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Assessing the costs and outcomes of control programmes for sexually transmitted infections: a systematic review of economic evaluations

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SB undertook the main analysis and prepared the initial manuscript. All other authors (LJ, JR, EF) contributed to the analysis and the development of the manuscript. All authors approved the final version. LJ is the guarantor of this review.

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ABSTRACT

Objective: To identify economic evaluations of interventions to control sexually transmitted infections (STIs) and HIV targeting young people, and to assess how costs and outcomes are measured in these studies.

Design: Systematic review.

Data sources: Seven databases were searched (Medline (Ovid), EMBASE (Ovid), Web of Science, PsycINFO, NHS EED, NHS HTA, and DARE) from January 1999 to April 2019. Key search terms were STIs (chlamydia, gonorrhoea, syphilis) and HIV, cost benefit, cost utility, economic evaluation, public health, screening, testing, and control.

Review methods: Studies were included that measured costs and outcomes to inform an economic evaluation of any programme to control STIs and HIV targeting individuals predominantly below 30 years of age at risk of, or affected by, one or multiple STIs and/or HIV in OECD countries. Data was extracted and tabulated and included study results and characteristics of economic evaluations. Study quality was assessed using the Philips and BMJ checklists. Results were synthesised narratively.

Results: 9,530 records were screened and categorised. Of these, 31 were included for data extraction and critical appraisal. The majority of studies assessed the cost-effectiveness or cost-utility of screening interventions for chlamydia from a provider perspective. The main outcome measures were major outcomes averted and quality-adjusted life years. Studies evaluated direct medical costs, e.g. programme costs and eleven included indirect costs, such as productivity losses. The study designs were predominantly model-based with significant heterogeneity between the models.

Discussion/Conclusion: None of the economic evaluations encompassed aspects of equity or context, which are highly relevant to sexual health decision-makers. The review demonstrated heterogeneity in approaches to evaluate costs and outcomes for STI/HIV control programmes. The low quality of available studies along with the limited focus, i.e. almost all studies relate to chlamydia, highlight the need for high-quality economic evaluations to inform the commissioning of sexual health services.

BACKGROUND

Economic evaluations of public health interventions are complex in nature but essential to support efficient allocation of healthcare spending and the optimal commissioning of clinical services. One reason for this complexity is that public health interventions encompass aims beyond just health such as equity and educational outcomes.[1,2] In contrast to healthcare interventions, public health interventions are often implemented in complex settings where there are multi-sectoral costs and outcomes.[3] Methodological guidance for economic evaluations in public health emphasises the importance of considering factors, such as: local decision-making processes; longer time horizons; broader costs and outcomes;[1,3,4] and adopting a societal perspective to include health and non-health costs and effects; as well as utilising different economic evaluation designs, depending on the needs of decision-makers.[3,4] In some countries, this contrasts to healthcare economic evaluations, for example in the United Kingdom (UK), Belgium, Croatia, Czech Republic, Estonia, and Latvia a healthcare perspective for costs and outcomes is generally recommended.[5] Improving sexual health and the control of sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) is an important dimension of public health. STI and HIV control encompasses treatment, screening, and testing, which aims to reduce the incidence and prevalence of infections.[6] Because STIs may be asymptomatic, screening for STIs is viewed as important to reduce onward transmission.[6]

Very few systematic reviews of economic evidence in sexual health have been conducted.[7-9] Initial scoping showed that there is a small existing base of robust evidence to inform economic evaluations in relation to the outcomes of STI and HIV screening programmes as well as assessing new modes of delivery in a sexual health context. This includes economic evaluations for the delivery of online sexual health services and services provided in community settings, such as in pharmacies.[7,9]

The aim of this systematic review was to identify economic evaluations of STI and HIV control programmes targeting young people (under 30 years) and to assess how costs and outcomes are measured, valued, and analysed in OECD countries.

METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the methods outlined in the University of York Centre for Review and Dissemination (CRD) guidelines.[10,11]

The search strategy involved three main search areas – STIs, economic evaluations, and public health. The STIs (chlamydia, gonorrhoea, syphilis) and HIV were chosen as a focus because they are the most common and serious STIs in OECD countries.[12-14]

Seven databases were searched (MEDLINE, EMBASE, Web of Science, PsycINFO, NHS Economic Evaluation Database [EED], NHS Health Technology Assessment [HTA], and the Database of Abstracts of Reviews of Effects [DARE]). In addition, the National Institute of Health and Care Excellence (NICE) was searched as this was the first organisation to provide guidance on economic evaluations for policy recommendations and was therefore viewed to be the most comprehensive.[15] The reference lists of the selected studies were reviewed. The initial search strategy was developed for MEDLINE database (Supplementary File 1). MeSH terms, truncation, and wild card symbols were adapted accordingly for the other databases.

