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Repeat screening for syphilis in pregnancy as an alternative screening strategy in the United Kingdom: a cost-effectiveness analysis

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Abstract

Objectives: To assess the cost-effectiveness of universal repeat screening for syphilis in late pregnancy, compared with the current strategy of single screening in early pregnancy with repeat screening offered only to high-risk women.

Design: A decision tree model was developed to assess the incremental costs and health benefits of the two screening strategies. The base case analysis considered short-term costs during pregnancy and the initial weeks after delivery. Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to assess the robustness of the results.

Setting: UK antenatal screening programme.

Population: Hypothetical cohort of pregnant women who access antenatal care and receive a syphilis screen in one year.

Primary and secondary outcome measures: The primary outcome was the cost to avoid one case of congenital syphilis (CS). Secondary outcomes were the cost to avoid one case of intrauterine fetal demise (IUFD) or neonatal death and the number of women needing to be screened/treated to avoid one case of CS, IUFD or neonatal death. The cost per quality-adjusted life year (QALY) gained was assessed in scenario analyses.

Results: Base case results indicated that for pregnant women in the UK (n=725,891), the repeat screening strategy would result in 5.5 fewer cases of CS (from 8.8 to 3.3), 0.1 fewer cases of neonatal death, and 0.3 fewer cases of IUFD annually compared to the single screening strategy. This equates to an additional £1.8 million per case of CS prevented. When lifetime horizon was considered, the incremental cost-effectiveness ratio (ICER) for the repeat screening strategy was £120,494.

Conclusions: Universal repeat screening for syphilis in pregnancy is unlikely to be cost-effective in the current UK setting where syphilis prevalence is low. Repeat screening may be cost-effective in countries with a higher syphilis incidence in pregnancy, particularly if the cost per screen is low.

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Strengths and limitations of this study

- This is the first health economic analysis to assess the cost-effectiveness of repeat screening strategy for syphilis in pregnancy compared to the single screen strategy within the UK setting.
- Experts provided input to inform the model inputs and validate the model structure and assumptions.
- Extensive sensitivity analyses were performed to assess uncertainty in the results.
- A lack of long-term data on the costs and utilities associated with congenital syphilis meant the focus of the analysis was on the short-term costs and health benefits, with the incremental cost-effectiveness ratio (ICER) being calculated in scenario analyses.

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Introduction

Syphilis is a bacterial sexually transmitted infection (STI) caused by *Treponema pallidum* subspecies *pallidum*. The prevalence of syphilis in the UK is low, however, the number of new diagnoses has increased over the last decade. In women, the number of cases rose from 345 in 2009 to 550 in 2018 [1].

Congenital syphilis (CS) occurs via vertical transmission of syphilis during pregnancy which can occur during any trimester and at any of the four stages of syphilis infection. The highest risk of transmission, however, occurs in primary syphilis when sores or chancres are present. Adverse pregnancy outcomes can include intrauterine fetal demise (IUFD), prematurity and neonatal death, with the risk being considerably higher in women with untreated syphilis than in pregnant women with no syphilis or in pregnant women who receive adequate treatment for syphilis following diagnosis at first trimester screening [2]. The risk of CS is difficult to quantify due to the small number of cases, the wide range of disease presentations and probable underdiagnosis. There is evidence, albeit limited, that the risk of CS is higher if women become infected whilst pregnant than if they have active syphilis at the time of conception [2,3]. In infants born with CS, the infection can cause reduced growth and development, neurological impairment, bone deformities, and hearing loss [4,5]. Infants treated with intravenous benzylpenicillin sodium in the first two months of life are reported to have a good short-term prognosis, but long-term outcomes have not been investigated in detail [6,7].

In the UK, routine antenatal screening for syphilis, hepatitis B and human immunodeficiency virus (HIV) is offered to all pregnant women at their first routine antenatal appointment, usually before 12 weeks gestation, or later, for the small proportion of women who first present in their second or third trimester [8,9]. Women who decline screening are formally re-offered and screening coverage currently exceeds 99.6% [9–11]. Blood samples are initially tested using an enzyme immunoassay (EIA) with a *T. pallidum* particle agglutination assay (TPPA) performed on the same specimen to confirm a positive result. Women with a positive TPPA result are referred to a sexual health clinic to assess whether they have an active infection which requires treatment or a previous infection not requiring treatment. It is possible that women who screen negative for syphilis become positive later in pregnancy, either because they become infected with syphilis, or because their infection was too recent for a detectable antibody response to have been mounted at the time of the first screen. Management guidelines, outside the national screening programme, recommend that women are offered repeat testing for syphilis in late pregnancy if they have been diagnosed and treated for syphilis in the first trimester, if they consider themselves to be at risk of infection, or have a single

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'high-risk' exposure [11,12]. Assessing women's risk can be problematic and risk can change during pregnancy. Data on coverage of repeat testing or management is not routinely collected. In 2011-13, the Surveillance of Antenatal Syphilis Screening (SASS) study was conducted to provide quantitative data on the performance of the screening pathway [13].

Syphilis prevalence in pregnant women is low, the SASS study found that 0.04% (1/2800) of pregnant women required treatment for syphilis in 2010-2011, although the prevalence may have subsequently increased [13]. CS incidence is also low and below the WHO elimination threshold of ≤0.5/1000 [14]. However, between March 2016 and January 2017, four cases of CS occurred in the UK in women who screened negative for syphilis in pregnancy [15]. None of whom had a repeat screen during pregnancy, and confirmatory testing later showed that they had acquired syphilis whilst pregnant. These infections would likely have been diagnosed and treated if repeat screening in late pregnancy was offered to all pregnant women, an approach that has not been assessed in the UK. Two models assessed the cost-effectiveness of universal repeat screening in the US, where the prevalence of syphilis in pregnant women is higher than in the UK. One found that universal repeat screening was cost saving [16], whilst the other found that it cost $419,842 per CS case avoided [17].

To inform the UK National Screening Committee (UK NSC) and in response to an increase in syphilis diagnoses in the UK and the continued occurrence of CS cases each year, albeit very small numbers, the clinical and cost-effectiveness of universal screening in the first and third trimesters, as an alternative strategy to universal screening in the first trimester only, was assessed.

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Methods

Model structure

A decision tree model in TreeAge (TreeAge Pro 2019, R2. TreeAge Software, Williamstown, MA, USA) was developed to assess the incremental costs and health benefits of universal repeat screening for antenatal syphilis compared with universal screening in the first trimester only (**Figure 1**). For both screening strategies, the decision tree followed the true disease state of women and the population was split into women screened in the first/second trimester and women screened in the third trimester (i.e. late presenters who would miss the opportunity for repeat screening). Women with a positive result received treatment at a sexual health clinic plus any additional testing required. Each branch (with or without syphilis) ended with the same pregnancy outcomes: IUFD or no IUFD, the latter resulting in a preterm or term delivery and either neonatal death, an infant with CS, or an infant with no CS (online supplement **Figure S1**).

Figure 1. Overview of decision tree comparing single screening with universal repeat screening of syphilis in pregnancy

Footnote:
PW, pregnant women; FN, false negative result; FP, false positive result; TN, true negative result; TP, true positive result.
With reference to the timing of 1st syphilis screen, 'early' refers to 1st or 2nd trimester and 'late' refers to the third trimester.
Where branches split, the probabilities are shown in the top branch, with # indicating (1-probability).
Blue circle indicates referral to specialist management for treatment and the same seven pregnancy outcomes (as is shown in the topmost branch). Each branch ends with the same outcomes, but with different probabilities for each branch. Pregnancy outcomes are presented in **Figure S1** in online supplement.

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The model included pregnant women in the UK who accessed antenatal care and received a syphilis screen in 2018 (the latest available data at the time). Pregnant women who were not screened (0.04%) were not included, since any change to the screening strategy would have no impact on their outcomes. Costs were considered from the UK healthcare system perspective. Social care costs were not included in the short-term. To assess the overall impact of the two screening strategies, the costs for all pregnancy outcomes for all women screened were considered, not just costs for women with syphilis. The model threshold for early versus late first screen was 28 weeks gestation, i.e. the start of the third trimester. The time horizon for the base case analysis considered short-term costs during pregnancy and the perinatal period. Lifetime costs and utilities were not used in the base case analysis (but were considered in scenario analysis) as the data available on the long-term costs and utilities associated with CS were limited and include too much uncertainty to provide a robust result. See **Table S1** for base case model assumptions.

Model parameters

Data were sought using PubMed, Google Scholar, online searches, references within papers, from experts and laboratory contacts and by data request to Public Health Agencies.

Clinical parameters

Key clinical parameters were derived from published data and national surveillance data. Where data were only available from outside the UK, they were scaled to reflect UK pregnancy outcomes and syphilis prevalence. See **Table 1** for clinical parameters and methods of estimation. Furthermore, data from a large meta-analysis [18] were adjusted to the UK setting to estimate the probability of each pregnancy outcome (online supplement **Tables S2-S5**).

