to predominantly assess healthcare and productivity costs related to paid labour. This is in line with previous research reporting that even when a societal perspective is adopted in economic studies these often only consider healthcare and labour costs (16). The focus on healthcare and productivity costs could be explained by the fact that traditional approaches to COI studies broadly divide costs into direct, indirect and intangible costs (93). The included studies reveal that the biggest impact of intersectoral costs was in the labour market. It was suggested that productivity losses could potentially be greater than healthcare costs (8).

The present findings suggest that the assessment of unpaid labour and non-paid opportunity costs such as leisure time, volunteering and care for children or elderly is rather limited in COI studies. Similar findings were found for full economic evaluations (i.e. cost-effectiveness analysis) (149), however, the inclusion of these types of economic evaluations associated with interventions for STIs is explored elsewhere (PROSPERO, Reference ID: CRD42019130940).

As mentioned earlier, intersectoral costs can have a big impact on the total cost burden. In fact, this review reveals that the inclusion of intersectoral costs attributed to STIs and HIV indicate a substantially higher cost burden to society than healthcare costs alone. This means that unless intersectoral costs are taken into account, the total cost implications of STIs will not be appreciated. This is in keeping with a review of COI studies by Pike and colleagues (2015) which reported that limiting the assessment of the economic burden to healthcare costs can substantially underestimate the total economic cost burden (150).

This review found that the heterogeneity of methodological approaches in COI studies, including the choice of study perspective(s) and what costs to include in analysis, made it rather difficult to analyse and compare the impact of intersectoral costs across studies. The use of different methods in cost analyses can affect how results are interpreted and subsequently affect policy decisions. This review raises awareness to the potential need for standardised guidelines for COI studies and a standard

quality assessment tool for COI studies to assess the consistency and transparency of these studies and improve comparability.

5.5.2 Policy implications

The present review shows that only a small number of COI studies of STIs and HIV include intersectoral costs. Those studies that do capture intersectoral costs tend to report a higher burden of STIs and HIV, which is important information for policy/decision-makers. These findings imply that if intersectoral costs are not included in cost analyses, the total cost burden of STIs and HIV to society is severely underestimated. If intersectoral costs are captured in COI studies this may change the overall results and is likely to improve the information developed for decision/policy-makers. Realising the higher cost burden of STIs and HIV might give more prioritisation to interventions targeted at reducing the number of STIs and HIV compared with other competing demands on the healthcare budget.

5.5.3 Strengths and weaknesses of the study

The strength of this review lies in its rigorous and systematic approach. A comprehensive search strategy was developed in collaboration with an information specialist. Studies were carefully screened to evaluate whether intersectoral costs had been captured and a cost component table (or sector-specific (cost) classification scheme) was established that can be adapted or expanded by future research, as needed. The present review considered studies conducted in all OECD member countries to account for a good representation of study results. Further, this review was able to synthesise evidence that addresses the impact intersectoral costs of STIs and HIV can have on the total economic burden. This review also has some limitations. One limitation is that other studies that potentially assessed intersectoral costs may have been missed. The articles were limited to the timeframe of 2009-2019. Five potentially relevant articles eligible for full-text analysis were only available in form of abstracts or posters. After finding that only six studies were eligible for data extraction and narrative synthesis and available in full the review team scanned a random number of excluded studies to check whether potentially relevant articles may have been missed. Further, the complex nature of STIs and HIV requires an examination of the wider societal impacts, and the included studies might not represent the fuller range of potentially relevant cost sectors. This however also means that the present sector-specific (cost) classification scheme could serve as a guide for future research and offers room for expansion.

Overall, this review has generated pertinent evidence and presents a clear message that the focus of most of the existing COI studies to date is largely on healthcare costs when it is evident that the impact of disease is wider and more substantial.

5.5.4 Further research

Future research could further investigate relevant cost sectors associated with STIs and HIV and validate or complement the findings of this review. Gathering more evidence could help propose a standardisation of sector-specific (cost) classification scheme for COI studies concerned with STIs and HIV. Economic evaluations could be reviewed to identify the different sector-specific costs as well as benefits associated with interventions targeting STIs and HIV.

5.6 Conclusion

It is evident that intersectoral costs associated with STIs and HIV are substantial and largely contribute to the total economic cost burden. However, studies tend to predominantly assess healthcare and productivity costs related to paid labour under a societal perspective. If relevant intersectoral costs are not included in cost analyses the total cost burden of STIs and HIV to society is severely underestimated. Therefore, intersectoral costs associated with STIs and HIV need to be addressed in order to ensure the total economic burden of STIs and HIV on society is assessed and communicated to policy/decision-makers.

5.7 Chapter summary

This chapter presented a systematic literature review of COI studies that explored the intersectoral costs associated with STIs and HIV and categorised these into cost sectors. As part of this, the impact of intersectoral costs on the total cost burden was demonstrated. This chapter also presented further evidence that there is a lack of a standard critical appraisal tool to review and assess COI studies. Chapter 8 and Chapter 9 both explore and address this research gap. The following chapter presents a systematic review of economic evaluations of interventions relating to STIs, exploring the intersectoral costs considered in these studies under a societal perspective.

CHAPTER 6 ARE INTERSECTORAL COSTS CONSIDERED IN ECONOMIC EVALUATIONS OF INTERVENTIONS RELATING TO SEXUALLY TRANSMITTED INFECTIONS (STIS)? A SYSTEMATIC REVIEW

6.1 Chapter overview

This chapter presents a systematic literature review of economic evaluations. The review is published in *BMC Public Health* and a link to the review is presented in Appendix 8. The review aimed i) to review and identify economic evaluations of interventions relating to STIs, which aimed to include a societal perspective; ii) to analyse the intersectoral costs included; iii) to categorise these costs by sector; and iv) to assess the impact of intersectoral costs on the overall study results. This chapter introduces the relevant intersectoral costs identified in the systematic literature review, categorising them by (policy) sector and illustrating them in a (cost) classification scheme. The findings reveal that the inclusion of intersectoral costs as presented in this scheme can result in more favourable cost estimates. This chapter concludes that economic evaluations of interventions relating to STIs that adopt a societal perspective tend to be limited in scope, and that there is an urgent need for economic evaluations to be more comprehensive.

The main article is kept the same as the original publication.

6.2 Background

Sexually transmitted infections (STIs) continue to rise worldwide and generate important impacts on society (46). STIs and their sequelae are shown to not only have an impact on the health sector but also the private resources of those affected, their families and other sectors of society (151). Living with an STI can, for instance, affect an individual's productivity and participation in the labour market (9, 152, 153). It can also have a considerable impact on an individual's mental health (i.e. stigma, depression), compromising an individual's overall quality of life (154-156). The wider societal impacts spilling over to other non-health sectors are also referred to as *societal* (101), *multisectoral* (102) or *intersectoral* costs and benefits (or consequences) (5, 13). This review will use the term *intersectoral* costs.

Interventions relating to STIs are essential but complex in nature (like many other public health problems). This complexity can, in part, be explained by the aforementioned wide-ranging, intersectoral impacts of public health programmes, and this can create challenges in adequately capturing them in economic evaluations (13, 107). The study perspective (or viewpoint) adopted in an economic evaluation ultimately determines the costs and benefits included in the analysis. A societal

perspective is increasingly being advocated for economic evaluations of public health interventions as it is expected to capture all relevant costs and benefits associated with an intervention both within and beyond health (18, 86). Depending on the study objective and stakeholder interests, it may be appropriate to assess costs and benefits from other perspectives (i.e. when estimating the financial costs of an intervention to a specific healthcare system or provider).

Even though a societal perspective has been advocated in methodological guidelines for some time (75), it is not always adopted or, if attempted, tends to be incomplete (149, 157-160). As indicated above, this can be due to the methodological challenges associated with quantifying the intersectoral impacts of public health interventions (15). However, evidence suggests that the societal costs associated with STI-related interventions can substantially contribute to the total economic cost burden (151, 152). This implies that excluding intersectoral costs from analyses could severely underestimate the total cost burden and present incomplete economic information to policy/decision-makers, potentially leading to suboptimal decision-making (i.e. inefficient allocation of resources) (149, 158, 161). Hence, more comprehensive economic evidence is needed that will allow policy/decision-makers to better understand the total cost burden associated with STIs.

Given the importance placed on the societal perspective and the potential for suboptimal policy decisions in the absence of a comprehensive evaluation, a systematic review of published economic evaluations which adopted a societal perspective was undertaken. The review aimed to explore the intersectoral costs considered under a societal perspective in economic evaluations of interventions relating to STIs, and the impact of including intersectoral costs on the overall study results. The specific objectives of this review were to i) identify economic evaluations of interventions relating to STIs which aimed to include a societal perspective; ii) analyse the intersectoral costs (i.e. costs broader than healthcare) included; iii) categorise these costs by sector (i.e. patient/family, productivity, other); and iv) assess the impact of intersectoral costs on the overall study results.

6.3 Methods

A protocol for this review was published in PROSPERO, the International Prospective Register of Systematic Reviews database (CRD42019130940). The review systematically followed the Centre for Review and Dissemination (CRD) guidance for undertaking reviews in health care (162) and a five-step approach on how to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions (141, 163, 164). PRISMA guidelines were followed for the reporting of this review (165) (Appendix 9).

6.3.1 Search strategy

A search strategy was developed in PubMed for MEDLINE together with an information specialist before adapting for use in other databases (Appendix 10). Seven electronic databases were searched (1999-2019): MEDLINE (via PubMed), EMBASE (via Ovid), Web of Science (Core Collection), CINAHL, PsycINFO, EconLit and NHS EED. The search strategy was updated for 2020-21 in Medline (PubMed) only. The year 1999 was initially chosen as a starting year to reflect the inception of the UK National Institute of Health and Care Excellence (NICE) and their implementation of guidance statements for the conduct of health economic evaluations. Key search terms included terms for economic evaluation and STIs including specific infections.

6.3.2 Inclusion criteria

This review considered both trial- and model-based economic evaluations of any intervention relating to STIs that were conducted in an Organisation for Economic Co-operation and Development (OECD) member country. OECD member countries were chosen due to their similarities in terms of health(care) systems and to better compare the methodology of studies concerned with similar health(care) systems. It focused on full economic evaluations that adopted a societal perspective, including cost-effectiveness analyses (CEA), cost-utility analyses (CUA) and cost-benefit analyses (CBA). The methods of CEA, CUA and CBA have varying theoretical foundations and outcomes are expressed differently. A CEA measures assesses outcomes (effects) in natural units, whereas a CUA assesses outcomes in health utilities such as quality-adjusted life years (QALYs). A CBA assesses both costs and outcomes in monetary values. No restrictions were placed on the type of comparator or outcomes. Participants in an intervention had to be at least 10 years of age to reflect international definitions of the start of adolescence (a period during which individuals establish sexual maturation and sexual activity) (166). See Appendix 11 for a PICO table.

6.3.3 Screening of data and data extraction

Search results were exported into EndNote X9. Citations were de-duplicated following the guidelines by Bramer and colleagues (2016) (139). The study selection was performed by two reviewers (LS, LJ). A systematic process was adopted to guide the screening of studies for inclusion (140). Stage I: title screening (LS), stage II: title/abstract screening and categorisation of selected studies by study type and disease group (LS), and stage III: full-text screening (LS). This process was checked by a second reviewer (LJ) and discrepancies were discussed. A standardised data extraction sheet was utilised to record data on study characteristics, intersectoral costs and cost-effectiveness estimates for those

studies that adopted a societal perspective in addition to a healthcare and/or provider perspective (to illustrate the difference in study results for each perspective) (141). Corresponding authors of selected studies were contacted for clarification where it was not clear what types of costs were considered. A PRISMA flowchart illustrates the selection process (Figure 3).

6.3.4 Analysis

Data were recorded using Microsoft Excel and Word. Intersectoral costs were identified, extracted and categorised by sector using Drummond's sector-specific classification scheme (75) (Table 6). Drummond and colleagues categorise costs into (i) healthcare, (ii) patient and family, (iii) productivity, and (iv) costs in other sectors such as informal care, educational costs, costs in the criminal justice system, household and/or leisure costs (5). The reported intersectoral costs were converted to US Dollars and the year 2021, adjusting the values by inflation. This was done using an online inflation tool (22) and a currency converter (21). A narrative synthesis was performed following CRD guidelines (162).

Table 6 Sector-specific cost classification scheme based on Drummond et al. (2015)

Sector	**Examples of cost components/resource items**
Healthcare	i.e. treatment, medication, hospitalisation, other
Patient and family	i.e. patient time, out-of-pocket costs, travel expenses, other
Productivity	i.e. lost working days (labour costs), lost income, other
Costs in other sectors	i.e. education, criminal justice, leisure, household, informal care, other*
*Examples are based on Drost et al. (2013) and Edwards et al. (2013)	

6.4 Results

The search strategy generated 23,895 studies after duplicates were removed. Studies were further limited to those published from 2009 onwards, excluding 6,483. Though this was due to a high number of records identified in the databases, the publication date reflects the period of time during which intersectoral costs and benefits have gained more prominence (15, 105, 107). Titles and then abstracts were screened, and a total of 572 economic evaluations were identified. Studies were further screened to exclude evaluations that considered healthcare or intervention costs only. In total, 48 studies were identified for full text screening and 29 studies were taken forward for data extraction and narrative synthesis (please refer to Appendix 12 for a list of excluded studies).

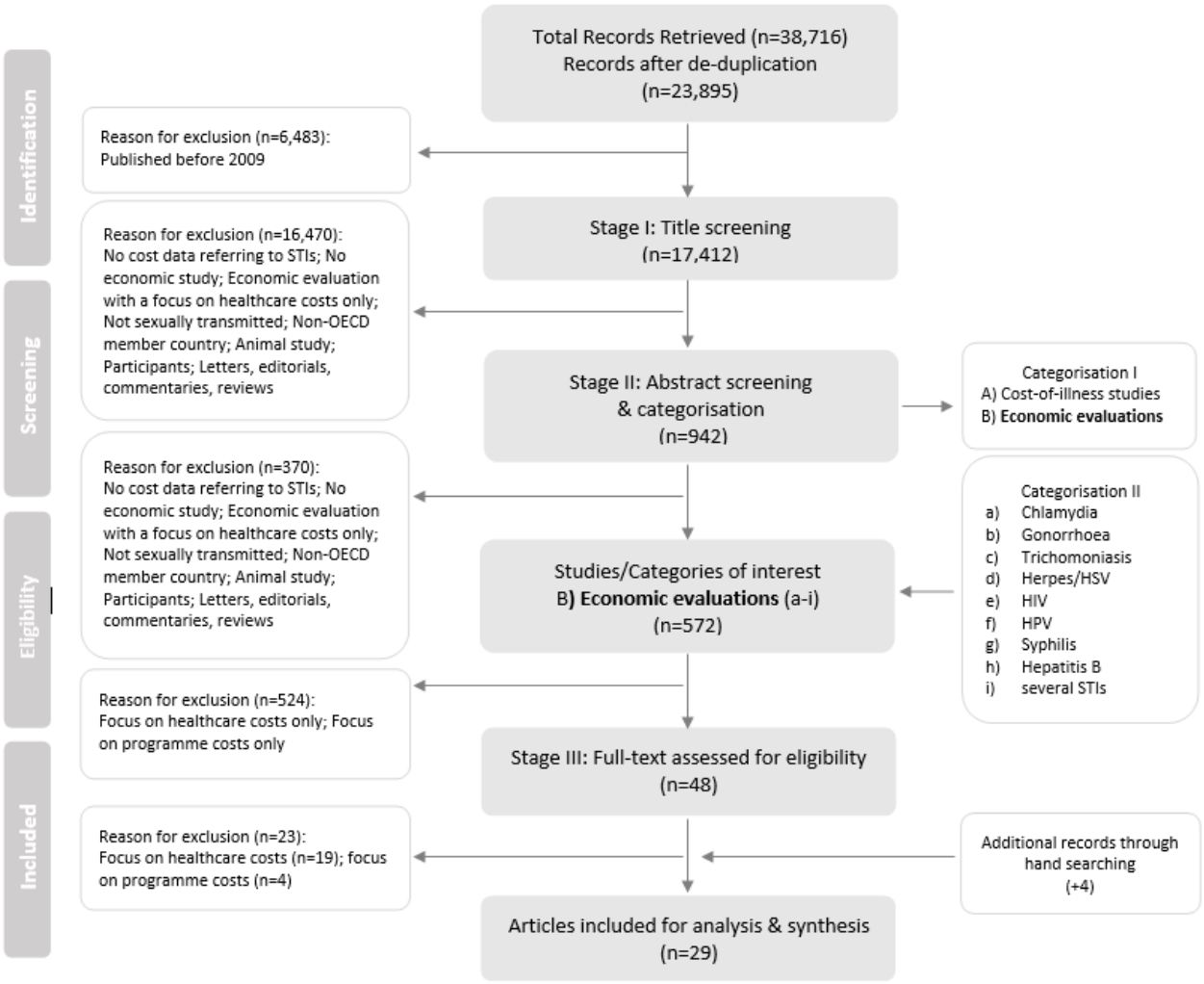

Figure 3 PRISMA flowchart

6.4.1 Study characteristics

Of the 29 studies identified, the majority focused on HPV (n=11), HIV (n=8) and chlamydia (n=7, two of which focused on both chlamydia and gonorrhoea) (Table 7). The remaining studies were concerned with gonorrhoea (n=1), hepatitis B (n=1) and hepatitis C (n=1). The countries of interest in the selected studies included the United States of America (USA) (n=10), The Netherlands (n=8), Canada (n=3), Sweden (n=3), Germany (n=2), Australia (n=1), Austria (n=1) and Israel (n=1). The overwhelming approach adopted was a CEA (considering the study authors' definition of their study as a CEA and CUA). However, not all studies explicitly stated whether they applied a CEA or CUA approach. Only three out of the 29 studies explicitly reported to have undertaken a CUA (167-169) and one study was explicit about having conducted both a CEA and CUA (170). Modelling was used in all but two studies, which were trial-based (168, 169). Most of the modelling studies applied a (dynamic) transmission model, which is the preferred method when evaluating infectious diseases (171-179). Twenty-eight

studies applied a societal perspective of which eight additionally adopted a healthcare or payer perspective, or both (169, 171, 172, 176, 179-181). One study used a modified payer perspective (182).

The types of interventions varied widely. Vaccination and screening interventions dominated, and involved stand-alone vaccination (12, 177, 182, 183)**,** vaccination in addition to screening (172, 184-187)**,** vaccination of girls and boys (175, 179), sex-neutral vaccination (181)**,** screening (stand-alone) (173, 188-190), screening in addition to testing (191) and screening after vaccination (192). Other interventions involved test and treat interventions including PrEP (Pre-Exposure Prophylaxis) (174, 193), testing and linkage to care (169) and opt-out testing strategy (178); expedited partner treatment (178), population-level treatment expansion (176), (on-demand) PrEP (167, 194), treatment adherence interventions (170), guided internet-based behaviour intervention (168) and financial incentives (171)

Table 7 Study characteristics

Nr	Authors	Year	Country	Type of STI	Perspective	Type of intervention	Comparator	Type of analysis*	Type of study	Outcome(s)	Year of valuation	Currency
1	Adamson et al.	2019	USA	HIV	Multiple (Societal, Healthcare)	Financial incentives for HIV viral suppression	Standard of care	CEA	Disease progression model and ongoing transmission	QALYs, viral suppression, reduced HIV infections prevented	2017	USD
2	Campos et al.	2021	USA	HPV	Modified payer perspective	HPV testing self-collection at home	Standard of care involving cytology and HPV co-testing at the Health Department clinics	CEA	Monte Carlo microsimulation model/ micro-costing study alongside RCT	Year of life saved	2019	USD
3	Coupe et al.	2009	NL	HPV	Societal	Cervical cancer screening strategies	Vaccination only	Not explicitly stated	Markov simulation model	QALYs	2006	EUR
4	Damm et al.	2017	GER	HPV	Multiple (Societal, Healthcare)	Vaccination in addition to screening	Screening alone	Not explicitly stated	Dynamic transmission model (SIRS)	LYs, QALYs	2010	EUR
5	De Kok et al.	2009	NL	HPV	Societal	Vaccination in addition to cervical cancer screening	Screening alone	CEA	Simulation model (MISCAN)	QALYs, CIN lesions detected, cervical cancer	2008	EUR

										diagnosis, cervical cancer deaths, life-years lost		
6	De Wit et al.	2015	NL	Chlamydia	Societal	Screening (six scenarios)	Another scenario, or no screening	Not explicitly stated	Analogous to the transmission dynamics model	QALYs	2010	EUR
7	Deogan et al.	2010	SWE	Chlamydia	Societal	Community based intervention (testing, treatment, contact tracing)	No intervention	CEA	Cost-effectiveness model	QALYs, reduced potential costs associated with medical sequels	2007	EUR
8	Drabo et al.	2016	USA	HIV	Societal	Testing (expanded), test-and-treat (expanded HIV testing combined with immediate treatment) and PrEP	Status quo	CEA	Economic model following a compartmental HIV transmission model	QALYs, HIV incidence	2010; 2013	USD
9	Fogelberg et al.	2020	SWE	HPV	Societal	Alternative screening strategies	Alternative screening strategies	CEA	Microsimulation model	QALE, measured in terms of QALYs,	2014	SEK to EUR

										incorporating disutility due to cervical cancer		
10	Gift et al.	2011	USA	Chlamydia, Gonorrhoea	Multiple (Societal, Payer, Healthcare)	Expedited partner treatment (EPT)	Unassisted standard partner referral (SR)	Not explicitly stated	Monte Carlo simulation model	QALYs	2008	USD
11	Ginsberg et al.	2020	ISR	HIV	Societal	PrEP use by MSM	No PrEP	CUA	Model (Excel-based)	DALYs	2018	USD
12	Kim et al.	2009	USA	HPV	Societal	Vaccination and cervical cancer screening in older women	Screening alone	CEA	Monte Carlo simulation model	QALYs, reductions in lifetime risk for cervical cancer	2006	USD
13	Kim & Goldie	2009	USA	HPV	Societal	Vaccination of girls and boys	screening alone; HPV vaccination of girls alone	CEA	Dynamic transmission model, incidence based models	QALYs, outcomes related to cervical disease and other cancers associated with HPV 16/18, HPV 6/11 associated genital	2006	USD

										warts, juvenile onset recurrent respiratory papillomatosis		
14	Krauth et al.	2020	GER	Hepatitis C	Societal	HCV screening strategies (including MSM as a target group)	No screening	Not explicitly stated	Markov Model	QALYs	2015	EUR
15	Mahumud et al.	2019	AUS	HPV	Multiple (Societal, Health System)	HPV vaccination	Three different vaccine delivery strategies	CEA	Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model	DALYs, LYs	2018	AUD
16	Nosyk et al.	2015	CAN	HIV	Multiple (Societal, Third-party payer)	Population-level HAART expansion (testing and treatment)	Constrained treatment access to HAART (75%, 50%)	CEA	Dynamic compartmental transmission model	QALYs, HIV prevalence, incidence	2010	CAD
17	Ouellet et al.	2015	CAN	HIV	Societal	On-demand PrEP	Lifetime costs of HIV infection	CEA	Model based on clinical trial	QALYs, LYs	2012	CAD
18	Owusu-Edusei et al. (2015)	2015	USA	Chlamydia	Societal	Vaccination	Various strategies of i.e. no screening, no	Not explicitly stated	Compartmental heterosexual transmission model	QALYs	2013	USD

							vaccination, tailored screening					
19	Owusu-Edusei et al. (2016)	2016	USA	Chlamydia	Societal	Opt-Out Chlamydia Testing	Risk-based screening (status quo)	Not explicitly stated	Compartmental heterosexual transmission model	QALYs	2014	USD
20	Regnier et al.	2014	USA	Gonorrhoea	Societal	Vaccination (meningococcal)	Standard of care (antibiotics)	Not explicitly stated	Decision-analysis model	QALYs	2012	USD
21	Rogoza et al.	2009	NL	HPV	Societal	Vaccination on top of screening	NCCSP only	Not explicitly stated	Markov model	QALYs, LYs	2009	EUR
22	Rossi et al.	2013	CAN	Hepatitis B	Societal	Universal vaccination, screening & vaccination, screening & treatment, combined screening	No targeted screening or vaccination	CEA	Markov model (decision-tree)	QALYs, HBV-associated morbidity and mortality	2011	CAD
23	Rours et al.	2016	NL	Chlamydia	Societal	Antenatal screening	No screening	CEA	Decision-analysis model	QALYs, pregnancy outcomes averted	2009	EUR
24	Van Luenen et al.	2019	NL	HIV	Societal	Guided Internet-based intervention	Attention only	CUA	Trial	QoL, QALYs	2017	EUR

25	Van Wifferen et al.	2021	NL	Chlamydia, Gonorrhoeae	Societal	Screening strategies 6 monthly	Screening strategies 3 monthly (current practice)	CEA	Dynamic infection model	QALYs, prevalence of chlamydia and gonorrhoea	2018	EUR
26	Wijnen et al.	2019	NL	HIV	Societal	Adherence Improving Self-management Strategy in HIV Care	Treatment as usual	CEA, CUA	Markov Model	QALYs	2013	EUR
27	Wolff et al.	2018	SWE	HPV	Multiple (Societal, Healthcare)	Sex-neutral vaccination	Girls-only vaccination	Not explicitly stated	Epidemiological model; Dynamic compartmental model (HPV-related cancers)	QALYs	2018	EUR
28	Zechmeister et al.	2009	AT	HPV	Multiple (Societal, Public payer)	Vaccination in addition to screening for girls only Vaccination in addition to screening for girls and boys	Screening only	CEA	Dynamic transmission model	LYG	2007	EUR
29	Zulliger et al.	2017	USA	HIV	Multiple (Societal, Payer)	HIV testing and linkage to care	5 main testing strategies	CUA	Trial	QALYs	2013	USD

*This was based on the study authors' reporting of a CEA or CUA. HPV=Human Papillomavirus

AT=Austria, CAN=Canada, GER=Germany, ISR=Israel, NL=Netherlands, SWE-Sweden, USA=United States of America
AUD=Australian Dollar
CEA=Cost-effectiveness analysis
CUA=Cost-utility analysis
DALY(s)=Disability-adjusted life year(s)
EUR=Euro, CAD=Canadian Dollar, USD=United States Dollar
LY(s)=Life year(s)
LYG(s)=Life year(s) gained
HAART=Highly Active Antiretroviral Therapy
HIV=Human Immunodeficiency Virus
NCCSP=National Cervical Cancer Screening Program
NR=Not reported
MISCAN= Microsimulation Screening Analysis
MSM=Men Having Sex With Men
PrEP=Pre-Exposure Prophylaxis
QALE=Quality-Adjusted Life-Expectancy
QALY(s)=Quality-Adjusted Life Year(s)
QoL=Quality of Life
SEK=Swedish Krona
SIRS=Susceptible-Infectious-Recovered-Susceptible

6.4.2 Identification, exploration and categorisation of intersectoral costs

Different intersectoral costs were identified, relating to the following sectors: patient and family, informal care, paid labour (productivity), non-paid opportunity costs (productivity), education and consumption (Table 8).

Patient and family

Patient and family costs were captured in 14 studies and included patient time, travel expenses, out-of-pocket costs and premature burial costs. Four studies estimated patient time and travel to seek care as part of healthcare costs (i.e. screening, treatment, vaccination) (175, 184, 185, 191); although it was not clear whether this time was equated to lost productivity. Nine studies included travel costs or expenses paid for by patients/families in their analyses (167, 169, 175, 180, 182, 185, 186, 190, 192). Most of the studies evaluated travel costs associated with the intervention being evaluated, though this was not made explicit in all studies. Studies were also not always explicit about whether this referred to travel time or financial expenses such as travel fares. Out-of-pocket costs related to costs paid for by patients/families and was accounted for by two studies (171, 187). Premature burial costs were considered in one study (167).

Informal care

Caregiver support (non-family) and unpaid help by family/friends was captured in four studies (12, 170, 174, 187). Two focused on informal care costs related to HIV/AIDS care (170, 174), one on caregiver time loss during treatment for cervical cancer patients (12)and one estimated the time taken by family members during patients' palliative care due to hepatitis B-related cancer (187).

Paid labour (productivity)

Productivity costs in terms of paid labour losses were assessed in 24 studies. The majority of studies measured these in terms of absenteeism (time off work). Of those, one study estimated productivity losses in a sensitivity analysis only (181). Two of the studies measured productivity in utilities and captured these in quality adjusted life year (QALY) estimates (174, 187). Here, productivity was attributable to the HIV-related morbidity and mortality and lost income due to death or disability from hepatitis B-related sequelae, both chronic conditions. Presenteeism was only accounted for by two studies (168, 189). Few studies estimated lost income (171, 183), lost revenue due to unemployment rate gap (194), fringe benefits (171), early retirement (189), avoided future production loss (in SA) (193) and intervention-related productivity gains (176, 183).

Non-paid opportunity costs (productivity)

Only four studies explicitly reported capturing the costs associated with non-paid work (i.e. domestic tasks, voluntary work) (12, 168, 170, 171). It was not clear if/how many studies equated non-paid opportunity costs (i.e. lost leisure time) to lost work hours (labour).

Education

School absence was captured in one study only (170). It refers to an individual missing out on potential productivity and educational attainment, but no further characteristics were stated for those who missed school. School absence was calculated by adding a unit price (based on the Dutch minimum wage) per hour missed.

Consumption

Future consumption costs unrelated to health were considered by one study (171). These consumption costs referred to national average age-specific expenditures outside of healthcare and were based on the U.S. Census Consumer Expenditures Survey. The study did not further specify what this entailed.