The search results were limited to the period January 1999 to April 2019 and to studies involving 'humans' only. The timeframe was selected due to the establishment of NICE in 1999 alongside guidelines for the conduct of economic evaluation, termed the 'reference case'.[15,16]

Inclusion criteria

Studies were included if they met the following criteria: the study population consisted of women and/or men predominantly below 30 years of age who were at risk of or affected by one of the specified STIs (chlamydia, gonorrhoea, syphilis) or HIV (or where the study's focus was on those aged under 30) and living in OECD countries; the focus was any intervention or programme to control STIs or HIV; and costs and outcomes were measured to inform an economic evaluation. Publication in all languages was included.

Selection of papers for review

For management and categorisation of the references, EndNote referencing manager (version X9) was utilised.[17] For the systematic selection of studies, the strategy recommended by the CRD, University of York was applied.[11] The records identified through the search strategy were categorised using a two-stage process as suggested by Roberts et al.[18] The first stage included categories from A to I and the second stage further categorised studies identified as A and B, which were then assigned to categories 1 to 5 (see Figure 1 and Supplementary File 2). The identification and initial categorisation were performed by one author (SB) and two authors (LJ, EF) checked the selection process (screening, eligibility, and

inclusion) to confirm the categorisation of studies. The final papers selected were studies that presented a complete economic evaluation

Data synthesis

The data was tabulated and synthesised narratively. For a list of data extraction categories see Supplementary File 3. This method of synthesis was chosen due to the diversity of studies found and is based on the narrative synthesis framework from the CRD of the University of York.[11] Based on the generated tables, the different studies were compared in a textual form. In combination with the quality assessment, it was then possible to appraise the robustness of evidence for studies conducting economic evaluations of STI/HIV control programmes.

Quality assessment

The quality of included studies was assessed by applying the BMJ checklist for reviewing economic evaluations.[19] For modelling studies, the Philips criteria were utilised.[20] The purpose of the quality assessment was to critically appraise the methodological characteristics of current economic evidence for STI and HIV control programmes rather than to exclude studies. The findings of the quality assessment were used to inform the main discussion of the results, instead of being reported separately.

RESULTS

The PRISMA diagram shows the different stages of the systematic review process (see Figure 1). A total of 9,522 records were obtained from the databases and an additional eight were found through initial hand searching. After removing 3,485 duplicates 433 records were screened as part of Stage I based on title, abstract, and keywords (see Supplementary File 3 for details of the categories used). This resulted in 64 records being considered for Stage II categorisation with two additional records identified from hand searching of reference lists. The assessment of full-texts resulted in 31 category A(1) studies identified for inclusion in the quality assessment and narrative synthesis.

Study characteristics

Table 1 provides an overview of the main characteristics of the 31 studies identified for inclusion. The main countries where the studies took place were the Netherlands (7)[21-27], UK (8)[28-35], and United States of America (12). The majority of studies compared the cost-effectiveness or cost-utility of two or more different screening options for chlamydia (25 studies). Six studies included gonorrhoea screening in their strategy[28,36-38] and one focussed on the cost-effectiveness of age-specific HIV screening.[39] The search did not

identify any study assessing interventions for syphilis. Two studies considered newer screening modes, such as pharmacy based screening[24] and internet-based testing.[40]

Study populations

The majority of studies (19) focussed on both men and women aged up to 30 years as the study population. Eleven interventions looked at women only, and the study by Jackson et al. was the only study that exclusively focused on the cost-effectiveness of screening men for STIs.[28]

Study findings

The general conclusion in 16 of 28 studies was that screening for chlamydia below the age of 30 years is likely to be cost-effective. Nine economic evaluations concluded that screening for chlamydia was likely to be cost-effective if certain assumptions, such as uptake rate and chlamydia prevalence were correct.[24,26,27,29,30,33,41-43] However, other studies have highlighted uncertainties about these assumptions. For example, one of the more recent studies used a much lower uptake rate for the screening programmes because the authors considered the rates used in previous studies to be too optimistic.[21] Four additional studies did not find the STI intervention to be cost-effective.[31,44-46] The cost-consequence analysis by Jackson et al. found that costs and outcomes were similar across the assessed interventions.[28]