Cost parameters

Cost parameters are presented in **Table 1**. National Health Service (NHS) tariff costs or published costs from the UK were used where possible. Where no UK data were available, micro-costing was used to calculate costs - informed by clinical guidelines, expert opinion and incorporating published NHS costs and tariffs where possible. To estimate the additional lifetime cost of CS, cost estimates from outside the UK were converted to pound sterling (£) [19]. Where necessary, costs were inflated to 2017/18 prices using mid-year conversion rates [20].

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Table 1. Clinical and cost parameters for model comparing single screening with universal repeat screening of syphilis in pregnancy in the UK

	Baseline value	Low	High	Distribution	Note
Clinical parameters					
Total number of women in model (representing one-year)	725,891	-	-	-	Based on number of deliveries in the UK in 2017/2018 and the screening uptake. See **Table S6**.
Probability of having syphilis at the start of pregnancy	0.00035	0.00028	0.00042	Beta	Data derived from 2011 SASS data [13] (England only [244/691,494]). Assume same risk in other UK countries.
Probability of becoming infected with syphilis during pregnancy	0.000017	0.0000017	0.00012	Beta	Incidence was estimated using published incidence and prevalence data from United States scaled to reflect UK prevalence [13,21].
Probability of receiving syphilis screen before 28 weeks gestation	0.947	0.936	0.984	Beta	Estimate based on gestational week at first antenatal attendance. **Table S7** in online supplement. The low value is in line with results from SASS study [13]. The high value is in line with data from Northern Ireland which (from the UK countries) has the highest proportion of women attending before 28 weeks.
Probability of true positive result	0.995	0.984	1.00	Beta	Based on the average test sensitivity of EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK [22,23].
Probability of false negative result[1]	0.005	0.016	0.00	Beta	Based on the average test sensitivity of EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK [22,23].
Probability of true negative result	0.998	0.999	0.99	Beta	Based on average test specificity of EIA assays (99.8%) used in the UK. High and low are estimates [22,23].
Probability of false positive result[1]	0.002	0.001	0.01	Beta	Based on average test specificity of EIA assays (99.8%) used in the UK. High and low are estimates [22,23].
Cost parameters					
Syphilis screen	13.36	6.68	26.72	Gamma	Estimated using micro-costing. Screening is performed at the same time as other antenatal blood tests – this would also be the case for repeat screening at 28 weeks gestation. See **Table S8**.

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	Baseline value	Low	High	Distribution	Note
Management women diagnosed with syphilis in pregnancy	314.09	251.27	376.91	Gamma	Clinical management by sexual health clinician estimate based on London Integrated Sexual Health Tariff [24]. See **Table S9**.
Intrauterine fetal demise	4,356.80	3,485.44	5228.16	Gamma	Estimate based on 2013/14 published estimate from UK inflated to 2017/2018 costs [25].
Preterm delivery	7,100.37	5,680.30	8,520.45	Gamma	Estimate based on UK costs for delivery at 32-33 weeks and 34-36 weeks gestation (inflated from 2010/11 costs) [26]. UK data on gestational age at delivery (**Table S10**) were then used to calculate the proportion of deliveries at 32-33 (28%) and 34-36 weeks (72%).
Term delivery (37+ weeks)	2,034.62	1,627.69	2,441.54	Gamma	Estimate based on published cost using inflated 2010/11 UK data [26].
Neonatal death	5,805.80	4,644.64	6,966.96	Gamma	Estimated using cost of IUFD plus additional hospital costs. See **Table S11**.
CS testing and treatment	6,607.68	5,286.14	7,929.21	Gamma	Estimated using micro-costing. See **Table S12** and **Table S13**.
CS neonatal screen	245.25	196.20	294.30	Gamma	Screening test for neonates born to women treated for syphilis in pregnancy. Estimated using micro-costing. See **Table S14**.
CS lifetime healthcare cost	80,423.37	-	-	Gamma	Average additional lifetime healthcare costs attributable to CS based on cost estimate for cerebral palsy (estimate from 2000) [27].
CS lifetime health and social care cost	651,387.47	-	-	Gamma	Average additional lifetime health and social costs attributable to CS based on cost estimate for cerebral palsy (estimate from 2000) [27].

[1] These probabilities refer to the final diagnosis after all diagnostic testing plus discussion with sexual health consultant if diagnostic tests result is positive for treponemal antibodies. EIA: Enzyme immunoassay. CS, congenital syphilis. For costs, high and low values are +/- 20% of baseline values with exception of syphilis screening cost where high and low values are +/- 50%.

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Outcomes

The primary outcome was cost to avoid one case of CS. Secondary outcomes were: cost to avoid one case of IUFD or neonatal death; the number of women who need to be screened to avoid one case of CS, IUFD or neonatal death; and the number of women who need to be treated for syphilis to avoid one case of CS, IUFD or neonatal death.

Sensitivity and scenario analyses

A univariate deterministic sensitivity analysis (DSA) was run for all probabilities and costs to determine which parameters had the greatest impact on the outcome of the model. This was done by selecting a high and low value for each input and generating outcomes. A probabilistic sensitivity analysis (PSA) using Monte Carlo simulation (1000 iterations) was used to assess the robustness of the results and calculate 95% credibility intervals (CIs) for each output using the mean and standard deviation. A beta distribution was used for clinical probability inputs, and a gamma distribution for cost inputs (**Table 1**).

As well as the base case analysis, seven scenarios were assessed to observe how changes in model assumptions and certain parameters impacted the main outcomes:

1) Lifetime time horizon with incremental cost-effectiveness ratio (ICER) in terms of cost per QALY as the main outcome.
2) Incomplete uptake of the repeat screen – where the probability of having a second screen was 99.6%, in line with the current uptake of screening in England.
3) Increased syphilis incidence - varying incidence at 10 intervals between the baseline and the high value used in sensitivity analysis (0.012%).
4) No late presentation to antenatal care – all women are screened twice in the repeat screening strategy.
5) 100% sensitivity and specificity of the syphilis screening process.
6) 100% specificity of the repeat screen (i.e. no false positives).
7) Examining the per screen cost required to meet NICE cost-effectiveness thresholds.

In scenario analysis 1, the lifetime healthcare and social care costs for infants born with CS were considered. Since no data on the lifetime cost of CS were available, cerebral palsy (CP) was used as a proxy as it can also lead to a range of disabilities, vary hugely in severity, and may sometimes be a result of CS. The lifetime health and social care costs of CP were taken from a single Danish study [21] adjusted to reflect UK life expectancy and gender split.

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As EuroQol-5D (EQ-5D) data has not been reported for CS or CP, a utility of 0.74 for infants with CS and 1.00 for infants born with no CS was used, adapted from a 2006 study of new-born screening strategies where 0.74 was used for infants with 'mild developmental delay' [22]. These utility values were used in a similar health economic model from the US [16] and were used to calculate quality adjusted life-years (QALY). Parental HRQoL or HRQoL for the other pregnancy outcomes were not considered.

The life expectancy of infants with CS was estimated as 70 years, in line with the estimate for CP [21] and in light of reports of CS diagnoses in a wide range of ages [23]. The life expectancy of infants with no CS was estimated as 81 years based on current UK data [24]. All costs and utilities were discounted at 3.5%, in line with NICE guidelines for England.

Patient and public involvement

There was no patient or public involvement (PPI) in the design of the evaluation. A report outlining the model was reviewed by the UK NSC which has PPI representation and was made available for public consultation.

Results

Base case analysis

The base case results indicate that in one year of screening pregnant women in the UK (n=725,891), the repeat screening strategy would result in 5.5 fewer cases of CS, 2 fewer cases of preterm delivery, 0.1 fewer cases of neonatal death (i.e. one less neonatal death every 10 years on average), and 0.3 fewer cases of IUFD compared to the single screening strategy (**Table 2**).

The healthcare costs would be £9,886,863 higher for the repeat screening strategy (£1,777,469,008 vs. £1,787,355,870 respectively when total annual screening costs, treatment costs, and delivery costs for all pregnant women screened were considered) with most of this increase (£9,162,355) being a result of the additional screening costs (**Table 3**).

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Table 2. Base case clinical outcomes for model comparing universal repeat screening of syphilis in late pregnancy with single screening

Screening strategy	Syphilis antenatal screens	Women treated for syphilis	False positive maternal syphilis	Intrauterine fetal demise (all causes)[1]	Preterm deliveries (all causes)[1]	Neonatal deaths (all causes)[1]	Congenital syphilis cases
Existing: single screen							
Estimate	725,891	1,705	1,451	2,904.4	54,228	1,446.5	8.8
95% CI[2]	725,891-725,891	1,698-1,737	1,443-1,482	2,890-2,916	53,905-54,282	1,441-1,457	8.7-8.9
Alternative: repeat screen							
Estimate	1,411,696	3,089	2,823	2,904.1	54,226	1,446.4	3.3
95% CI[2]	1,411,456-1,411,503	3,074-3,150	2,806-2,883	2,889-2,915	53,903-54,280	1,441-1,457	3.3-3.3
Difference	685,805	1,384	1,372	-0.3	-2	-0.1	-5.5

[1] These adverse pregnancy outcomes are all-cause outcomes for all 725,891 women screened, including the small number with syphilis infection.

