

Assessing the costs and outcomes of control programmes for sexually transmitted infections

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

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20

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22 EF) contributed to the analysis and the development of the manuscript. All authors approved
23 the final version. LJ is the guarantor of this review.

24

25 Keywords: economic evaluation, control, testing, screening, sexually transmitted infections,
26 STIs, HIV

27

28 Word count: 3,194

29 **ABSTRACT**

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

33 **Design:** Systematic review.

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

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

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

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

57 **BACKGROUND**

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

76

77 Very few systematic reviews of economic evidence in sexual health have been conducted.[7-
78 9] Initial scoping showed that there is a small existing base of robust evidence to inform
79 economic evaluations in relation to the outcomes of STI and HIV screening programmes as
80 well as assessing new modes of delivery in a sexual health context. This includes economic
81 evaluations for the delivery of online sexual health services and services provided in
82 community settings, such as in pharmacies.[7,9]

83

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

87

88 **METHODS**

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

92

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

96

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

106

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

111

112 **Inclusion criteria**

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

119

120 **Selection of papers for review**

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

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

131

132 **Data synthesis**

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

140

141 **Quality assessment**

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

148

149 **RESULTS**

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

158

159 **Study characteristics**

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

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

168

169 Study populations

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

174

175 Study findings

176 The general conclusion in 16 of 28 studies was that screening for chlamydia below the age of
177 30 years is likely to be cost-effective. Nine economic evaluations concluded that screening for
178 chlamydia was likely to be cost-effective if certain assumptions, such as uptake rate and
179 chlamydia prevalence were correct.[24,26,27,29,30,33,41-43] However, other studies have
180 highlighted uncertainties about these assumptions. For example, one of the more recent
181 studies used a much lower uptake rate for the screening programmes because the authors
182 considered the rates used in previous studies to be too optimistic.[21] Four additional studies
183 did not find the STI intervention to be cost-effective.[31,44-46] The cost-consequence analysis
184 by Jackson et al. found that costs and outcomes were similar across the assessed
185 interventions.[28]

186

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* |

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 | | | | |
| 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 completed¹, 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; ¹Under 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 immunochromatographic 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

188 **Methodological considerations**

189 Types of economic evaluations

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

201

202 Outcome measures

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

212

213 Perspective

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

220

221 Study designs

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

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

229

230 Comparators

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

235

236 Costing approaches and costs included

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

243

244 Time period

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

250

251 Sensitivity analysis

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

257

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% | ✓ |

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 | | | | | | | |
| 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; ¹Broad approach: Gross costs are listed; ²Direct medical costs: Costs for testing (including clinician time), treatment (including the cost of a return visit), and sequelae costs, such as PID; ³Indirect costs refer to cost of lost productivity due to illness; ⁴PID; ⁵Ectopic pregnancy; ⁶(Tubal) infertility; ⁷Chronic pelvic pain; ⁸Neonatal pneumonia; ⁹Neonatal conjunctivitis; ¹⁰Epididymitis in men; ¹¹Urethritis in men; ¹²Cervicitis; [‡]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

259 **Critical appraisal of studies**

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

272

273 **DISCUSSION**

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

282

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

294

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

305

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

310

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

321

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

328

329 **Comparison with other literature**

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

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

335

336 **Policy implications**

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

342

343 **Strengths and weaknesses of this review**

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

355

356 **Further research**

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

363

364 **CONCLUSION**

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

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

371 **CONFLICT OF INTEREST**

372 The authors declare no conflict of interest.

373

374 **KEY MESSAGES**

375 ➤ This systematic review identifies and assesses economic evaluations of control
376 programmes for sexually transmitted infections and HIV targeting young people.

377 ➤ The economic evaluations found had limitations in terms of measuring costs and
378 benefits beyond health and considering aspects of context and equity, which are of
379 particular importance to local public health decision-makers.

380 ➤ There is a need for further high quality economic evaluations, which can directly inform
381 improvements in sexual health services.

382

383 **LEGEND**

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

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

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

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

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