Table 1. Characteristics of economic evaluations of control programmes for STIs

Author (year)	*Country*	*Study aims and context*	*STIs*			*Target population*	*Screening interval*	*Intervention was found to be cost-effective (✓=yes, X=no, ✓/X*, NA)*	*Main CE results*
			CT	*NG*	*HIV*				
Neilan (2018)	USA	Identify the optimal age for one-time HIV screening for adolescents and young adults			✓	Adolescents and young adults 13-24 years without identified risk factors	One-off screening	✓	ICER = $96,000/YLS (cost-effective by U.S. standards: less than $100,000/YLS)
Owusu-Edusei (2016)	USA	Explore the CE of a patient-directed, universal, opportunistic *CT* Opt-Out Testing strategy for all women aged 15-24 years	✓			High risk women; 15-24 years†	Unclear	✓	ICER estimated range from cost-saving to $19,974/QALY saved
de Wit (2015)	NL	Evaluate the CE of repeated CT screening and its influence on incidence and prevalence	✓			16-29 year old men and women	Annual, every 2 years, every 5 years	X	More than 5,000€/MOA; Minimum 50,000€/QALY*
Jackson (2015)	UK	Compare costs and outcomes of two STI screening interventions (CT, NG) targeted at men in football club settings in England	✓	✓		Men (18 years and over) within six amateur football clubs in London	One-off screening	NA	Average cost: £82, £88, £89 per intervention
Teng (2015)	USA	Incorporate the age dependency of the infection risk into an economic study of CT screening; Optimise age-dependent screening strategies	✓			14-25 year old women; intercity cohort	Various intervals	✓	Considering age-dependency is cost-saving
Gillespie (2012)	IRE	Estimate the cost and CE of opportunistic CT screening	✓			Men and women; 18-29 years	Annual	X	ICER/MOA=6,093€ and ICER/QALY=94,717€
Huang (2011)	USA	Model a hypothetical cohort of 10,000 women/year who order an internet-based CT screening kit	✓			Women (no defined age; CDC recommendation: 15-24 years)	Annual	✓	36 cases of PID prevented; $41,000 saved (direct medical costs)
Turner (2011)	UK	Compare the cost, CE, and sex equity of different intervention strategies within the English NCSP	✓			Women and men eligible for the NCSP (15-24 years)	Unclear	✓/X	Increasing male screening to 24%=£528 costs per infection treated; PN efficacy to 0.8=£449 costs per infection diagnosed
de Vries (2008)	NL	Estimate the CE of repeated screening for CT at various time intervals	✓			Heterosexual men and women; 15-29 years	Annual, every 2, 5, 10 years	✓	ICER: below 20,000€ (Dutch threshold) for interval strategies for CT screening
Gift (2008)	USA	Examine the impact on men and their female partners of screening men for CT	✓			Women and men; 15-24 years; equal distribution of gender†	Annual	✓	ICER/QALY gained ranged from cost-saving to $97,789*
Adams (2007)	UK	Estimate the CE of the NCSP and its alternatives in England	✓			Men and women under 25 years	Annual	✓/X	Average CE ratio is about £27,000*
Low (2007)	UK	Examine the CE of active CT screening approaches in preventing major clinical outcomes	✓			Women and men; 12-62 years; 50% women	Annual, 6 monthly	X	ICER for women screening only = 28,000 £/MOA; ICER for screening men and women = 25,700 £/MOA
Andersen (2006)	DK	Estimate the incremental effects and costs of home sampling screening for CT over the current in-office screening practice	✓			Men and women; 15-24 years	Annual	✓/X	Total costs/MOA= $3,186; from year 4 the programme was cost-saving
Bernstein (2006)	USA	Identify an optimal screening algorithm for NG infection among women in private sector care		✓		Hypothetical population of women; 15-35 years; mixed race/ethnicity; 15% drug users	Unclear	✓	No screening was cost-saving over all screening strategies; Screening at risk women under 25 years is most cost-effective
de Vries (2006)	NL	Estimate the impact of a screening programme on CT incidence and prevalence in the population	✓			Men and women; 15-29 years	One-off screening	✓	Net costs/MOA=373€*
Evenden (2006)	UK	Model the dynamics of infection recovery and sequelae to quantify CE of various CT screening strategies	✓			No details on target population; aim was to identify high risk groups concerning age, gender, partnership frequency†	Unclear (opportunistic screening)	✓	£1,500/month saved when high-risk person screened; £200/month saved when low-risk person screened
Walleser (2006)	AU	Examine the CE of a hypothetical screening programme for CT based on annual opportunistic testing of women consulting a GP	✓			Women 25 years or younger consulting a GP	Annual	✓	Cost/QALY=$2,968
Aledort (2005)	USA	Assess the CE of screening women for NG seeking care in urban EDs using two different testing devices		✓		Women; 15-29 years; sexually active; presenting to the ED with non-genitourinary symptoms	Unclear	✓	ICER=$6,490/QALY
Evenden (2005)	UK	Capture CT infection dynamics within a population, incorporating the behaviour of different risk groups, and provide a cost-benefit study for screening	✓			Men and women; 16-24 years†	Unclear	✓/X	5% high-risk group screening=£1,500 saved/person screened; 1% screening=£200 saved/person screened*