[2] 95% CI, confidence intervals calculated using probabilistic sensitivity analysis.

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Table 3. Base case short-term annual healthcare costs from model comparing universal repeat screening of syphilis in late pregnancy with single screening

Screening strategy	Total healthcare costs	Cost breakdown[1]		
		Antenatal syphilis screening	Syphilis treatment (in pregnant women found positive)	Perinatal costs (for all pregnancies)
Existing: single screen				
Estimate	£ 1,777,469,008	£ 9,697,904	£ 535,434	£ 1,767,235,670
Lower 95% CI	£ 1,769,393,140	£ 9,661,636	£ 532,820	£ 1,759,111,560
Upper 95% CI	£ 1,778,772,048	£ 9,822,870	£ 545,591	£ 1,768,490,710
Alternative: repeat screen				
Estimate	£ 1,787,355,870	£ 18,860,259	£ 970,254	£ 1,767,525,357
Lower 95% CI	£ 1,779,322,118	£ 18,786,836	£ 964,636	£ 1,759,402,583
Upper 95% CI	£ 1,788,703,813	£ 19,100,346	£ 989,342	£ 1,768,782,187
Cost difference	£ 9,886,863	£ 9,162,355	£ 434,820	£ 289,687

[1] Costs to the NHS in the UK for all 725,891 pregnant women screened. Costs are spilt into 1) antenatal screening costs, which includes sample collection and laboratory testing; 2) syphilis treatment within sexual health clinics; and 3) perinatal costs, which includes the costs of delivery and neonatal care for all infants.

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Table 4. Requirements to prevent one outcome – from model comparing universal repeat screening of syphilis in late pregnancy with single screening

Outcome	Cost	Women screened in third trimester	Women treated for syphilis – TP and FP	Additional false positives
Congenital syphilis	£ 1,791,880	124,294	251	249
Intrauterine fetal demise	£ 37,852,707	2,625,664	5,300	5,251
Neonatal death	£ 79,507,578	5,515,066	11,133	11,030

FP, false positive; TP, true positive for syphilis infection.

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The model calculated that 124,292 women would need to be rescreened in the third trimester to prevent one case of CS, 2.6 million to prevent one case of IUFD (i.e. one case prevented approximately every 3.6 years if every pregnant woman was rescreened), and 5.5 million to prevent one case of neonatal death (i.e. one case prevented approximately every 7.6 years if every pregnant woman was rescreened, **Table 4**). It would cost an additional £1,791,880 per case of CS prevented, £37,852,707 per case of IUFD prevented, and £79,507,578 per neonatal death prevented. An additional 251 women need to receive treatment for syphilis to prevent one case of CS (**Table 4**).

Sensitivity and scenario analyses

The DSA results indicated that even accounting for parameter uncertainty, the total cost of the repeat screening strategy was always higher than the cost of the single screening strategy (see **Figure S2** in online supplement for Tornado diagram). Total costs were most sensitive to changes in the per screen cost, but also to changes in the specificity of the screening process, the proportion of women first attending antenatal care before their third trimester, syphilis incidence, and the cost of syphilis treatment (**Figure S2**). In the DSA examining the impact of clinical and cost parameters on the number of CS cases, the model was most sensitive to syphilis incidence during pregnancy and the probability of CS in infants born to women infected with syphilis during pregnancy who did not receive treatment (i.e. were undiagnosed; see **Figure S3**). In all iterations in the 1,000 PSA Monte Carlo simulations, the repeat screening strategy cost more than the single screening strategy and resulted in fewer cases of CS. The incremental cost and incremental cases of CS prevented are shown online in online **Figure S4**.

When lifetime costs and utilities were considered (Scenario 1), the health and social care cost per additional QALY gained for the repeat screening strategy (ICER) was £120,494 (see **Table S15** in online supplement). In further scenario analyses, reducing the uptake of repeat testing to 99.6% (in line with current uptake of the first screen, Scenario 2), including all women who attended antenatal care before their third trimester (i.e. no late first screen, Scenario 4), including 100% sensitivity and specificity of the screening process (Scenario 5), or including no false positives in the second screen (Scenario 6) had very little impact on the model outcomes, reducing the base case cost per CS case avoided by <10% (data not shown).

When the probability of becoming infected with syphilis between screens was increased seven-fold to 0.00012 (Scenario 3), repeat screening resulted in 39 fewer cases of CS compared to single screening, 0.9 fewer neonatal deaths, 13 fewer preterm deliveries, and 1.8 fewer cases of IUFDs whilst the repeat strategy cost an additional £9,638,476 (**Table S16** and **S17** in online supplement).

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In this scenario, the cost per CS case prevented was £247,284 (**Table S18**). **Table S19** in the online supplement presents the cost per case of CS avoided and the ICER when the probability of becoming infected with syphilis between screens is higher than baseline (at 10 intervals between 0.00003 and 0.00012). As anticipated, with each increase in incidence, the repeat screening strategy resulted in more CS cases prevented and a lower cost per CS case prevented. When lifetime healthcare and social-care costs were considered, the ICER was £11,171 (below the £20-£30k threshold used by NICE), when syphilis incidence in pregnancy was 0.004% and became cost saving at an incidence of 0.005% (1 in 100,000) or higher.

Scenario 7 examined the cost per screen needed to meet NICE ICER thresholds (at the current syphilis incidence) (see supplementary material **Table S20**). The per screen cost would need to decrease from £13.36 to £6.46 to take the ICER below £30k and £5.70 to take it below £20k when lifetime health and social care costs and utilities of CS were considered.

Discussion

We report on the cost-effectiveness of repeat universal syphilis antenatal screening in the UK. Our results indicate that this screening strategy would not be cost-effective in the current UK setting where the prevalence and incidence of syphilis among pregnant women is low. Although the repeat screening strategy is likely to result in fewer cases of CS, the number of cases prevented would be small, 5-6 a year, and would cost an additional £9.9 million, equivalent to £1.8 million per case prevented. Most of the increase in cost is a result of the additional costs related to providing the second screen rather than treatment or delivery costs for women with syphilis.

The PSA and DSA indicated that the model results are robust to changes in the inputs. When lifetime health and social-care costs and health-related quality of life were considered (Scenario 1), the cost per QALY gained was £120,494 for the repeat screening strategy compared to the single screening strategy. This is well above the £20k-30k cost per QALY threshold that NICE uses to assess interventions, and also exceeds the £100,000 threshold used to assess drugs/interventions for rare conditions (the threshold used when the intervention results in <10 additional QALYs to an individual in their lifetime) [25].

Only two previous economic evaluations from the United States (US) have assessed universal repeat syphilis screening in pregnancy compared to single screening in early pregnancy. Albright *et al.* found that universal third-trimester syphilis rescreening was not cost-effective, while Hersh *et al.* reported repeat screening was cost saving [17,26]. These economic evaluations did not account for late

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presentation to antenatal care and syphilis prevalence and incidence were considerably higher as were healthcare costs.

It is important to note that changes to the screening strategy would not change the number of adverse pregnancy outcomes in women who decline screening, in women who present late to antenatal care and have one screen but no opportunity for a repeat screen, or in women who first present at the time of delivery, thereby missing the opportunity for any antenatal screening or treatment. For this reason, and because treatment for syphilis is not universally effective at preventing adverse pregnancy outcomes, it is likely that there would continue to be a very small number of infants born with CS each year irrespective of changes made to the screening strategy.

Strengths and weaknesses

This is the first health economic analysis to assess the costs and clinical benefits of a repeat screening strategy for syphilis compared to a single screen strategy within the UK setting. The input values in the model were based on the best available evidence from the published literature, UK-specific surveillance data, NHS tariffs and published costs, and with input from experts in the field were data were lacking. These inputs were rigorously tested in sensitivity and scenario analyses to add confidence to the results, despite limited data in some areas.

There were sparse UK data available on pregnancy outcomes in women treated for syphilis or in infants born with CS. We therefore used the additional lifetime cost of CP, estimated in a study from Denmark [21], as a proxy for the lifetime cost of CS. As such, the primary focus of the analysis was the short-term costs and CS cases avoided since it was difficult to have confidence in the estimate used for lifetime CS cost.