Table 8 Classification of intersectoral costs included in the identified studies

Sector	Cost component/resource item	N
Patient and family	Patient time (and travel)	4
	Travel costs/expenses	9
	Out-of-pocket costs	2
	Premature burial costs^	1
	*Total**	*14*
Informal care	Informal caregiver support (non-family)	1
	Care provided by family/friends	4
	*Total**	*4*
Paid labour (productivity)	Productivity loss due to absenteeism	2
	Productivity loss due to presenteeism	2
	Lost income	2
	Lost revenue due to unemployment rate gap	1
	Fringe benefits	1
	Early retirement	1
	Avoided future production loss	1
	Intervention-related productivity gains (cost savings)	2
	*Total**	*24*
Non-paid opportunity costs (productivity)	Inability to perform non-paid work/activities i.e. domestic tasks or voluntary work	4
	Total	*4*
Education	School absence	1
	Total	*1*
Consumption	Future consumption unrelated to health	1

Total	*1*

N=Number of studies that captured the specific cost component(s)/resource item(s).

*Some studies captured multiple cost components/resource items in the same sector, in which case the number of studies is lower than the number would be when adding up N for each cost component/resource item in the same sector.

^Premature burial costs were defined as 'the discounted value of burial costs of the person dying from AIDS less the discounted burial costs of dying in the future from causes other than AIDS'. It was not clear where these costs incurred but in this review it was assumed that they were borne by patients/families.

More information on the different cost components identified in each individual study can be found in Appendix 13.

6.4.3 The impact of intersectoral costs on the study results

All studies that applied a societal perspective in addition to a healthcare and/or payer perspective presented more favourable cost-effectiveness results under the societal perspective (Table 9). Four studies reported that interventions were cost-saving from a societal perspective, whereas they were 'only' cost-effective under a healthcare or payer perspective (8, 171, 172, 176). Two studies found the incremental cost-effectiveness ratios (ICERs) of their interventions decreased when applying a societal perspective in addition to a healthcare or payer perspective (179, 181). One study found their intervention to be cost-effective from both the health system and societal perspective (12).

Table 9 Comparison of cost-effectiveness results from a healthcare or payer perspective and societal perspective

Authors	Intervention	Perspectives	Cost- effectiveness results from a healthcare or payer perspective	Cost- effectiveness results from a societal perspective
Adamson et al.	Financial incentives for HIV viral suppression	Societal, Healthcare	Intervention: Cost-effective US$ 49,877/QALY [US$ in 2021: 53,819]	Intervention: Cost-saving (dominant) Threshold used: range from $50,000 to $150,000 per QALY gained
			Excluding productivity and non-health care expenditures, financial incentives for viral suppression [intervention] cost US$ 3,033 more per patient compared to the standard-of-care cost [comparator] (US$ 487,993 vs. US$ 484,961) [US$ in 2021: 526,562 vs. 523,290]	The total discounted lifetime societal cost was US$ 4,210 lower for financial incentive patients [intervention] than for the standard-of-care patients [comparator] (US$ 268,255 vs. US$ 272,464 per patient, respectively) [US$ in 2021: 289,457 vs. 293,998]
			The greatest change among cost categories was the US$ 3685 per patient increase in lifetime ART drug costs for financial incentives compared to standard of care [US$ in 2021: 3,976]	A majority of financial incentive cost savings were attributable to lifetime productivity gains of US$ 10,686 per patient. [US$ in 2021: 11,530]
			Excluding non-health care costs and productivity, financial incentives for viral suppression were cost-effective with an ICER of US$ 49,877 per QALY gained	Financial incentives for viral suppression gained 0.06 QALYs per patient and avoided US$ 4210 per patient compared to the standard of care.

			compared to the standard of care [US$ in 2021: 53,819]	[US$ in 2021: 4,543] Financial incentives “dominated” the standard of care because patients and partners had better health outcomes for a lower cost.
			NA	Lifetime productivity gains of US$ 10,686 per patient [US$ in 2021: 11,530]
Damm et al.	HPV vaccination in addition to screening	Societal, Healthcare	Intervention (2-dose): Cost-effective 19,450€ per QALY for the bivalent [US$ in 2021: 27,305] 3645€ per QALY for the quadrivalent vaccine [US$ in 2021: 5,117]	Intervention (2-dose): Cost-saving Threshold used: €50,000 Under certain scenarios: A 2-dose approach using the quadrivalent vaccine was a cost-saving strategy while using the bivalent vaccine resulted in an ICER of 13,248€ per QALY [US$ in 2021: 18,598]
			Intervention (3-dose): ICERs of a 3-dose schedule were 53,807€ per LY and 34,249€ per QALY for the bivalent vaccine [US$ in 2021: 75,539 and 48,082] and 30,910€ per LY and 14,711€ per QALY for the quadrivalent vaccine [US$ in 2021: 43,394 and 20,653]	Intervention (3-dose): Inclusion of indirect costs decreased the ICERs to 28,047€ and 8,984€ per QALY for the bivalent and the quadrivalent vaccine, respectively. [US$ in 2021: 39,375 and 12,613]

				Sensitivity analysis: In scenarios with low coverage, the use of the quadrivalent vaccine led to cost savings from a societal perspective
Gift et al.	Expedited partner treatment (EPT) for Chlamydia and Gonorrhoea	Societal, Healthcare, Individual payer	Intervention (individual payer perspective): Cost-effective (under a wide range of assumptions) When EPT was not cost saving from the individual payer perspective, the incremental cost per QALY gained through EPT compared with Standard Referral (SR) was less than US$ 13,000 a cost per QALY that is typically considered to be very cost-effective [US$ in 2021: 16,124]	Intervention (societal or healthcare perspective): Cost saving Threshold used: NR It resulted in more partners treated at lower cost
Mahumud et al.	HPV vaccination	Societal, Health System	Intervention: Cost-effective From the health system and societal perspectives, the 9vHPV vaccination was very cost-effective in comparison with the status quo, with an ICER of A$47,008 and A$44,678 per DALY averted, respectively	Intervention: Cost-effective Threshold used: heuristic cost-effectiveness threshold as defined by the WHO Commission on Macroeconomics and Health (A$73,267) From the health system and societal perspectives, the 9vHPV vaccination was very cost-effective in comparison with the

				status quo, with an ICER of A$47,008 and A$44,678 per DALY averted, respectively
Nosyk et al.	HIV Population-level HAART expansion (testing and treatment)	Societal, Third-party payer (TPP)	Intervention: Cost-effective From a TPP perspective, 'observed HAART access' cost CAN$ 23,679 per QALY gained, compared to the '75% observed access' scenario, and CAN$ 24,250 per QALY gained compared to the '50% observed access' scenario, making observed HAART scale-up highly cost-effective [US$ in 2021: 22,625 and 23,171]	Intervention: Cost-saving Threshold used: WHO thresholds for cost-effectiveness Observed HAART access resulted in savings of CAN$ 25.1M and CAN$ 66.5M in present value compared to 75% and 50% HAART access scenarios, respectively [US$ in 2021: 23,955,214 and 63,467,001] Productivity gains due to HAART access more than offset the additional costs of treatment, resulting in 'Observed HAART access' being a dominant strategy (lower total costs, higher QALY gains)
Wolff et al.	Sex-neutral HPV vaccination	Societal, Healthcare	Intervention: Likely to be cost-effective ICER was higher from a healthcare perspective, which did not include gains from decreased production losses: 40,821€ [US$ in 2021: 50,461]	Intervention: Likely to be cost-effective Threshold used: €50,000 ICER was lower from a societal perspective, which considered cost of production loss: 38,237€

				[US$ in 2021: 47,265]
Zechmeister et al.	HPV vaccination in addition to screening	Societal, Public payer	Intervention: Not cost-effective Applying a shorter time frame and a payer's perspective or vaccinating boys may not be cost-effective without reducing the vaccine price	Intervention: Cost-effective Threshold used: NR HPV-vaccination for girls should be cost-effective when adopting a longer time-horizon and a societal perspective
			Discounted ICER for HPV-vaccination of girls only was 64,000€ per LYG [US$ in 2021: 79,111]	Discounted ICER for HPV-vaccination of girls only was 50,000€ per LYG (lower compared to a healthcare perspective) [US$ in 2021: 61,800]
			For vaccinating girls and boys compared to girls only, the corresponding ICERs were 311,000€ per LYG [US$ in 2021: 384,399]	For vaccinating girls and boys compared to girls only, the corresponding ICERs were 299,000€ per LYG (lower compared to a healthcare perspective) [US$ in 2021: 369,564]
Zulliger et al.	HIV testing and linkage to care among men having sex with men (MSM)	Societal, Payer	NA [*Results for payer and societal perspective were not reported separately*]	Intervention (venue-based testing program in all cities): Cost-saving Threshold used: $100,000 (The cost-saving threshold for HIV testing was $20,645 per new HIV diagnosis) Cost-utility analysis of the MSM Testing Initiative (MTI) programmes demonstrated

		that all venue-based testing programmes were cost-saving
		Intervention (voluntary counselling and testing strategies, social network strategies): Partially not cost-effective, depending on the city

CAN=Canadian Dollar
HAART=Highly Active Antiretroviral Therapy
HIV=Human Immunodeficiency Virus
HPV=Human Papillomavirus
ICER=Incremental Cost-Effectiveness Ratio
QALY=Quality-Adjusted Life Year
LY(G)=Life Year (Gained)
US$=United States Dollar

6.5 Discussion

This study is the first to systematically review economic evaluations of interventions relating to STIs and explore and categorise the different types of intersectoral costs captured under a societal perspective. It also presents evidence that the inclusion of intersectoral costs has an impact on the overall study results.

6.5.1 Principal findings

This review found that the identified studies took a rather narrow approach to the societal perspective and only considered costs relating to a limited range of non-health sectors. For the majority of studies this meant primarily estimating paid labour losses. For others, this meant the inclusion of patient and family costs in their analyses. Very few studies considered informal care costs and other non-paid opportunity costs. Only one study included educational costs and another captured non-medical consumption costs. These findings indicate that even where a societal perspective is adopted, this may often be limited in scope, potentially omitting relevant costs from other sectors. The theoretical definition of a societal perspective, however, does not limit the potential scope to the aforementioned sectors (195).

Even though the inclusion of intersectoral costs was limited to a few cost sectors, where intersectoral costs were accounted for, this resulted in more favourable cost-effectiveness estimates.

It is important to note that a societal perspective can improve the cost-effectiveness of an intervention and can subsequently policy/decision-making processes such as resource allocation. However, even when the cost-effectiveness of an intervention improves this does not necessarily mean that the conclusion on cost-effectiveness changes. The decision-making based on a cost-effectiveness analysis can vary across countries, given the different reference cases and thresholds in place. For example, UK NICE recommends an NHS and personal social services (PSS) perspective for interventions funded by the NHS and PSS. For interventions funded by the public sector and with health and non-health outcomes, a broader societal perspective is recommended. It needs to be clear to the policy/decision-makers as to which costs were included in the analysis irrespective of the perspective adopted and the cost-effectiveness results presented.

6.5.2 Methodological challenges to the study perspective

A primary reason for studies applying a narrow societal perspective could be the methodological challenges associated with capturing these wider costs such as with data collection processes or

unavailable data (107). The identification, measurement and valuation of intersectoral costs and benefits in economic evaluations is recognised as one of four methodological challenges when assessing public health interventions (196). This review highlights that despite methodological difficulties, it is important to be transparent and if a narrower societal perspective is applied, this needs to be explained and justified.

6.5.3 Classification of costs

This review's sector-specific (cost) classification scheme was established to assess whether (or not) and to what extent intersectoral costs were considered and reported explicitly and transparently. The findings suggest that there is considerable scope for exploring other wider societal costs in relation to interventions addressing STIs. This would help improve understanding of the wider societal impacts of STI-related interventions and inform the design of future, more comprehensive economic evaluations.

Informal care

This review shows that informal care was rarely captured in the evaluations, but where it was considered, it related to chronic conditions including HIV/AIDS, HPV-related cervical cancer and hepatitis B-related cancer. Where (long-term) care is provided informally this makes the inclusion of such costs in economic evaluations crucial. If informal care is not considered (or discussed as a study limitation) this can omit important information and underestimate the total cost burden. Future research is needed to further investigate informal care costs related to STIs, particularly those that can have chronic impacts (i.e. HIV/AIDS, hepatitis B) and those with severe long-term sequelae (i.e. pelvic inflammatory disease, chronic pelvic pain).

Non-paid opportunity costs

This review also found that the costs associated with unpaid work remained largely excluded from economic evaluations relating to STIs. This was difficult to judge as not all studies were explicit about which cost components/resource items they accounted for when referring to productivity costs – i.e. paid labour, volunteering or household work. A number of study authors were approached to clarify whether productivity losses accounted for paid or unpaid labour, or both. The majority responded that only paid labour losses were included due to missing data or the methodological challenges of including unpaid productivity. These findings suggest that greater transparency is needed when a societal perspective is adopted to clarify which costs and benefits are included/excluded and the justification for these decisions.

Education

School absence was only captured in one study. Absence from school due to an STI or seeking treatment for an STI can refer to potential productivity loss or loss of educational attainment. The study that captured absence from school valued each hour missed at school based on the national minimum wage, as informal care and domestic activities. No other costs relating to education were identified.

Consumption

Where future consumption costs unrelated to health were accounted for it was not clear what this involved. Examples of non-medical consumption costs can include travel expenditures or future costs for housing and food (197). This adds to the call from this review that more transparency is needed in economic evaluations, in particular on the different cost components included (or not included), to increase consistency in terms of the costs included and improve comparability of results across studies.

Distinct health impacts

Other potentially important distinct health impacts can include costs in the reproductive health and mental health sphere. However, these impacts were not captured in the selected studies. The prevention of STIs can reduce the risk of cervical cancer, pelvic inflammatory disease and infertility among women (198), which is often related to their sexual, reproductive and psychological health (199). This implies there might be intangible costs related to STIs and their sequelae such as pain, anxiety and psychological suffering that could have an impact on people's overall quality of life and contribute to the cost burden. Research shows that intangible costs could potentially outweigh healthcare costs and its inclusion in economic evaluations potentially result in more favourable cost-effectiveness estimates (161). This study acknowledges there are difficulties associated with measuring and valuing intangible costs and the demonstration of attribution, and more research is needed in this area.

6.5.4 Comparison to other literature

Relatively few economic evaluations related to STIs have adopted a societal perspective. This is in line with recent findings by Bloch and colleagues (2021) who assessed how costs and outcomes are measured in economic evaluations relating to interventions to control STIs. Their study revealed that multiple studies did not adopt a broader perspective to account for outcomes beyond health, despite

national recommendations advocating to do so (19). The present review focused on those economic evaluations that did adopt a societal perspective and demonstrated that often this perspective is limited to certain cost sectors, predominantly the labour sector. Kim and colleagues similarly found that the CEAs they considered rarely captured impacts on sectors outside health, but if so, productivity losses were the most commonly estimated (158). Krol and colleagues' (2013) findings also show that economic evaluations tend to predominantly assess paid labour costs (149). Unpaid work, in comparison, has tended to receive little attention (17). The present review confirms that non-paid work is almost entirely ignored, or not explicitly reported, in economic evaluations. As indicated above, sexual health is closely related to other sectors, including education. In 2010, Shepherd and colleagues found that school-based behavioural interventions for the prevention of STIs can improve knowledge and increase self-efficacy (200). Research by Chong and colleagues (2013) showed that online sexual-health education have an impact on an individual's knowledge and attitudes (201). Overall, it is evident that public health issues and interventions can impact other sectors of society, and that the application of a societal perspective is important. This has recently been highlighted using COVID-19 as an example and demonstrating the broader societal impacts of such disease on other sectors outside health (57).

6.5.5 Policy Implications

A societal perspective is generally recommended to allow for all relevant costs and benefits to be considered and for an economic evaluation to be as comprehensive as possible. However, where economic studies adopt a societal perspective, but this only includes certain costs in certain sectors, relevant societal implications may be ignored. As a result, decisions based on an analysis with a limited scope might not be optimal (158). As shown in this review, adopting a societal perspective and capturing intersectoral costs relating to STIs resulted in more favourable cost-effectiveness estimates (202). Again, where diseases such as STIs can be prevented, treated or managed this can have an impact on an individual's physical, mental and social health and wellbeing, their productivity as well as wider society (202). In order to improve information communicated to policy/decision-makers all potentially relevant intersectoral costs need to be included in analyses, and if a narrow societal perspective is adopted, the exclusion of relevant costs needs to be made transparent and justified.

6.5.6 Implications for research

The costs considered and included under a societal perspective differed across studies, resulting in heterogeneity of study results. This highlights that there is a need for a clear understanding of which costs were included and excluded under any perspective when reviewing and synthesising the existing

literature, or when combining results from different studies undertaken in different settings. This is particularly important because the different elements of costs (i.e. care practices, wages) can differ between countries and time points. When researchers adopt data from the existing literature for use in their own work, they need to carefully assess what costs were captured before the results can be relied on and utilised.

6.5.7 Strengths and limitations

The main strength of this review is that it followed a structured and rigorous process. To our knowledge, this is the first review in sexual health to apply a classification scheme in order to explore and categorise the intersectoral costs considered by sector. The sector-specific (cost) classification scheme provides a valuable foundation for the critical appraisal of economic evaluations, in particular with regard to the consideration and identification of societal costs. The results of this study can inform the design of future, more comprehensive economic evaluations of public health interventions, building on the classification scheme presented. Another key strength of this review is the exhaustive search strategy that was developed in cooperation with an information specialist, searching nine databases and a wide range of key search terms relating to sexual health. It is however possible that some relevant search terms may have been missed. In addition, the update of the review focused on Medline only, which may have resulted in some studies being omitted, although this was mitigated by extensive hand searching. A potential weakness of the review is that because of the high volume of studies identified in the databases, an initial screening was undertaken to exclude studies where the abstract suggested that the study adopted a healthcare perspective only. This means that relevant studies could have been missed. Future research could review economic analyses that adopted a healthcare (system) perspective to assess in detail which costs these studies captured, i.e. direct medical costs, patient costs, or other costs. Another limitation of this review is that it focused on OECD member countries. Reviewing studies in non-OECD member countries could have identified other potentially relevant costs associated with interventions relating to STIs. Further, this review focused on STIs that are sexually transmitted and interventions related to infections transmitted other than sexually, could have revealed additional cost sectors.

6.5.8 Future research

Further research is needed to investigate wider intersectoral costs related to STIs that were not (sufficiently) captured in this review but that could be important to inform policy/decision-making. Such research could also help explore the intersectoral costs relating to other sexual health aspects beyond disease such as sexuality, sexual behaviour, and related areas. Given the complexity of sexual

health future research could explore wider intersectoral costs relating to STIs that have been considered outside of the health economics literature such as in educational journals or journals relating to social services. Furthermore, future research could explore in greater depth the distinction between intersectoral consequences associated with the disease and the intersectoral costs incurred by the intervention being evaluated, as this was not always fully clear.

6.6 Conclusion

This systematic review suggests that economic evaluations of interventions relating to STIs that adopt a societal perspective tend to be limited in scope. This risks omitting potentially relevant intersectoral costs that could be important information for policy/decision-making. There is an urgent need for economic evaluations to be more comprehensive in order to allow policy/decision-makers to make better informed decisions.

6.7 Chapter summary

This chapter presented a systematic literature review of economic evaluations that explored the intersectoral costs relating to sexual health intervention considered under a societal perspective. It illustrated a sector-specific (cost) classification scheme, listing these intersectoral costs by sector. As part of this review, the impact of intersectoral costs on the overall study results was demonstrated. The following chapter (Chapter 7) explores the intersectoral costs and benefits (ICBs) relating to sexual health in the wider context, looking beyond the area of disease and beyond the health economics literature; using expert interviews.

CHAPTER 7 EXPLORING THE WIDER SOCIETAL IMPACTS OF SEXUAL HEALTH ISSUES AND INTERVENTIONS TO BUILD A FRAMEWORK FOR RESEARCH AND POLICY: A QUALITATIVE STUDY BASED ON IN- DEPTH SEMI-STRUCTURED INTERVIEWS WITH EXPERTS IN OECD MEMBER COUNTRIES

7.1 Chapter overview

This chapter presents a qualitative research study based on in-depth semi-structured online interviews with experts from OECD (Organisation for Economic Co-operation and Development) member countries. This study is published in *BMJ Open* and a link to the article is presented in Appendix 14. The aim of this study was i) to explore the different intersectoral costs and benefits associated with sexual health problems and interventions, ii) to categorise these into (policy) sectors, and iii) to subsequently develop a preliminary framework (sector-specific (cost) classification scheme) to better understand these impacts and to guide future research and policy. The main findings generated from a total of 28 interviews confirm that sexual health is complex and can generate wide-ranging impacts on other areas of health and other non-health sectors of society. The findings illustrate that these sectors can be affected and should be accounted for when evaluating interventions in sexual health and making policy decisions. [Please note that the term framework and (cost) classification scheme may be used interchangeably in this thesis.]

The main article in this chapter is kept the same as the original publication.

7.2 Background

Sexual health is a complex public health challenge and can generate wide-ranging health, social and economic impacts (13, 203, 204). Public health challenges relating to sexual health include sexually transmitted infections (STIs), HIV/AIDS, sexual violence, coercion and discrimination, sexual dysfunction, and unintended pregnancies. With the recent COVID-19 pandemic the wider societal impacts of public health issues became more apparent (205). This has emphasised the need to look at public health issues and interventions from a wider societal perspective, taking into account the impacts on health and non-health sectors (i.e. labour, education). The pandemic also made even more apparent some of the most prominent health inequalities, and how sexual health is part of these inequalities (206). For example, the pandemic caused disruptions in the provision of essential sexual health services (i.e. access to pre-exposure prophylaxis (PrEP), STI/HIV testing) (64, 207), disproportionately affecting certain population groups (i.e. people with lower average incomes, young people) (208, 209).

Sexual health is a broad concept and defined by the World Health Organization (WHO) as 'a state of physical, emotional, mental and social well-being related to sexuality'. It acknowledges that sexual health involves a 'positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence'. The WHO's definition is expansive and reflects the complexity of sexual health, recognising and advocating for a more holistic approach to sexual health. For example, the effect of an STI can extend well beyond the acute infection, and people living with an STI are at an increased risk of acquiring other STIs or HIV (210). STIs can often be asymptomatic, which can result in missed or delayed treatment as well as increased risk of transmission (211). Beyond the physical health impact sexual health problems are often associated with shame, (self-)stigma and/or psychological distress, which can have an impact on an individual's relationships and can result in difficulties in a marriage, partnership or with a sexual partner (6). In contrast, optimal sexual health, sexual functioning, sexual pleasure and intimacy can have a positive impact on relationships and an individual's physical and mental wellbeing (3). On a societal level, adverse sexual health outcomes, like other public health consequences, can generate wide-ranging impacts both within and outside the health sector. Those impacts that occur outside the health sector could include costs due to lost work/labour productivity, school absence, housing insecurity, and reduced physical, mental, or social well-being (205, 212, 213). In this paper, we will use the term *intersectoral costs and benefits* to refer to costs and benefits beyond the health sector (15, 214).

Existing evidence suggests that very few economic studies in sexual health adopt a broader perspective in their analyses, and for those that claim to adopt such a perspective the types of costs considered tend to be narrow (214). Missing to capture relevant intersectoral costs and benefits in economic studies can potentially underestimate the true societal impact of a sexual health issue or intervention and can lead to sub-optimal policy decisions (15).

The objectives of this study were (i) to explore the different intersectoral costs and benefits associated with sexual health issues and interventions, (ii) to categorise these into sectors, and (iii) to develop a preliminary framework to better understand these intersectoral impacts and to guide future research and policy; using in-depth semi-structured interviews.

7.3 Methods

A qualitative study was conducted based on in-depth semi-structured interviews with experts in OECD member countries.

7.3.1 Sampling and recruitment of participants

Sampling of participants was undertaken purposively based on experts' knowledge and expertise. We distributed e-mail invitations to the study authors' network as well as experts in the area. This was followed by snowball sampling. In this study, we use the term 'experts' to refer to professionals that are knowledgeable in a particular area, in this case in sexual health. Purposive sampling was used to ensure a spread of expertise across different areas and in relation to different roles. The purpose of this study was to develop a framework that could be used to inform evaluation and health policy in Organisation for Economic Co-operation and Development (OECD) member countries and hence we included participants from these countries to ensure comparability of healthcare systems. We included potential participants with diverse expertise, affiliations and experience in the field of sexual health including clinicians, medical practitioners, sexologists, researchers, professionals working for international governmental or non-governmental health (policy) organisations, and professionals involved in the implementation and/or evaluation of sexual health interventions. We approached experts via e-mail and invited them to participate in semi-structured, one-to-one online interviews in English with the lead researcher (LS). A participant information leaflet was attached to the e-mail including more detailed information on the purpose and background of the study, voluntary participation in the study, confidentiality and anonymity, duration of the interview, and dissemination of study findings. Interviews were conducted until data saturation was reached, meaning when no new insights emerged from additional interviews (215).

7.3.2 Data collection and analysis

Semi-structured in-depth online interviews were conducted to allow for a systemic coverage of key topics and to allow for new ideas and themes to emerge (216). Online interviews were chosen due to the circumstances relating to the COVID-19 pandemic. The videoconferencing platform Zoom was used to conduct the interviews. We used a topic guide to structure the interviews (Appendix 15). The topic guide was developed based on a review of the existing literature (e.g., on sexual health and intersectoral costs and benefits) and the information generated through the two systematic reviews (Chapter 5 and Chapter 6). The list of questions was pilot tested in two pilot interviews and amended accordingly. The interviewer was a doctoral candidate, and the interviewees were all experts in sexual health. All interviews were audio-recorded, with the participant's consent. Detailed field notes were taken during the interviews to provide further information for analysis. The interviewer (LS) utilised an interview protocol, containing a set of open-ended questions to discuss potentially relevant wider societal costs and benefits associated with sexual health services or interventions.

We applied the Framework approach as presented by Gale and colleagues (2013) for the thematic data analysis. It is a widely used approach to manage the qualitative data derived that allows for systematic analysis, and comparison and contrasting of data (217). All audio-recorded interviews were transcribed verbatim and entered into NVivo 12 (a software for qualitative data analysis) by one author (LS) (step I). A sample of the transcripts was cross-checked for reliability by a second researcher (LJ). Both authors (LS, LJ) familiarised themselves with a set of the data and repeatedly coded several transcripts independently, identifying emerging themes and sub-themes (step II and III). The authors then compared their themes and sub-themes and discussed these with all co-authors, resulting in a coding framework (in form of a matrix) that all authors agreed upon. Discrepancies were discussed, where needed (step IV). LS applied the established coding framework to the remaining transcripts (step V). A matrix was developed, charting all themes and sub-themes, which was discussed with all authors (step VI and VII). LS reviewed, analysed and summarised a set of the coded themes and sub-themes, which was again discussed with all authors. We followed the guidance outlined in the Standards for Reporting Qualitative Research (SRQR) for the reporting of the study context, methods and findings (Appendix 16).

Consent form

All participants that agreed to take part in the interviews signed and returned their written consent to the lead researcher (LS) via e-mail prior to the start of the interview.

Ethical approval

Ethical approval was granted by the University of Birmingham (ERN_19-1371) and Maastricht University (FHML-REC/2020/017/02).

7.4 Results

7.4.1 Interviews

A total of 28 experts (16 female, 12 male) were interviewed between November 2020 and June 2021. The duration of the interviews ranged between 30-60 minutes each.

7.4.2 Participant characteristics

All participants had expertise in the field of sexual health including the provision of clinical sexual health services, or the design, implementation or evaluation of (clinical and non-clinical) sexual health interventions. At the time of the interviews, participants worked in Australia, Canada, The

Netherlands, Switzerland, the United Kingdom or the United States (Table 10). Among those were Clinicians or Clinical Academics (n=8), Non-clinical Academics or Researchers (n=15), Programme Managers (n=3), and Technical Advisors (n=2). Many experts were affiliated with a university or research institute (n=16). Others worked at governmental (n=3), non-governmental (n=4) or international policy organisations (n=4). Some participants had training in sexology (n=2), medical anthropology (n=2) or health economics (n=3).

Table 10 Interview sample

Role	Affiliation	Country	Male/Female	ID
Clinician/	Hospital	United Kingdom	M	I.1
Clinical academic	University/ Research Institute	United Kingdom	F	I.2
	University/ Research Institute	Australia	M	I.3
	University/ Research Institute	The Netherlands	M	I.4
	Non-governmental Organisation	The Netherlands	F	I.5
	International Policy Organisation	Switzerland	M	I.6
	International Policy Organisation	Switzerland	M	I.7
	International Policy Organisation	Switzerland	F	I.8
	University/ Research Institute	The Netherlands	M	I.9
	University/ Research Institute	USA	F	I.10
	University/ Research Institute	Australia	F	I.11
	University/ Research Institute	The Netherlands	F	I.12
	University/ Research Institute	USA	F	I.13
	University/ Research Institute	USA	M	I.14
Non-clinical	University/ Research Institute	USA	F	I.15
Academic/Researcher	University/ Research Institute	USA	M	I.16
	University/ Research Institute	The Netherlands	F	I.17

	University/ Research Institute	The Netherlands	F	I.18
	University/ Research Institute	USA	M	I.19
	University/ Research Institute	The Netherlands	F	I.20
	University/ Research Institute	Canada	F	I.21
	International Policy Organisation	Switzerland	M	I.22
	Governmental Organisation	United Kingdom	F	I.23
Programme Manager	Governmental Organisation	The Netherlands	F	I.24
	Governmental Organisation	The Netherlands	F	I.25
	Non-governmental Organisation	The Netherlands	F	I.26
Technical Advisors	Non-governmental Organisation	United Kingdom	M	I.27
	Non-governmental Organisation	United Kingdom	M	I.28
Total				*28*

7.4.3 Themes (sector-specific cost classification scheme)

The participants in the interviews highlighted the holistic nature of sexual health, which meant that there were a wide range of impacts on other areas of health and other sectors. As shown in Figure 4, six themes emerged from the interviews that established a sector-specific cost classification scheme (or framework): (1) Interconnections to other areas of health, (2) Relationships and family, (3) Productivity and labour, (4) Education, (5) Criminal justice/sexual violence, (6) Housing, addiction, and other sectors.