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Author (year)	*Country*	*Study aims and context*	*STIs*			*Target population*	*Screening interval*	*Intervention was found to be cost-effective (✓=yes, X=no, ✓/X*, NA)*	*Main CE results*
			CT	*NG*	*HIV*				
Gift (2005)	USA	Conduct a CEA of five interventions to encourage public STI clinic patients infected with CT/NG to return for re-screening	✓	✓		Men and women; 14-30 years; diagnosed with and treated for CT/NG in two STI clinics	Unclear (one-off screening)	✓	$622/infection treated (programme perspective); $813/infection treated (societal perspective)
Hu (2004)	USA	Assess the CE of new strategies for CT screening	✓			Sexually active women; 15-29 years	Annual, semi-annual	✓	$2,350 to $7,490 cost/QALY
Norman (2004)	UK	Determine CE of screening for CT in antenatal, gynaecology and family planning clinics	✓			Women; up to 20 years; 20-24 years; 25-29 years; 30 and above; Aberdeen and Glasgow	Unclear	✓	Net cost £771.36/MOA
Novak (2004)	SE	Assess the CE of identifying and treating asymptomatic carriers of CT	✓			Women and men; 20-24 years; in Umea, Sweden	Unclear (one-off screening)	✓/X	Female screening cost-saving when >5.1% CT prevalence; male screening cost-saving when 12.3% CT prevalence
Tao (2004)	USA	Evaluate a mixed-integer programme to model CT in women visiting publicly funded family planning clinics aiming to maximise number of infected women cured of CT	✓			Women below 20 years, 20-24 years and above 24 years in family planning clinics	Unclear (annual, six monthly)	✓/X	Re-screening: number of cases cured 89-283; cost savings $61,779-$166,779; Rescreening vs. no re-screening; Additional cases cure 7-20; Additional cost savings $3,088-$16,820
van Bergen (2004)	NL	Assess the effectiveness and CE of a pharmacy-based screening programme for CT in a high-risk health centre population in Amsterdam using mailed home collected urine samples	✓			Women aged 14-29 years; multicultural, lower income area in Amsterdam; 50% of population had a Surinamese/ Antillean background	Unclear (one-off screening)	✓/X	Cost-saving to 3,872€/PID case averted
Gift (2002)	USA	Examine the CE of routine dual treatment of women with NG infection with or without separate testing for CT and restricting treatment for CT to women testing positive for CT	✓	✓		Asymptomatic women infected with NG; no defined age range	Unclear (one-off screening)	X	-$130 (cost saving) to $557 cost/ PID case averted
Mehta (2002)	USA	Evaluate the CE of enhanced screening for NG and CT in an ED setting	✓	✓		Men and women; 18-31 years; ED setting	Unclear (one-off screening)	✓	-$437 (cost saving) to $1694 per case treated*
van Valkengoed (2001)	NL	Evaluate the CE of a systematic screening programme for asymptomatic CT infections	✓			Women aged 15-40 years	Unclear (one-off screening)	X	Net cost $15,800/MOA
Postma (2000)	NL	Estimate the CE of screening women for asymptomatic infection with CT in general practice	✓			Men and women below the age of 30; different age sub-groups; general practice setting	Unclear (one-off screening)	✓/X	$386/MOA for women aged 20-24 $644/MOA for women aged 25-29 $2,583/MOA for women aged 30-34
Townshend (2000)	UK	Evaluate impacts of a variety of screening interventions with a focus on the incidence of sequelae of CT	✓			Women and men; age groups:12±15, 16±20, 21±25, 26±40 years†	One-off, every year, every 2 years	✓	Intervention is cost-saving; after 5 years around 30,000 PIDs, 7,000 infertility and 700 cases of ectopic pregnancies would be prevented per year*
Welte (2000)	NL	Develop a novel dynamic approach for the economic evaluation of CT prevention measures; determine the CE of a general practice-based screening programme	✓			Men and women (15-64 years)	Annual	✓/X	-$492/MOA for direct costs; -$1,086/MOA including indirect costs*

✓=Done, ✓/X = To some extent completed[1], X=Not cost-effective; NA = Not applicable

†Risk factor was sexual activity groups; *Further results on differences between men and women reported in the study; [1]Under certain assumptions and conditions, the intervention was found to be cost-effective;
ART=Anti-retroviral treatment; AYA=Adolescents and young adults; CDC=Center for Disease Control; CE=cost-effectiveness; CEA=cost-effectiveness analysis; CEAC=cost-effectiveness acceptability curve; CT=*Chlamydia trachomatis*; ED=Emergency department; GP=general practitioner; HIV=Human immunodeficiency virus; ICER=Incremental cost-effectiveness ratio; MO= Major outcome; MOA=Major outcome averted; NCSP=National Chlamydia Screening Programme; NG=*Neisseria gonorrhoeae*; PID=Pelvic inflammatory disease; QALY=Quality-adjusted life years; RIS=rapid immunochromotographic strip test; SA=Sensitivity analysis, YLS=Years of Life Saved
Country abbreviations: AU=Australia; DK=Denmark; IRE=Ireland; NL=Netherlands; SE=Sweden; UK=United Kingdom; USA=United States of America

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Methodological considerations

Types of economic evaluations

The predominant method of economic evaluation applied was cost-effectiveness analysis (20 studies) followed by cost-utility analysis (9 studies)[21,22,30,37,46-50]. The latter measures outcomes in quality-adjusted life years (QALYs) whereas a cost-effectiveness analysis assesses outcomes in natural units, i.e. life years gained, or major outcome averted, which in this context refers to pelvic inflammatory disease (PID) or infertility. One study self-identified as a cost-benefit analysis[33] where costs and consequences are expressed in monetary units.[51] The studies by Jackson et al. and Tao et al. conducted cost-consequence analyses.[28,43] Cost-consequence analyses list all costs and a catalogue of different outcomes of alternatives are listed separately, which results in no definite cost-outcome ratio.[52] Across the 20 years considered within this review, cost-utility analyses were more frequently applied from the year 2005 onwards (see Table 2).