The model assumed that women could not become infected with syphilis between the repeat screen and delivery. As the incidence estimate relates to the full duration of pregnancy, this assumption would overestimate the number of women diagnosed at the repeat screen and treated, therefore overestimating the benefits of the repeat screen strategy. However, the number of women who become infected with syphilis is small and thus this would likely have little impact on the overall results. Since we do not know what repeat screening coverage would be, the model assumed 100% coverage, since all women in the model had already agreed to a first screen. This is optimistic since it assumes continued engagement with antenatal services. However, scenario analysis 2 showed that even when uptake was <100% it would be unlikely to have much impact on the cost per CS case avoided.

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It was also assumed that all women and neonates diagnosed with syphilis receive the appropriate full course of treatment and all infants born to women diagnosed with syphilis in pregnancy receive syphilis testing at birth. However, the SASS study [13] found that in 2010-11, not all women diagnosed with syphilis received complete treatment and inadequate paediatric follow-up was identified as an issue. Lack of treatment in these women and neonates is likely to make the repeat screening even less cost-effective.

Implications for clinicians and policymakers

The number of CS cases was most sensitivity to changes in the syphilis incidence between screens. It may be cost-effective to repeat screen for a period of time where there is a known syphilis outbreak or if there are multiple cases of CS in a short period within the same geographical area in women who tested negative for syphilis at the first screen - as this would indicate a much higher syphilis incidence in pregnancy in that area.

Our model focused on the UK but is relevant to other European countries with similar syphilis prevalence and healthcare costs. Our analyses, using UK cost estimates, suggest that a universal second screen in late pregnancy could become cost-effective if the incidence of syphilis in pregnancy were to increase (to 5 per 100,000 pregnant women), indicating that in countries that have far higher syphilis prevalence than the UK, a second screen could be cost saving. For example, recent estimates suggest that the prevalence of syphilis in the WHO African region is more than 10-fold higher than in the WHO European Region [27]. In such a high prevalence setting, combined with lower local healthcare costs, a second syphilis screen in late pregnancy could be cost-effective.

There could be some negative impact associated with repeat screening. A false positive result may lead to additional costs, unnecessary anxiety for mothers and their families, impact the mother's relationships, possibly even damage their confidence in the screening programme, as well as lead to overtreatment. It is vital to minimise unnecessary use of antibiotics where possible given growing concerns around antimicrobial resistance and because there is some evidence that antibiotic use in pregnancy increases the risk of childhood epilepsy, obesity, and asthma [28].

Alternative approaches to reduce the number of CS cases and other adverse pregnancy outcomes could be more cost-effective and should be explored. These include better targeting of high-risk individuals and sexual health promotion in pregnancy. Furthermore, of the 20 CS cases in the UK since 2010, 11 had no record of the mother receiving antenatal screening. It remains unknown whether this was because testing was refused or due to very late/no first antenatal attendance [15].

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This highlights the need to ensure timely screening in pregnancy, particularly in women who present late who are already at increased risk of adverse pregnancy outcomes. Education for pregnant women around sexual health and STI prevention might be cost-effective and could be considered.

Unanswered questions and future research

Our model had a single disease focus. At present however, pregnant women are screened for syphilis, HIV and hepatitis B. It would be useful to assess the potential cost-effectiveness of a repeat screen for all three infections since treatment for these infections during late pregnancy and/or at birth would reduce the risk of vertical transmission. Screening for all three infections may yield more benefits in terms of clinical outcomes and may make this strategy more cost-effective.

Furthermore, data collection including gestational week of first screen, coverage of repeat screen in high-risk women, pregnancy outcome for women treated for syphilis, stage of infection in women diagnosed with syphilis, and cost estimation for lifetime costs of being born with CS, would help inform future evaluations of screening strategies.

Conclusions

The results of this health economic analysis indicate that implementing universal repeat screening for syphilis in pregnancy is unlikely to be cost-effective in the current UK setting where the prevalence and incidence of syphilis in pregnant women is low. Repeat screening could be considered in areas with a high syphilis incidence in pregnancy and may then be cost-effective, particularly if the cost per screen were low.

If syphilis prevalence continues to increase, the cost-effectiveness of the repeat screening strategy should be re-examined, highlighting the importance of continued monitoring of syphilis in pregnant women, screening uptake, CS cases and long-term follow-up.

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Author contributions: All authors contributed to developing the final model structure and data inputs and informing the micro-costing calculations. SH built the model and drafted the paper, with input from GW and FS. All authors contributed to the interpretation of the results and drafting of the final paper and have approved the final submitted version.

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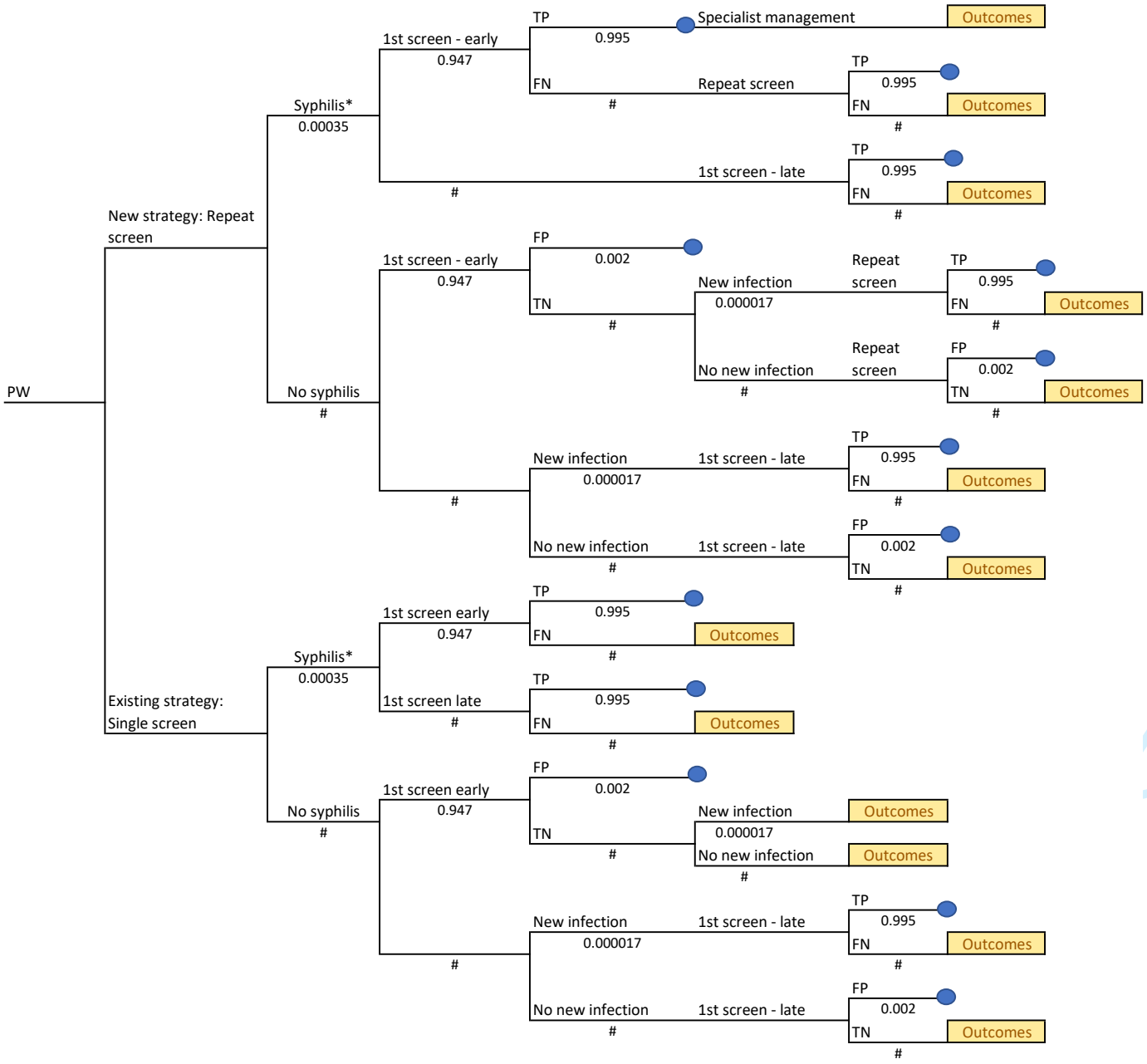
PW
New strategy: Repeat screen
Existing strategy: Single screen
Syphilis*
0.00035
No syphilis
#
1st screen - early
0.947
1st screen late
1st screen early
TP
0.995
FN
FP
0.002
TN
Specialist management
Repeat screen
New infection
0.000017
No new infection
1st screen - late
Outcomes

Online Supplement

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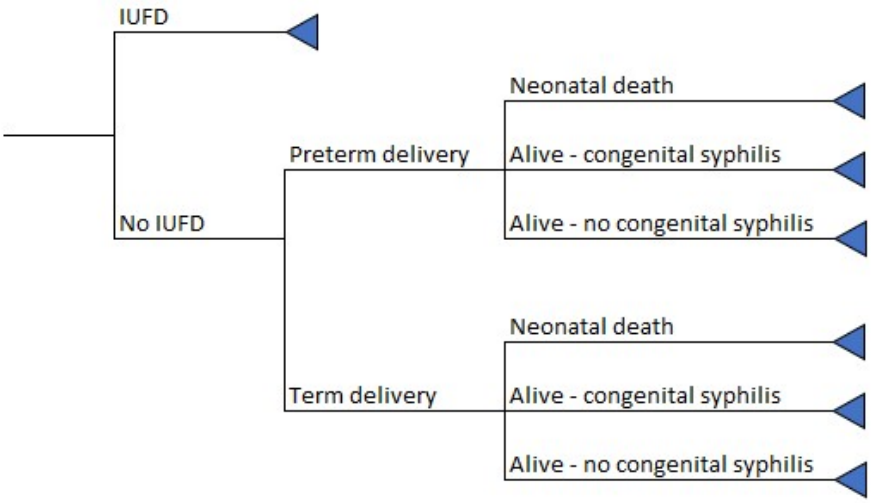
Figure S1. Pregnancy outcomes used in the decision tree comparing universal repeat screening of syphilis in late pregnancy with single screening



Footnote:

IUFD, intrauterine fetal demise; preterm refers to <37 weeks gestation. The blue triangle indicates the branch end point.