THE HOLISTIC NATURE OF SEXUAL HEALTH					
(1) Interconnections to other areas of health	(2) Relationships and family	(3) Productivity and labour	(4) Education	(5) Criminal justice/ sexual violence	(6) Housing, addiction, and other sectors

Figure 4 Themes (sector-specific cost classification scheme)

Theme 1: Interconnections to other areas of health

When considering the societal impacts of STIs, the holistic nature of sexual health and interconnections to other areas of health became evident. Although not strictly an 'intersectoral' impact, we include this as a theme, as participants felt that it was important to highlight these connections to other areas of health, as they may otherwise be overlooked. The inextricable link between sexual and reproductive health as well as the relationship to mental health was expressed by almost all clinicians repeatedly.

Long-term consequences

When first asked about potential societal impacts of any sexual health aspect, almost all experts instantly described the impact of STIs as being potentially serious, with long term consequences for the physical and mental health of an affected individual. These long-term consequences included pelvic inflammatory disease (PID), chronic pelvic pain, infertility and adverse pregnancy outcomes.

> *"Chlamydia is most likely to be asymptomatic in women and yet can have one of the worst sequelae in terms of say tubal infertility, ectopic pregnancy and that sort of thing. That obviously has a huge impact on women and also pelvic inflammatory disease from chlamydia and gonorrhoea can be really devastating, even as an illness when treatment can be offered." (I.2, University/Research Institute, UK)*

> *"You still have people that get ectopic pregnancy or infertility, and this is directly related to chlamydia. I think these are also important things to look at and also PID [pelvic inflammatory disease]." (I.25, Governmental Organisation, The Netherlands)*

> *"About syphilis we know that it can have adverse effects on pregnancy outcomes, and we know that there is significant foetal and natal death every year because of not detecting syphilis. It would be greater than that when it comes to loss or miscarriage." (I.27, Non-governmental Organisation, UK)*

The inextricable link between sexual and reproductive health

The majority of experts highlighted the inextricable link between sexual and reproductive health. They expressed the importance of providing more holistic care, which means ensuring that essential services around sexual, reproductive and potentially other areas of health are addressed.

"When you look at sexual health provisionally for women that's very much bundled in with reproductive health. […] I've seen this a lot in STI clinics, women who come in for screening but also get a LARC [long-acting reversible contraception] while they are there. Women who talk to you about contraception while they've come in for let's say a pep [smear test]. Even though contraception isn't what we do in sexual health the two things overlap quite a lot." (I.2, University/Research Institute, UK)

"What we try to ensure within our clinics is that we get those essential service areas around contraception, abortion care, issues around HIV, the wider STIs covered, we know that a lot of STIs are not always included." (I.27, Non-governmental Organisation, UK)

Mental health problems relating to sexual health

Alongside those physical sexual and reproductive health concerns, experts highlighted the serious impacts STIs can have on an individual's mental health and psychological well-being. In particular, syphilis, Herpes Simplex Virus (HSV) and HIV were listed among those causing serious psychological consequences.

"Syphilis, I mean goodness, it causes horrible psychological illness and it's a systemic illness, it has a huge impact." (I.2, University/Research Institute, UK)

"HSV which is herpes simplex virus is a very common infection and depends on the individuals most of them have minor symptoms some have more severe symptoms. That can be very psychologically damaging." (I.1, Hospital, UK)

"I argue there is a mental health cost to living with an HIV infection." (I.23, Government Researcher, UK)

Theme 2: Relationships and family

Most participants highlighted the need to think beyond health aspects, and family, friendships and relationships was seen as an important part of this.

"Beyond the health sector you want to look at what is my relationship with my family and peers, do I have access to safe shelter, do I have food, do I have a job." (I.28, Non-governmental Organisation, UK)

Several interviews revealed that the use of PrEP (pre-exposure prophylaxis) was expected to have additional non-health benefits, in particular, for people's relationships with partners and peers. Similarly partner notification interventions were perceived to have a positive impact on interpersonal relationships for various STIs including HIV, genital warts, among other

> *"What we see with PrEP when people are not afraid of HIV, we think that people enjoy sex more. Or positive sexual relation, pleasure, connection with people. It impacts your relationship, how you stand in your sexual network." (I.5, Non-governmental Organisation, The Netherlands)*

> *"They feel that PrEP is giving people a lot more confidence of having new relationships, it makes them be more confident in their sex life, knowing that they can't pass the virus on." (I.23, Government Researcher, UK)*

Theme 3: Productivity and labour

A link was drawn between sexual health and productivity by many experts. They indicated that STIs that are left untreated can continue to affect an individual's health and can have a 'knock-on effect' on an individual's productivity and participation in the labour market. One concern was also that untreated STIs will continue to spread and infect more and more people and create an even bigger impact on society's productivity and ability to work.

> *"I think the impact on the labour market and the impact on the health sector are very similar in that every single STI has horrible consequences down the line if it isn't treated. […] If it's not treated then you're going to get more people that are incredibly unwell. And yes, that's going to have a huge impact." (I.2, University/Research Institute, UK)*

> *"It will be in terms of work productivity so they would not be able to work or there are some mental health issues that then kind of snowballs into the need for disability pensions, but this would be a very small minority of my patients." (I.3, University/Research Institute, Australia)*

The loss of income and productivity was often linked to chronic conditions, illustrating the relationship between health and work. For example, many clinicians explained that the development of PID can have an impact on women's productivity as well as economic consequences.

"In terms of the labour market, so treating every single STI has huge health impacts down the line. If you've got women who then develop PID a couple years down the line they will be out work for a while, they are going to be hospitalised for a while, etc. […] The provision of healthcare you need when you don't treat an STI is huge. […] and that's going to have an impact on their productivity as well." (I.2, University/Research Institute, UK)

One expert highlighted the possibility of people living with well-managed HIV to work effectively.

"Similarly, if HIV is well managed then you've got people coming in once or twice a year getting their blood sample done, getting their medications checked, it's all very easy and they probably aren't taking a huge amount of time off work. However, if HIV progresses to AIDS people are incredibly ill and probably have to be off work for quite some time." (I.2, University/Research Institute, UK)

Theme 4: Education

Other wider societal impacts raised by experts included those in the education sector. For example, one described the impact of teenage pregnancy on future educational and professional attainment.

"The same applies to all the broader levels of for instance teenage pregnancy, teenage mothers. […] But also there, of course, they miss out on further education. They miss out on getting a good job or being economically independent. All that ripple effect is happening and this all needs to be taken into consideration." (I.12, University/Research Institute, The Netherlands)

Experts also explained the relationship between sexual health and education in terms of the costs and benefits of comprehensive sexuality education and sexual health education in schools.

"For example, in our implementation research on comprehensive sexuality education, we are working to build linkages between education provision and linkages to health and social services and studying how these linkages function." (I.7, International Policy Organisation, Switzerland)

The benefits of providing sexual health education as outlined by experts included the prevention of STIs, unwanted pregnancies, sexual coercion, sexual abuse and/or unwanted sexual experiences.

> *"And of course there is the more direct benefit [of school-based sexual health interventions], the more prepared young people are the less likely they are to be at risk of sexual health issues and that includes HIV and STIs but also unplanned pregnancies and sexual coercion or abuse or unwanted sexual experience." (I.20, University/Research Institute, The Netherlands)*

> *"The implications are huge. […] If we do these [school-based sexual health] programmes better and we get to prevent STIs or unwanted pregnancies even more, the cost in the STI testing clinics should in the best scenario go down." (I.12, University/Research Institute, The Netherlands)*

The need for sexual health education programmes to be more comprehensive and integrate, among other, sexuality education was expressed.

> *"It's not only about knowledge but it's also about sexual norms, attitude, skills on how to communicate, how to negotiate, that's very important but still it's a challenge." (I.26, Non-governmental Organisation, The Netherlands)*

> *"For me it is very important, complementary to add interventions for example comprehensive sexuality education because it can boost here. Even where it exists the young people might understand what sexuality means and what sexual life and sexual health means but in real life they can still face some issues." (I.6, International Policy Organisation, Switzerland)*

Theme 5: Criminal justice/sexual violence

Sexual health was also linked to criminal justice, mainly discussing the wider societal impacts of sexual violence, abuse or assault. Victims of sexual abuse were seen as not only having to bear the direct physical and emotional burden of being violated but also serious mental health consequences.

> *"For sexual abuse, this is also a double sword, there is this immediate impact of being violated which of course has a mental health impact but behind that there always sits a trauma that is about the rumination, the reliving, but also the thought of what did I do wrong. And society somehow reinforces that." (I.20, University/Research Institute, The Netherlands)*

The prevention of sexually violent behaviour(s) can help to avoid significant wider societal impacts, according to experts.

> *"If we can prevent that violent behaviour then we can also prevent societal costs you know in the mental health part, and broader, people might have depression or other mental health problems, and they don't work anymore or have less participation in labour because of their mental health problems." (I.24, Governmental Organisation, The Netherlands)*

The important role of sexual health services in identifying and signposting cases of sexual violence and abuse was emphasised by some experts.

> *"In terms of victims of crime, you definitely get a lot of that coming through sexual health services. The role of sexual services usually is to funnel them through the system in terms of trying to get justice. Often a lot of support services are available including psychosexual counselling and that sort of stuff is. From STI clinics you can kind of funnel them into the type of services that they might need." (I.2, University/Research Institute, UK)*

> *"Especially for sexual health interventions there's a lot of testing and referrals. For example, in a situation where you're experiencing partner violence you may be constantly exposed to whatever sexual health outcome, so we need to direct that to services." (I.16, Researcher, USA)*

One expert drew further links between sexual health and the criminal justice system, explaining that those incarcerated are vulnerable to STI outbreaks and are at an increased risk to acquire STIs.

> *"I think also when you think about the criminal justice system healthcare provision for people that are incarcerated is also really important. STI outbreaks in prisons happen a lot and you know a lot of people go in to prison risking STIs or with STIs and those are often very vulnerable populations." (I.2, University/Research Institute, UK)*

Theme 6: Housing, addiction, and other sectors

The interviews revealed that sexual health can often relate to other issues including housing insecurity, drug use or other issues. Although such issues and sectors were less frequently mentioned, important links were highlighted.

"I was interviewing clients to find out how these (HIV care) services are really influencing people's engagement and experience going through the care continuum. And these things keep popping up you know saying 'I am housing insecure' or 'I also use injection drugs' or 'there is so much stigma' or 'I need social support'." (I.16, Researcher, USA)

"The clinic that I used to work we had health advisors so people with complex sexual health needs got support from the health advisors who would then talk to them about all sorts of things you know housing, chemsex, relationships all that sort of stuff." (I.2, University/Research Institute, UK)

7.5 Discussion

7.5.1 Principal findings

This study is the first to comprehensively explore the intersectoral costs and benefits of sexual health issues and interventions and systematically categorise these into sectors to develop a preliminary framework for understanding and considering these intersectoral impacts, and guiding future research and policy. The study findings confirm that sexual health is complex and can generate wide-ranging impacts relating to (1) other areas of health including reproductive and mental health; (2) relationships and family, (3) labour and productivity, (4) education, (5) criminal justice in particular relating to sexual violence, and (6) housing, addiction and other sectors.

Furthermore, the participants all felt that sexual health is holistic in nature and there were important impacts on other sectors outside health. This study reveals that there is a need to also consider the wider impacts sexual health issues and interventions can have on an individual's family, friendships and relationships. Experts explained that if STIs are left untreated or unmanaged they can continue to spread and can have a 'knock-on effect' on an individual and society's productivity and participation in the labour market, potentially causing economic consequences. The education sector and, in particular, the provision of sexual health education was perceived to play a key role in the promotion of good sexual health and well-being, the prevention of STIs, and the prevention of unwanted teenage pregnancy. Sexual violence, abuse and assault and the risk of developing mental health problems because of such traumatic experience was also discussed, drawing a link to the criminal justice sector.

7.5.2 Comparison to other literature

There is a growing body of evidence that advocates for a more holistic approach to sexual health (218). Studies have shown important links to mental health, i.e. finding a need to support people's mental health and sexual health needs holistically (219-221), as well as housing, employment status and alcohol use (222, 223). More and more evidence call for an integrated approach to address the complexity of sexual health by providing holistic services that include health practitioners, mental health professionals, social workers, youth services, employment services, and other (224, 225). This study contributes to this emerging literature by providing a comprehensive analysis of the broader impacts relating to sexual health and providing an initial framework.

7.5.3 Implications for policy

This study presents a preliminary framework of relevant intersectoral impacts of sexual health issues and interventions by policy sector, which researchers and policy/decision-makers can use to ensure evaluations are holistically capturing costs and benefits. The findings of this research are in line with the Action Framework by the WHO, which suggests the need for a 'multisectoral framework' (49). This study highlights the need to take such multisectoral (intersectoral, societal) approach when evaluating interventions and programmes in sexual health to provide policy/decision-makers in the field of sexual health with optimal and comprehensive estimates of the costs and benefits of sexual health interventions.

7.5.4 Implications for research

The findings of this study have important implications for the design of health economic studies. There is acknowledgment that capturing wider societal implications is (methodologically) challenging (15). Methods to capture intersectoral costs and benefits are needed, and this study's preliminary framework of intersectoral costs can help guide future research in sexual health and other public health issues. Future research is recommended to explore other potentially relevant links between sexual health and additional sectors not covered in this study, and to expand the preliminary framework.

7.5.5 Strengths and limitations of the study

One of the key strengths of this study is the use of semi-structured, open-ended interviews that allowed for a systemic, rigorous and structural coverage of key topics while, at the same time, allowing for a degree of freedom and adaptability in seeking information from the interviewees. Another strength is the depth of information generated by including 28 experts from six different countries and covering a wide range of different professions. As the interviews were conducted with participants

based in OECD member countries, it would be important to explore the views and experiences of those based in other settings.

The use of online interviews allowed for more flexibility with regard to the recruitment of participants and therefore ensured a larger sample of participants over a short period of time. Participants did not have to travel to take part in the interviews, which was considered timesaving. The online interviews also allowed participants to join the interviews from a setting most convenient and comfortable to them (226). We acknowledge that the facilitation of online interviews can be challenging, for example due to internet issues, power cuts, etc., particularly in some low-and middle-income countries. Further, as the interviewees were all experts in sexual health it could be important to conduct interviews with other stakeholders outside of this area. There could be additional sectors affected by sexual health issues and interventions that are not covered in this study, and further research is warranted in this area.

7.6 Conclusion

Sexual health issues and interventions can generate costs and benefits across different sectors of society. These need to be considered when evaluating interventions relating to sexual health to ensure well-informed, optimal (political) decisions are made. This preliminary framework developed by this study can help guide future research and policy.

7.7 Chapter summary

This chapter presented a qualitative research study based on in-depth semi-structured online interviews with experts in sexual health to explore the different ICBs associated with sexual health problems and interventions. It identified and categorised relevant ICBs in a preliminary framework (cost classification scheme) to better understand and illustrate these impacts and to guide future research and policy. While this chapter was part of addressing the first aim of thesis, the following chapter (Chapter 8) relates to the second aim of this thesis, which was to develop a consensus-based checklist for the quality appraisal of COI studies. Chapter 8 presents this checklist, describing the six-step process to develop this tool.

CHAPTER 8 A CONSENSUS-BASED CHECKLIST FOR THE CRITICAL APPRAISAL OF COST-OF-ILLNESS (COI) STUDIES

8.1 Chapter overview

This chapter presents a consensus-based checklist for the critical appraisal of cost-of-illness (COI) studies and is accepted for publication in the *International Journal of Technology Assessment in Health Care*, alongside a companion paper (see Chapter 9). While conducting a critical appraisal of COI studies as part of a systematic literature review (see Chapter 5), it became evident that there is currently no single standard quality assessment tool for COI studies. This presented itself as an opportunity to explore and to address this research gap further. Scoping work revealed that there was a need to develop a checklist for the critical appraisal of COI studies that can be used as a minimum standard to appraise the comprehensiveness, transparency and consistency of COI studies and that is based on expert consensus. This chapter describes the six-step development process of the checklist. It then presents the consensus-based checklist for the critical appraisal of COI studies, comprising 17 main questions (and some additional sub-questions) across three domains: (1) study characteristics; (2) methodology and cost analysis; and (3) results and reporting. Following the checklist, guidance statements were developed.

The main article in this chapter is kept the same as the original publication.

8.2 Background

Cost-of-illness (COI) studies can help identify, measure and value the economic burden an illness or disease can impose on society (93). It is a useful decision-making tool as their estimates can be used as a foundation for projecting disease expenses and a framework to address a certain health problem, among others (97, 227). COI studies are a commonly used tool to provide researchers and policy/decision-makers with relevant information regarding the different cost components and cost categories (or sectors) associated with an illness or disease and can describe healthcare spending as well as costs beyond healthcare (i.e. intersectoral costs) (97).

In order to allow for COI studies to optimally inform researchers and policy/decision-makers, these studies need to be methodologically sound (95, 96). Various checklists and guidance tools exist for full economic evaluations including, for instance, the Drummond Methods for the Economic Evaluation of Health Care Programmes (75), the Consensus on Health Economic Criteria checklist (CHEC-list) (228), and others. These checklists and guidelines play an important role in assessing the (methodological or

reporting) quality of economic evaluations and are widely used. In comparison, there is an evident lack of guidance for COI studies and poor consensus on how to review and assess those studies and what tool(s) to use for a critical or critical appraisal (227, 229-233).

To the best of our knowledge, there are only two tools that are specifically designed to assist in developing and assessing COI studies (143, 234). Both tools require a deeper level of technical and methodological detail and are extensive in length. The issue of length is critical because a checklist is often expected to be rigorous but also practical to use. The objective of one of the two tools, the Checklist for the Development and Assessment of Cost-of-Illness Studies by Mueller et al., was to develop a checklist in German and specifically for the German context (234). The objective of the second tool, a Guide to Critical Evaluation by Larg & Moss, was to develop a guide for understanding and evaluating COI studies (143). However, it is unclear whether this guide was developed based on consensus and expert opinion.

Methodological approaches for COI studies can differ in a variety of aspects (i.e. objectives, study perspective, costs included, time horizon), giving rise to considerable methodological heterogeneity (235, 236). This makes comparability across COI studies difficult and the assessment of the generalisability or transferability of study results almost impossible. Because of the lack of available tools to review and assess existing COI studies, researchers often develop their own one-off list of questions as part of their work (e.g., literature reviews).

An internationally applicable, standardised checklist is needed to review and critically appraise the methodological approaches taken and reported in a COI study, to assess a study's comprehensiveness, transparency and consistency, to reflect on a study's strengths and weaknesses, and to potentially increase comparability across COI studies.

Aims and objectives

The aim of this paper was to develop a consensus-based checklist that can be used as a minimum standard to appraise the comprehensiveness, transparency and consistency of COI studies. This is important when, for instance, reviewing and assessing COI studies for example as part of a systematic review) or when building an economic model.

8.3 Methods

The development process of the consensus-based checklist involved six sequential steps, as presented in Figure 5. These steps were based on previous approaches to the development of other relevant checklists and guidelines in health economics and related areas (228, 234, 237).

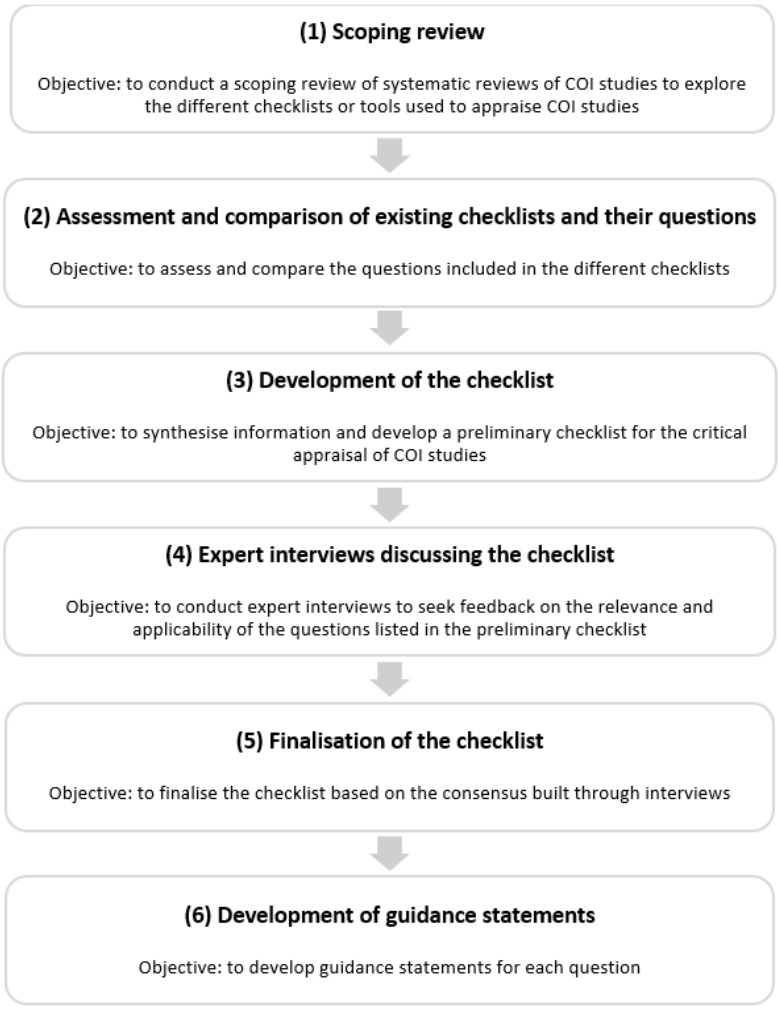

Figure 5 Development process of the consensus-based checklist

8.3.1 Scoping review (step 1)

A targeted scoping review of systematic reviews of COI studies was conducted in MEDLINE (Ovid) to explore the different checklists or other tools used. This was complemented by hand searching and searches in Google scholar, checking the reference lists of included articles, and reviewing articles, studies, checklists, and guidelines suggested by experts working in health economics and with COI studies. A search strategy was developed in MEDLINE using keywords and terminology relating to cost-of-illness, burden of illness, economic burden, systematic review(s), and checklist(s), focusing on papers published from 2010 (Appendix 17). The search strategy combined search terms using Boolean

operators ‘AND’ and ‘OR’ and searched for these keywords and terms in a paper’s title, abstract and beyond. This date was selected as a previous study had considered papers prior to this date, which were reviewed (234). Studies were included in the scoping review that reported on applying at least one checklist or a similar tool for the critical appraisal of COI studies. The aim was to identify all checklists and tools used by researchers for the critical appraisal of COI studies, even if these checklists were not specifically designed for COI studies.

8.3.2 Assessment and comparison of the different checklists and their questions (step 2)

The different checklists identified in the scoping review in Step 1 were listed, compared, and critically reviewed to determine whether they had been specifically designed for COI studies or were based on other existing health economic guidelines. This involved developing a matrix, charting all the questions and sub-questions included in the identified checklists, to allow discussion and comparison by all authors. Due to the fact that not all checklists identified in Step 1 were specifically designed for COI studies (for example they may be for full economic evaluations), the questions (or criteria) included in these different checklists were carefully and critically reviewed in terms of their applicability and relevance for COI studies to identify and synthesise a set of key questions for assessing these studies. This meant that questions that were listed in existing checklists but were only applicable to full economic evaluations were excluded.

8.3.3 Development of a checklist for COI studies (step 3)

This step involved synthesising the output of the scoping review (Step 1) and the results of the critical assessment (Step 2) to determine key areas that would need to be included in a checklist for COI studies. This was further refined to develop a list of the key questions that would be relevant and applicable and that could be used as a minimum standard for the critical appraisal of COI studies. From here on this will be referred to as the ‘preliminary checklist’. This provided an initial outline for discussion with the experts engaged in COI studies in the next step.

8.3.4 Expert interviews (step 4)

Semi-structured, open-ended interviews were conducted with health economists and other experts from different countries working with COI studies to seek their expert opinion on the preliminary checklist and potentially identify questions to be added, removed, or revised. This process is fully described in Chapter 9. In this study, we use the term ‘experts’ to refer to individuals that are knowledgeable in a particular area, in this case in health economics/COI studies, and are/were actively involved in doing research around COI studies, including professors, assistant or associate professors,

research fellows, among other. Experts were selected purposively based on their knowledge and expertise in relation to COI studies using network and snowball sampling. Interviews were audio-recorded, with the participant's consent, and anonymised. A Framework approach was applied for the thematic analysis of the interviews, following systematic steps (217): interview recordings were transcribed verbatim by one author (LS); transcripts were entered and coded in NVivo, identifying themes and sub-themes (LS); a set of transcripts and the coding framework were cross-checked by another author (LJ); both authors familiarised themselves with the transcripts and agreed on a final framework listing relevant themes and sub-themes; the framework and findings were discussed among the author team (AP, LJ, LS, SE, TR); findings were reported narratively. More detailed information on the methodology, conduct and analysis of the interviews is provided in Chapter 9.

8.3.5 Finalisation of the checklist (step 5)

Experts' feedback, suggestions and recommendations on the preliminary checklist were carefully considered. The checklist was modified based on the experts' feedback, removing certain questions, adding relevant questions, and rephrasing other questions, where applicable. The checklist was also presented at internal seminars in the Health Economics Unit at the University of Birmingham and at international health economics conferences, including the lolaHESG 2021 (The lowlands Health Economists' Study Group) and the iHEA Conference 2021 (International Health Economics Association) to seek further feedback from experts in health economics. This step also involved the development of a list and description of answer categories suggested for use when answering the questions in the checklist, based on discussions with experts during the interviews and at the international conferences.

8.3.6 Development of guidance statements (step 6)

Guidance statements were developed for each question listed in the checklist to provide further information on the purpose and meaning behind each question and to give an example of a best practice. These guidance statements were based on existing health economic guidelines and best practices, to align the language and terminology in the checklist with the existing economic literature (95, 97, 228, 238-241).

Ethical approval to conduct this study was obtained from the University of Birmingham (ERN_20-1240).

8.4 Results

The result was a consensus-based checklist for the critical appraisal of COI studies covering relevant questions in relation to study characteristics, methodology and cost analysis, and results and reporting (Table 11). Guidance statements explaining the questions and suggested answer categories were also established (Table 12 and Table 13). This study further generated relevant interview findings that are summarised and presented in a separate paper (Chapter 9).

8.4.1 Scoping review (step 1)

The scoping review of systematic reviews of COI studies published between 2010-2020 identified 26 studies that reported to have used a checklist or similar tool to assess COI studies. Six different checklists and guidelines were identified: the BMJ Checklist (n=8), the CHEC-list (n=3), the CHEERS checklist (n=5), the Drummond 10-point checklist (n=3), and the Drummond Methods for the Economic Evaluation of Health Care Programmes (n=4), and the Guide to Critical Evaluation by Larg & Moss (n=3) (75, 143, 228, 238, 242). (The Drummond 10-point checklist is adapted from the Drummond Methods, but we followed the study authors' ways of reporting). A seventh tool was identified through handsearching, the Checklist for the Development and Assessment of Cost-of-Illness Studies by Mueller et al. (n=0) (Appendix 18) (234). This scoping review revealed that most of the studies predominantly applied critical appraisal tools that are intended for the assessment of full economic evaluations to assess the quality of COI studies. For example, eight studies identified in the scoping review reported to have used (part of) the BMJ Checklist, five studies used the CHEERS Checklist, four studies used the Drummond Methods, three studies used the Drummond 10-point Checklist, and another three studies used the CHEC-list. Some studies reported to have used more than one checklist or other tool/source; in part to develop their own checklist based on existing tools or guidelines. Where checklists and guidelines for full economic evaluations were applied, many studies only adopted a sub-set of the questions included in the checklists or guidelines for full economic evaluations.

Only two of the identified tools are designed for the assessment of COI studies: the Guide to Critical Evaluation by Larg & Moss, and the Development and Assessment of Cost-of-Illness Studies by Mueller et al. Where these tools were applied, studies mostly modified the original checklist by removing some questions or changing the wording of questions.

Some of the studies reported to have developed their own ad-hoc checklist for their study or systematic reviews - which simply had a one-off purpose - based on existing guidelines, previous studies and/or health economic guidelines.

8.4.2 Assessment and comparison of the different checklists and their questions (step 2)

The matrix analysis charting all the questions and sub-questions included in the identified checklists showed similarities in terms of key areas (dimensions) covered in the checklists such as study characteristics, the detailed methods that were used in the cost analysis, and how the study had been reported. There were some key differences between the checklists for full economic evaluations and the two tools specifically designed for COI studies. The latter two are more extensive and require the user/researcher to look at COI studies in more (technical) detail. The number of questions (criteria) in each checklist was recorded: the BMJ Checklist (n=35), the CHEC-list (n=19), the CHEERS checklist (n=24, or n=27 when including sub-questions), the Drummond 10-point checklist (n=10), and the Drummond Methods for the Economic Evaluation of Health Care Programmes (n=NA), the Guide to Critical Evaluation by Larg & Moss (n=37), and the Checklist for the Development and Assessment of Cost-of-Illness Studies by Mueller et al. (n=35) (Appendix 18).

8.4.3 Development of a checklist for COI studies (step 3)

Following the assessment of the questions and sub-questions in Step 2, a list of key questions relevant and applicable to COI studies that would need to be included in a checklist was developed, and the CHEC-list was used as a foundation for further development. The CHEC-list was chosen as a foundation because a rigorous process had been followed to build the checklist. This process included literature searches, taking into consideration existing health economic checklists and criteria, and building consensus using Delphi methods involving a panel of international experts. In addition, the CHEC-list is concise and comprehensive in its format as well as manageable with a total of 19 questions. This was considered an advantage as the aim of this study was to develop a checklist for COI studies that is concise but comprehensive and can be expanded, where needed. Due to the fact that the CHEC-list is intended for full economic evaluations, the author team reviewed all 19 questions in terms of their applicability and relevance to COI studies. We excluded those questions that were only relevant for full economic evaluations (i.e. a description of competing alternatives; an identification, measurement and valuation of relevant outcomes for each alternative; information on an incremental analysis of costs and outcomes). This resulted in a preliminary list of 14 questions applicable to COI studies (Appendix 19). Findings from a previous study comparing the original CHEC-list to two other checklists (the BMJ checklist and the Quality of Health Economic Studies (QHES) checklist) suggested that the

original CHEC-list is missing a question assessing whether study limitations are specified (243). Hence, the author team added a question on study limitations to the preliminary checklist for COI studies, resulting in a total of 15 questions for the preliminary checklist. The order and wording of the 14 questions were kept almost identical to the original CHEC-list as health economists and other experts working with COI studies that were to be interviewed were likely to be familiar with the questions and terminology, and this was considered helpful for the interviews. The questions could (preliminarily) be divided into the following three dimensions: study characteristics; Methodology and cost analysis; and Results and reporting.