Outcome measures

With respect to outcome measures, 22 out of the 31 studies applied major outcomes averted (MOAs), such as pelvic inflammatory disease (PID), ectopic pregnancy or infertility (see Table 2). The study by Gift et al. looked at the number of chlamydia and gonorrhoea cases treated[38] due to the inclusion of both men and women, and as PID is specific to women, MOAs would not be appropriate. The nine cost-utility analyses utilised QALYs as an outcome measure and largely derived the estimates from the existing literature[53,54] with six out of nine studies[22,37,47-50] not highlighting any associated issues (e.g. estimates based on expert opinion or assumptions). Multiple studies (12) also applied other outcome measures, such as monetary outcomes or the number of patients cured.[43,55]

Perspective

Thirteen studies applied a healthcare and eleven a broader societal perspective. Whilst studies from the Netherlands and Sweden collected and analysed their data from a societal perspective as required by their national guidance, the economic evaluations from the UK were conducted from a narrower healthcare perspective. Two studies analysed their data from both a societal and provider perspective.[38,41] Five studies did not report their perspective.[24,31-33,36]

Study designs

The study design of the included studies were mostly model-based (30 studies). However, heterogeneity was found when looking at the range of model types applied. Out of the 30 studies, fourteen applied dynamic models, which are recommended for economic evaluations of infectious diseases,[51] one study utilised a mixed approach of static and dynamic

modelling[50] and the remainder exclusively applied static models (15 studies). One study consisted of an economic evaluation only as it was based on a pilot cluster randomised controlled trial.[28]

Comparators

A range of screening interventions were considered, such as organised screening for chlamydia targeting a certain age group and/or setting, and they were generally compared to a no organised screening programme (16 studies). For three studies the comparator was not explicitly stated.[23,32,33]

Costing approaches and costs included

The cost data incorporated by the studies mostly used a bottom-up costing approach (22 studies). Nine studies chose a broad costing approach, which lists general programme costs but does not provide information on all costs per unit.[29,32,33,35,36,39,43,47,56] Overall, the studies focussed on direct medical costs, such as programme costs, which consisted of invites for screening and costs for testing and treatment. Eleven studies included indirect costs, which were mainly loss of productivity due to illness.

Time period

Out of the 31 studies, 29 did state a time period for their intervention and model calculations. Two studies did not provide clear information on the time period under consideration.[34,42] There was a variety in the time horizons applied ranging from a patient's lifetime to 2 years. Justification for the time periods varied and included the time onset of sequelae, such as PID, following an infection.

Sensitivity analysis

All studies, except for three, conducted some form of assessment of uncertainty.[22,24,56] The most common method applied was a univariate sensitivity analysis (26 studies) followed by multivariate sensitivity analysis (8 studies).[30,36,39,40,47-49,57] This involved the variation of selected parameters, such as MOAs including PID probability, the discount rate or the probability of screening uptake.

Table 2. Methodological specifications on economic evaluations of STI control programmes