This diagram complements **Figure 1** in the main body of the paper. The probability of each of these outcomes occurring for each branch of the tree is presented in **Table S2**.

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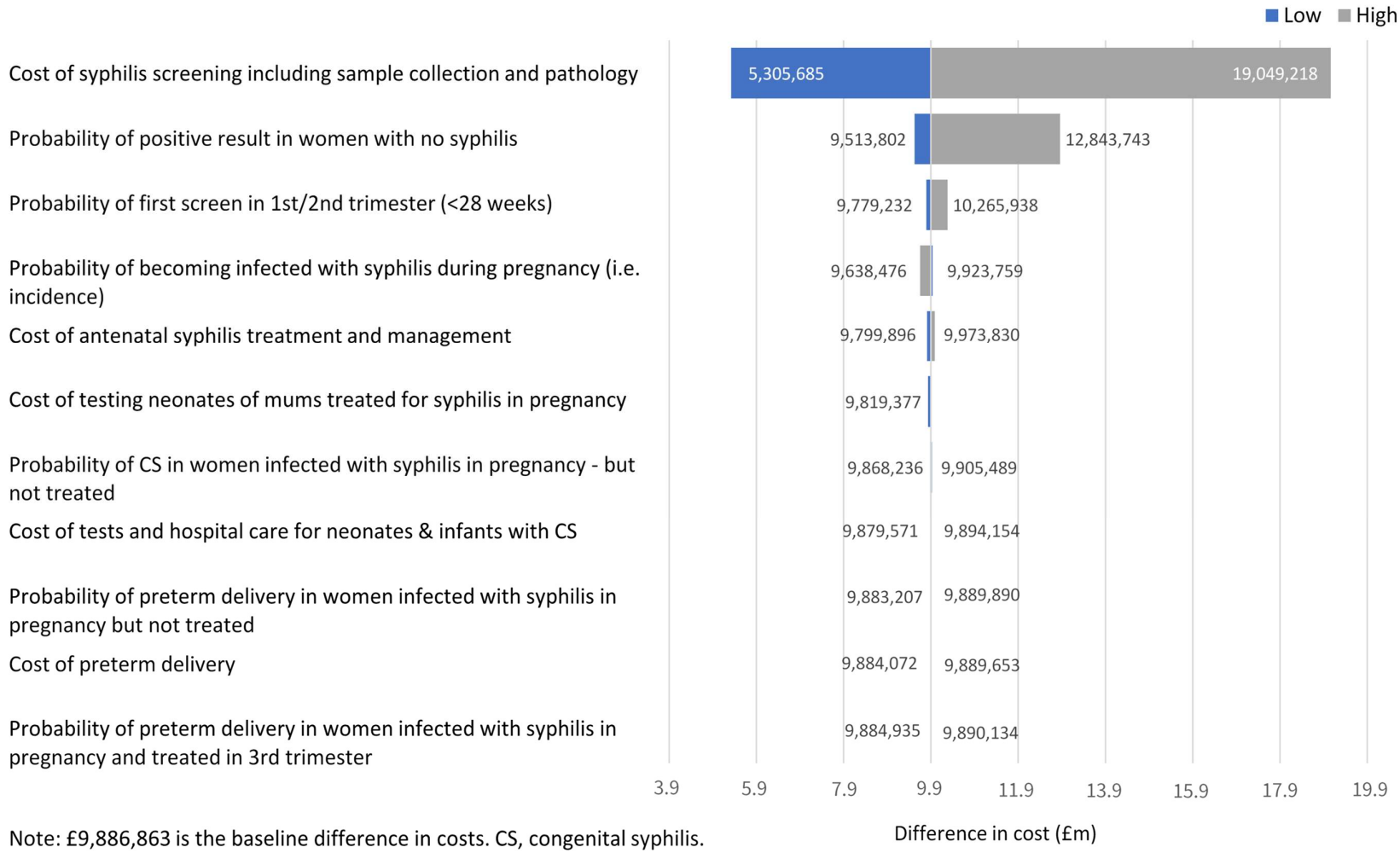
Figure S2. Tornado diagram – one-way deterministic sensitivity analysis of total costs - parameters with least impact removed



Note: £9,886,863 is the baseline difference in costs. CS, congenital syphilis.

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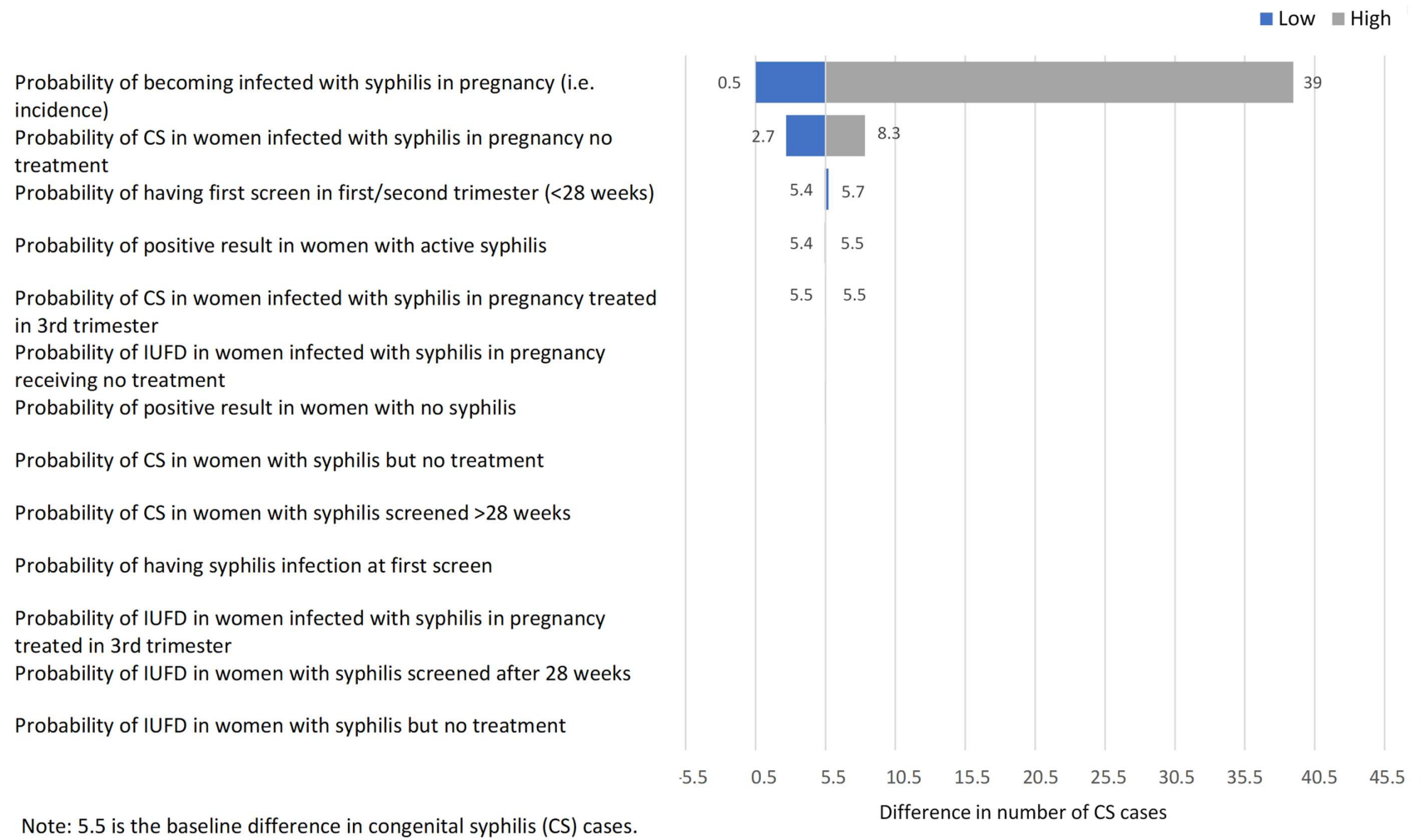
Figure S3. Tornado diagram - one-way deterministic sensitivity analysis of CS cases - parameters with least impact removed



Note: 5.5 is the baseline difference in congenital syphilis (CS) cases.