8.4.4 Expert interviews (step 4)

Between October 2020 and April 2021, 21 professionals (11 male, 10 female) from 11 different countries and with expertise in health economics (n=17), economics, (n=1), health policy (n=2) and psychology (n=1) participated in the interviews and provided feedback on the checklist. Experts were affiliated with academia, international policy organisations, governmental organisations, and consulting firms. More detailed information on the interview sample is provided in Chapter 9.

This study reached data saturation and consensus after those 21 interviews, finding similarities across those interview findings with little to no new findings emerging. Overall, experts were in favour of the checklist and expressed the urgent need for a checklist for COI studies. They suggested to remove, add, or rephrase some of the questions. Their feedback was considered and discussed carefully to finalise the checklist (before further presenting this checklist to experts at international health economic conferences). A more detailed analysis of the interview findings including relevant quotations is provided in Chapter 9.

8.4.5 Finalisation of the checklist (step 5)

Following expert feedback and discussions with experts at international health economic conferences, the final version of the checklist was agreed upon. The final checklist comprised 17 main questions (and some additional sub-questions) across three domains: study characteristics; methodology and cost analysis; and results and reporting (Table 11). These domains are briefly described below.

Domain 1 - study characteristics: This dimension aims to assist the user of this checklist in assessing whether a COI study formulated (Item 1.) an objective, described (Item 2.) the characteristics of the study population, and is explicit about (Item 3.) the perspective chosen for the cost analysis.

Domain 2 - methodology and cost analysis: This dimension aims to assist the user of this checklist in assessing whether a COI study reported their choice for their (Item 4.) epidemiological approach, (Item 5.) costing approach, and (Item 6.) data collection approach as well as whether it stated which resources their study (Item 7.) identified, (Item 8.) measured, and (Item 9.) valued. It also guides the user in assessing whether a COI study stated their (Item 10.) time horizon for analysis, reported whether they (Item 11.) discounted future costs and conducted (Item 12.) sensitivity analysis/analyses.

Domain 3 - results and reporting: This dimension aims to assist the user of this checklist in assessing whether a COI study presented (Item 13.) study results by cost category/sector (depending on their study perspective) and discussed (Item 14.) generalisability of study results, (Item 15.) study limitations, and (Item 16.) ethical and/or distributional issues. It also asks whether the study reported any (Item 17.) conflict of interest.

Table 11 The consensus-based checklist for cost-of-illness (COI) studies

Item	Question	Answer*	Supportive information
STUDY CHARACTERISTICS			
Question/objective	1. Is a well-defined research question or objective stated?		
Population	2. Is the study population described?		
Perspective	3. a) Is (are) the chosen study perspective(s) stated?		
	b) If so, is (are) the chosen study perspective(s) justified?		
METHODOLOGY AND COST ANALYSIS			
Epidemiological approach	4. Is the epidemiological approach reported (i.e. prevalence, incidence)?		
Costing approach	5. Is the costing approach reported (i.e. top-down, bottom-up)?		
Data collection approach	6. Is the data collection process reported (i.e. prospective, retrospective)?		
Identification	7. a) Are all components of resource use identified that are relevant to the condition/disease, population, intervention, study objectives and study perspective?		
	b) If not, is a justification provided for excluding relevant components of resource use?		
Measurement	8. a) Are all included components of resource use measured?		
	b) If not, is a justification provided for not measuring certain components of resource use?		
Valuation	9. a) Are all included components of resource use valued in monetary terms?		
	b) If not, is a justification provided for not valuing certain components of resource use?		
Time horizon	10. a) Is the chosen time horizon specified?		
	b) If so, is the chosen time horizon justified?		

Discounting	11.	a) Are future costs discounted?
		b) If so, is a justification provided for the discount rate?
Sensitivity	12.	a) Are all variables whose values are uncertain subjected to sensitivity analysis?
		b) If so, is a justification provided for which variables are subjected to sensitivity analysis?
		c) Are analyses done on relevant sub-groups?
RESULTS AND REPORTING		
Cost sectors	13.	Are the study results presented transparently by cost category/ sector?
Generalisability	14.	Do the authors discuss the generalisability of study results (i.e. comparing the results to other patient/client groups or/in other settings)?
Limitations	15.	Do the authors discuss important limitations?
Ethical & distributional issues	16.	a) Do the authors discuss ethical issues?
		b) Do the authors discuss distributional issues?
Conflict of interest	17.	Do the authors report any potential conflicts of interest?

*Suggested answer categories: *yes, partially, no, not applicable (NA)* or *unclear*. See Table 12 and 13 for further detail and guidance.

Application of the checklist

Based on the consensus built throughout the interviews and at international conferences, the following answer categories are suggested to be applied when answering the questions in the checklist: *yes, partially, no, not applicable (NA)* or *unclear* (Table 13). The checklist contains one column listing all questions and sub-questions, one column to note down the answer, and one column to add *Supporting Information*. Users are advised to extract relevant information from COI studies when answering the questions to support or justify their answer narratively and to increase accountability. Further detail on the above answer categories is given in Table 13, and the reasons for choosing intermediate categories are summarised and published in a separate paper (see Chapter 9*)*.

It is considered sufficient if one reviewer completes the checklist, assuming that they use the data extraction column to add information that justifies their answer. It is recommended to seek out to a second reviewer where information is not clear, and discrepancies need to be discussed. This checklist does not require the user to add scores to their answers or produce a total score for each study and a ranking of studies by score. Where desired or needed, it is however open to and possible for users to add scores to their answers (i.e. *yes*=1, *partially*=0.5, *no*=0). When answering the questions as suggested in the guidelines, users will be able to reflect on the number of *yeses* or *nos*, which could give them an idea of the comprehensiveness, transparency and consistency of the study.

Where needed, the checklist can be modified and/or expanded, but it is suggested to clearly report any modifications or expansions to maintain consistent use.

8.4.6 Development of guidance statements (step 6)

Additional guidance was developed describing the purpose and meaning behind each question and listing examples of best practice, see Table 12.

Table 12 Guidance statements

Item	Question	Guidance
STUDY CHARACTERISTICS		
1. Question/objective	Is a well-defined research question or objective stated?	A research question or objective should be stated and identify the study population and the type of disease(s)/condition(s) that is being assessed. The objective (or purpose) for why this study is conducted and needed should be described and be economically important (i.e. why this study is important to decision-makers). The objective of the study ultimately determines the study perspective and subsequently resources captured in the analysis. Ideally, the research question or objective should include the chosen study perspective and indicate the costs that are being assessed.
2. Population	Is the study population described?	The study population should be described including information on patient characteristics (i.e. age, sex, ethnicity), geographic location and clinical characteristics (i.e. disease stage, previous treatments, co-morbidities). The study population described should be consistent with the population data in the study analysis. This information should be relevant to the motivation and objective of the study.
3. Perspective(s)	a) Is (are) the chosen study perspective(s) stated?	The study perspective(s) to address the research question or objective should be clearly stated. The study perspective ultimately depends on the study objective and stakeholder interests (i.e. government, provider, payer, decision/policy maker). The study needs to be specific about whether it assesses the economic burden of, for instance, society as a whole or a particular agent (i.e. provider, payer). The study perspective should ideally include a description of what payers are included. Examples: Societal, provider, health system, government, other.
	b) If so, is (are) the chosen study perspective(s) justified?	A clear justification should be provided for the chosen study perspective as it determines the cost components to be included in analysis. For example, the study might have followed national guidelines or reference cases. In some cases, national guidelines recommend adopting a narrower (i.e.

		healthcare, payer), perspective. The authors should always justify why a narrower perspective was applied and is valid. For example, a narrower perspective is accepted if the aim is to maximise the health outcome from a given (healthcare) budget.
METHODOLOGY AND COST ANALYSIS		
4. Epidemiological approach	Is the epidemiological approach reported (i.e. prevalence, incidence)?	The epidemiological approach should be clearly reported. The prevalence approach estimates the economic burden of a disease/condition over a defined period of time (usually one year). The incidence approach estimates the economic burden of a disease/disease over (usually) over a lifetime.
5. Costing approach	Is the costing approach reported (i.e. top-down, bottom-up)?	The data quantification method should be clearly reported. The top-down approach uses aggregated data to estimate the attributable resources. The bottom-down approach uses individual-level data to estimate the quantity of inputs used and the unit costs of the inputs used.
6. Data collection	Is the data collection process reported (i.e. prospective, retrospective)?	The data collection process should be clearly reported. COI studies can be performed either prospectively or retrospectively depending on the relationship between the start of the study and the data collection. In a retrospective study, the events and resources have already occurred, and data has already been collected by the time the study is initiated. The previously collected data is then used for analysis. In a prospective study, the events and resources have not yet occurred by the time the study is initiated. This requires data to be collected by following individuals over time.
7. Identification of resource(s)	a) Are all components of resource use* identified that are relevant to the condition/disease, population, intervention, study objectives and study perspective?	A full identification and documentation of relevant resources should be provided. This includes the identification and inclusion of different categories of costs (i.e. healthcare, productivity). The definition of 'relevant' costs is dependent on the disease/condition, study objective and study perspective. Each cost component should be clearly stated. Where a study adopted more than one perspective (i.e. healthcare and societal perspective), the inclusion of the different resources under each perspective should be reported separately.

		Recommended sub-items: Healthcare, individual/family, productivity losses (labor), other sectors (i.e. education, criminal justice).
	b) If not, is a justification provided for excluding relevant components of resource use?	A clear justification should be provided for any excluded resources, including potentially relevant cost categories and cost components.
8. Measurement of resource(s)	a) Are all identified and included components of resource use measured?	Ideally, all identified and included resources should be measured. The methods (sources, instruments) for obtaining and quantifying the different components of resource use should be valid and clearly stated (i.e. interview, questionnaire, survey, cost-diary, etc.). If relevant, it should be stated if only costs specific to the disease/condition were included or if additional or excess costs were measured (i.e. costs related to comorbidities).
	b) If not, is a justification provided for not measuring certain components of resource use?	A justification should be provided for those resources that were not (or could not be) measured.
9. Valuation of resource(s)	a) Are all included components of resource use valued in monetary terms?	The sources of valuation for each unit price of every component of resource use should be valid and clearly stated. The currency and costing/reference year should be stated. The different approaches to valuing costs should be justified (i.e. what approach was taken to measure and value productivity costs, and why). If relevant, price adjustments over time should be reported. If relevant, it should be reported if prices were taken from other countries.
	b) If not, is a justification provided for not valuing certain components of resource use?	A justification should be provided for those resources that were not (or could not be) valued.
10. Time horizon	a) Is the chosen time horizon specified?	The chosen time horizon should be clearly stated. It refers to the period of analysis over which resources are assessed and is often associated with the choice of the epidemiological approach for analysis (prevalence, incidence). The time horizon should be long enough to capture all resources relevant to the disease/condition.

	b) If so, is the chosen time horizon justified?	A clear justification should be provided for the chosen time horizon. For example, the study might have followed national guidelines or reference cases.
11. Discounting	a) Are future costs discounted?	Where discounting is applicable the method for discounting future costs should be stated. Discounting indicates that costs that occur at different points in time (i.e. present costs and future costs) are valued differently. Hence, the timing of when costs incur plays a role when discounting future costs. For example, discounting is crucial for any study that adopted a time horizon longer than one year, i.e. when applying an incidence approach where costs are estimated over a lifetime. Where studies used a time horizon of less than 1 year it might not be applicable (NA) to discount future costs.
	b) If so, is a justification provided for the discount rate?	The discount rate used in the study should be justified. For example, the study might have followed national guidelines or reference cases.
12. Sensitivity	a) Are all variables whose values are uncertain subjected to sensitivity analysis?	All variables in the analysis are potential candidates for the sensitivity analysis and should be presented or discussed. Different types of sensitivity analysis can include, for example, univariate and multivariate sensitivity analysis.
	b) b) If so, is a justification provided for which variables are subjected to sensitivity analysis?	A clear justification should be provided describing the range of the variables used in the sensitivity analysis. Only variables that are certain or which have a minimal impact on the study results (based on the preliminary analysis) can be excluded from the sensitivity analysis.
	c) Are analyses done on relevant sub-groups?	Resource use or costs can vary across populations and sub-groups (i.e. disease severity, gender, age, and ethnicity). In other words, characteristics of sub-groups can influence the resource use or costs. Such heterogeneity of sub-groups should be explored and, where relevant, separate analyses should be done on sub-groups. For example, healthcare costs may be higher for males compared to females, older people compared to younger people, or other.
RESULTS AND REPORTING		
13. Cost sectors	Are the study results presented	The presentation of cost components for each cost category is dependent on the study perspective.

	transparently by cost category/sector?	Where a study adopted more than one perspective (i.e. healthcare and societal perspective), the inclusion of the different cost components under each perspective should be reported separately. Recommended sub-items: Healthcare, individual/family, productivity losses (labor), other sectors (i.e. education, criminal justice)
14. Generalisability	Do the authors discuss the generalisability of study results (i.e. comparing the results to other patient/client groups or/in other settings)?	Generalisability refers to the applicability of the study results based on a (patient/client) sample to another sample (or setting). The study should clearly describe how research findings could be applied to other patient/client groups or settings and indicate how particular findings (or costs) could vary by patient/client groups, population, setting, location, care provider, etc.
15. Limitations	Do the authors discuss important limitations?	The study should discuss relevant limitations. Limitations can relate to, for instance, certain data, sources, cost components, assumptions, and (measurement, valuation) methods chosen for analysis. The reader should be able to understand the choice for certain methods and their main limitations. Recommended sub-items: data, sources, cost components, assumptions, methods, other.
16. Ethical and distributional issues	a) Do the authors discuss ethical issues?	Where applicable, the study should note ethical aspects that may raise some controversy. For example, placing a value on life/health and the methodological approach to do so may raise some ethical issues.
	b) Do the authors discuss distributional issues?	Where applicable, the study should elaborate on the characteristics of the population experiencing the disease/condition (young, old, poor, wealthy) and how this may have distributional implications.
17. Conflict of interest	Do the authors report any potential conflict of interest?	The study should declare whether there is a potential conflict of interest. For example, a study should declare if an external agency financed the study to guarantee transparency in the relationship between the researcher and sponsor.

An explanation of the answer categories is given in Table 13 (next page).

Table 13 Suggested answer categories to assess the questions in the checklist for COI studies

Answer categories	Explanation
Yes	Yes can be applied to indicate if a study reported on the requested information
No	No can be applied to indicate if a study missed to report on the requested information
Partially	Partially can be applied to indicate when a question was addressed or mentioned, but the information is not clearly or only sub-optimally described
Not Applicable (NA)	Not Applicable (NA) can be applied to indicate where a question might not be applicable to a COI study or in the context of the study
Unclear	Unclear can be applied when a question is addressed but it is not clear how exactly

*Other international literature might also refer to the components of resource use as resources or costs.

8.5 Discussion

8.5.1 Principal findings

The aim of this study was to develop a consensus-based checklist that can be used as a minimum standard to appraise the comprehensiveness, transparency and consistency of COI studies. This study is the first to establish a checklist to review and assess the methodological approaches taken and reported in COI studies that is internationally applicable. The checklist was developed with the engagement of international experts from relevant backgrounds such as health economics, health policy, and psychology who had conducted or provided guidance for COI studies. The checklist is based on existing checklists and guidelines for health economic studies, expert qualitative interviews, and feedback from stakeholders at international health economic conferences. It can be considered a pragmatic, reliable tool, and a minimum standard to review COI studies and to assess whether a study generates reliable COI estimates. It is generic, concise, and comprehensive and can be applied in several scenarios, for instance, when reviewing and assessing a COI study for example as part of a systematic review or when building an economic model. Additionally, this study addresses the inconsistency in the use of checklists and guidelines to appraise COI studies. More details and evidence on the important need for a standardised checklist to review and assess COI studies are provided in Chapter 9. It is the first study to fill this gap and provide a tool that could be used by users/researchers more consistently and internationally.

8.5.2 Comparison to other checklists

Those checklists identified in the scoping review of this study cover similar questions and show methodological parallels. Those checklists, in particular the CHEC-list, provided a starting point to the development of a consensus-based checklist for COI studies. The Guide to Critical Evaluation by Larg & Moss and the Checklist for the Development and Assessment of Cost-of-Illness Studies by Mueller et al. are designed for COI studies but may require a deeper level of technical and methodological detail and are extensive in length. It was unclear as to how the guide by Larg & Moss had been developed and whether it is based on expert opinion and consensus (244). The checklist by Mueller et al. was developed using expert opinion but it was first and foremost established for the German context and is officially only published in German (234). Both tools have been taken into consideration for the development of the present consensus-based checklist for COI studies.

8.5.3 Strengths and weaknesses of the study

This study established and followed an extensive, structured, and iterative approach to the development of the checklist, involving literature searches, expert interviews, and further discussions among experts at international health economic conferences. The involvement of 21 international experts working in health economics, health policy, and psychology, and users as well as developers of existing critical appraisal tools is one of the key strengths of this study. The checklist is a generic tool that can be applied to different disease areas and scenarios. A potential weakness of this study is that the checklist has not yet been formally pilot-tested. The checklist has, however, been applied by staff and students at Maastricht University and the University of Birmingham who have provided constructive feedback. The author team will undertake further piloting and testing of the checklist across different disease areas, and potentially refine its criteria, where relevant. This will be undertaken by students and researchers (initially by the authors and their research groups) using this tool for reviewing and assessing COI studies as part of future systematic reviews. It is planned that the appraisal tool will also be published on a university website (Maastricht University) alongside other critical appraisal tools. This will allow us to monitor use of the checklist and to provide details on correspondence, in order to collect feedback from a wider range of users (outside of our research groups). Another limitation of this study is that due to the iterative process of development, the feedback collected during the interviews and the feedback collected at conferences were merged for analysis, making it difficult to compare the changes made based on the interviews and those made due to conference discussions. Further, the use of the CHEC-list as a starting point may be a limitation. This is because the CHEC-list was developed for full economic evaluations and given COI studies cannot be defined as economic evaluations there is a risk that questions pertinent to COI studies may not

have been included. However, other tools and checklists including the guide by Larg & Moss and the checklist by Mueller et al. were carefully considered during the development of the new checklist.

8.6 Conclusion

There is currently no standard checklist for the critical appraisal of COI studies and, as a result, the use of checklists for COI studies is inconsistent and heterogeneous. The consensus-based checklist for COI studies is a first step toward standardising the critical appraisal of COI studies and is one that could be considered a minimum standard, with international applicability. The checklist can help to assess the comprehensiveness, transparency and consistency of COI studies, to address potential heterogeneity and to allow for comparability of methodological approaches.

8.7 Chapter summary

This chapter presented the development and finalisation of a consensus-based checklist for the critical appraisal of cost-of-illness (COI) studies. The checklist comprises 17 main questions (and some additional sub-questions) across three domains: (1) study characteristics; (2) methodology and cost analysis; and (3) results and reporting. Alongside the checklist, guidance statements were developed and included to explain the meaning behind each question in the checklist. While this chapter presented the new checklist, the following chapter (Chapter 9) presents a qualitative study, exploring expert interviews to inform the development of the consensus-based checklist for the quality appraisal of COI studies as well as their expert opinion on the use and relevance of COI studies and tools to assess these studies.

CHAPTER 9 EXPERT OPINION ON A CONSENSUS-BASED CHECKLIST FOR THE CRITICAL APPRAISAL OF COST-OF-ILLNESS (COI) STUDIES: QUALITATIVE INTERVIEWS

9.1 Chapter overview

This chapter presents a qualitative paper that is accepted for publication in the *International Journal of Technology Assessment in Health Care*, alongside the new consensus-based checklist for the critical appraisal of COI cost-of-illness (COI) studies (please refer to Chapter 8). The aim of this study was to explore experts' views on the development of a proposed checklist for COI studies (developed by the PhD student and supervisory team), using qualitative interviews. Simultaneously, it explored experts' perspectives on the of COI studies and of critical appraisal tools used for COI studies as well as their experiences with existing critical appraisal tools. Experts included individuals that are knowledgeable in health economics/COI studies and are/were actively involved in doing research around COI studies. As part of presenting the rationale for this work, the chapter briefly discusses the controversy around COI studies to date. Following this, the chapter then presents the main findings from a total of twenty-one interviews. It concludes that the interviews provided relevant input for the development and refinement of the consensus-based checklist for COI studies and confirmed the important need for a checklist for the critical appraisal of COI studies.

The main article in this chapter is kept the same as the original publication.

9.2 Background

Cost-of-illness (COI) studies aim to assess the economic burden of an illness (or disease, health condition, risk factor) on society (93). This generally involves the identification, measurement, and valuation of healthcare costs and/or non-healthcare costs across different sectors of society (i.e. intersectoral costs), depending on the study perspective (i.e. healthcare, societal). For example, a societal perspective is expected to capture all relevant costs associated with an illness both within and beyond the health sector (i.e. productivity losses, informal care) (95).

An accurate estimation of COI is essential to optimally inform different stakeholders. In the context of health policy/decision-making, this can be essential to prioritise certain health interventions or policies and to allocate resources accordingly and under budget constraints (95, 96). In health economics research, this can be relevant to provide adequate information on valuable cost estimates, for example, to inform the conduct of full economic evaluations (75, 227, 245-247). This requires COI studies to be of solid methodological quality and to be as comprehensive and transparent as possible.

There is, however, an extensive methodological heterogeneity among COI studies due to poor consensus on methodological approaches and a lack of a standard tool to assess COI studies in terms of their comprehensiveness, transparency and consistency (227, 229-233). Different methodological approaches can be found, for instance, in relation to the objective(s), study perspective(s), and costs captured. Heterogeneity can also be a result of the different data sources available for COI studies. Such heterogeneity can hinder comparison and transferability of study results (235, 248). This highlights the important need for a standard tool to critically appraise COI studies that could be used as a minimum standard.

The controversy around COI studies and its importance for research and policy/decision-making is briefly described below before presenting the objectives of the study and methodological approaches.

9.2.1 Controversy around COI studies

While COI studies have an important role to play in health economics and are a useful economic tool for policy/decision-making, these studies have been the subject of extensive debate. One argument against COI studies that is often articulated is that they simply identify an area of high expenditure and could lead to those illnesses being focused on that are the most costly (97), rather than those that are judged as the highest priority.

The controversy on the usefulness of COI studies largely concerns its methodology. They are criticised for only considering the costs of resources and not the utility loss associated with an illness. It is argued that COI studies do not capture information on the benefits (outcomes) associated with interventions and that the lack of understanding and comparison of the costs and benefits makes it impossible to determine whether resources are being spent efficiently (94). This controversy has resulted in COI studies being overlooked and their role as an important economic tool being questioned (97).

However, a number of alternative arguments have been put forward in relation to the importance of COI studies, in particular in relation to the true total cost to society (97, 249). First, COI studies reveal relevant information on how much society is spending on an illness. COI estimates can be used as a foundation for projecting disease expenses or a framework to address a certain health problem (97, 227). Second, COI studies are used to provide policy/decision-makers with information regarding the different cost components and cost categories (or sectors) associated with an illness. It is argued that identifying the main cost components is essential in order for policy/decision-makers to define cost

containment strategies, in particular for main cost drivers (97). The consideration of both health and non-health (i.e. intersectoral) costs (or resources) is crucial to reflect the most comprehensive total costs to society. Unless both health and non-health costs are captured total cost estimates can be insufficient, and this can lead to suboptimal decision-making (250). A recent systematic review of COI studies found that the intersectoral costs associated with sexually transmitted infections and HIV can largely contribute to the total economic cost burden of those diseases (251). Further, findings arising from COI studies can be used as a justification of the necessity associated with health interventions or policy (95, 245). COI estimates are also needed to inform decision-analytic modelling on the cost-effectiveness of interventions (227, 245, 252).

This study aimed to explore experts' views on the development of a proposed checklist for COI studies developed by the author team (Chapter 8), using qualitative interviews. It also investigated experts' perspectives on both the use and relevance of COI studies and of critical appraisal tools used for COI studies as well as their experiences with the use of existing critical appraisal tools. In this study, we use the term 'experts' to refer to individuals that are knowledgeable in a particular area, in this case in health economics/COI studies, and are/were actively involved in doing research around COI studies.

This paper is complementary to the study that published the consensus-based checklist for COI studies and provides a broader context and in-depth analysis of the interviews (Chapter 8).

9.3 Methods

Semi-structured, open-ended interviews were conducted with health economists and other experts working with COI studies and with experience developing health economic guidelines or checklists, to seek their opinion on the relevance and use of COI studies, existing critical appraisal tools for COI studies, and to contribute to the development of a checklist for COI studies.

9.3.1 Sampling and recruitment of participants

Interview participants were selected purposively based on their expertise in health economics, their knowledge on COI studies and their experience in developing health economic guidelines or checklists. Using network and snowball sampling, experts were approached via E-mail and invited to participate in a one-to-one online interview with the lead researcher (LS). An information leaflet was shared with all potential participants to provide more information on the background and purpose of the study and the dissemination of study findings. Prior to their interviews, participants received the preliminary checklist for COI studies developed by the author team and a consent form (Appendix 19). All

participants received the same version of the checklist and had been given the opportunity to review the checklist prior to the interview.

9.3.2 Data collection and analysis

A semi-structured approach was chosen for the conduct of the interviews as it allows for a systematic coverage of key topics alongside flexibility and spontaneity (216). Online interviews were chosen due to the circumstances relating to the COVID-19 pandemic. A topic guide was developed to guide the interviews, containing a set of open-ended questions (Appendix 20). Some of the questions involved asking whether participants had used any form of quality assessment(s) for COI studies to date, and if so, why they chose to apply certain tools, and what these entailed. Participants were also invited (i) to share their feedback on the preliminary checklist, (ii) to comment on the relevance of individual questions included in the checklist, (iii) to suggest additional questions, and (iv) to state whether the checklist was comprehensive. Interviews were audio-recorded, with the participant's consent, and anonymised.

A Framework approach was applied for the thematic analysis, allowing for systematic analysis (217). The interview recordings were transcribed in full and entered into NVivo 12 (a software for qualitative data analysis) by the lead researcher (LS) (step I). The same researcher (LS) and a second author (LJ) both familiarised themselves with a number of the recordings and transcripts (step II) and independently coded several transcripts, identifying emerging themes and sub-themes (step III). The authors compared their themes and sub-themes, discussed discrepancies, and discussed those themes with all co-authors (step IV). This resulted in a coding framework that all study authors agreed upon. The lead researcher (LS) then coded the remaining transcripts, applying the established coding framework (step V). A matrix was developed, charting all themes and sub-themes found in all transcripts (step VI). This was again shared with all co-authors for discussion (step VII). The findings are reported narratively.

Consent

All interview participants signed and returned their written consent prior to the start of their interview.

Ethical approval

Ethical approval to conduct this study was obtained from the University of Birmingham (ERN_20-1240).

9.4 Results

9.4.1 Study characteristics

Twenty-one experts (eleven male, ten female) with experience of undertaking or working with COI studies from eleven different countries participated in the interviews between October 2020 and April 2021 (Table 14). This involved experts from Europe (n=13), Australia (n=1), Canada (n=1), the Middle East (n=1), and the United States (n=5). Experts had expertise in health economics (n=17), economics, (n=1), health policy (n=2) and psychology (n=1). Most of them were affiliated with academia or research institutes (n=17); others with international policy organisations (n=1), governmental organisations (n=1), and consulting firms (n=2). Three of the experts had experience in developing checklists for health economic studies. The interviews ranged between 45-75 minutes.

Table 14 Interview sample

Participants	**21**
>10 years of experience (approximately)	11
<10 years of experience (approximately)	10
Country	
Australia	1
Canada	1
Denmark	1
France	1
Germany	2
Ireland	1
Italy	1
Lebanon	1
Netherlands	1
United Kingdom	5
United States	5

Expertise	Affiliation	ID
Health Economics	University/ Research Institute	I.1-I.9; I.11-I.15
	International Policy Organisation	I.16
	Consultancy	I.17; I.18
Economics	Governmental Organisation	I.19
Health Policy	University/ Research Institute	I.10; I.20
Psychology	University/ Research Institute	I.21

9.4.2 Interview findings

COI studies were generally found to be relevant to estimate the overall burden of a disease, to draw attention to disease areas and their impacts, to understand the different cost components and the total costs, to explain cost variability, to inform decision-making, and to provide input for cost-effectiveness analyses.

One expert explained that 'we as health economists usually get the request to do cost-of-illness studies to help inform decision-making around new vaccines and whether introducing a vaccine against a disease, or even earlier in the development chain, whether even investing in R&D in a new vaccine is relevant. […] This is where that cost-of-illness information comes in, as a first step. It's also used as an input for cost-effectiveness analysis eventually.' (Economist, I.19)

Some differing opinions were identified, with one participant raising the concern that COI studies 'are often used as an advocacy tool, saying that a specialty is important as it costs a lot of money' (Psychologist, I.21). Another claimed, 'Cost-of-illness tends to be used as an attempt to draw attention to a disease in the hope that [it] will encourage a greater amount of funding' (Health Economist, I.15).