Author (year)	*Type of economic evaluation*	*Outcome measure*			*Perspective (healthcare provider/ societal)*	*Study design (dynamic or static model/ trial)*	*Comparator**	*Costing approach and included costs*	*Data source for costs and outcomes*	*Time period and discount rate*	*Sensitivity analysis*
		QALY	*MOA*	*Other*							
Neilan (2018)	Cost-effectiveness analysis			✓	Healthcare provider	Dynamic model (microsimulation model)	Routine care	Broad approach[1]; direct medical costs[2]	Secondary	Lifetime; 3%	✓
Owusu-Edusei (2016)	Cost-utility analysis	✓	✓[4-7,10]		Societal	Dynamic model (compartmental transmission model)	Risk-based screening (30% coverage)	Broad approach; direct medical costs and indirect costs[3]	Secondary	50 years; 3%	✓
de Wit (2015)	Cost-utility analysis	✓	✓[4-6]		Societal	Static model (Outcome tree)	No organised screening	Bottom-up approach; programme costs, direct medical costs, indirect costs	Secondary	10 years; 4% costs and 1.5% effects	✓
Jackson (2015)	Cost-consequence analysis			✓	Healthcare provider	Trial	Two STI screening interventions	Bottom-up approach; direct medical costs and some private costs	Primary	NA; NA	✓
Teng (2015)	Cost-effectiveness analysis			✓	Societal cost-saving	Dynamic model (compartmental model)	No organised screening	Broad approach; direct medical costs	Secondary	Depending on the age; No discount rate stated	X
Gillespie (2012)	Cost-utility analysis	✓	✓[4-6,8-10]		Healthcare provider	Dynamic model (decision model)	No organised screening	Bottom-up approach; direct medical costs	Primary and secondary	10 years; 3.5%	✓
Huang (2011)	Cost-effectiveness analysis		✓[4-6]	✓	Healthcare provider	Static model (decision tree)	Routine care	Bottom-up approach; direct medical costs	Primary and secondary	10 years, 5 years, 2 years; 3%	✓
Turner (2011)	Cost-effectiveness analysis			✓	Healthcare provider	Static model (simple economic model)	Base case data[†]: NCSP (2008/9)	Broad approach; programme costs, direct medical costs	Primary	NA; NA	✓
de Vries (2008)	Cost-utility analysis	✓	✓[4-8]		Societal	Dynamic model (susceptible-infected-susceptible model)	One-off screening	Bottom-up approach; direct and indirect medical costs; programme costs	Primary and secondary	20 years; 4%	X (previously applied in the 2006 study)
Gift (2008)	Cost-utility analysis	✓	✓[4]		Societal	Dynamic model (compartmental model)	Screening programme for women	Bottom-up approach; direct medical costs, programme costs, indirect costs	Primary and secondary	Model: 5 years, analytic horizon 20 years; 3%	✓
Adams (2007)	Cost-utility analysis	✓	✓[4-6,8-10]		Healthcare provider	Dynamic model (stochastic model)	No organised screening	Bottom-up approach; direct medical costs	Secondary	10 years; 3.5%	✓
Low (2007)	Cost-effectiveness analysis		✓[4-6,8-10]		X	Dynamic model (transmission model)	No organised screening	Bottom-up approach; direct medical costs, programme costs	Primary and secondary	Around 20.5 years; 3.5%	✓
Andersen (2006)	Cost-effectiveness analysis		✓[4-8]	✓	Societal and healthcare provider	Dynamic model (Monte Carlo model)	In-office screening	Bottom-up approach; direct medical costs, programme costs, indirect costs	Primary and secondary	10 years; 3%	✓
Bernstein (2006)	Cost-effectiveness analysis			✓	X	Static model (decision analytical model)	No organised screening	Broad approach; direct medical costs	Primary and secondary	10 years; 3%	✓
de Vries (2006)	Cost-effectiveness analysis		✓[4-8]		Healthcare provider	Dynamic model (susceptible-infected-susceptible model)	X	Bottom-up approach; direct and indirect medical costs; programme costs	Primary and secondary	10 years; 4%	✓
Evenden (2006)	Cost-effectiveness analysis			✓	X	Dynamic model (system dynamics model)	X	Broad approach; direct medical costs	Primary (expert opinion/trial) and secondary	2 years; No discount rate applied	✓
Walleser (2006)	Cost-utility analysis	✓	✓[4-7]		Healthcare provider	Static model (decision analytical model)	No organised screening	Bottom-up approach; direct medical costs	Secondary (expert opinion if no data)	25 years; 5%	✓

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		QALY	*MOA*	*Other*							
Aledort (2005)	Cost-utility analysis	✓	✓[4-7]	✓	Societal	Static model (state transition Markov model)	Routine care	Bottom-up approach; direct medical costs	Secondary	A woman's lifetime; 3%	✓
Evenden (2005)	Cost-benefit analysis/ cost-effectiveness analysis			✓	X	Dynamic model (system dynamics model)	X	Broad approach; direct medical costs	Secondary (expert opinion)	2 years; No discount rate applied	✓
Gift (2005)	Cost-effectiveness analysis			✓	Healthcare provider & societal	Static model (mathematical model, decision tree)	Baseline intervention 1 and 4‡	Bottom-up approach; counselling costs, direct medical costs, and indirect costs	Primary and secondary	10 years; 3%	✓
Hu (2004)	Cost-effectiveness analysis	✓	✓[4-6]	✓	Modified societal	Static and dynamic model (state transition simulation model)	No organised screening	Bottom-up approach; direct medical costs	Secondary	Lifetime; discounting applied, rate not stated	✓
Norman (2004)	Cost-effectiveness analysis		✓[4-11]	✓	Healthcare provider	Static model (decision model)	No organised screening	Bottom-up approach; direct medical costs	Primary and secondary	No time period stated; 5% and 3%	✓
Novak (2004)	Cost-effectiveness analysis		✓[4-9,11]		Societal	Static model (cost-effectiveness model)	No organised screening	Bottom-up approach; direct medical costs	Primary and secondary	No time period or discount rate stated	✓
Tao (2004)	Cost-consequence analysis		✓[4-6]	✓	Healthcare provider	Static model (mathematical model)	Different screening strategies	Broad approach; direct medical costs	Secondary	NA; NA	✓
van Bergen (2004)	Cost-effectiveness analysis		✓[4-7]		X	Static model (pharmacoeconomic and funnel model)	No organised screening	Bottom-up approach; direct medical costs, indirect costs	Primary and secondary	Programme evaluation after 2 years; 4%	X
Gift (2002)	Cost-effectiveness analysis		✓[4-7]		Healthcare provider	Static model (decision analytical model)	Different screening strategies	Bottom-up approach; direct medical costs	Secondary	Patient's lifetime; 3%	✓
Mehta (2002)	Cost-effectiveness analysis			✓	Healthcare provider	Static model (outcome decision model)	Routine care	Bottom-up approach; direct medical costs, programme costs	Primary and secondary	10 years; 3%	✓
van Valkengoed (2001)	Cost-effectiveness analysis		✓[4-9]		Societal	Static model (decision tree)	No organised screening	Bottom-up approach; direct medical costs, programme costs, indirect costs	Primary and secondary	5 years; 3%	✓
Postma (2000)	Cost-effectiveness analysis		✓[4-8]	✓	Societal	Static model (decision analytical model)	No organised screening	Bottom-up approach; direct medical costs, indirect costs	Primary and secondary	5 years, 10 years; 3%	✓
Townshend (2000)	Cost-effectiveness analysis		✓[4-6]	✓	Healthcare provider	Dynamic model (system dynamics model)	No organised screening	Broad approach; direct medical costs	Secondary	10 years for costs and 40 years for MOs; 6%	✓
Welte (2000)	Cost-effectiveness analysis		✓[4-8]		Societal	Dynamic model (stochastic simulation model)	No organised screening	Bottom-up approach; direct medical costs, indirect costs	Secondary	20 years; 3%	✓