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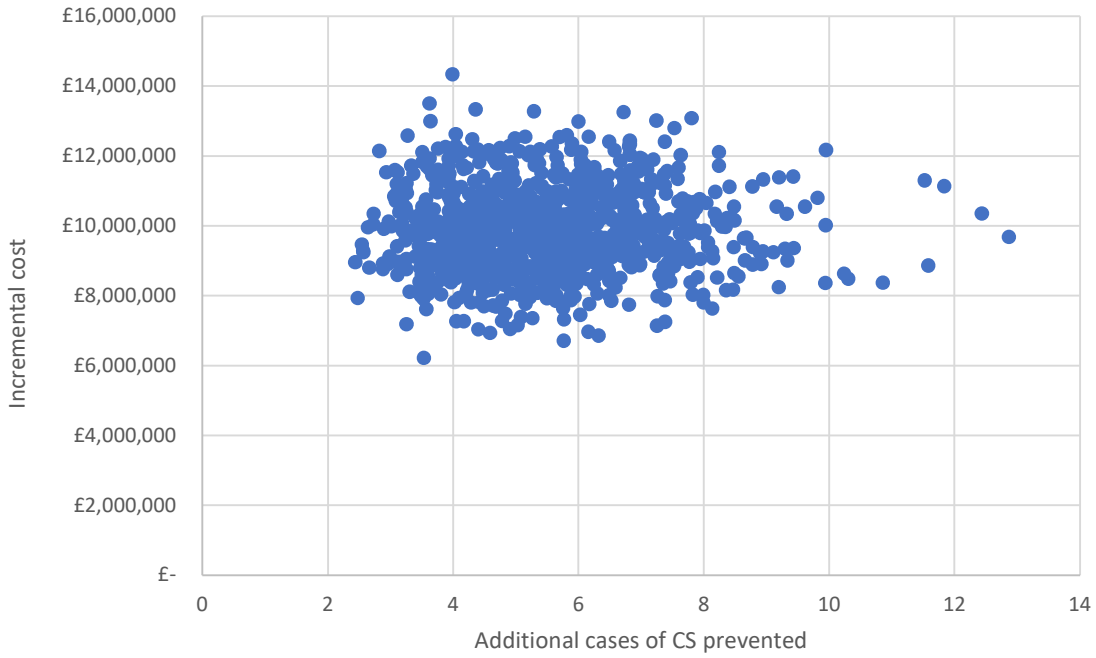
Figure S4. Incremental cost versus additional cases of CS prevented



This figure is an output from the Probabilistic Sensitivity Analysis (PSA) and shows the impact of parameter uncertainty on the cost per additional case of CS prevented in universal repeat screening of syphilis in late pregnancy versus single screening.

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Table S1. Assumptions applied to screening strategies and rationale

Assumption	Note
All women found positive for syphilis, at their first or repeat screen, are referred to care within a sexual health clinic and are successfully treated within that setting.	As per clinical guidelines [1]. Uptake of treatment in diagnosed women is thought to be high. No published data were found to support or refute this assumption.
The clinical management of women who are diagnosed with syphilis at their first screen includes repeat testing of syphilis and as such they do not receive a repeat screen as part of the IDPS in either screening strategy.	Recommendation from experts. This is hypothetical, as repeat screening is not current practice.
Infants born with CS display signs of CS, 40% at birth and 60% some weeks/months after delivery and are tested and treated accordingly.	Based on expert opinion and evidence indicating that most infants with CS develop signs by 5 weeks. Lack of data on the proportion of CS cases with late presentation (after two years) [1].
There is no loss to follow-up, i.e. all women who are identified as needing treatment receive it.	Inclusion of loss to follow-up in the model would add unnecessary complexity to the model. Also, there is lack of data on loss to follow-up in this setting.
There is 100% uptake of repeat screening in women who were initially screened.	Assessed in Scenario Analysis 2.
The model inputs are not correlated.	To avoid over complexity in the model and due to lack of evidence around correlation.
Pregnant women who attend first antenatal care late receive their first screen at that point and therefore miss the opportunity for a repeat test.	Recommendation from experts. This is hypothetical, as repeat screening is not current practice.
Preterm vs. term delivery impacts costs but the model assumes it has no impact on the risk of pregnancy outcomes (neonatal death or congenital syphilis).	Lack of data around correlation between timing of delivery and pregnancy outcome.
The repeat screen would be performed at 28 weeks gestation to coincide with existing routine anaemia blood tests. It was assumed that no new syphilis infection could occur between this screen and delivery.	No data could be found on the incidence of syphilis or the impact of a new syphilis infection that late in pregnancy. Timing of repeat screen based on expert advice – and is hypothetical as repeat screening is not current practice.
No women undergo a repeat screen in the current care pathway (i.e. the single screening strategy).	Following expert advice that few high-risk women receive repeat screening at present. Lack of data around uptake of repeat screening and pregnancy outcomes for low risk vs. high risk women.

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Table S2. Pregnancy outcomes - parameter inputs for decision tree comparing universal repeat screening of syphilis in late pregnancy with single screening

Parameter	Baseline value	Low	High	Note
Pregnant women with no syphilis				
IUFD	0.004	0.003	0.005	**Tables S3-S5**
Preterm delivery	0.075	0.058	0.097	**Tables S3-S5**
Neonatal death	0.002	0.001	0.003	**Tables S3-S5**
Congenital syphilis	0.000	-	-	Assumption
Pregnant women with syphilis diagnosed and treated <28 weeks				
IUFD	0.005	0.002	0.012	**Tables S3-S5**
Preterm delivery	0.079	0.042	0.143	**Tables S3-S5**
Neonatal death	0.003	0.001	0.014	**Tables S3-S5**
Congenital syphilis	0.011	0.008	0.016	**Tables S3-S5**
Pregnant women with syphilis diagnosed and treated ≥28 weeks				
IUFD	0.023	0.018	0.028	**Tables S3-S5**
Preterm delivery	0.183	0.119	0.275	**Tables S3-S5**
Neonatal death	0.013	0.005	0.032	**Tables S3-S5**
Congenital syphilis	0.038[1]	0.029	0.047	**Tables S3-S5**
Pregnant women with syphilis not diagnosed or treated				
IUFD	0.028	0.023	0.033	**Tables S3-S5**
Preterm delivery	0.241	0.188	0.305	**Tables S3-S5**
Neonatal death	0.014	0.009	0.022	**Tables S3-S5**
Congenital syphilis	0.034[1]	0.026	0.042	**Tables S3-S5**
Pregnant women infected with syphilis in pregnancy and diagnosed and treated in 3rd trimester				
IUFD	0.006	0.002	0.013	Assumed to have same risk as women diagnosed and treated for syphilis infection in 1st trimester.
Preterm delivery	0.071	0.038	0.127	
Neonatal death	0.003	0.001	0.015	
Congenital syphilis	0.010	0.007	0.014	
Pregnant women infected with syphilis during pregnancy not diagnosed or treated				
IUFD	0.028	0.023	0.033	Assumed to have same risk as women with syphilis not diagnosed or treated. Estimate based on expert opinion.
Preterm delivery	0.241	0.188	0.305	
Neonatal death	0.014	0.009	0.022	
Congenital syphilis	0.500	0.250	0.750	

IUFD, intrauterine foetal demise. Low and high values are based on the 95% confidence intervals (CIs) from the meta-analysis Qin *et al.* [2] adjusted to the UK setting in the same way as the baseline values (See **Tables S3-S5**).

[1]The probability of congenital syphilis in women with syphilis is higher in women treated at ≥28 weeks gestation than in women receiving no treatment. This is because estimates are from a meta-

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analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.

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Table S3. Pregnancy outcome data taken from published large meta-analysis of international studies [2]

Pregnancy outcome	Women with no syphilis	Syphilis infection at time of conception					New syphilis infection during pregnancy	
		a	b	c	d	e	f	g
		First screen + treatment 1st trimester	First screen + treatment 2nd trimester	First screen + treatment 1/2nd trimester	First screen + treatment 3rd trimester	No treatment	Repeat screen + treatment 3rd trimester	No treatment
Congenital syphilis	0.0%	10.4%	17.6%	12.1%	40.6%	36.0%	10.4%	50%
Preterm delivery	7.2%	6.8%	10.1%	7.6%	17.6%	23.2%	6.8%	23.2%
IUFD (stillbirth)	3.7%	5.3%	4.2%	5.0%	21.3%	26.4%	5.3%	26.4%
Neonatal death	2.0%	3.8%	3.0%	3.6%	15.1%	16.2%	3.8%	16.2%

These data are from a systematic review and meta-analysis which measured pregnancy outcomes in women with and without syphilis (Qin *et al.* [2]). Each estimate is an average calculated by combining data from 2-33 different studies.