Further, experts reported a lack of a standardised critical appraisal tool for COI studies. Their experience with existing critical appraisal tools primarily related to guidelines and checklists designed for full economic evaluations such as the Drummond Methods for Economic Evaluation in Healthcare and the CHEERS guidelines. Some experts were familiar with the Guide for Critical Evaluation by Larg & Moss (2011). When assessing COI studies, experts stated they often referred to previous studies or reviews of COI studies to adopt their methodology or their set of questions for quality assessment. The main purpose for assessing COI studies was as part of a (systematic) review.

The following themes emerged from the interviews when discussing the preliminary checklist: (i) the need for a critical appraisal tool, (ii) format and practicality, (iii) assessing the questions (how to answer them), (iv) addressing subjectivity, and (v) guidance requirements.

(i) The need for a critical appraisal tool

The interviews validated that at the time there was currently no consensus on either a standard guideline for the methodology of COI studies or a standard critical appraisal tool to review and assess COI studies. Experts considered the proposed preliminary checklist to be important to address this gap. Those who previously conducted COI studies explained they relied on their own knowledge and experience or what other researchers have done before in terms of methodology. This could result in heterogeneity across studies and challenge any comparison. This could be appraised and assessed with the use of a checklist.

> *"There is no consensus, there is no standard way to think about methodology. People could have different opinions and it's really hard to say one [study] is better than the other." (Health Economist, I.5)*

> *"To begin with, I think it's brilliant that you have this idea of creating a checklist because there aren't any." (Psychologist, I.21)*

> *"There is not a normative guideline that we use in developing some of the cost-of-illness studies. We are more building on what has been done internally. For example, there has been an influenza economic burden tool developed by WHO and then we used that tool to then do an influenza burden of disease study in other countries." (Economist, I.19)*

It was highlighted that guidelines for economic evaluations are often used to conduct COI studies or assess its quality, but that this is methodologically suboptimal.

> *"At the end of the day, we work alongside the guidelines for economic evaluation. However, they don't really fit. We mostly rely on our own experience, and we look at literature, what other researchers are doing." (Health Economist, I.14)*

The important need for a checklist for COI studies specifically was expressed repeatedly.

"There is an importance of having a strong checklist and a good guidance in order to assess whether we are working in a methodologically sound way, 'yes or no'. […] So we need such checklist or guidance in order to know if what we are doing is optimal." (Health Economist, I.4)

(ii) Format and manageability

The interviews elicited views on the overall format and manageability of the checklist. It was suggested to keep it concise, and experts felt that a balance was needed between being comprehensive and ensuring the checklist was practical for use.

"First, I certainly understand the thought behind developing this checklist. […] It is not appreciated to have to use a long checklist when having to evaluate existing studies. […] It is not practical. I think it makes sense to cut down on criteria as you did with the [CHEC-list]." (Health Economist, I.12)

"The checklist is high-level. I think that the way that you drafted it is OK. Otherwise, you need to go too much into detail. […] and this can become too cumbersome." (Health Economist, I.9)

"I prefer a shorter checklist and if there are a lot of 'no's' you kind of take a closer look and see what exactly is going on here, also in terms of limitations." (Health Economist, I.2)

Only a minority of the experts suggested to add more directed and technically detailed questions but argued that this was primarily helpful to guide the conducting of COI studies.

"But maybe it's a bit short because if you conduct a cost-of-illness study it comes down to very specific questions." (Health Economist, I.14)

"I mean it's a quality assessment tool, it's not a guideline. I think guidelines are more detailed and explain why you have to choose certain approaches. I don't think that's necessary for a checklist. […] I don't think you have to be too detailed in a checklist, details are for guidelines." (Health Economist, I.14)

Dividing the questions listed in the checklist by domain (study characteristics, methods and data analysis, results and reporting) was welcomed by the experts.

"I think it's nice and simple. The main, top level categories, study characteristics, methods, results and reporting [...]. This is following pretty much the economic evaluation kind of checklists. I think the questions are all relevant, I can't see any here which are not needed." (Health Economist, I.16)

"It's clear first of all, and it's good that you divided it based on study characteristics, methodology and cost analysis, this is very helpful." (Health Economist, I.4)

(iii) Assessing the questions (how to answer them)

A discussion evolved in many interviews around how to answer the questions in the checklist. There was consideration of whether the response should be scored or simply an assessment of whether an item was present or absent.

"When I saw your checklist my first reaction was 'how are you going to score each of the questions?' […] Nobody knows what the most ideal way is of doing the scoring." (Health Economist, I.5)

Most experts suggested to avoid applying a numerical score when assessing the questions (i.e. yes=1, no=0). The main argument was that not all questions are equally important and have the same weight.

"But the main issue is how to score the items. And second, are the items given the same weight. Are there any relatively more important items. […] Or are there more important items that truly affect the results of the study." (Health Economist, I.4)

"As part of one of our reviews we were thinking on whether we want to add a score and add up the scores, but we didn't because working with scores is not appropriate. Because we were unable to decide which questions should be given more weight compared to others." (Health Economist, I.14)

"I'm always a bit more cautious about giving a score in a checklist because that implies something about how important each criterion is compared to another. A scoring process is another piece of work, so I guess I'm against scoring." (Health Economist, I.6)

"We saw in the pre-test of our checklist that people wanted a quantification, so a total score. […] But this is not in the nature of cost-of-illness studies. Cost-of-illness studies might have scored well on some criteria but should the one or two criteria that they didn't score well on really ruin the quality of the study. In that case a score can be treacherous." (Health Economist, I.12)

There was some controversy around whether the answers to questions should be limited to just 'yes-or-no' responses, with some experts arguing in favor of this.

"My preference has been yes-or-no and have an accumulative score. But I don't know if all of these elements are equally weighted." (Economist, I.19)

"A checklist with a yes-or-no process would actually be quite useful because I could get quite a lot from that checklist quite quickly." (Health Economist, I.6).

Whereas many others felt that a more nuanced response would be needed. As they felt that some aspects might be very clear, but others might be less well covered.

"For example, 'The research question was posed in an answerable form'. It might be clear to some, it might not entirely be clear to others, so a yes or no could be a bit too strict." (Health Economist, I.9)

"Question 2 is a yes-or-no question and what do I do if my answer is somewhere between 1 and 2." (Health Economist, I.12)

It was also argued that yes-or-no answers would be unfair for those studies that did not have all the necessary resources or data available for the COI study.

"Maybe there should be a place somewhere in the middle because for us as low-middle income-country sometimes you don't find the source of the costs or you are expected to value them in a way that is not optimal but at least you did something. So yes-or-no answers are a bit harsh." (Health Economist, I.4)

Instead, intermediate answer categories were suggested for use to avoid misjudgement when an answer is not clear.

> *"Thinking about whether it makes sense to include intermediate answer categories. I always think it makes sense because there are often questions where the answer is not clear. Similar to the COCHRANE risk of bias tool with low, medium and high risk. […] I find it difficult if the in-between answers are not provided or not an option. If I have to decide on whether it is a yes or no, this may risk a misjudgement." (Health Economist, I.12)*

> *"It doesn't have to be numerical scoring. For example, the GRADE one where you have low, medium and high risk and at the end of your review you can give the reader an understanding of what is the quality of the literature." (Health Economist, I.7)*

> *"Perhaps I would prefer it kind of a gradient scale instead of saying yes-or-no. […] A scale could be more flexible and could also provide the reviewers with more opportunities to express their opinion about the study." (Health Economist, I.9)*

The idea of adding a data extraction column to the checklist was expressed. This would allow the users of the checklist to add supportive information to their answers, which in turn could enhance accountability.

> *"I do think it makes sense to have a separate column to fill in your answers much like a data extraction." (Health Economist, I.12)*

> *"In the PRISMA checklist it is like that, adding a page number or sometimes you have to add an excerpt depending on the journal. But I do think that this really forces accountability." (Economist, I.19)*

> *"That's a problem with the CHEERS checklist, it's incredibly long and it gets very tedious. […] I quite like the idea of having a data extraction column and putting the information in there rather than referring to that sentence on a page number." (Health Economist, I.1)*

(iv) Addressing subjectivity

Questions should be as clear as possible, as suggested by experts, to avoid or reduce subjectivity. There was particular concern about the interpretation of the word 'appropriate' which could be interpreted in different ways.

> *"People have different ideas of what is appropriate. People would argue vehemently for a friction approach to measure productivity losses. Other people would argue vehemently the human capital approach is appropriate. And they're going to give completely different estimates." (Health Economist, I.17)*

> *"Appropriateness; you talk about whether it's relevant or not. That requires interpretation and so the difficulty is, it's not necessarily repeatable." (Health Economist, I.2)*

> *"Obviously the tricky part is how do you gauge whether someone did something appropriately or not versus they are just limited to what they are doing. Especially if you start to think about a societal perspective, it gets tricky. At some level you're going to have to cut it even though you are adopting a societal perspective. […] Obviously, people have their own incentives in terms of thinking about whether these are appropriate versus not appropriate." (Health Policy, I.20)*

Suggestions were given by experts to rephrase some of the questions to avoid such subjectivity, such as:

> *"Sometimes it's not really clear what you mean by appropriate. I would probably use something more like 'Was the study design described or motivated?'" (Health Economist, I.3)*

> *"It's very subjective to use the term 'appropriate', I would just ask 'Is the study design stated?'" (Health Economist, I.14)*

(v) Guidance requirements

The inclusion of guidance statements to explain each of the questions was recommended. This was suggested as important to give further detail and provide examples of best practice. Guidance statements were also seen as helpful in reducing subjectivity in answers.

"You might need an accompanying piece to your checklist and explain the questions, like a table that explicates what each of the questions are really getting at and with an example. Because unless you give people a tool that says here is an example of appropriate […], you just can't answer it. (Economist, I.19)

"If you kept the questions like this you can have another paper of what you actually mean by the questions." (Health Economist, I.7)

"When you have an article that goes through these different domains and criteria and then at the end almost have an appendix or a table where you'd have the checklist." (Health Economist, I.16)

9.5 Discussion

9.5.1 Principal findings

This study is the first to explore experts' views to inform the development of a checklist for COI studies and to simultaneously investigate experts' perspectives on the use and relevance of COI studies and critical appraisal tools for COI studies (please refer to Chapter 8 for more detailed information on how the checklist was developed).

The research findings highlight that at the time of the interviews there was no standard, consensus-based checklist for the critical appraisal of COI studies available that is internationally applicable. This risks inconsistency in the methodology across COI studies and increases heterogeneity. Consequently, optimal comparability across study findings and transferability of results are challenging, if not impossible (229, 232, 233, 248, 253-257). This study gathered data on the relevance and need for such checklist as well as what the checklist would need to entail to be considered comprehensive, practical, and a minimum standard for use. It presents findings about the format, ways of assessment, wording, and guidance requirements such a checklist should best fulfil.

Overall experts appreciated that the checklist was short but comprehensive. A longer and more technically detailed checklist was seen as burdensome, in particular, when having to apply it to a larger number of studies as part of a review. Opinions differed slightly regarding how to best to answer the questions in the checklist. There was general agreement among the participants around the need to provide guidance statements explaining each question to help avoid potential misunderstanding and to reduce subjectivity.

9.5.2 Comparison with other studies

Methods adopted by other existing studies to develop checklists/guidance were taken into consideration for the development of the present checklist (143, 228, 234). Like this study, previous studies made use of stakeholder interviews or Delphi panels to develop guidelines or checklists for full economic evaluations including the CHEC-list (228, 258, 259). To the best of our knowledge, only one other study exists that developed a checklist specifically for COI studies and incorporated stakeholder interviews in the development process; the checklist by Mueller et al. (2017). However, their checklist was established for the German context and is officially only published in German (234). The Guide to Critical Evaluation by Larg & Moss (2011) was also designed for COI studies, but it is not clear whether they had considered expert opinion as part of their development process (244).

9.5.3 Strengths and weaknesses of the study

This paper provides a thorough overview of experts' perspectives elicited from qualitative interviews. Participants had direct experience of working with COI studies, undertaking COI studies, developing health economic guidelines and checklists, and applying such; which is a key strength of this study. The involvement of consultations with 21 experts from eleven different countries with professional experience in health economics, economics, health policy, and/or psychology, and with a range of different affiliations, adds to the strengths of this study. Another strength is the use semi-structured, open-ended interviews, which allowed for a structured approach to guide the interviews as well as the opportunity for new themes to emerge and be explored. The author team acknowledges that there could inevitably be some limitations associated with the study. There might be additional considerations regarding the checklist that were not captured, and it is suggested that future research is undertaken to explore such factors. In particular, as the interviews were conducted with participants based in OECD countries, it would be important to capture the views and experiences of those based in other settings. Another limitation could be that experts might not have felt comfortable stating that they did not feel there was a need to develop and implement a checklist for COI studies given the research had already started and a preliminary checklist been developed. However, interviewees were encouraged to provide their honest professional opinion both prior to and throughout the interviews.

9.6 Conclusion

The interviews provided relevant input for the development of a consensus-based checklist for COI studies that could be used as a minimum standard and for international application. The interviews also confirmed the important need for a checklist for the critical appraisal of COI studies.

9.7 Chapter summary

This chapter presented a qualitative paper that explored experts' views on the development of a proposed checklist for COI studies as well as experts' perspectives on the of COI studies and of critical appraisal tools used for COI studies, using semi-structured, open-ended interviews. The interview findings provided relevant input for the development and refinement of the consensus-based checklist for COI studies. The controversy around COI studies to date was also briefly discussed in this chapter, as part of the rationale for this thesis. Where Chapter 8 and Chapter 9 addressed the second aim of this thesis, the following chapter (Chapter 10) discusses the objectives and findings resulting from all chapters, including a summary of each of the research projects outlined in Chapter 5-9.

CHAPTER 10 GENERAL DISCUSSION

10.1 Chapter overview

Sexual health is a public health area that is complex by nature and can generate wide-ranging health, social and economic implications across various sectors of society. Interventions in sexual health such as those to prevent, treat and manage sexual health challenges can result in better sexual health outcomes and improve overall wellbeing. At the same time, these interventions can generate spillover costs and benefits on other areas of health (i.e. reproductive health, mental health) as well as other non-health sectors (or intersectoral costs and benefits, ICBs) such as productivity, informal care or education. Accounting for these ICBs in economic studies is often fundamental to capturing the true total (economic) burden associated with sexual health problems and interventions. This is subsequently essential to comprehensively inform societal policy/decision-making processes such as the allocation of (scarce) resources and the prioritisation of demanding interventions. However, these ICBs are not always considered in economic studies, which could risk to suboptimally inform societal policy/decision-making. In fact, many studies still adopt a rather narrow perspective for analysis (i.e. healthcare), potentially omitting relevant societal impacts. This is often because a narrow perspective might be sufficient when stakeholders or decision-makers are interested in the costs connected with a budget relating to one area of health only. It is important to note that the perspective chosen for an economic analysis is often based on the national guidelines or reference case (e.g., UK NICE recommends a 'NHS and Personal Social Service' perspective. In other words, researchers often need to follow the guidelines and have no choice in perspective. Another reason might relate to a restricted timeframe for the analysis, or limitations in terms of the resources or data available for analysis. Yet another reason, however, might be a lack of realisation of the importance of wider societal impacts relating to sexual health problems and interventions. The latter is addressed and explored in this thesis.

The primary aim of this thesis was to explore and identify relevant ICBs relating to sexual health and to develop a sector-specific (cost) classification scheme that would categorise these ICBs into different sectors of society. The motivation behind this aim was to create comprehensive and transparent evidence to provide a stronger foundation for future research and policy/decision-making processes. In working towards this aim and as part of a systematic review of cost-of-illness (COI) studies presented in this thesis, it became apparent that a validated critical appraisal tool for these studies would be beneficial in order to explore the methodological approaches of the identified studies. This is, in part, because COI studies estimate the costs (or resources) associated with an illness or disease,

but also can include *intersectoral* costs. Thus an additional aim emerged, which was to develop a consensus-based checklist for the critical appraisal of COI studies that can be used as a minimum standard to review and assess existing studies. Among other methodological approaches, such a checklist could help to critically appraise the choice of study perspective and the different costs included in the analysis.

This chapter briefly revisits the objectives of the thesis before it discusses the principal findings that contributed to addressing these objectives. Objective 1 to 3 addressed the first aim of this thesis, whereas objective 4 and 5 addressed the second aim of this thesis.

10.2 Overview and objectives of the thesis

The objectives were:

1. to gain insight into whether and to what extent existing COI studies of STIs and HIV consider intersectoral costs in their analyses by conducting a systematic literature review and to categorise these costs by sector;
2. to undertake a second systematic literature review of economic evaluations relating to STIs to assess whether they consider intersectoral costs in their analyses and to categorise these costs by sector;
3. to explore potentially relevant ICBs associated with sexual health problems and interventions through expert interviews and to develop a sector-specific (cost) classification scheme that categorises these ICBs into different cost sectors;
4. to develop a consensus-based checklist for the critical appraisal of COI studies that can be used as a minimum standard to review and assess these studies; and
5. to explore expert perspectives on the development process of the checklist for COI studies and on the use of COI studies and of critical appraisal tools for COI studies, using semi-structured interviews.

10.3 Summary of principal findings

The following section discusses the main findings from each of the research phases.

10.3.1 Findings from the systematic literature review of COI studies

The first objective of this thesis was to systematically review COI studies relating to STIs and HIV with the aim to identify and categorise the intersectoral costs considered in these studies under a societal perspective by (policy) sector. The review also explored whether the intersectoral costs included in

analyses contributed to the total cost burden of STIs and HIV. Reviewing these studies revealed that only a small number of COI studies adopted a societal perspective for their analyses, which would, in theory, allow for intersectoral costs to be considered. This indicates that most COI studies in this area adopted a narrower perspective, and potentially omitted relevant intersectoral costs that could be important, for instance, to inform societal policy/decision-making. Where a societal perspective was applied, the following intersectoral cost sectors were identified:

- patient and family
- informal care
- productivity (paid labour)

The selected studies estimated costs in at least one (or more) of these sectors, but not in all of them. Most studies considered productivity costs related to paid labour. Productivity costs can, however, involve productivity losses for paid and non-paid opportunity costs. The findings show that the assessment of unpaid labour and non-paid opportunity costs (i.e. leisure time, volunteering, care for children or elderly) might be rather limited in COI studies in this area. Patient and family costs such as out-of-pocket costs and travel expenses were addressed in some of the studies. Few studies estimated informal care costs in terms of unpaid (home) care support by family or friends. This review demonstrates that the inclusion of intersectoral costs attributed to STIs and HIV indicate a substantially higher cost burden to society than healthcare costs alone, which again emphasises the importance of a societal perspective. If intersectoral costs are not captured, the total cost burden to society could be underestimated.

Additionally, this review revealed that the use of different methodological approaches (i.e. study perspective, costs included) can affect how results are interpreted and impact the information communicated to policy/decision-makers. One of the original aims of the systematic review of COI studies was to critically assess the included COI studies. However, it became evident that there was no standardised, international applicable, critical appraisal tool for COI studies to do so. Based on these findings, it was concluded that future research was needed to explore and address this gap in literature and the potential need for such a tool. This thesis addressed this long-standing gap and opportunity to develop a tool, which is presented in Chapter 8 and 9.

10.3.2 Findings from the systematic literature review of economic evaluations

The second objective of this thesis was to review and assess existing economic evaluations of interventions targeting STIs to identify and categorise the intersectoral costs captured in these studies under a societal perspective. This review also assessed whether the inclusion of intersectoral costs had an impact on the overall study results. It revealed that a societal perspective in these economic evaluations is less represented in the literature in comparison to a healthcare perspective. Economic evaluations that are restricted to estimating 'fixed budget costs', such as from a healthcare or payer perspective, might omit potentially relevant societal costs and result in suboptimal societal policy or decision-making. Where specific costs based on a fixed budget need to be assessed this could be done as part of a societal perspective by differentiating these costs and presenting these separately. Where a societal perspective was applied in economic evaluations of this review, studies considered a limited range of costs in non-health sectors:

- patient and family
- informal care
- productivity (paid labour)
- productivity (non-paid opportunity costs)
- education
- consumption (non-medical)

Most studies estimated paid labour losses (i.e. absenteeism, sick leave) and patient and family costs (i.e. out-of-pocket costs, travel costs). In comparison, informal care costs, non-paid opportunity costs, education costs and non-medical consumption costs were captured less in their analyses. The identification of these different intersectoral costs highlighted that there are important impacts relating to sexual health interventions that fall on other sectors outside health. Where these costs are overlooked, this could potentially underestimate the total cost burden attributable to these interventions and omit important information for policy/decision-makers. This thesis acknowledges that the above list of non-health sectors is non-exhaustive given that it is based on economic evaluations of interventions relating to STIs only. Therefore, it was concluded that further research was needed to explore the intersectoral impacts relating to the wider remit of sexual health, beyond the area of disease (STIs, HIV), and this was addressed and presented in Chapter 7 (qualitative interviews).

The review also found that those studies that applied a societal perspective in addition to a healthcare or payer perspective presented more favourable cost-effectiveness results under the societal

perspective. This, again, demonstrates the growing importance of capturing wider societal impacts in health economic analyses under a broader perspective to ensure the true total cost burden to society is estimated. Only then can societal (including intersectoral) costs be captured, and policy/decision-makers faced with societal decisions around resource allocation and the prioritisation of interventions be fully informed.

10.3.3 Findings from the expert interviews in sexual health to investigate ICBs

The third objective of this thesis was to explore potentially relevant ICBs relating to the wider remit of sexual health (moving beyond the systematic reviews which focused on disease alone) and to categorise these ICBs into different (policy) sectors. This was done by conducting in-depth semi-structured interviews with experts in sexual health. The experts emphasised the holistic nature of sexual health and discussed a wide range of impacts associated with STIs and HIV, sexuality, sexual violence and abuse, unplanned pregnancies, and related interventions. Given there is no framework or tool available that systematically, carefully and explicitly illustrates the holistic nature and the relevant societal impacts of sexual health, this thesis developed a sector-specific (cost) classification scheme for sexual health (research and policy). This scheme was based on the findings from the interviews:

- interconnections to other areas of health (reproductive health and mental health)
- relationships and family
- productivity (paid labour and non-paid opportunity costs)
- education
- criminal justice/sexual violence
- housing, addiction, and other sectors

The interconnections to other areas of health became evident and involved the inextricable link between sexual and reproductive health as well as the relationship to mental health. The interviews suggested that there is an important need to also think beyond health aspects when evaluating the societal impact of sexual health problems and interventions, with impacts on family, friendships and relationships being one of them. The findings also showed that sexual health problems and interventions can have a 'knock-on effect' on an individual's productivity, participation in the labour market and on the education sector (i.e. reduced educational attainment due to illness). A link was further drawn between sexual health and criminal justice, for example, due to sexual violence, abuse

or assault. Though evidence was scarce the interviews revealed that sexual health concerns can also relate to other problems including housing insecurity, drug use or other issues.

It is acknowledged that the sector-specific (cost) classification scheme (set out above) is not exhaustive, but rather should be seen as a first step towards identifying and categorising relevant impacts relating to sexual health. Identifying and categorising these intersectoral impacts helped to first organise and present these wider impacts more comprehensively and transparently. It can help to ensure a more comprehensive approach to future research and policy/decision-making. The findings from the interviews not only confirmed the findings from the systematic reviews but also revealed relevant additional intersectoral costs and cost sectors. However, there is room for opportunity to further explore additional intersectoral costs and to expand this cost classification scheme.

10.3.4 Findings from the development process of the consensus-based checklist for COI studies

The fourth objective of this thesis (addressing the second aim of this thesis) was to develop a consensus-based checklist for the critical appraisal of COI studies. The development process of the checklist involved six sequential steps: (1) reviewing existing literature, checklists and guidelines in this area, (2) assessing these different guidelines and checklists and their questions, (3) developing a preliminary checklist for COI studies, (4) conducting semi-structured interviews with experts to discuss the preliminary checklist, (5) finalising the checklist based on these interviews, and (6) developing guidance statements to explain the meaning behind each of the questions included in the checklist.

The findings from the scoping review revealed that most of the studies identified predominantly applied critical appraisal tools that are intended for the assessment of full economic evaluations to assess the quality of COI studies (i.e. BMJ Checklist, CHEC-list). Only two of the identified tools are designed for COI studies; however, it was found that these were not consensus-based and internationally applicable. Hence the need for the development of a critical appraisal tool was identified. A preliminary checklist for COI studies was developed based on the CHEC-list given the rigorousness in its own development process (literature searches, the consideration of existing health economic checklists, and the conducting of Delphi panels to build consensus). The expert interviews discussed the format and practicality of the preliminary checklist, the questions included and how to answer these questions, among others (see section 10.3.5 for more details). The findings from these discussions were used to develop the final consensus-based checklist, entailing 17 main questions

(and some additional sub-questions) across three domains: study characteristics, methodology and cost analysis, and results and reporting.

Overall, the interviews suggested to keep the checklist concise and pragmatic, and a balance was needed between the checklist being comprehensive and ensuring it was practical for use. The use of intermediate answer categories (*yes, partially, no, not applicable (NA)* or *unclear*) to assess the questions in the checklist was suggested by most experts and is hence recommended when applying the checklist. A data extraction column was added to the checklist that allows users to add supportive information to their answers and to enhance accountability of answers. Guidance statements explaining each question in the checklist were developed, as recommended by most experts.

The checklist is a first step toward standardising the critical appraisal of COI studies and is one that could be considered a minimum standard to review and critically assess the comprehensiveness, transparency and consistency of these studies.

Next steps suggested for the checklist of COI studies include the publishing and sharing the checklist internally and externally as well as piloting the checklist and monitoring the use of it. Next steps can include:

1. *Sharing the checklist for use internally at the University of Birmingham and Maastricht University (e.g., with students, researchers, staff)*
2. *Introducing the checklist in Bachelor and Master programmes (e.g., for students to use when conducting a systematic review of COI studies)*
3. *Publishing the checklist on the University website for both internal and external use*
4. *Monitoring the volume of downloads of the checklist through the website*
5. *Collecting feedback from a range of users e.g., include a comment field on the University website where the checklist can be downloaded, share a short questionnaire with the users*
6. *Analysing the feedback e.g., on the use and applicability of the checklist*

10.3.5 Findings from the expert interviews to inform a checklist for cost-of-illness (COI) studies and the use of COI studies and critical appraisal tools

The fifth and last objective of this thesis was to explore expert perspectives on the development process of the checklist for COI studies and on the use of COI studies and of critical appraisal tools for COI studies, using semi-structured interviews. The interviews not only informed the development process of the checklist but also confirmed the lack of and important need for a tool or checklist to

critically appraise COI studies, which had already been identified in a previous research phase (Chapter 5). The proposed checklist was perceived by experts as an important step toward addressing this need for a checklist to assess the comprehensiveness, transparency, and consistency of these studies. Given the lack of guidance and assessment tools for COI studies, experts reported they had previously relied on their own knowledge, existing literature, and guidelines and checklists designed for full economic evaluations. This meant that different approaches and methodologies were often applied across studies that could lead to inconsistency and heterogeneity, making it difficult to compare study findings. This also meant that a new checklist could be used more consistently to help review, identify and understand different methodological choices, present these differences (for instance as part of a systematic review) and reflect on the comprehensiveness, transparency and consistency studies.

Additionally, and despite the controversy around COI studies (as outlined in Chapter 9), the interviews revealed that these studies can be an important tool to estimate the overall burden of a disease, to draw attention to disease areas and their impacts, to understand the different cost components and the total costs, to explain cost variability, to inform decision-making, and to provide input for cost-effectiveness analyses.

10.3.6 Synthesis of the main findings

This thesis is the first to thoroughly explore, identify, categorise and present the wider ICBs relating to sexual health problems and interventions. The research findings collectively highlight the holistic nature of sexual health and related interventions, and the complexity associated with evaluations in this area. It is also the first to develop a consensus-based checklist for the critical appraisal of COI studies that could be used as a minimum standard and be applied internationally.

Summarising the findings addressing the first three objectives, this thesis demonstrates:

- The number of COI studies of STIs and HIV that adopt a societal perspective is small, indicating there is limited data on intersectoral costs relating to the cost burden of STIs and HIV. Those intersectoral costs identified in COI studies were limited to a few cost sectors: patient/family, informal care, and productivity (paid labour).
- The number of economic evaluations of interventions targeting STIs that adopt a societal perspective is small, but intersectoral costs have been identified in the following sectors: patient/family, informal care, productivity (paid labour, non-paid opportunity costs), education, consumption.

- Sexual health problems and interventions can generate relevant ICBs for other areas of health (reproductive health and mental health) and other sectors of society. The latter include relationships and family, productivity losses (paid labour and non-paid opportunity costs), costs in education, criminal justice/sexual violence costs, and costs relating to housing, addiction, among others.
- To illustrate the ICBs relating to sexual health and to address the lack of a tool to inform and guide future research and policy, this thesis synthesised and presented these ICBs in a sector-specific (cost) classification scheme.
- The majority of COI studies and economic evaluations adopting a societal perspective tend to focus on patient and family costs and productivity losses and have generally neglected the wider ICBs relating to sexual health.
- Overall, the findings show it is evident that interventions attributed to STIs can impact other sectors of society, and that the application of a societal perspective can be important.

Summarising the findings addressing the last two objectives, this thesis demonstrates:

- COI studies can be relevant to estimate the overall burden of a disease, to draw attention to disease areas and their impacts, to understand the different cost components and the total costs, to explain cost variability, to inform decision-making, and to provide input for cost-effectiveness analyses, according to experts in health economics.
- There was a lack of and important need for a standard critical appraisal tool to review and assess the comprehensiveness, transparency and consistency of COI studies that is internationally applicable, comprehensive, concise and practical in use.
- This need was addressed in this thesis by developing a checklist that is based on existing literature and expert opinion and that could be used as a minimum standard by users/researchers to review and assess COI studies (i.e. as part of a systematic review).

10.4 Strengths and limitations

The following section discusses the main strengths and limitations of this thesis and the PhD research undertaken.