✓=Done, X=Not reported; NA = Not applicable

*As stated by the authors; [1]Broad approach: Gross costs are listed; [2]Direct medical costs: Costs for testing (including clinician time), treatment (including the cost of a return visit), and sequelae costs, such as PID; [3]Indirect costs refer to cost of lost productivity due to illness; [4]PID; [5]Ectopic pregnancy; [6](Tubal) infertility; [7]Chronic pelvic pain; [8]Neonatal pneumonia; [9]Neonatal conjunctivitis; [10]Epididymitis in men; [11]Urethritis in men; [12]Cervicitis; †Base-case data: A base case is the average scenario; ‡Baseline intervention 1 and 4: The interventions were closest to the standard care

CT=*Chlamydia trachomatis*; MO=Major outcome; MOA=Major outcome averted; NA=Not applicable; NCSP=National Chlamydia Screening Programme; NG=*Neisseria gonorrhoeae;* PID=Pelvic inflammatory disease; PN=Partner notification; QALY=Quality-adjusted life year

Critical appraisal of studies

All economic evaluations were subject to a critical assessment as a measure of study quality using one checklist for economic models and one for other economic evaluations (Supplementary File 4-5).[19,20] In general, the modelling studies frequently neglected to argue for the scope and perspective of the study. Studies were also unclear in reporting their modelling types, which made it challenging to classify some economic evaluations.[33,43] The uncertainties associated with model structures were often not completely assessed. Most studies did review parameter uncertainty in the form of a univariate analysis or probabilistic sensitivity analysis. However, they neglected methodological uncertainty, i.e., running alternative versions of the model with different methodological assumptions, as well as sub-group analysis making the reliability of model results uncertain. The study by Jackson et al. did fulfil most of the BMJ checklist criteria except for stating the research question and for explaining the choice of the study type in relation to the research question.[28]

DISCUSSION

This systematic review identified 31 economic evaluations of control programmes for STIs and HIV targeting young people. In general, the studies applied a cost-effectiveness or cost-utility analysis for interventions that mainly focussed on chlamydia screening. The results show that there was a great variety in the approaches adopted to evaluate the control programmes for STIs/HIV. This comprises the overall heterogeneity in methods including measurement of outcomes and differences in the perspectives applied, partly due to differences between national guidance documents for economic evaluations across OECD countries. The studies were also of variable quality.

One might expect that over a twenty-year period, there would be more convergence among the studies to allow better comparability and understanding of the overall results, such as whether, overall, the intervention was cost-effective or not. However, due to the large variance in methods applied along with the low quality of models, it is difficult to draw a final conclusion from most of the studies. Static models, among other aspects, do not take interdependences of individuals into account and therefore jeopardise the interpretation of the model results. The studies reviewed applied a mix of static and dynamic models (14 out of 30 were dynamic models) and there was no evidence that since the review by Roberts et al. in 2006[58], which highlighted the importance of dynamic modelling for infectious diseases, more dynamic models are being used. It was noted, however, that when a dynamic model was not used, authors acknowledged the limitations of this.

The evaluations did not consider equity of service provision for individuals nor the intervention's context, which are vital for local decision-makers in public health. Consideration of equity issues is required by guidance in some countries[59] and is important for public health interventions due to their focus on population health and the distribution of health (fairness). In order to enable outcomes beyond health to be considered, a broader perspective for economic evaluation would be required. This is particularly relevant to sexual health as it is associated with factors, such as housing problems and substance use.[60,61] Despite the recommendations by several national guidance bodies, such as NICE in 2012 for performing economic evaluations of public health interventions[4], this was not the case for multiple studies..