The risk of neonatal death was reported for the whole of pregnancy but was not calculated separately for treatment in each pregnancy trimester. For the model, the risk of intrauterine fetal demise (IUFD) in each trimester compared to the overall risk in pregnancy was used to estimate the risk of neonatal death in each trimester compared to the overall risk in pregnancy.

Column c, the risk of pregnancy outcomes if syphilis is diagnosed and treated in the 1st or 2nd trimester, was calculated using data from the 1st and 2nd trimesters (column a and b) and using UK data to calculate the proportion of women first attending antenatal care in their 1st or 2nd trimester (75.9% and 24.1% respectively). For example, the risk of congenital syphilis (CS) was calculated as follows: (0.759*0.104) + (0.241*0.176) = 0.121.

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Column e: no treatment group due to a false negative test result. The probability of CS in women with syphilis is higher in women treated in 3rd trimester (column d) than in women receiving no treatment (column e). This is because estimates are from a meta-analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.

Column f: women infected with syphilis during pregnancy but diagnosed and treated at their repeat screen (in third trimester) are assumed to have the same risk of adverse pregnancy outcomes as women who are diagnosed and treated in their first pregnancy trimester (column a) (from expert opinion).

Column g: the risk of preterm delivery, IUFD and neonatal death is assumed to be the same as for women who have syphilis at conception but who are not treated in pregnancy (column e). However, the risk of CS is estimated as 50%, since the risk is known to be high in primary infection (from expert opinion).

The risk of adverse pregnancy outcomes in women with no syphilis in the meta-analysis data (Qin *et al*) [2] were considerably higher than the numbers seen in pregnant women in the UK. The risk of CS in women with syphilis was also considerably higher in the meta-analysis results than seen in the UK [3,4]. Therefore, these inputs were adjusted to the UK settings (See **Table S4**).

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Table S4. Comparing the risk of adverse pregnancy outcomes in meta-analysis with risk observed in the UK in order to scale meta-analysis data

Pregnancy outcome	Meta-analysis data [2] A	UK data [n/N] B	UK vs. meta-analysis C	UK data reference
Women with no syphilis				
Preterm delivery	7.2%	7.485% [57,079/762,594]	104.0%	**Table S10**
IUFD (stillbirth)	3.7%	0.393% [3.93/1000] [1]	10.6%	[5]
Neonatal death	2.0%	0.172% [1.72/1000] [1]	8.6%	[5]
Women with syphilis				
Congenital syphilis (any trimester)	13.7%	1.28% [3.4/266][2]	9.4%	[3,4]

[1]The most recent data on pregnancy outcomes from the UK were from 2016 when the total number of pregnancies in the UK was 780,043 [5]. Pregnancy outcomes reported from the UK as a whole are used for the no syphilis group.

[2] Based on the numbers in our model, we would expect at total of 266 women in 2017/18 to have syphilis in pregnancy i.e. 254 women at the start of pregnancy [0.00035*725,891] plus 12 women infected during pregnancy [0.000017*725,637].

No data on the risk of the different pregnancy outcomes during each trimester were available from the UK. Therefore, the difference in overall risk in pregnancy between the UK and the metanalysis data was used to adjust data from the meta-analysis to calculate the risk of outcomes in each trimester for women in the UK. The calculated risks, used in the model, are presented in **Table S5** and an example of how they were calculated is included in the **Table S5** footnotes.

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Table S5. Pregnancy outcome data used in the model – adjusted from published large meta-analysis of international studies [2] to reflect UK risks

Pregnancy outcome	Women with no syphilis	Syphilis infection at time of conception					Becomes infected during pregnancy	
		First screen + treatment 1st trimester	First screen + treatment 2nd trimester	First screen + treatment 1/2nd trimester	First screen + treatment 3rd trimester	No treatment	Repeat screen + treatment 3rd trimester	No treatment
Congenital syphilis	0.0%	0.97%	1.65%	1.14%	3.80%	3.37%	0.97%	50.0%
Preterm delivery	7.48%	7.07%	10.50%	7.90%	18.03%	24.12%	7.07%	24.12%
IUFD (stillbirth)	0.39%	0.56%	0.45%	0.53%	2.26%	2.80%	0.56%	2.80%
Neonatal death	0.17%	0.32%	0.26%	0.31%	1.30%	1.39%	0.32%	1.39%

These numbers were calculated using data from a meta-analysis (**Table S3**) adjusted by the difference in the (overall) risk of pregnancy outcomes between the UK and the meta-analysis (**Table S4**, column C).

For example, the risk of congenital syphilis (CS) in women treated for syphilis in the 1st/2nd trimester (1.14%) was calculated as follows: (0.121*0.094) = 0.0114 i.e. the risk of CS in the 1st/2nd trimester from the meta-analysis (**Table S3**, column C) multiplied by the proportional in of risk of CS in pregnancy in the UK vs. the meta-analysis (**Table S4**, column C).

The published 95% confidence intervals were adjusted in the same way to calculate the low and high values used in the sensitivity analysis.

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Table S6. Overall number of women screened for syphilis in pregnancy, 2017/18

Country	Total number of deliveries	Estimated number screened	Reference
England	626,203	623,698	[36]
Northern Ireland	23,045	23,038	[38]
Scotland	51,197	50,992	[39]
Wales	28,361	28,248	[40]
UK total	728,806	725,976	

In England, Wales and Scotland, these data exclude women giving birth at home or in non-NHS hospitals.

Screening uptake in 2017/2018 for England, Wales and Scotland was estimated as 99.6% i.e. the same as uptake in England in 2016/2017 [15].

The uptake of screening in 2017/2018 for Northern Ireland was 99.97%, based on data collected by Public Health Agency Northern Ireland 2017/2018.

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Table S7. Gestational week at first antenatal care attendance – by UK country

UK country	<12 weeks		12-28 weeks		≥28 weeks		No data	With data available	Total	Reference
	n	%	n	%	n	%				
England	299,634	70.1%	103,137	24.1%	24,935	5.8%	~200,000	427,706	-	[6]
Northern Ireland	15,069	65.4%	7,607	33.0%	365	1.6%	4	23,041	23,045	[7]
Scotland	42,840	84.2%	5,876	11.5%	2,165	4.3%	316	50,881	51,197	[8]
Wales	22,878	82.2%	4,226	15.2%	745	2.7%	512	27,849	28,361	[9]
UK total	380,421	71.8%	120,846	22.8%	28,210	5.3%		529,477		

All data are for year 2017/18. The SASS study [3] found that in women screening positive for syphilis, 6.4% (81/1271) had their first antenatal attendance at 27 weeks or later. These data were used to calculate pregnancy outcomes and the percentage of women receiving a first syphilis screen before 28 weeks gestation (94.7% i.e. 501,267/529,477).

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Table S8. Calculating the cost per antenatal syphilis screen

Activity	Cost per item (£)	Proportion with cost	Average cost/person (£)	Notes
Blood sample collection	0.23	1.00	0.23	Includes only equipment costs. Syphilis screening is performed at the same time as other antenatal screening tests – and therefore does not incur additional staff time.
Laboratory testing (higher cost)	16.50	0.50	8.25	Price quoted in London Sexual Health full STI screen tariff [10].
Laboratory testing (lower cost)	9.00	0.50	4.50	Price quoted by laboratory manager in Leeds. This is the price charged per screen. It covers consumables, internal quality control (IQC), external quality assessment (EQA), laboratory staff time, and overheads. It accounts for the ratio of negative (which require only one test), positive (which require confirmatory work) test results.
Input from multi-disciplinary team	37.50	0.002	0.08	Estimate 1/500 women require 30 minutes input from the MDT based on expert opinion.
Reference laboratory testing	40.00	0.003	0.10	Estimate 1/400 samples sent to reference laboratory for confirmatory testing based on England's central reference lab receiving ~1300 samples/year (personal communication with laboratory manager).
Repeat test blood collection	3.86	0.01	0.04	1/100 women require a repeat test due to inconclusive test results. This cost is taken from London Sexual Health full STI screen tariff [10].
Laboratory testing (higher cost)	16.50	0.005	0.08	Repeat test due to inconclusive test result from first assay.
Laboratory testing (lower cost)	9.00	0.005	0.05	Repeat test due to inconclusive test result from first assay.
Referral to sexual health clinic	56.60	0.0006	0.04	Women with positive result for antibodies are referred to Sexual Health Clinic for sexual history and risk assessment. Cost based on a 30-minute appointment with a consultant plus 5 mins of receptionist time (staff costs taken from PSSRU 2017/18 [11]). Proportion taken from SASS study [3] which found 607/961,494 women had positive antibody result but did not then require treatment.
Total			**13.36**	

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Footnote: A 50:50 split between the higher and lower costs for laboratory tests was used. The cost of a repeat screen was assumed to be the same as the cost of a first screen since in both cases, samples would be taken at a routine antenatal appointment when other blood tests are performed, i.e. HIV and hepatitis B screening at first screen and routine anaemia blood tests at 28 weeks gestation.