10.4.1 Strengths

This PhD research presents several strengths. One of the main strengths of this thesis is that it identified and addressed two significant gaps in research and subsequently developed and proposed two new tools to address these gaps. One research gap being the lack of or limited awareness and

exploration of the importance of intersectoral impacts relating to sexual health. To address this gap and illustrate its importance, a sector-specific (cost) classification scheme for sexual health was developed in this thesis. The second research gap being the lack of a standard critical appraisal tool for COI studies. To address this gap, a consensus-based checklist was developed in this thesis to assist in reviewing and critically appraising COI studies.

Another main strength of this thesis is the triangulation of the different qualitative research methodologies. Triangulation can help to increase the credibility and validity of research findings, which was done in this thesis. Qualitative research methods have increasingly become more widely embraced in health economics research, in part, because they allow for an in-depth understanding of complex topics (260), and are hence considered advantageous in this thesis. This thesis combined two systematic reviews and expert interviews to address the first aim of the PhD research. The two systematic reviews were rigorous and structured in their approach and provided a first insight into which types of intersectoral costs are typically captured in economic studies. For both reviews, a robust and systematic methodology was applied including a comprehensive search strategy, which was developed in collaboration with an information specialist to ensure an optimal and extensive search. The search strategy was pilot tested before translating it for use in multiple other databases to identify and account for as many articles as possible. Both reviews focused on studies conducted in OECD member countries to ensure a good representation of study results. The conduct of the in-depth semi-structured interviews was valuable in complementing, validating and expanding the findings from the two systematic reviews. The interviews complemented the reviews by exploring intersectoral impacts relating to the wider remit of sexual health, by looking beyond the area of disease and beyond the health economics literature. This is a strength of this thesis and was essential because of the holistic nature of sexual health and the spillover effects it can have on other areas of health and other sectors of society, and vice versa. Another key strength was the involvement of 28 interviewees that allowed in-depth analysis of information from a wide range of experts (in terms of their expertise and experience in sexual health). The use of semi-structured interviews with open-ended questions guaranteed both a systematic coverage of key topics as well as a degree of freedom and adaptability in the discussions. This allowed for new themes to emerge and be explored.

Furthermore, an extensive, structured, and iterative six-step development process was established to address the second aim of the thesis, which was to develop a checklist for COI studies. This process also involved a combination of qualitative methodologies, a scoping review and in-depth semi-structured expert interviews. One of the main strengths in this research phase was the involvement

of 21 semi-structured interviews with experts from eleven countries and with expertise in health economics, health policy, and psychology to build the checklist. This ensured substantial coverage of a range of expertise and experience. Further, the interview participants had direct experience of working with relevant studies and were involved in undertaking COI studies and/or developing health economic guidelines and checklists, which was considered an important advantage. The presentation of the checklist at international health economic conferences sought further feedback from a broader group of experts to ensure internal and external feedback and mitigate any potential (selection) bias.

10.4.2 Limitations

It is acknowledged, there are also some limitations associated with this PhD research. First, the research methodologies employed in this thesis were exploratory in nature. Despite exploring the area of interest in depth, limitations may naturally exist by applying these approaches. For example, the conduct of expert interviews to explore potentially relevant intersectoral impacts relating to sexual health might have included a degree of subjectivity. The same accounts for the interviews conducted as part of the development of the consensus-based checklist for COI studies. However, a larger number of interview participants were ensured to mitigate any limitation. Second, given that there was no standard approach to developing a checklist for COI studies, a six-step iterative approach was developed by the authors, which again might have included a degree of subjectivity. However, this approach involved interviews with experts external to the research team developing this checklist.

There are also some limitations are associated with each of the research phases. The focus of both systematic reviews was on OECD member countries, which may have potentially missed identifying other relevant intersectoral costs and cost sectors relevant for other non-OECD settings. The reviews were limited to studies published between 2009-2019 and there may have been some relevant articles published outside of this timeframe. Further, the reviews explored the impacts of STIs and HIV that are sexually transmitted and may have not identified additional intersectoral costs and cost sectors relating to other areas of sexual health. However, the interviews with experts in sexual health subsequently explored sexual health more broadly. The interviews involved experts within sexual health, and it is acknowledged that those working in other areas might have had interesting perspectives on the topics considered and an 'external' perspective might have been helpful. Similarly, this thesis did not capture the views from experts outside of OECD member countries but recommends this be explored in future research.

There are also several limitations associated with the development process of the checklist for COI studies. Although the checklist is based on international literature and expert interviews, it has not yet been formally pilot-tested. However, the checklist has been applied by staff and students at Maastricht University and the University of Birmingham and their feedback has been taken into consideration. The use of the CHEC-list as a starting point to develop the current checklist could be seen as a potential limitation. This is because the CHEC-list was developed for the assessment of full economic evaluations and hence this might have influenced the subsequent development processes. However, other tools and checklists were taken into consideration when developing the current checklist for COI studies, and a consensus-based approach was adopted. Although the checklist was developed based on discussions with 21 experts with professional experience in health economics, economics, health policy, and psychology to account for a good representation of views, there might be additional viewpoints that were not captured. Online interviews were chosen due to the circumstances relating to the COVID- 19 pandemic. This thesis acknowledges that the facilitation of online interviews can be challenging (i.e. internet issues). However, the use of online interviews facilitated the recruitment of participants and therefore ensured a larger sample of participants over a short period of time.

10.5 Comparison with existing literature

There has been an increasing recognition across international literature that economic evaluations of public health interventions, including those relating to sexual health, need to adopt a broader societal perspective to consider relevant societal costs and benefits (83, 250, 261). This is to ensure that a comprehensive assessment of the societal impacts of an intervention is achieved, in particular, when the aim is to inform societal policy/decision-making (250). However, to date most economic evaluations of public health interventions still mainly consider those impacts falling on the healthcare sector (16). While research has already been done to identify relevant ICBs relating to mental health and alcohol prevention programmes (136, 262), the wider impacts of sexual health problems and interventions have received little attention and are yet to be fully explored. This thesis addresses the paucity of existing evidence on ICBs relating to sexual health problems and interventions.

As outlined under 'Principal findings', the two systematic reviews conducted for this PhD research found that only a minority of COI studies and economic evaluations relating to sexual health interventions have adopted a societal perspective. Moreover, within those studies that did adopt a societal perspective, there was only very limited consideration of ICBs, with an almost exclusive focus on productivity losses in the labour market. These findings are in line with other literature that has

described the limited scope that many COI studies have adopted in their analyses, predominantly estimating productivity losses in terms of paid labour costs (150). Kim and colleagues previously found that cost-effectiveness analyses seldomly capture impacts on other sectors outside health, but when they do, this most commonly relates to productivity losses (158). Krol and colleagues report similar findings and argue that the loss of unpaid work receives little attention in economic studies compared to paid labour losses (17).

It is evident from the findings in this thesis that sexual health problems and interventions can generate relevant impacts both within health and beyond the health sector such as education. This has also been shown in previous studies. A review by Shepherd et al. that assessed the effectiveness and cost-effectiveness of schools-based skills-building behavioural interventions to prevent the transmission of STIs found that these interventions can improve knowledge on sexual health and increase self-efficacy more generally (200). Research by Chong et al. showed that online sexual-health education has an impact on an individual's broader knowledge and attitudes (201). Wellings and Johnson describe a number of interconnections between sexual health and other areas of health and wellbeing as well as links from sexual health to other sectors of society that call for a broader perspective of sexual health (218). They explain, for instance, that the prevention of STIs and infertility has a positive and preventative effect on the quality of life of an individual and the quality of sexual relationships. These findings are also reflected in this thesis, which found that sexual health (problems) can have an impact on family, friendships and other interpersonal relationships. Wellings and Johnson argue that positive sexual experiences and sexual activity are linked to lower rates of depressive symptoms, among other aspects, positively impacting the quality of life of an individual (218). They also iterate that negative sexual experience, such as sexual abuse or non-consensual sex, can result in physical as well as psychological pain. Similar findings are presented in this thesis, which found that sexual violence is often linked to physical, emotional and mental health issues.

In terms of literature in the area of COI studies (and appraisal tools), existing research has not only emphasised the lack of standard guidance to conduct COI studies, but also the lack of a standard tool to review and critically appraise COI studies (227, 229-233). The findings presented in Chapter 9 validated this gap in research, and this PhD research addresses this gap. As shown in Chapter 8 and 9, there are currently only two other tools that were specifically designed for the appraisal of COI studies, which show methodological parallels: the Guide to Critical Evaluation by Larg & Moss and the Checklist for the Development and Assessment of Cost-of-Illness Studies by Mueller et al. (103, 234). However, both tools have limitations, and were either not consensus-based or internationally applicable. This

thesis thus presents the initial development of a consensus-based checklist to critically appraise COI studies.

Overall, this thesis contributes to the existing economic literature and addresses two important gaps in research and proposes two new tools: a sector-specific (cost) classification scheme for sexual health and a consensus-based checklist was developed to assist in reviewing and critically appraising COI studies.

10.6 Implications for research and future research recommendations relating to intersectoral costs

There are relevant implications for research in relation to the first aim of the thesis, exploring the intersectoral impacts associated with sexual health. Based on the findings in this thesis, there are important intersectoral costs relating to sexual health across a range of different sectors of society that need to be considered under a societal perspective in economic studies. In particular when the aim is to assess the total cost burden to society. There is acknowledgment that capturing these wider intersectoral impacts of sexual health interventions (and public health interventions in general) is methodologically challenging (15). The sector-specific (cost) classification scheme developed in this thesis, listing relevant intersectoral impacts relating to sexual health, is a first step towards more explicitly and transparently illustrating these impacts to guide future comprehensive research in this area.

Future research could further explore relevant cost components and cost sectors associated with sexual health in order to validate or complement the findings from the systematic reviews and expert interviews. Reviewing economic literature in other non-OECD member settings could help to identify other potentially relevant intersectoral costs that were not captured in this thesis. Future research could also capture the views and experiences of experts based in other non-OECD countries to ensure a global representation. Given the holistic nature of sexual health future research could further investigate the intersectoral costs relating to sexual health that have been discussed outside of the health economics literature, such as in journals relating to education, criminal justice, drug and alcohol consumption and social services. By doing so, the sector-specific (cost) classification scheme could be validated and expanded, where needed. There is also an opportunity to pilot the current cost classification scheme within research that is concerned with developing a COI study and an economic evaluation in sexual health.

10.7 Implications for research and future research recommendations relating to the checklist for COI studies

There are relevant implications for research in relation to the second aim of the thesis, the development of a consensus-based checklist for COI studies. First of all, it is important to highlight that with the development and publication of the checklist, an important gap in research was addressed. This thesis addresses the inconsistency in the use of checklists and guidelines to appraise COI studies and provides evidence that there is an important need for a standardised checklist to review and assess COI studies. The checklist will allow researchers/users to assess the methodological approaches taken and reported in existing COI studies (for instance as part of a systematic review) and to review and critically appraise the comprehensiveness, transparency and consistency of these studies. This can, for instance, assist in assessing whether a study generated reliable COI estimates that could be important when researchers adopt data from existing literature.

Future research is needed to formally pilot-test the checklist. To date, the checklist has been applied and tested by staff and students at Maastricht University and the University of Birmingham. Further piloting and testing of the checklist across different disease areas is recommended to investigate the applicability of the checklist and potentially to refine the questions in the checklist. It is recommended that future research monitors the use of the checklist and collects feedback from a range of users. In particular, it could be relevant to investigate the use and applicability of the checklist in non-OECD settings. This is because the checklist was predominantly informed by experts in OECD member countries and hence it would be important to capture the views and experiences of those based in other settings.

10.8 Implications for policy/decision-makers relating to intersectoral costs

There are relevant implications for policy/decision-makers in relation to the intersectoral impacts associated with sexual health. As set out in this thesis, sexual health problems and interventions can generate wide-ranging costs and benefits across various sectors of society. It is important that these wider impacts are understood and considered in policy/decision-making processes such as decisions relating to the allocation of (scarce) resources and the prioritisation of demanding or competing interventions in healthcare and public health. This thesis demonstrates that the consideration of intersectoral costs under a societal perspective in both COI studies and economic evaluations can have an impact on the overall study results and the total cost burden. These are economic tools that are often used to inform policy/decision-making.

This thesis shows that COI studies that consider intersectoral costs tend to report a higher burden of disease. It shows that the total cost burden of STIs and HIV could be severely underestimated when intersectoral costs are excluded from analyses. The inclusion of intersectoral cost scan thus portray a more complete picture of the total cost burden. For policy/decision-makers in health and public health, this means that where a higher cost burden of STIs and HIV is portrayed, this could give more prioritisation to interventions targeted at the prevention, treatment and management of STIs and HIV that might be competing with other demands on the healthcare budget. Similarly, it shows that economic evaluations that consider intersectoral costs in their analyses can present more favourable cost-effectiveness estimates, as compared to studies that adopt a narrower perspective for analysis. In general, a societal perspective is recommended for economic evaluations of public health interventions (including those relating to sexual health) to allow the capture of all relevant costs and benefits of an intervention and to inform policy/decision-makers comprehensively. Again, failing to capture relevant intersectoral costs can underestimate the true total costs associated with an intervention and relevant societal implications may be ignored that could be relevant information for societal policy/decision-makers.

Overall, the sector-specific (cost) classification scheme of intersectoral costs relating to sexual health as presented in this thesis can be useful for researchers, health economists as well as policy/decision-makers to better and more comprehensively understand the wider societal impacts relating to sexual health. Such overview of potentially relevant societal impacts can help to illustrate and improve information communicated to policy/decision-makers.

10.9 Implications for policy/decision-makers relating to the checklist for COI studies

There are relevant implications for policy/decision-makers in relation to the consensus-based checklist for COI studies. COI studies have been shown to be a useful tool for policy/decision-makers. This thesis highlighted the controversy around COI studies but demonstrated their important role as a tool in health economics and policy/decision-making. Briefly, COI estimates can be used to project disease expenses, to address a certain health problem, and to provide policy/decision-makers with relevant information regarding the different (health and non-health) cost components and cost categories (or sectors) associated with an illness. This thesis presents a consensus-based checklist for the critical appraisal of COI studies, one that can be applied internationally and be used as a minimum standard. This checklist can help to improve the comprehensiveness, transparency and consistency of COI studies. This is important for decision-makers as there is a need to ensure the information

communicated to policy/decision-makers is comprehensive, of optimal quality, and that any limitations in the evidence are identified.

10.10 Concluding remarks

This thesis generated relevant evidence that demonstrates the holistic nature of sexual health and the wider societal impacts that sexual health problems and interventions can have on society. It confirms the importance of the identification of ICBs relating to sexual health and the need to capture these in economic analyses, in particular when the aim is to estimate the economic burden on society and inform/support societal decision-making. This thesis highlights the complexity associated with evaluating ICBs relating to sexual health problems and interventions under a societal perspective. The sector-specific (cost) classification scheme established and presented in this thesis helps to begin to understand and illustrate the wider societal impacts relating to sexual health, which can be helpful in guiding future (more comprehensive) research and policy/decision-making.

This thesis also confirmed the lack of a standard tool to review COI studies and to critically appraise the comprehensiveness, transparency and consistency of these studies. It addressed this gap in research by developing a consensus-based checklist for the critical appraisal of COI studies that can be used as a minimum standard to review and assess these studies. This thesis recommends future research is undertaken to pilot this checklist and assesses global applicability.

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APPENDICES

Appendix 1: Long-term complications and sequelae of STIs

Sexually transmitted infection	(Long-term) Complications in women*	(Long-term) Complications in men*
Chlamydia (Chlamydia trachomatis)	Pelvic inflammatory disease (PID), tubal scarring leading to infertility, ectopic pregnancy, chronic pelvic pain, perihepatitis, Reiter's syndrome (urethritis, conjunctivitis, and arthritis)	Inflammation of the testicles, epididymis, or urethra, leading to urethritis, epididymitis, orchitis, or prostatitis
Gonorrhoeae (Neisseria Gonorrhoeae)	Pelvic inflammatory disease (PID), infertility, ectopic pregnancy, chronic pelvic pain, perihepatitis, gonococcal infection presenting with arthritis, tenosynovitis, and dermatitis (tender necrotic pustules)	Infection in the testicles and prostate gland, leading to epididymitis, infertility
Syphilis	Primary syphilis, secondary syphilis causing skin rashes, fever, and swollen lymph nodes, latent or tertiary syphilis causing neurological disease (neurosyphilis), cardiovascular disease (cardiosyphilis) and granuloma (gummatous lesions or gumma); ulcers around the mouth, anus, vagina rashes, swollen glands, wart-like lumps on your body, hair loss, headaches, tiredness, pain in the muscles, bones and joints, damage to the nerves and large vessels near the heart; congenital syphilis, with risk of miscarriage, premature birth and stillbirth	Primary syphilis, secondary syphilis causing skin rashes, fever, and swollen lymph nodes, latent or tertiary syphilis causing neurological disease (neurosyphilis), cardiovascular disease (cardiosyphilis) and granuloma (gummatous lesions or gumma); ulcers around the mouth, anus, penis rashes, swollen glands, wart-like lumps on your body, hair loss, headaches, tiredness, pain in the muscles, bones and joints, damage to the nerves and large vessels near the heart
Trichomoniasis (Trichomonas vaginalis)	Genital inflammation, vaginitis, cervicitis, pelvic	Genital inflammation, urethritis, prostatitis, reduced fertility

	inflammatory disease (PID), increased cervical cancer risk, adverse birth outcomes such as premature rupture of membranes, low birth weight, preterm birth, infertility	
Hepatitis B virus (HBV)	Acute or chronic Hepatitis B, possibly leading to cirrhosis and hepatocellular carcinoma, liver cancer, liver failure	Acute or chronic Hepatitis B, possibly leading to cirrhosis and hepatocellular carcinoma, liver cancer, liver failure
Human immunodeficiency virus (HIV)	Acquired Immune Deficiency Syndrome (AIDS); weakened immune system, possibly leading to other severe illnesses such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma; psychological, sequelae such as depression, anxiety	Acquired Immune Deficiency Syndrome (AIDS); weakened immune system, possibly leading to other severe illnesses such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma; psychological, sequelae such as depression, anxiety
Human papillomavirus (HPV)	Cervical cancer, cancer of the vulva, anal cancer, oral cancer, condylomata acuminata (genital warts), recurrent respiratory papillomatosis	Penile cancer, anal cancer, oral cancer, condylomata acuminata (genital warts), recurrent respiratory papillomatosis
Herpes simplex virus (HSV)	Genital herpes, genital ulcers; HSV-1 infection can lead to more severe complications such as encephalitis (brain infection) or keratitis (eye infection); HSV-2 can lead to meningoencephalitis (brain infection) and disseminated infection.	Genital herpes, genital ulcers; HSV-1 infection can lead to more severe complications such as encephalitis (brain infection) or keratitis (eye infection); HSV-2 can lead to meningoencephalitis (brain infection) and disseminated infection.
*This list is non-extensive. Sources: (263) (128) (264-271)		

Appendix 2: The broader societal impacts of COVID-19 and the growing importance of capturing these in health economic analyses

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Appendix 3: Intersectoral costs of sexually transmitted infections (STIs) and HIV: a systematic review of cost-of-illness (COI) studies

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Appendix 4: PRISMA checklist (systematic revie of cost-of-illness (COI) studies)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	See title, p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See abstract, p.2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p.6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional file 2
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p.7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Appendix 5: PubMed search strategy

(((((((("Sexual Behavior"[MeSH] OR sexual behavior*[tiab] OR sexual behaviour*[tiab] OR sexual activit*[tiab] OR sexual education[tiab] OR sex education[tiab] OR sexuality education[tiab] OR sexual health[tiab] OR "Sexual Health"[MeSH] OR safe sex[tiab] OR unsafe sex[tiab] OR "Unsafe Sex"[MeSH] OR "Contraception"[MeSH] OR contracepti*[tiab] OR birth control[tiab]) OR ("Sexually Transmitted Diseases"[MeSH] OR sexually transmitted disease*[tiab] OR sexually transmitted infection*[tiab] OR STD[tiab] OR STDs[tiab] OR STI[tiab] OR STIs[tiab] OR venereal disease*[tiab] OR "Acquired Immunodeficiency Syndrome"[MeSH] OR acquired immune deficiency syndrome*[tiab] OR Acquired Immunodeficiency Syndrome*[tiab] OR acquired immuno deficiency syndrome*[tiab] OR Acquired Immunologic deficiency Syndrome*[tiab] OR AIDS[tiab] OR herpes genitalis[tiab] OR genital herpes[tiab] OR "Syphilis"[MeSH] OR syphilis[tiab] OR "Chlamydia"[MeSH] OR "Chlamydia infections"[MeSH] OR chlamydia[tiab] OR "HIV"[MeSH] OR HIV[tiab] OR human immunodeficiency virus*[tiab] OR "Gonorrhea"[MeSH] OR gonorrh*[tiab] OR "Trichomonas Infections"[MeSH] OR trichomonas infection*[tiab] OR trichomonias*[tiab] OR "Pelvic Inflammatory Disease"[MeSH] OR pelvic inflammatory disease*[tiab] OR inflammatory pelvic disease*[tiab] OR HPV[tiab] OR human papillomavirus*[tiab] OR condylomata acuminata[tiab] OR genital wart*[tiab] OR venereal wart*[tiab] OR "Hepatitis B"[MeSH] OR "Hepatitis B"[tiab])) AND ((cost[tiab] OR costs[tiab] OR "costs and cost analysis"[MeSH:noexp] OR (cost benefit analyses[Tiab] OR cost benefit analys*[Tiab]) OR "cost benefit analysis"[MeSH] OR "health care costs"[MeSH:noexp]) OR (("Cost of Illness"[MeSH] OR (health expenditure[tiab] OR health expenditure*[tiab]))))))))

Appendix 6: Quality assessment of cost-of-illness (COI) studies

Criteria/First author	Kuhlman	Lopez-Bastida	Mostardt	Owusu-Edusei	Shon	Yang
1. Is the study population clearly described?	Y	Y	Y	-	Y	Y
2. Is a well-defined research question posed in answerable form?	Y	Y	Y	Y	Y	Y
3. Is the economic study design appropriate to the stated objective?	Y	Y	Y	Y	Y	Y
4. Is the actual perspective chosen appropriate?	Y	Y	Y	Y	Y	Y
5. Are all important and relevant costs identified?	Y	Y	Y	-	Y	Y
6. Are all costs measured appropriately?	Y	Y	Y	Y	Y	Y
7. Are costs valued appropriately?	Y	Y	Y	Y	Y	Y
8. Are all future costs discounted appropriately?	-	-	-	-	-	-
9. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	-	-	-	-	-	Y
10. Do the conclusions follow from the data reported?	Y	Y	Y	Y	Y	Y
11. Does the study discuss the generalisability of the results to other settings and patient/client groups?	Y	Y	Y	Y	-	Y
12. Does the article indicate that there is (no) potential conflict of interest of study researcher(s) and funder(s)?	Y	Y	Y	Y	Y	*
13. Does the study discuss important limitations regarding the cost components, data, assumptions and methods?	Y	Y	Y	Y	Y	Y

Y=Yes

* The study, however, indicated under 'Acknowledgments' that it was supported in part by a research grant from a pharmaceutical corporation.

The checklist is based on the following material:

- Criteria 1-12: Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care. 2005;21(2):240-245.
- Criteria 13: Larg, A., & Moss, J. R. (2011). Cost-of-illness studies. *Pharmacoeconomics*, *29*(8), 653-671.

Appendix 7: List of studies not available for full-text screening

E. C. Wolf, S. 2016. Health-related costs in chronic HIV infection: A case-control study versus general population using a claims-based approach in Germany http://www.natap.org/2016/GLASGOW/2016posterComCostGermany_P153.pdf
M. K. Tatar, G.; Ozelgun, B.; Elbir, T. Z.; Senturk, A.; Tuna, E.; Unal, S.; Tumer, A.; Inkaya, C. 2016. Indirect Cost of Hiv/Aids: Results of a Survey from a Turkish Research Center http://polarsaglik.com/uploads/polar/Indirect2.pdf
M. K. Stoll, A.; Hower, M.; Heiken, H.; Gerschmann, S.; Klauke, S.; Lutz, T.; Bogner, J.; Degen, O.; Van Lunzen, J.; Bachmann, C.; Stellbrink, H.; Schmidt, W.; Leistner, I.; Mahlich, J. C.; Ranneberg, B. 2012. Corsar-study (cost and resource utilisation study in antiretroviral treated patients) https://www.sciencedirect.com/science/article/pii/S1098301512028136?via%3Dihub
L. L. Smylie, P.; Lerch, R.; Kennedy, C.; Bennett, R.; Clarke, B.; Diener, A. 2011. The economic burden of chlamydia and gonorrhoea in Canada https://sti.bmj.com/content/87/Suppl_1/A156.1
R. W. B. Baran, R.; Kleinman, N.; Beren, I.; Dietz, B. 2012. Employees living with human immunodeficiency virus: Impact of disease and antiretroviral therapies on health care costs and productivity https://betterhealthworldwide.com/wp-content/uploads/2015/05/Comparative-HIV-AMCP20121.pdf

Appendix 8: Are intersectoral costs considered in economic evaluations of interventions relating to sexually transmitted infections (STIs)? A systematic review

Published in BMC Public Health

https://doi.org/10.1186/s12889-022-14484-z

Appendix 9: PRISMA checklist (systematic revie of economic evaluations)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	See title, p1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	p2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p5-6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p7-8
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	See supplemental file 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p7-8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p7-8

Section and Topic	Item #	Checklist item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p7-8
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p7-8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	p9, supplemental file 4
Study characteristics	17	Cite each included study and present its characteristics.	p9-10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p16-20
	23b	Discuss any limitations of the evidence included in the review.	p22
	23c	Discuss any limitations of the review processes used.	p22
	23d	Discuss implications of the results for practice, policy, and future research.	p21, 23
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p31
Competing interests	26	Declare any competing interests of review authors.	p31
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplemental files on data collection forms and data extracted from

Section and Topic	Item #	Checklist item	Location where item is reported
			included studies are available upon request

Appendix 10: Search strategies

PubMed (MEDLINE) [24 May 2019]

(((((((("Sexual Behavior"[MeSH] OR sexual behavior*[tiab] OR sexual behaviour*[tiab] OR sexual activit*[tiab] OR sexual education[tiab] OR sex education[tiab] OR sexuality education[tiab] OR sexual health[tiab] OR "Sexual Health"[MeSH] OR safe sex[tiab] OR unsafe sex[tiab] OR "Unsafe Sex"[MeSH] OR "Contraception"[MeSH] OR contracepti*[tiab] OR birth control[tiab]) OR ("Sexually Transmitted Diseases"[MeSH] OR sexually transmitted disease*[tiab] OR sexually transmitted infection*[tiab] OR STD[tiab] OR STDs[tiab] OR STI[tiab] OR STIs[tiab] OR venereal disease*[tiab] OR "Acquired Immunodeficiency Syndrome"[MeSH] OR acquired immune deficiency syndrome*[tiab] OR Acquired Immunodeficiency Syndrome*[tiab] OR acquired immuno deficiency syndrome*[tiab] OR Acquired Immunologic deficiency Syndrome*[tiab] OR AIDS[tiab] OR herpes genitalis[tiab] OR genital herpes[tiab] OR "Syphilis"[MeSH] OR syphilis[tiab] OR "Chlamydia"[MeSH] OR "Chlamydia infections"[MeSH] OR chlamydia[tiab] OR "HIV"[MeSH] OR HIV[tiab] OR human immunodeficiency virus*[tiab] OR "Gonorrhea"[MeSH] OR gonorrh*[tiab] OR "Trichomonas Infections"[MeSH] OR trichomonas infection*[tiab] OR trichomonias*[tiab] OR "Pelvic Inflammatory Disease"[MeSH] OR pelvic inflammatory disease*[tiab] OR inflammatory pelvic disease*[tiab] OR HPV[tiab] OR human papillomavirus*[tiab] OR condylomata acuminata[tiab] OR genital wart*[tiab] OR venereal wart*[tiab] OR "Hepatitis B"[MeSH] OR "Hepatitis B"[tiab])) AND ((cost[tiab] OR costs[tiab] OR "costs and cost analysis"[MeSH:noexp] OR (cost benefit analyses[Tiab] OR cost benefit analys*[Tiab]) OR "cost-benefit analysis"[MeSH] OR "health care costs"[MeSH:noexp]) OR (("Cost of Illness"[MeSH] OR (health expenditure[tiab] OR health expenditure*[tiab])))))))
NOT (developing countr*[Title] OR third world[Title] OR underdeveloped countr*[Title] OR under developed countr*[Title] OR "Latin America"[Mesh] OR "Africa"[MeSH] OR "Asia, Northern"[MeSH] OR "Asia, Central"[MeSH] OR "Asia, Southeastern"[MeSH] OR "Asia, Western"[MeSH] OR "Central America"[MeSH] OR "Caribbean Region"[MeSH] OR Latin America[Title] OR Africa[Title] OR Central America[Title] OR Caribbean Region[Title] OR "Sensory Aids"[Mesh] OR hearing aids[Title] OR sensory aids[Title])))

Note: The term "cost-benefit analysis"[MeSH], which (among other) searches for the following terms: Cost Effectiveness; Effectiveness, Cost; Cost-Effectiveness Analysis; Analysis, Cost-Effectiveness; Cost Effectiveness Analysis.