Further, only two studies focussed their economic evaluation on the newer modes of delivery for screening, such as online services and services provided in community settings.[24,40] However, it was acknowledged by some authors that their economic models were limited in this respect.[45]

To compare different types of economic evaluations is challenging since the differences in methodology result in different outcome measures, including intermediate (MOAs) and long-term (QALYs) outcomes. Several studies highlighted that due to the lack of data about the risk of clinical progression following acute gonorrhoea infection and its impact on quality of life, they were unable to calculate QALYs.[36,37] In addition, where studies included QALYs they mainly relied on a limited set of values, an issue which has been highlighted in previous literature as a methodological limitation.[7,58] The overall lack of data on sexual behaviour, transmission patterns, and transition probabilities[27,41] (for example the probability of developing PID is estimated to range anywhere from 10% - 40%[21,41,44,49,57]) intensifies uncertainty in interpreting study results.

The quality assessment of the studies showed that a significant number did not fulfil all the requirements for an economic evaluation,[19] and this was particularly the case for uncertainty assessment. Most of the authors did not justify why they omitted certain steps in assessing uncertainty and rarely was subgroup analysis conducted to understand the differential costs and effects on certain vulnerable population groups, which is an important aspect since resources may be wasted and opportunities for a specific sub-group may be lost.[51]

Comparison with other literature

Our findings update and confirm those from previous systematic reviews in this area. The predominant utilisation of cost-effectiveness analyses with static models to evaluate costs and

outcomes of screening and testing for STIs and HIV has been highlighted previously.[7,58] Despite this, methodological issues seem to persist, which may be explained partially by a lack of suitable data to include within analyses.[28]

Policy implications

The results of this systematic review show that current economic evidence has limitations, which may impact on its interpretation and use in policy decision-making. The important focus of public health interventions on equity in addition to health improvement, as well as the context within which they are delivered, indicates that future economic evaluations also need to address these multiple domains.

Strengths and weaknesses of this review

This review has several strengths. A robust methodology incorporating a thorough search strategy across multiple databases along with article hand searching was applied. Further, it focusses on young people who are particularly vulnerable with regard to STIs. One weakness of the review is that by focussing on young people, other vulnerable groups, such as men who have sex with men or minority ethnic groups, may have been omitted and additional important economic evaluations specific to these groups may have been missed. Hand searching was undertaken of the NICE database and a wider search of relevant databases might have generated additional results. In addition, some of the studies included people who were aged over 30, however, this did not seem to affect the overall results. Further, in some studies the comparator arm was not clearly defined. Applying different inclusion and categorisation criteria may yield further future insights into economic evaluations for these groups.

Further research

There is a tension between following recommendations for conducting an economic evaluation for a public health programme and ensuring real world applicability, for example utilising QALYs for comparability vs. the needs of local decision-making. Future research needs to address these tensions with the aim to improve knowledge translation between health economists and public health decision-makers and ensure the wider applicability of health economic findings.

CONCLUSION

This review has highlighted some limitations in existing economic evaluations which focus on STI and HIV control programmes, particularly in terms of context, equity, an appopriate time horizon, and wider costs and benefits beyond health. It has illustrated wide heterogeneity in the published economic evaluations of STI and HIV control programmes and this, combined

with limited study quality, demonstrates a need for further economic evaluations, which can directly inform improvements in patient care.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY MESSAGES

- This systematic review identifies and assesses economic evaluations of control programmes for sexually transmitted infections and HIV targeting young people.
- The economic evaluations found had limitations in terms of measuring costs and benefits beyond health and considering aspects of context and equity, which are of particular importance to local public health decision-makers.
- There is a need for further high quality economic evaluations, which can directly inform improvements in sexual health services.

LEGEND

Figure 1. PRISMA flow-diagram of study categorisation stages I and II.

Stage I categorisation: A) Economic evaluation of a STI/HIV control programme targeting young people, containing primary or secondary data on both costs and outcomes; B) Contains original data (primary research) on the cost and/or economic outcomes of STI/HIV control programmes of the target population, e.g. QALY, DALY etc.; C) Incomplete economic evaluation; D) Focus on other STIs; E) Target population was not young people; F) Economic evaluation of diagnostic test; G) Systematic review; H) Unclear; I) No relevance;

Stage II categorisation: 1) Complete economic evaluation; 2) Study presents an economic evaluation; 3) Different methods for an economic evaluation are described; 4) Review of economic features of control programmes for STIs/HIV; 5) No relevance; (see Supplementary File 3);

DALY, Disability-adjusted life years; DARE, Database of Abstracts of Reviews of Effects; HTA, Health Technology Assessment; NHS EED, NHS Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; QALY, Quality-adjusted life years; STI, Sexually transmitted infection

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