EMBASE (via Ovid) [24 May 2019]

1. sexual health/
2. sexual education/
3. (sexual behaviour or sexual behaviour).kw.
4. safe sex.kw.
5. unsafe sex.kw.
6. (contraception or contraceptions or contraceptive or contraceptives or birth control).kw.
7. exp Sexually Transmitted Diseases/

8. (STIs or STI or STDs or STD or venereal disease or venereal diseases).kw.
9. (AIDS or acquired immun* deficiency syndrome or human immunodeficiency virus).ti,ab,kw.
10. (HIV or human immun* deficiency virus or human immunodeficiency virus).ti,ab,kw.
11. (Herpes Genitalis or genital herpes or genital infection or genital infections).ti,ab,kw.
12. Syphilis.ti,ab,kw.
13. Chlamydia.ti,ab,kw.
14. Gonorrh*.ti,ab,kw.
15. (trichomonas or trichomoniasis).ti,ab,kw.
16. Pelvic Inflammatory Disease*.ti,ab,kw.
17. (HPV infection* or Papillomavirus Infection or Papillomavirus Infections).ti,ab,kw.
18. (Genital wart or genital warts or venereal wart or venereal warts or condylomata acuminata).ti,ab,kw.
19. Hepatitis B.ti,ab,kw.
20. cost of illness/
21. (healthcare cost* or health care cost*).kw.
22. (cost or costs).tw.
23. 20 or 21 or 22
24. exp sensory aid/ or exp hearing aids/
25. ("sensory aid*" or "hearing aid*").ti,ab,kw.
26. 24 or 25
27. exp developing country/ or exp Africa/ or exp Caribbean/ or exp Central America/ or exp Southeast Asia/ or exp USSR/ or exp Melanesia/ or exp "Federated States of Micronesia"/ or exp Polynesia/ or exp French Polynesia/ or exp Atlantic islands/ or exp Indian Ocean/ or exp Central Africa/
28. "Macedonia (republic)"/ or Russian Federation/ or China/ or Afghanistan/ or Albania/ or Bahrain/ or Belarus/ or Brazil/ or Bhutan/ or Bolivia/ or "Federation of Bosnia and Herzegovina"/ or "Bosnia and Herzegovina"/ or Bulgaria/ or Congo/ or Ecuador/ or Guyana/ or "Punjab (India)"/ or India/ or Iran/ or Iraq/ or Jordan/ or Kuwait/ or Lebanon/ or Moldova/ or Mongolia/ or Montenegro/ or Nepal/ or Oman/ or Pakistan/ or Paraguay/ or Puerto Rico/ or Peru/ or Philippines/ or Kosovo/ or Yemen/ or Romania/ or Saudi Arabia/ or Serbia/ or Sri Lanka/ or Suriname/ or Syria/ or Uruguay/ or Venezuela/ or Qatar/ or United Arab Emirates/ or Colombia/
29. (Afghanistan or Africa or Albania or Algeria or Angola or Antigua or Argentina or Armenia or Azerbaijan or Bangladesh or Barbados or Barbuda or Bahrain or Belarus or Belize or Brazil or Bhutan or Bolivia or Bosnia or Botswana or Bulgaria or Burkina Faso or Burundi or Cambodia or Cameroon or Chad or Comoros or Congo or Costa Rica or Croatia or Cuba or Congo or Djibouti or Dominica or Dominican or East Timor or Ecuador or Egypt or El Salvador or Equatorial Guinea or Eritrea or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea or Guyana or Haiti or Honduras or India or Indonesia or Iran or Iraq or Jamaica or Jordan or Kazakhstan or Kenya or Kiribati or Kyrgyzstan or Kuwait or Laos or Lebanon or Lesotho or Liberia or Libya or Madagascar or Malawi or Malaysia or Maldives or Mali or Mauritania or Mauritius or Micronesia or Moldova or Mongolia or Montenegro or Morocco or Mozambique or Myanmar or Namibia or Nepal or Nicaragua or Niger or Nigeria or Oman or Pakistan or Palau or Panama or Paraguay or Benin or China or Peru or Philippines or Georgia or Kosovo or Macedonia or Yemen or Romania or Russia or Rwanda or Saint Kitts or Saint Vincent or Saint Lucia or Sao Tome Principe or Saudi Arabia or Senegal

or Serbia or Seychelles or Sierra Leone or South Africa or Solomon Islands or Somalia or Sri Lanka or Sri-Lanka or Sudan or Suriname or Swaziland or Syria or Tajikistan or Tanzania or Thailand or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkmenistan or Uganda or Ukraine or Uruguay or Uzbekistan or Vanuatu or Venezuela or Vietnam or Samoa or Zambia or Zimbabwe or Qatar or United Arab Emirates or Colombia).ti.

30. 27 or 28 or 29

31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

32. 23 and 31

33. 32 not 26

34. 33 not 30

35. 34 not ((exp animal/ or nonhuman/) not exp human/)

36. limit 35 to ((dutch or english or german) and last 20 years)

Web of Science Core Collection [24 May 2019]

31 (#29 not #30)

30 (ti=("sensory aids" or "hearing aids"))

29 (#27 not #28)

28 (ti=(Afghanistan or Africa or Albania or Algeria or Angola or Antigua or Argentina or Armenia or Azerbaijan or Bangladesh or Barbados or Barbuda or Belarus or Belize or Brazil or Bhutan or Bolivia or Bosnia or Botswana or Bulgaria or Burkina Faso or Burundi or Cambodia or Cameroon or Central African Republic or Chad or Chile or Colombia or Comoros or Congo or Costa Rica or Croatia or Cuba or Czech* or Congo or Djibouti or Dominica or Dominican or East Timor or Ecuador or Egypt or El Salvador or Equatorial Guinea or Eritrea or Estonia or Ethiopia or Fiji or Gabon or Gambia or Ghana or Grenada or Guatemala or Guinea-Bissau or Guyana or Haiti or Honduras or Hungary or India or Indonesia or Iran or Iraq or Ivory Coast or Jamaica or Jordan or Kazakhstan or Kenya or Kiribati or Kyrgyzstan or Laos or Latvia or Lebanon or Lesotho or Liberia or Libya or Lithuania or Madagascar or Malawi or Malaysia or Maldives or Mali or Marshall Islands or Mauritania or Mauritius or Mexico or Micronesia or Moldova or Mongolia or Montenegro or Morocco or Mozambique or Myanmar or Namibia or Nepal or New Guinea or Nicaragua or Niger or Nigeria or Oman or Pakistan or Palau or Panama or Papua New Guinea or Paraguay or Benin or China or Peru or Philippines or Poland or Cape Verde or Georgia or Kosovo or Macedonia or Yemen or Romania or Russia or Rwanda or Saint Kitts or Saint Vincent or Saint Lucia or Sao Tome Principe or Saudi Arabia or Senegal or Serbia or Seychelles or Sierra Leone or Slovak* or South Africa or Solomon Islands or Somalia or Sri Lanka or Sri-Lanka or Sudan or Suriname or Swaziland or Syria or Tajikistan or Tanzania or Thailand or Togo or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Uganda or Ukraine or Uruguay or Uzbekistan or Vanuatu or Venezuela or Vietnam or Samoa or Zambia or Zimbabwe))

27 #26 AND #21

26 #25 OR #24 OR #23 OR #22

25 (ti=(cost* or "cost benefit analys*" or "health care cost*" or "economic evaluation"))

24 (ts=("cost benefit analys*" or "health care cost*" or "economic evaluation"))

23 (ts=("cost of illness*" or "burden of illness*" or "burden of disease*" or "economic burden"))
22 (ti=("cost of illness*" or "health expenditure*" or "burden of illness*" or "burden of disease*" "economic burden"))
21 #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
20 (ti=(Hepatitis B))
19 (ti=(Genital wart* or venereal wart*))
18 (ti=(HPV infection* or Human Papillomavirus Infection* or Papillomavirus Infection*))
17 (ti=(Pelvic Inflammatory Disease*))
16 (ti=(trichomonas infection or trichomoniasis))
15 (ti=(Gonorrh*))
14 (ti=(Chlamydia))
13 (ti=(Syphilis))
12 (ti=(Herpes Genitalis or genital herpes))
11 (ti=(HIV or human immuno deficiency virus or human immunodeficiency virus or human immune deficiency virus))
10 (ti=(AIDS or acquired immuno deficiency syndrome or acquired immune deficiency syndrome))
9 (ti=(sexually transmitted infection* or sexually transmitted disease* or STI or STIs or STD or STDs or venereal disease*))
8 (ts=(sexually transmitted disease*))
7 (ts=(sexually transmitted infection*))
6 (ti=(contracept* or birth control))
5 (ti=(sexual health or sexual behavi* or sexual activit* or sex* education))
4 (ts=(contracept*))
3 (ts=(sexual behavi*))
2 (ts=(sexual health))
1 (ts=(sex* education))

For Web of Science the following indexes were searched: SCI-EXPANDED (Science Citation Index Expanded), SSCI (Social Sciences Citation Index), A&HCI (Arts & Humanities Citation Index), ESCI (Emerging Sources Citation Index). Timespan=1999-2019.

CINAHL (EBSCO) [26 May 2019]

Limitation Date: 19990101-20191231
Interface: EBSCOhost Research Databases

S29 S26 NOT (MH "Animals" NOT MH "Human)
S28 S26 NOT (MH "Animals" NOT MH "Human)
S27 S26 NOT (MH "Animals" NOT MH "Human)
S26 S24 NOT S25 NOT S19
S25 S20 OR S21 OR S22

S24 S18 AND S23

S23 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S22 (MH "Developing Countries") OR (MH "Low and Middle Income Countries")

S21 "developing countr*" or "underdeveloped countr*" or "under developed countr*" or "third world" or "least developed countr*" or "less developed countr*" or "under developed nation*" or "developing nation*"

S20 TI ("Russia" or "China" or "Brazil" or "Brasil" or "Bosnia" or "Herzegovina" or "Kuwait" or "Moldova" or "Mongolia" or "Montenegro" or "Nepal" or "Oman" or "Pakistan" or "Paraguay" or "Puerto Rico" or "Kosovo" or "Yemen" or "Romania" or "Saudi Arabia" or "Sri Lanka" or "Suriname" or "Syria" or "Uruguay" or "Venezuela" or "Qatar" or "United Arab" or "United Arab Emirates" or "Colombia" or "Afghanistan" OR "Africa" OR "Albania" OR "Algeria" OR "Angola" OR "Antigua" OR "Argentina" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Barbados" OR "Barbuda" OR "Bahrain" OR "Belarus" OR "Belize" OR "Bhutan" OR "Bolivia" OR "Botswana" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cambodia" OR "Cameroon" OR "Chad" OR "Comoros" OR "Congo" OR "Costa Rica" OR "Croatia" OR "Cuba" OR "Congo" OR "Djibouti" OR "Dominica" OR "Dominican" OR "East Timor" OR "Ecuador" OR "Egypt" OR "El Salvador" OR "Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "Gambia" OR "Ghana" OR "Grenada" OR "Guatemala" OR "Guinea" OR "Guyana" OR "Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhstan" OR "Kenya" OR "Kiribati" OR "Kyrgyzstan" OR "Laos" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Myanmar" OR "Namibia" OR "Nicaragua" OR "Niger" OR "Nigeria" OR "Palau" OR "Panama" OR "Benin" OR "Peru" OR "Philippines" OR "Georgia" OR "Macedonia" OR "Rwanda" OR "Saint Kitts" OR "Saint Vincent" OR "Saint Lucia" OR "Sao Tome Principe" OR "Senegal" OR "Serbia" OR "Seychelles" OR "Sierra Leone" OR "South Africa" OR "Solomon Islands" OR "Somalia" OR "Sudan" OR "Swaziland" OR "Tajikistan" OR "Tanzania" OR "Thailand" OR "Togo" OR "Tonga" OR "Trinidad" OR "Tobago" OR "Tunisia" OR "Turkmenistan" OR "Uganda" OR "Ukraine" OR "Uzbekistan" OR "Vanuatu" OR "Vietnam" OR "Samoa" OR "Zambia" OR "Zimbabwe") or AB ("Russia" or "China" or "Brazil" or "Brasil" or "Bosnia" or "Herzegovina" or "Kuwait" or "Moldova" or "Mongolia" or "Montenegro" or "Nepal" or "Oman" or "Pakistan" or "Paraguay" or "Puerto Rico" or "Kosovo" or "Yemen" or "Romania" or "Saudi Arabia" or "Sri Lanka" or "Suriname" or "Syria" or "Uruguay" or "Venezuela" or "Qatar" or "United Arab" or "United Arab Emirates" or "Colombia" or "Afghanistan" OR "Africa" OR "Albania" OR "Algeria" OR "Angola" OR "Antigua" OR "Argentina" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Barbados" OR "Barbuda" OR "Bahrain" OR "Belarus" OR "Belize" OR "Bhutan" OR "Bolivia" OR "Botswana" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cambodia" OR "Cameroon" OR "Chad" OR "Comoros" OR "Congo" OR "Costa Rica" OR "Croatia" OR "Cuba" OR "Congo" OR "Djibouti" OR "Dominica" OR "Dominican" OR "East Timor" OR "Ecuador" OR "Egypt" OR "El Salvador" OR "Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "Gambia" OR "Ghana" OR "Grenada" OR "Guatemala" OR "Guinea" OR "Guyana" OR "Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhstan" OR "Kenya" OR "Kiribati" OR "Kyrgyzstan" OR "Laos" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Myanmar" OR "Namibia" OR "Nicaragua" OR "Niger" OR "Nigeria" OR "Palau" OR "Panama" OR "Benin" OR "Peru" OR

“Philippines” OR “Georgia” OR “Macedonia” OR “Rwanda” OR “Saint Kitts” OR “Saint Vincent” OR “Saint Lucia” OR “Sao Tome Principe” OR “Senegal” OR “Serbia” OR “Seychelles” OR “Sierra Leone” OR “South Africa” OR “Solomon Islands” OR “Somalia” OR “Sudan” OR “Swaziland” OR “Tajikistan” OR “Tanzania” OR “Thailand” OR “Togo” OR “Tonga” OR “Trinidad” OR “Tobago” OR “Tunisia” OR “Turkmenistan” OR “Uganda” OR “Ukraine” OR “Uzbekistan” OR “Vanuatu” OR “Vietnam” OR “Samoa” OR “Zambia” OR “Zimbabwe”)

S19 "sensory aid*" or "hearing aid*" or "decision aid*" or "smoking cessation aid*"

S18 "cost analys*" or "cost benefit" or "cost effectiv*" or "cost minimi*" or "cost utility" or "health cost*" or "healthcare cost*" or "direct cost*" or "indirect cost*" or "health care cost*" or "health expenditure*" or "burden of illness*" or "burden of disease*" or "economic burden" or "economic evaluation*" or "health* economic*" or "cost* of illness*" or "illness* cost*" or "cost* of disease*" or "disease* cost*" or "sickness cost*" or "productivity cost*" or "cost* and benefit*"

S17 TI ("Hepatitis B") or AB ("Hepatitis B")

S16 TI ("Genital wart*" or "venereal wart*" or "condylomata acuminata") or AB ("Genital wart*" or "venereal wart*" or "condylomata acuminata")

S15 TI ("HPV infection*" or "Human Papillomavirus Infection*") or AB ("HPV infection*" or "Human Papillomavirus Infection*")

S14 TI ("Pelvic Inflammatory Disease*") or AB ("Pelvic Inflammatory Disease*")

S13 TI ("trichomonas vagin*") or AB ("trichomonas vagin*")

S12 TI ("Gonorrh*") or AB ("Gonorrh*")

S11 TI ("Chlamydia trachomatis") or AB ("Chlamydia trachomatis")

S10 TI ("Syphilis") or AB ("Syphilis")

S9 TI ("genital herpes" or "Herpes Genitalis" or "genital infection") or AB ("genital herpes" or "Herpes Genitalis" or "genital infection")

S8 TI ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus") or AB ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus")

S7 TI ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome") or AB ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome")

S6 TI ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”) OR AB ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”)

S5 (MH "Sexually Transmitted Diseases")

S4 (MH "Contraception")

S3 "sexual behavior" or "sexual behaviour"

S2 (MH "Sex Education")

S1 (MH "Sexual Health")

PsycINFO (EBSCO) [26 May 2019]

Limiters - Publication Year: 1999-2019

S26 S25 NOT (PO Animal NOT PO Human)

S25 S24 NOT S21 NOT S22

S24 S18 AND S23

S23 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15

S22 S19 OR S20

S21 "sensory aid*" or "hearing aid*" or "decision aid*" or “smoking cessation aid*”

S20 TI (“Russia” or “China” or “Brazil” or “Brasil” or “Bosnia” or “Herzegovina” or “Kuwait” or “Moldova” or “Mongolia” or “Montenegro” or “Nepal” or “Oman” or “Pakistan” or “Paraguay” or “Puerto Rico” or “Kosovo” or “Yemen” or “Romania” or “Saudi Arabia” or “Sri Lanka” or “Suriname” or “Syria” or “Uruguay” or “Venezuela” or “Qatar” or “United Arab“ or “United Arab Emirates” or “Colombia” or “Afghanistan” OR “Africa” OR “Albania” OR “Algeria” OR “Angola” OR “Antigua” OR “Argentina” OR “Armenia” OR “Azerbaijan” OR “Bangladesh” OR “Barbados” OR “Barbuda” OR “Bahrain” OR “Belarus” OR “Belize” OR “Bhutan” OR “Bolivia” OR “Botswana” OR “Bulgaria” OR “Burkina Faso” OR “Burundi” OR “Cambodia” OR “Cameroon” OR “Chad” OR “Comoros” OR “Congo” OR “Costa Rica” OR “Croatia” OR “Cuba” OR “Congo” OR “Djibouti” OR “Dominica” OR “Dominican” OR “East Timor” OR “Ecuador” OR “Egypt” OR “El Salvador” OR “Guinea” OR “Eritrea” OR “Ethiopia” OR “Fiji” OR “Gabon” OR “Gambia” OR “Ghana” OR “Grenada” OR “Guatemala” OR “Guinea” OR “Guyana” OR “Haiti” OR “Honduras” OR “India” OR “Indonesia” OR “Iran” OR “Iraq” OR “Jamaica” OR “Jordan” OR “Kazakhstan” OR “Kenya” OR “Kiribati” OR “Kyrgyzstan” OR “Laos” OR “Lebanon” OR “Lesotho” OR “Liberia” OR “Libya” OR “Madagascar” OR “Malawi” OR “Malaysia” OR “Maldives” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Morocco” OR “Mozambique” OR “Myanmar” OR “Namibia” OR “Nicaragua” OR “Niger” OR “Nigeria” OR “Palau” OR “Panama” OR “Benin” OR “Peru” OR “Philippines” OR “Georgia” OR “Macedonia” OR “Rwanda” OR “Saint Kitts” OR “Saint Vincent” OR “Saint Lucia” OR “Sao Tome Principe” OR “Senegal” OR “Serbia” OR “Seychelles” OR “Sierra Leone” OR “South Africa” OR “Solomon Islands” OR “Somalia” OR “Sudan” OR “Swaziland” OR “Tajikistan” OR “Tanzania” OR “Thailand” OR “Togo” OR “Tonga” OR “Trinidad” OR “Tobago” OR “Tunisia” OR “Turkmenistan” OR “Uganda” OR “Ukraine” OR “Uzbekistan” OR “Vanuatu” OR “Vietnam” OR “Samoa” OR “Zambia” OR “Zimbabwe”) or AB (“Russia” or “China” or “Brazil” or “Brasil” or “Bosnia” or “Herzegovina” or “Kuwait” or “Moldova” or “Mongolia” or “Montenegro” or “Nepal” or “Oman” or “Pakistan” or “Paraguay” or “Puerto Rico” or “Kosovo” or “Yemen” or “Romania” or “Saudi Arabia” or “Sri Lanka” or “Suriname” or “Syria” or “Uruguay” or “Venezuela” or “Qatar” or “United Arab“ or “United Arab Emirates” or “Colombia” or “Afghanistan” OR “Africa” OR “Albania” OR “Algeria” OR “Angola” OR “Antigua” OR “Argentina” OR “Armenia” OR “Azerbaijan” OR “Bangladesh” OR “Barbados” OR “Barbuda” OR “Bahrain” OR “Belarus” OR “Belize” OR “Bhutan” OR “Bolivia” OR “Botswana” OR “Bulgaria” OR “Burkina Faso” OR “Burundi” OR “Cambodia” OR “Cameroon” OR “Chad” OR “Comoros” OR “Congo” OR “Costa Rica” OR “Croatia” OR “Cuba” OR “Congo” OR “Djibouti” OR “Dominica” OR “Dominican” OR “East Timor” OR “Ecuador” OR “Egypt” OR “El Salvador” OR “Guinea” OR “Eritrea” OR “Ethiopia” OR “Fiji” OR “Gabon” OR “Gambia” OR “Ghana” OR “Grenada” OR “Guatemala” OR “Guinea” OR “Guyana” OR “Haiti” OR “Honduras” OR “India” OR “Indonesia” OR “Iran” OR “Iraq” OR “Jamaica” OR “Jordan” OR “Kazakhstan” OR “Kenya” OR “Kiribati” OR “Kyrgyzstan” OR “Laos” OR “Lebanon” OR “Lesotho” OR “Liberia” OR “Libya” OR “Madagascar” OR “Malawi” OR “Malaysia” OR “Maldives” OR “Mali” OR “Mauritania” OR “Mauritius” OR “Morocco” OR “Mozambique” OR “Myanmar” OR “Namibia” OR “Nicaragua” OR “Niger” OR “Nigeria” OR “Palau” OR “Panama” OR “Benin” OR “Peru” OR “Philippines” OR “Georgia” OR “Macedonia” OR “Rwanda” OR “Saint Kitts” OR “Saint Vincent” OR “Saint Lucia” OR “Sao Tome Principe” OR “Senegal” OR “Serbia” OR “Seychelles” OR “Sierra Leone” OR “South Africa” OR “Solomon Islands” OR “Somalia” OR “Sudan” OR “Swaziland” OR “Tajikistan”

OR “Tanzania” OR “Thailand” OR “Togo” OR “Tonga” OR “Trinidad” OR “Tobago” OR “Tunisia” OR “Turkmenistan” OR “Uganda” OR “Ukraine” OR “Uzbekistan” OR “Vanuatu” OR “Vietnam” OR “Samoa” OR “Zambia” OR “Zimbabwe”)

S19 "developing countr*" or "underdeveloped countr*" or "under developed countr*" or "third world" or "least developed countr*" or "less developed countr*" or "under developed nation*" or "developing nation*"

S18 S16 OR S17

S17 "cost analys*" or "cost benefit" or "cost effectiv*" or "cost minimi*" or "cost utility" or "health cost*" or "healthcare cost*" or "direct cost*" or "indirect cost*" or "health care cost*" or "health expenditure*" or "burden of illness*" or "burden of disease*" or "economic burden" or "economic evaluation*" or "health* economic*" or "cost* of illness*" or "illness* cost*" or "cost* of disease*" or "disease* cost*" or "sickness cost*" or "productivity cost*" or "cost* and benefit*"

S16 DE "Costs and Cost Analysis" OR DE "Health Care Costs" OR DE "Health Care Economics"

S15 TI ("Hepatitis B") or AB ("Hepatitis B")

S14 TI ("Genital wart" or "Genital warts" or "venereal wart" or "venereal warts" or "condylomata acuminata") or AB ("Genital wart" or "Genital warts" or "venereal wart" or "venereal warts" or "condylomata acuminata")

S13 TI ("HPV infection*" or "Human Papillomavirus Infection*") or AB ("HPV infection*" or "Human Papillomavirus Infection*")

S12 TI ("Pelvic Inflammatory Disease*") or AB ("Pelvic Inflammatory Disease*")

S11 TI ("trichomonas vagin*") or AB ("trichomonas vagin*")

S10 TI ("Gonorrh*") or AB ("Gonorrh*")

S9 TI ("Chlamydia trachomatis") or AB ("Chlamydia trachomatis")

S8 TI ("Syphilis") or AB ("Syphilis")

S7 TI ("genital herpes" or "Herpes Genitalis" or "genital infection") or AB ("genital herpes" or "Herpes Genitalis" or "genital infection")

S6 TI ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus") or AB ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus")

S5 TI ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome") or AB ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome")

S4 TI ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”) OR AB ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”)

S3 DE "Birth Control"

S2 DE "Sexual Health" OR DE "Sexually Transmitted Diseases"

S1 DE "Sex Education"

EconLit (EBSCO) [26 May 2019]

Limiters - Published Date: 19990101-20181231

S30 S26 NOT S22

S29 S26 NOT S22

S28 S26 NOT S22

S27 S26 NOT S22

S26 S24 NOT S19 NOT S25

S25 S20 OR S21

S24 S18 AND S23

S23 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17

S22 "animal" or "animals" or "nonhuman"

S21 "developing countr*" or "underdeveloped countr*" or "under developed countr*" or "third world" or "least developed countr*" or "less developed countr*" or "under developed nation*" or "developing nation*"

S20 TI ("Russia" or "China" or "Brazil" or "Brasil" or "Bosnia" or "Herzegovina" or "Kuwait" or "Moldova" or "Mongolia" or "Montenegro" or "Nepal" or "Oman" or "Pakistan" or "Paraguay" or "Puerto Rico" or "Kosovo" or "Yemen" or "Romania" or "Saudi Arabia" or "Sri Lanka" or "Suriname" or "Syria" or "Uruguay" or "Venezuela" or "Qatar" or "United Arab" or "United Arab Emirates" or "Colombia" or "Afghanistan" OR "Africa" OR "Albania" OR "Algeria" OR "Angola" OR "Antigua" OR "Argentina" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Barbados" OR "Barbuda" OR "Bahrain" OR "Belarus" OR "Belize" OR "Bhutan" OR "Bolivia" OR "Botswana" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cambodia" OR "Cameroon" OR "Chad" OR "Comoros" OR "Congo" OR "Costa Rica" OR "Croatia" OR "Cuba" OR "Congo" OR "Djibouti" OR "Dominica" OR "Dominican" OR "East Timor" OR "Ecuador" OR "Egypt" OR "El Salvador" OR "Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "Gambia" OR "Ghana" OR "Grenada" OR "Guatemala" OR "Guinea" OR "Guyana" OR "Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhstan" OR "Kenya" OR "Kiribati" OR "Kyrgyzstan" OR "Laos" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Mauritania" OR "Mauritius" OR "Morocco" OR "Mozambique" OR "Myanmar" OR "Namibia" OR "Nicaragua" OR "Niger" OR "Nigeria" OR "Palau" OR "Panama" OR "Benin" OR "Peru" OR "Philippines" OR "Georgia" OR "Macedonia" OR "Rwanda" OR "Saint Kitts" OR "Saint Vincent" OR "Saint Lucia" OR "Sao Tome Principe" OR "Senegal" OR "Serbia" OR "Seychelles" OR "Sierra Leone" OR "South Africa" OR "Solomon Islands" OR "Somalia" OR "Sudan" OR "Swaziland" OR "Tajikistan" OR "Tanzania" OR "Thailand" OR "Togo" OR "Tonga" OR "Trinidad" OR "Tobago" OR "Tunisia" OR "Turkmenistan" OR "Uganda" OR "Ukraine" OR "Uzbekistan" OR "Vanuatu" OR "Vietnam" OR "Samoa" OR "Zambia" OR "Zimbabwe") or AB ("Russia" or "China" or "Brazil" or "Brasil" or "Bosnia" or "Herzegovina" or "Kuwait" or "Moldova" or "Mongolia" or "Montenegro" or "Nepal" or "Oman" or "Pakistan" or "Paraguay" or "Puerto Rico" or "Kosovo" or "Yemen" or "Romania" or "Saudi Arabia" or "Sri Lanka" or "Suriname" or "Syria" or "Uruguay" or "Venezuela" or "Qatar" or "United Arab" or "United Arab Emirates" or "Colombia" or "Afghanistan" OR "Africa" OR "Albania" OR "Algeria" OR "Angola" OR "Antigua" OR "Argentina" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Barbados" OR "Barbuda" OR "Bahrain" OR "Belarus" OR "Belize" OR "Bhutan" OR "Bolivia" OR "Botswana" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cambodia" OR "Cameroon" OR "Chad" OR "Comoros" OR "Congo" OR "Costa Rica" OR "Croatia" OR "Cuba" OR "Congo" OR "Djibouti" OR "Dominica" OR "Dominican" OR "East Timor" OR "Ecuador" OR "Egypt" OR "El Salvador" OR "Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "Gambia" OR "Ghana" OR "Grenada" OR "Guatemala" OR "Guinea" OR "Guyana" OR "Haiti" OR "Honduras" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhstan" OR "Kenya" OR "Kiribati" OR "Kyrgyzstan" OR "Laos" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR

“Mauritania” OR “Mauritius” OR “Morocco” OR “Mozambique” OR “Myanmar” OR “Namibia” OR “Nicaragua” OR “Niger” OR “Nigeria” OR “Palau” OR “Panama” OR “Benin” OR “Peru” OR “Philippines” OR “Georgia” OR “Macedonia” OR “Rwanda” OR “Saint Kitts” OR “Saint Vincent” OR “Saint Lucia” OR “Sao Tome Principe” OR “Senegal” OR “Serbia” OR “Seychelles” OR “Sierra Leone” OR “South Africa” OR “Solomon Islands” OR “Somalia” OR “Sudan” OR “Swaziland” OR “Tajikistan” OR “Tanzania” OR “Thailand” OR “Togo” OR “Tonga” OR “Trinidad” OR “Tobago” OR “Tunisia” OR “Turkmenistan” OR “Uganda” OR “Ukraine” OR “Uzbekistan” OR “Vanuatu” OR “Vietnam” OR “Samoa” OR “Zambia” OR “Zimbabwe”)

S19 "sensory aid*" or "hearing aid*" or "decision aid*" or "smoking cessation aid*"

S18 "cost analys*" or "cost benefit" or "cost effectiv*" or "cost minimi*" or "cost utility" or "health cost*" or "healthcare cost*" or "direct cost*" or "indirect cost*" or "health care cost*" or "health expenditure*" or "burden of illness*" or "burden of disease*" or "economic burden" or "economic evaluation*" or "health* economic*" or "cost* of illness*" or "illness* cost*" or "cost* of disease*" or "disease* cost*" or "sickness cost*" or "productivity cost*" or "cost* and benefit*"

S17 TI ("Hepatitis B") or AB ("Hepatitis B")

S16 TI ("Genital wart*" or "venereal wart*" or "condylomata acuminata") or AB ("Genital wart*" or "venereal wart*" or "condylomata acuminata")

S15 TI ("HPV infection*" or "Human Papillomavirus Infection*") or AB ("HPV infection*" or "Human Papillomavirus Infection*")

S14 TI ("Pelvic Inflammatory Disease*") or AB ("Pelvic Inflammatory Disease*")

S13 TI ("trichomonas") or AB ("trichomonas")

S12 TI ("Gonorrh*") or AB ("Gonorrh*")

S11 TI ("Chlamydia trachomatis") or AB ("Chlamydia trachomatis")

S10 TI ("Syphilis") or AB ("Syphilis")

S9 TI ("genital herpes" or "Herpes Genitalis" or "genital infection") or AB ("genital herpes" or "Herpes Genitalis" or "genital infection")

S8 TI ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus") or AB ("HIV" or "human immun* deficiency virus" or "human immunodeficiency virus")

S7 TI ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome") or AB ("AIDS" or "acquired immun* deficiency syndrome" or "acquired immunodeficiency syndrome")

S6 TI ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”) OR AB ("STI" or "STIs" or "STD" or "STDs" OR “venereal disease” OR “venereal diseases”)

S5 "Sexually Transmitted Disease*" or "Sexually Transmitted infection*"

S4 "contraception*" or "contraceptions" or "contraceptive" or "contraceptives" or "birth control"

S3 "sexual behavior*" or "sexual behaviour*"

S2 "sex* education"

S1 "sexual health"

NHS EED [27 May 2019]

1 (sexual health) IN NHSEED

2 (sex* behavi*) IN NHSEED

3 (safe sex) IN NHSEED
4 (unsafe sex) IN NHSEED
5 MeSH DESCRIPTOR Sex Education EXPLODE ALL TREES
6 (STI or STIs or STD or STDs) IN NHSEED
7 MeSH DESCRIPTOR Syphilis EXPLODE ALL TREES
8 MeSH DESCRIPTOR Syphilis, Congenital EXPLODE ALL TREES
9 MeSH DESCRIPTOR Chlamydia trachomatis EXPLODE ALL TREES
10 MeSH DESCRIPTOR Neisseria gonorrhoeae EXPLODE ALL TREES
11 MeSH DESCRIPTOR Gonorrhea EXPLODE ALL TREES
12 MeSH DESCRIPTOR Trichomonas Infections EXPLODE ALL TREES
13 MeSH DESCRIPTOR Trichomonas vaginalis EXPLODE ALL TREES
14 MeSH DESCRIPTOR Pelvic Inflammatory Disease EXPLODE ALL TREES
15 MeSH DESCRIPTOR Papillomaviridae EXPLODE ALL TREES
16 MeSH DESCRIPTOR Hepatitis B EXPLODE ALL TREES
17 MeSH DESCRIPTOR Hepatitis B virus EXPLODE ALL TREES
18 (contraception):TI OR (contraceptions):TI IN NHSEED
19 (contraceptive):TI OR (contraceptives):TI IN NHSEED
20 (HIV):TI OR (Human immunodeficiency virus):TI OR (Human immun* deficiency virus):TI IN NHSEED
21 (AIDS):TI OR (acquired immun* deficiency syndrome):TI OR (acquired immunodeficiency syndrome):TI IN NHSEED
22 (herpes genitalis):TI OR (genital herpes):TI OR (genital infection):TI IN NHSEED
23 (syphilis):TI IN NHSEED
24 (chlamydia trachomatis):TI IN NHSEED
25 (Gonorrh*):TI IN NHSEED
26 (Trichomonas vaginali*):TI OR (Trichomonas infection*):TI IN NHSEED
27 (Pelvic inflammatory infection):TI OR (Pelvic inflammatory infections):TI IN NHSEED
28 (Human papillomavirus):TI OR (Human Papilloma Virus):TI IN NHSEED
29 (Genital wart):TI OR (Condylomata Acuminata):TI OR (Genital warts):TI IN NHSEED
30 MeSH DESCRIPTOR Condylomata Acuminata EXPLODE ALL TREES
31 (hepatitis B):TI IN NHSEED
32 (MeSH DESCRIPTOR Sex Education EXPLODE ALL TREES) IN NHSEED
33 (MeSH DESCRIPTOR Sexually Transmitted Diseases EXPLODE ALL TREES) IN NHSEED
34 (MeSH DESCRIPTOR Contraception Behavior EXPLODE ALL TREES) IN NHSEED
35 (MeSH DESCRIPTOR Contraception EXPLODE ALL TREES) IN NHSEED
36 (MeSH DESCRIPTOR HIV EXPLODE ALL TREES) IN NHSEED
37 (MeSH DESCRIPTOR Acquired Immunodeficiency Syndrome EXPLODE ALL TREES) IN NHSEED
38 (MeSH DESCRIPTOR Herpes Genitalis EXPLODE ALL TREES) IN NHSEED
39 (MeSH DESCRIPTOR Syphilis EXPLODE ALL TREES) IN NHSEED
40 (MeSH DESCRIPTOR Syphilis, Congenital EXPLODE ALL TREES) IN NHSEED
41 (MeSH DESCRIPTOR Chlamydia trachomatis EXPLODE ALL TREES) IN NHSEED
42 (MeSH DESCRIPTOR Neisseria gonorrhoeae EXPLODE ALL TREES) IN NHSEED
43 (MeSH DESCRIPTOR Gonorrhea EXPLODE ALL TREES) IN NHSEED
44 (MeSH DESCRIPTOR Trichomonas Infections EXPLODE ALL TREES) IN NHSEED

45 (MeSH DESCRIPTOR Trichomonas vaginalis EXPLODE ALL TREES) IN NHSEED
46 (MeSH DESCRIPTOR Pelvic Inflammatory Disease EXPLODE ALL TREES) IN NHSEED
47 (MeSH DESCRIPTOR Papillomaviridae EXPLODE ALL TREES) IN NHSEED
48 (MeSH DESCRIPTOR Hepatitis B EXPLODE ALL TREES) IN NHSEED
49 (MeSH DESCRIPTOR Hepatitis B virus EXPLODE ALL TREES) IN NHSEED
50 (MeSH DESCRIPTOR Condylomata Acuminata EXPLODE ALL TREES) IN NHSEED FROM 1999 TO 2019
51 #1 OR #2 OR #3 OR #4 OR #6 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50
52 (sensory aid*) OR (hearing aid*) OR (decision aid*) IN NHSEED
53 (animal) OR (animals) OR (nonhuman) IN NHSEED
54 (#1 OR #2 OR #3 OR #4 OR #6 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50) IN NHSEED FROM 1999 TO 2019
55 (#1 OR #2 OR #3 OR #4 OR #6 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50) FROM 1999 TO 2019

PUBMED [30 June 2021]

Note: The original search was updated to also include studies between 2019 and June 2021 (time of update). Studies were only searched in PubMed.

Search: (((((("Sexual Behavior"[MeSH] OR sexual behavior*[tiab] OR sexual behaviour*[tiab] OR sexual activit*[tiab] OR sexual education[tiab] OR sex education[tiab] OR sexuality education[tiab] OR sexual health[tiab] OR "Sexual Health"[MeSH] OR safe sex[tiab] OR safe* sex[tiab] OR "Unsafe Sex"[MeSH] OR "Contraception"[MeSH] OR contracepti*[tiab] OR birth control[tiab] OR ("Sexually Transmitted Diseases"[MeSH] OR sexually transmitted disease*[tiab] OR sexually transmitted infection*[tiab] OR STD[tiab] OR STDs[tiab] OR STI[tiab] OR STIs[tiab] OR venereal disease*[tiab] OR "Acquired Immunodeficiency Syndrome"[MeSH] OR acquired immune deficiency syndrome*[tiab] OR Acquired Immunodeficiency Syndrome*[tiab] OR acquired immuno deficiency syndrome*[tiab] OR Acquired Immunologic deficiency Syndrome*[tiab] OR AIDS[tiab] OR "HIV"[MeSH] OR HIV[tiab] OR human immunodeficiency virus*[tiab] OR herpes genitalis[tiab] OR genital herpes[tiab] OR "Syphilis"[MeSH] OR syphilis[tiab] OR "Chlamydia"[MeSH] OR chlamydia[tiab] OR "Gonorrhea"[MeSH] OR gonorrh*[tiab] OR "Trichomonas Infections"[MeSH] OR trichomonas infection*[tiab] OR trichomonias*[tiab] OR "Pelvic Inflammatory Disease"[MeSH] OR pelvic inflammatory disease*[tiab] OR inflammatory pelvic disease*[tiab] OR HPV[tiab] OR human papillomavirus*[tiab] OR condylomata acuminata[tiab] OR genital wart*[tiab] OR venereal wart*[tiab] OR "Hepatitis B"[MeSH] OR "Hepatitis B"[tiab]))))) AND ((cost*[tiab] OR "costs and cost analysis"[MeSH:noexp] OR cost benefit analys*[Tiab] OR "cost-benefit analysis"[MeSH] OR "health care costs"[MeSH:noexp] OR "Cost of Illness"[MeSH] OR health expenditure[tiab] OR health

expenditure*[tiab])))) NOT (((Afghanistan[Title] OR Africa[Title] OR Albania[Title] OR Algeria[Title] OR Angola[Title] OR Antigua[Title] OR Argentina[Title] OR Armenia[Title] OR Azerbaijan[Title] OR Bangladesh[Title] OR Barbados[Title] OR Barbuda[Title] OR Belarus[Title] OR Belize[Title] OR Brazil[Title] OR Bhutan[Title] OR Bolivia[Title] OR Bosnia[Title] OR Botswana[Title] OR Bulgaria[Title] OR Burkina Faso[Title] OR Burundi[Title] OR Cambodia[Title] OR Cameroon[Title] OR Central African Republic[Title] OR Chad[Title] OR Colombia[Title] OR Comoros[Title] OR Congo[Title] OR Costa Rica[Title] OR Croatia[Title] OR Cuba[Title] OR Czech*[Title] OR Congo[Title] OR Djibouti[Title] OR Dominica[Title] OR Dominican[Title] OR East Timor[Title] OR Ecuador[Title] OR Egypt[Title] OR El Salvador[Title] OR Equatorial Guinea[Title] OR Eritrea[Title] OR Estonia[Title] OR Ethiopia[Title] OR Fiji[Title] OR Gabon[Title] OR Gambia[Title] OR Ghana[Title] OR Grenada[Title] OR Guatemala[Title] OR Guinea-Bissau[Title] OR Guyana[Title] OR Haiti[Title] OR Honduras[Title] OR Hungary[Title] OR India[Title] OR Indonesia[Title] OR Iran[Title] OR Iraq[Title] OR Ivory Coast[Title] OR Jamaica[Title] OR Jordan[Title] OR Kazakhstan[Title] OR Kenya[Title] OR Kiribati[Title] OR Kyrgyzstan[Title] OR Laos[Title] OR Latvia[Title] OR Lebanon[Title] OR Lesotho[Title] OR Liberia[Title] OR Libya[Title] OR Lithuania[Title] OR Madagascar[Title] OR Malawi[Title] OR Malaysia[Title] OR Maldives[Title] OR Mali[Title] OR Marshall Islands[Title] OR Mauritania[Title] OR Mauritius[Title] OR Micronesia[Title] OR Moldova[Title] OR Mongolia[Title] OR Montenegro[Title] OR Morocco[Title] OR Mozambique[Title] OR Myanmar[Title] OR Namibia[Title] OR Nepal[Title] OR New Guinea[Title] OR Nicaragua[Title] OR Niger[Title] OR Nigeria[Title] OR Oman[Title] OR Pakistan[Title] OR Palau[Title] OR Panama[Title] OR Papua New Guinea[Title] OR Paraguay[Title] OR Benin[Title] OR China[Title] OR Peru[Title] OR Philippines[Title] OR Poland[Title] OR Cape Verde[Title] OR Georgia[Title] OR Kosovo[Title] OR Macedonia[Title] OR Yemen[Title] OR Romania[Title] OR Russia[Title] OR Rwanda[Title] OR Saint Kitts[Title] OR Saint Vincent[Title] OR Saint Lucia[Title] OR Sao Tome Principe[Title] OR Saudi Arabia[Title] OR Senegal[Title] OR Serbia[Title] OR Seychelles[Title] OR Sierra Leone[Title] OR Slovak*[Title] OR South Africa[Title] OR Solomon Islands[Title] OR Somalia[Title] OR Sri Lanka[Title] OR Sri-Lanka[Title] OR Sudan[Title] OR Suriname[Title] OR Swaziland[Title] OR Syria[Title] OR Tajikistan[Title] OR Tanzania[Title] OR Thailand[Title] OR Togo[Title] OR Tonga[Title] OR Trinidad[Title] OR Tobago[Title] OR Tunisia[Title] OR Turkey[Title] OR Turkmenistan[Title] OR Uganda[Title] OR Ukraine[Title] OR Uruguay[Title] OR Uzbekistan[Title] OR Vanuatu[Title] OR Venezuela[Title] OR Vietnam[Title] OR Samoa[Title] OR Zambia[Title] OR Zimbabwe[Title]))))) NOT ((developing countr*[Title] OR underdeveloped countr*[Title] OR under developed countr*[Title] OR "Latin America"[Mesh] OR "Africa"[MeSH] OR "Asia, Northern"[MeSH] OR "Asia, Central"[MeSH] OR "Asia, Southeastern"[MeSH] OR "Asia, Western"[MeSH] OR "Central America"[MeSH] OR "Caribbean Region"[MeSH] OR Latin America[Title] OR Africa[Title] OR Central America[Title] OR Caribbean Region[Title])) Filters: Humans, from 2019/5/25 - 2021/6/30

Appendix 11: PICO table

Participants/population This review focuses on full (trial-based or model-based) economic evaluations of interventions including individuals (10 years and older) living in Organisation for Economic Co-operation and Development (OECD) member countries and at risk of contracting STIs and individuals infected with an STI
Intervention(s), exposure(s) This review considers different types of interventions implemented in OECD member countries and aimed at preventing, controlling or treating STIs or promoting healthy (sexual) behaviour
Comparator(s)/control Any comparator including usual care, treatment as usual or no intervention are considered
Main outcome(s) Any cost and outcome relevant to a full economic evaluation
Study design Trial-based or model-based economic evaluations that adopted a societal perspective

Appendix 12: List of studies excluded based on full-text screening

Brisson, M., Laprise, J. F., Chesson, H. W., Drolet, M., Malagón, T., Boily, M. C., & Markowitz, L. E. (2016). Health and economic impact of switching from a 4-valent to a 9-valent HPV vaccination program in the United States. *JNCI: Journal of the National Cancer Institute*, *108*(1).
Colchero, M. A., Bautista-Arredondo, S., Cortés-Ortiz, M. A., Romero-Martinez, M., Salas, J., Sosa-Rubí, S. G., & Uribe, P. (2016). Impact and economic evaluations of a combination prevention programme for men who have sex with men in Mexico. *Aids*, *30*(2), 293-300.
Dowdy, D. W., Rodriguez, R. M., Bradley Hare, C., & Kaplan, B. (2011). Cost-effectiveness of targeted human immunodeficiency virus screening in an urban emergency department. *Academic Emergency Medicine*, *18*(7), 745-753.
Farnham, P. G., Sansom, S. L., & Hutchinson, A. B. (2012). How much should we pay for a new HIV diagnosis? A mathematical model of HIV screening in US clinical settings. *Medical Decision Making*, *32*(3), 459-469.
Leibowitz, A. A., Harawa, N., Sylla, M., Hallstrom, C. C., & Kerndt, P. R. (2013). Condom distribution in jail to prevent HIV infection. *AIDS and Behavior*, *17*(8), 2695-2702.
Holtgrave, D. R., Maulsby, C., Kharfen, M., Jia, Y., Wu, C., Opoku, J., ... & Pappas, G. (2012). Cost–utility analysis of a female condom promotion program in Washington, DC. *AIDS and Behavior*, *16*(5), 1115-1120.
Hutchinson, A. B., Patel, P., Sansom, S. L., Farnham, P. G., Sullivan, T. J., Bennett, B., ... & Branson, B. M. (2010). Cost-effectiveness of pooled nucleic acid amplification testing for acute HIV infection after third-generation HIV antibody screening and rapid testing in the United States: a comparison of three public health settings. *PLoS medicine*, *7*(9), e1000342.
Ladapo, J. A., Elliott, M. N., Bogart, L. M., Kanouse, D. E., Vestal, K. D., Klein, D. J., ... & Schuster, M. A. (2013). Cost of talking parents, healthy teens: A worksite-based intervention to promote parent–adolescent sexual health communication. *Journal of Adolescent Health*, *53*(5), 595-601.
Long, E. F., Brandeau, M. L., & Owens, D. K. (2010). The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. *Annals of internal medicine*, *153*(12), 778-789.
Stevens, E. R., Nucifora, K., Zhou, Q., Braithwaite, R. S., Cleland, C. M., Ritchie, A. S., ... & Gwadz, M. V. (2018). Cost-effectiveness of peer-versus venue-based approaches for detecting undiagnosed HIV among heterosexuals in high-risk new York City neighborhoods. *Journal of acquired immune deficiency syndromes (1999)*, *77*(2), 183.
Suijkerbuijk, A., Over, E., Aar, F., Götz, H., Benthem, B., & Lugnér, A. (2017). VP35 Economic Consequences Of A Restricted Dutch Sexually Transmitted Infection-Testing Policy. *International Journal of Technology Assessment in Health Care*, *33*(S1), 165-165.
Tuite, A. R., Jayaraman, G. C., Allen, V. G., & Fisman, D. N. (2012). Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. *Sexually transmitted diseases*, 260-267.
Juusola, J. L., Brandeau, M. L., Owens, D. K., & Bendavid, E. (2012). The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Annals of internal medicine*, *156*(8), 541-550.

Spaulding, A. C., Pinkerton, S. D., Superak, H., Cunningham, M. J., Resch, S., Jordan, A. O., & Yang, Z. (2013). Cost analysis of enhancing linkages to HIV care following jail: a cost-effective intervention. *AIDS and Behavior*, *17*(2), 220-226.
Hersh, A. R., Megli, C. J., & Caughey, A. B. (2018). Repeat screening for syphilis in the third trimester of pregnancy: a cost-effectiveness analysis. *Obstetrics & Gynecology*, *132*(3), 699-707.
Wang, L. Y., Hamilton, D. T., Rosenberg, E. S., Aslam, M. V., Sullivan, P. S., Katz, D. A., ... & Goodreau, S. M. (2020). Cost-effectiveness of pre-exposure prophylaxis among adolescent sexual minority males. *Journal of Adolescent Health*, *66*(1), 100-106.
Kazemian, P., Costantini, S., Kumarasamy, N., Paltiel, A. D., Mayer, K. H., Chandhiok, N., ... & Freedberg, K. A. (2020). The Cost-effectiveness of Human Immunodeficiency Virus (HIV) Preexposure Prophylaxis and HIV Testing Strategies in High-risk Groups in India. *Clinical Infectious Diseases*, *70*(4), 633-642.
Bogaards, J. A., Coupé, V. M., Meijer, C. J., & Berkhof, J. (2011). The clinical benefit and cost-effectiveness of human papillomavirus vaccination for adult women in the Netherlands. *Vaccine*, *29*(48), 8929-8936.
Anderson, J., Wilson, D., Templeton, D. J., Grulich, A., Carter, R., & Kaldor, J. (2009). Cost-effectiveness of adult circumcision in a resource-rich setting for HIV prevention among men who have sex with men. *The Journal of infectious diseases*, *200*(12), 1803-1812.

Appendix 13: Intersectoral cost components included per individual study

	Patient & Family				Informal Care		Paid Labour (productivity)								Non-paid opportunity costs (productivity)	Education	Consumption
	Patient time (and travel)	Travel expenses	Out-of-pocket costs	Premature burial costs	Informal caregiver support (non-family)	Care provided by family/friends	Productivity loss due to absenteeism	Productivity loss due to presenteeism	Lost income	Lost revenue due to unemployment rate gap	Fringe benefits	Early retirement	Avoided future production loss	Intervention-related productivity gains (cost savings)	Inability to perform unpaid work/activities i.e. domestic tasks or voluntary work	School absence	Future consumption unrelated to health
Adamson et al.			X				X		X		X				X		X
Campos et al.	X	X															

Coupe et al.		X					X										
Damm et al.							X										
De Kok et al.	X																
De Wit et al.							X										
Deogan et al.							X						X				
Drabo et al.					X	X	X										
Fogelberg et al.	X																
Gift et al.		X					X										
Ginsberg et al.		X		X			X										
Kim et al.	X	X															
Kim & Goldie	X	X															
Krauth et al.							X	X				X					

Mahmud et al.						X	X								X		
Nosyk et al.														X			
Ouellet et al.							X			X							
Owusu-Edusei et al. (2015)							X										
Owusu-Edusei et al. (2016)							X										
Regnier et al.									X					X			
Rogoza et al.		X					X										
Rossi et al.			X			X	X										
Rours et al.							X										

Van Luenen et al.							X	X							X		
Van Wiffer en et al.		X					X										
Wijnen et al.						X	X								X	X	
Wolff et al.							X										
Zechmeister et al.							X										
Zulliger et al.		X					X										

Appendix 14 Exploring the wider societal impacts of sexual health issues and interventions to build a framework for research and policy: a qualitative study based on in- depth semi-structured interviews with experts in OECD member countries

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Appendix 15: Interview topic guide (to explore the intersectoral costs relating to sexual health)

Introduction

- First, can you tell me a little bit about your current role?
    - Have you been working in the field of sexual health or public health in general?
    - What other (related) professions/roles have you worked in?
- In your current profession, do you use any economic/cost data?
    - What type of economic/cost data are you working with?
    - Do you work with any economic/cost data specifically related to sexual health (or public health)?
    - What costs does that involve?
    - What do you use it for?
    - Do you use any economic studies in your profession? (e.g. decision making)
    - Are you familiar with economic evaluations?
    - Do you work with health economists?
- Are you currently working on/with any sexual health interventions?

Questions on intersectoral costs and benefits

- If I asked you to think of an example of a sexual health issue or intervention – what comes to mind?
    - Is this one you're currently working with?
- Which impact(s) do you expect to occur as a result of this sexual health issue or intervention? Can you think of an example?
    - Which impact does this issue or intervention have on an individual/ society/ economy?
    - Are there any specific types of costs you're thinking of?
        - Are they any costs you would expect to incur on the health sector?
        - Are they any costs you would expect to incur outside of the health sector?
    - Are there any specific benefits/ outcomes/ effects you're thinking of?
        - Are they any benefits you would expect to incur on the health sector?
        - Are they any benefits you would expect to incur outside of the health sector?
    - Are there any other sectors outside health that could be affected by a sexual health issue or intervention?
    - *[We define those impacts outside of health as intersectoral costs and benefits]*
- Do you (have to) evaluate any sexual health interventions/ programmes?
    - Do you (have to) consider any types of costs and benefits when you evaluate a sexual health programme?
        - What do you use it for?
        - When do you use it?
        - Why do you use it?
    - What about costs outside the health sector (i.e. intersectoral costs and benefits)?

- In your opinion, how relevant (or helpful) is it to consider intersectoral costs and benefits as part of an evaluation of an intervention or programme?
    - How would you identify and measure intersectoral costs and benefits?
- In your opinion, is there an extent to which intersectoral costs and benefits could contribute to the public health budget?
    - Would you say intersectoral costs and benefits contribute to the total cost burden of sexual health services or public health?
- For participants working in research, health economics, or other]
    - What are some elements to consider when you evaluate an intervention or programme from a societal perspective?
    - Can you provide some examples of how to identify and measure intersectoral costs and benefits?
    - What are some challenges?
- Policy context
    - How could you convince decision/policymakers to invest (more) in sexual health?
    - Do you think they consider economic evidence?
    - Do you think illustrating a ICBs - higher (cost) burden or cost savings - would change policy decisions?

Closing

- Is there anything else you would like to add?
- Do you have any questions for me?

Appendix 16: Standards for Reporting Qualitative Research (SRQR)

Title and abstract		**Page number(s)**
1	**Title** - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	1
2	**Abstract** - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	2

Introduction		
3	**Problem formulation** - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	4-5
4	**Purpose or research questio**n - Purpose of the study and specific objectives or questions	5

Methods		
5	**Qualitative approach and research paradigm** - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., postpositivist, constructivist/ interpretivist) is also recommended; rationale**	5
6	**Researcher characteristics and reflexivity** - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	5-6
7	**Context** - Setting/site and salient contextual factors; rationale**	5
8	**Sampling strategy** - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	5
9	**Ethical issues pertaining to human subjects** - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	6
10	**Data collection methods** - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	5-6

11	**Data collection instruments and technologies** - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	5-6
12	**Units of study** - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	7
13	**Data processing** - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	6
14	**Data analysis** - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	6
15	**Techniques to enhance trustworthiness** - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	6

Results/findings

16	**Synthesis and interpretation** - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	7
17	**Links to empirical data** - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	8-15

Discussion

18	**Integration with prior work, implications, transferability, and contribution(s) to the field -** Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	15-16
19	**Limitations** - Trustworthiness and limitations of findings	16-17

Other

20	**Conflicts of interest** - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	18
21	**Funding** - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	18

Appendix 17: Search strategy for Medline (Ovid)

As part of the scoping review for the development process of the checklist for cost-of-illness (COI) studies

cost-of-illness.mp. or "Cost of Illness"/
burden-of-illness.mp. or "Cost of Illness"/
(cost of illness).m_titl.
cost.ti,ab.
costs.ti,ab.
(economic burden).ti,ab.
(burden of disease).ti,ab.
AND
Systematic Review.mp. or "Systematic Review"/
Review.ti,ab.
checklist.mp. or Checklist/
quality assessment.mp.

Appendix 18: Checklists identified in the scoping review that used a quality appraisal to assess cost-of-illness (COI) studies

Checklist/tool	Year	Nr of questions included in the tool	Nr of studies* that used the tool
Designed for full economic evaluations			
BMJ Checklist	1996	35	8
CHEC-list	2005	19	3
CHEERS Checklist	2013	24^	5
Drummond 10-point Checklist**	2005/2007	10	3
Drummond Methods for the Economic Evaluation of Health Care Programmes	2005	NA	4
Designed for COI studies			
Checklist for the Development and Assessment of COI Studies (Mueller et al.)~	2017	37	-
Guide to Critical Evaluation (Larg & Moss)	2011	35	3

*A total of 26 studies were included in the scoping review. Some studies reported to have used more than one checklist or other tool/source.
**The Drummond 10-point checklist is adapted from the Drummond Methods, but we followed the study authors' ways of reporting.
^A total of 27 when including the sub-questions.
~The Mueller checklist was not identified through the scoping review, but through hand searching.

Appendix 19: Preliminary checklist for the critical appraisal of cost-of-illness (COI) studies

Study characteristics
1. Is the study population clearly described?
2. Is a well-defined research question posed in answerable form?
3. Is the economic study design appropriate to the stated objective?
4. Is the chosen time horizon appropriate in order to include relevant costs?
5. Is the actual perspective chosen appropriate?
Methodology and cost analysis
6. Are all important and relevant costs identified?
7. Are all costs measured appropriately?
8. Are costs valued appropriately?
9. Are all future costs discounted appropriately?
10. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?
Results and reporting
11. Do the conclusions follow from the data reported?
12. Does the study discuss the generalizability of the results to other settings and patient/client groups?
13. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?
14. Are ethical and distributional issues discussed appropriately?
15. Does the study discuss any limitations (i.e. cost components, data assumptions, methods)?
Question 1 to 14 is based on the CHEC-list (2005) *Question 15 is adopted from Larg & Moss (2011)*

Appendix 20: Interview topic guide to inform the checklist for cost-of-illness (COI) studies

Introduction

- Can you shortly describe your current profession?
- How long have you been working in health economics?

COI studies and quality appraisal tools

- Do you currently work with COI studies?
- In your opinion, why are COI studies important (or not important)?
- In your opinion, what can COI studies be used for? What is the objective?
- What is your professional opinion on the use of COI studies in health economics and in health policy?
- Are you familiar with a guide for COI studies?
- Are you familiar with a quality appraisal tool for COI studies?
- In your opinion, what is the main purpose of conducting a quality appraisal of COI studies?
- Do you currently work with a quality appraisal tool for COI studies (or have you recently?)
- If so, which tools (or checklists) have you worked with so far to assess the quality of COI studies? Why did you choose this checklist or tool? How did you hear about this tool or checklist?
- If not, where would you search for a quality appraisal tool for COI studies, if you sought one?
- Are there any other tools or checklists you know of that could be used for the quality assessment of COI studies?
- In your opinion, what would an ideal checklist entail when assessing the quality of COI studies?
- How would you design it?
- Where would you start looking for and developing a new checklist for the quality appraisal of COI studies?

Feedback on the preliminary checklist

- Having had the opportunity to look at the preliminary checklist - what are your thoughts on the checklist in general?
- What are your thoughts on the outline in the checklist?
- What are your thoughts on the three dimensions (background, methodology, results) of the checklist?
- Are the questions included in the checklist comprehensive?
- Is there a question that is less comprehensive?
- Do you understand the purpose and meaning behind each question?
- Is there a question for which the purpose or meaning could be made clearer or more explicit?
- Could you go over the questions with me and explain which question is relevant (or less relevant) for COI studies?

- Could you go over the questions with me and give me your feedback on the applicability of each question for COI studies?
- In your opinion, is there any question that is less relevant or applicable? Would you recommend removing this specific question from the checklist?
- In your opinion, is there anything missing in this checklist?
- Is there a question you would add to the checklist?
- In your opinion, is the checklist complete?
- How would you answer (or rate or score) the questions in the checklist? Any preference and why?
- What would you do with the answers?
- In your opinion, would you add up the answers? Please explain why (or why not)?
- What do you think about giving answers a score or weight? Why is this important (or not important)?
- What would you use this checklist for? (i.e. to conduct of a COI study, to review COI studies)
- Who would benefit from the implementation of this checklist?
- Would you recommend this checklist to other researchers, analysts, economists, or other?

Closing

- Is there anything else you would like to add?
- Is there anything else you would like to ask me?