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Table S9. Calculating the cost of treatment and management of women diagnosed with syphilis in pregnancy

Activity	Cost per woman (£)	Notes
STI Intervention C - Management of reactive treponemal serology	262.34	Cost taken from the London Integrated Sexual Health Tariff 2017/18 which includes 5 visits to clinic for treatment with penicillin regimen appropriate for the stage of infection [1,10]. In pregnant women diagnosed in the first trimester, all 5 visits would occur before delivery, in women diagnosed in final trimester, 3/5 visits would occur before delivery and 2 after delivery (personal communication with senior sexual health consultant).
Additional cost at 1st visit	16.50	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Additional cost at 2nd visit	8.25	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Additional cost at 5th visit	27.00	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Total	**314.09**	

There would be no change to the staff grade (from the tariff) at the 3rd or 4th visit, when the patient would be seen by a nurse.

This cost was calculated based on expert opinion from a senior consultant in sexual health.

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Table S10. Gestational week at delivery (used for calculating delivery costs and estimating pregnancy outcomes)

Country	≤33 weeks		34-36 weeks		>36 weeks		No data	With data available	Total	Ref	Notes
	n	%	n	%	n	%					
England	13,846	2.1%	35,533	5.4%	607,972	92.5%		657,351	-	[19]	2014 data
Northern Ireland	470	2.0%	1,385	6.0%	21,190	92.0%	0	23,045	23,045	[7]	2017/18 data
Scotland	868	1.7%	2,444	4.9%	46,791	93.4%	207	50,103	50,310	[8]	2017/18 data
Wales	723	2.3%	1,810	5.6%	29,562	92.1%	141	32,095	32,236	[20]	2017 data
UK total	15,907	2.1%	41,172	5.4%	705,515	92.5%		762,594			

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Table S11. Calculating the average healthcare costs associated with a neonatal death

Activity	Resource/ Activity	Quantity	Cost per unit	Total cost	Ref	Notes:
Cost of IUFD	-	-	-	£4,356.80	[12]	
Hospital stay	Day	3	£483.00	£1,449.00	[1,13]	Based on NHS tariff for Paediatric Major Infections with CC Score 0 - HRG code PW16E.
Total cost				**£5,805.80**		

The cost of neonatal death is calculated using the cost of intrauterine fetal demise (IUFD), which includes the cost of post-mortem, parental counselling and a subsequent pregnancy, plus an additional 3-days in a paediatric intensive care unit for the neonate. Three days hospital stay is an estimate based on expert opinion.

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Table S12. Calculating the cost of testing for syphilis in neonates with clinical signs of congenital syphilis (CS)

Activity	Number		Resource type	Resource/ Activity	Quantity /minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
	At birth	After birth							
Clinical assessment for signs of CS	1		Staff time	Consultant paediatrician	30	108.00	54.00	[11]	
Review of syphilis test results		8	Staff time	Consultant paediatrician	10 per review	108.00	144.00	[11]	
RPR/VDRL blood test	1	4	Staff time	Blood taken by nurse (band 6)	10 per test	45.00	37.50	[11]	Test at birth, 1, 3, 6 and 12 months.
IgM EIA blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	Test at birth, 1 and 3 months.
Syphilis blood tests (as above)	2	6	Diagnostics	Laboratory tests	5 (3 combined + 2 single)	12.75	63.75		Same cost if both tests are performed or only RPR/VDRL blood test performed.
Blood tests: full blood count, liver function, electrolytes	1		Staff time	Blood taken by nurse	10	45.00	7.50	[11]	
Blood tests (as above)	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
Lumbar puncture (white blood cell, protein, RPR, TPPA)	1		Staff time	Paediatric registrar	45	43.00	32.25	[11]	
Blood tests (as above)	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
X-ray of long bones	1		Staff time	Consultant Radiographer	30	93.00	46.50	[11]	Based on cost of Band 8c Radiographer

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Table S12 Continued from previous page.

Activity	Number At birth	Number After birth	Resource type	Resource/ Activity	Quantity /minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
Chest x-ray	1		Staff time	Consultant Radiographer	30	93.00	46.50	[11]	Based on cost of Band 8c Radiographer
X-ray film	1		Diagnostics	Diagnostic tests	2	25.00	50.00	[14]	
Ophthalmic assessment	1		Staff time	Consultant Ophthalmologist	30	108.00	54.00	[11]	
Audiology review	1		Staff time	Audiologist (Associate specialist)	10	105.00	17.50	[11]	
Sample taken for microscopy/PCR	1		Staff time	Nurse (band 6)	10	45.00	7.50	[11]	
Dark ground microscopy and PCR for *T. pallidum*	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
Results review and liaison with sexual health team	1		Staff time	Consultant paediatrician	60	108.00	108.00	[11]	
Total cost							**751.50**		

RPR/VDRL, rapid plasma reagent/venereal disease research lab test. Detailed testing protocol was obtained from Clinical Guidelines [1] and expert opinion.

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Table S13. Calculating the cost of treating neonates with congenital syphilis (CS)

Activity	N	Resource type	Resource/ Activity	Unit	Cost per unit (£)	Cost per neonate (£)	Reference	Notes
Neonates with signs of CS at delivery (40%)								
Treatment for CS	23	Medication	Penicillin (dose 30mg/kg)	105mg dose	3.00 /600mg vial	12.08	[1,15,16]	Dose calculated using average birthweight of 3.5kg.
Treatment for CS	23	Medication	Glucose 5% or sodium chloride 0.9%	Infusion bag	2.14	49.22	[1,15,16]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	721.00	7,210.00	[1,13,17]	Based on NHS tariff for Neonatal Diagnoses with CC Score 0 - HRG code PB04D.
Neonates with signs of CS days/weeks after delivery (60%)								
Treatment for CS	30	Medication	Penicillin (dose 30mg/kg)	123.75mg dose	3.00 /600mg vial	18.56	[1,15,16]	Dose calculated using average weight at 1 month of 4.125kg.
Treatment for CS	30	Medication	Glucose 5% or sodium chloride 0.9%	Infusion bag	2.14	64.20	[1,15,16]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	483.00	4,830.00	[1,13,17]	Based on NHS tariff for Paediatric Major Infections with CC Score 0 - HRG code PW16E.
Total cost of treating neonates with CS (based on 40%/60% split)						5,856.18		
Total cost of testing and treating neonates with clinical signs of CS						6,607.68		

CS, congenital syphilis. Clinical guidelines recommend that treatment is given every 12 hours (for infants ≤7 days of age) and every 8 hours (for infants >7 days of age) for a total of 10 days with treatment typically starting on the day of delivery.

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Table S14. Calculating the cost of neonate screening in infants born to mothers treated for syphilis in pregnancy

Activity	Number		Resource type	Resource/ Activity	Quantity/ minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
	At birth	After birth							
Clinical assessment for signs of CS	1		Staff time	Consultant paediatrician	30	108.00	54.00	[11]	
Review of test results		6	Staff time	Consultant paediatrician	10 per review	108.00	108.00	[11]	
RPR/VDRL blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	Tests every three months until RPR is negative (this usually occurs by six months). Cost based on band 6 nurse.
IgM EIA blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	
Syphilis blood tests (as above)	2	4	Diagnostics	Laboratory tests	3 sets of tests	12.75	38.25	[10]	Based on average combined cost for tests.
Total cost							**£245.25**		

CS, congenital syphilis; IgM EIA, immunoglobulin M enzyme immunoassay; RPR/VDRL, rapid plasma reagent/venereal disease research lab test.

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Table S15. Long-term health care and social care costs associated with congenital syphilis (CS) – results of the model comparing universal repeat screening of syphilis in late pregnancy with single screening

	Short-term costs [Antenatal + postnatal]	Long-term costs[1]	Lifetime costs [short + long-term]	Total QALYs
Single screen	£1,777,469,008	£5,754,176	£1,783,223,184	19,464,817
Universal repeat screen	£1,787,355,870	£2,160,086	£1,789,515,957	19,464,869
Difference	£9,886,863	-£3,594,090	£6,292,773	52.2
ICER				£120,494

ICER, Incremental cost-effectiveness ratio. Lifetime costs and utilities were discounted at 3.5%. Data presented are for all women screened for syphilis in one year (n=725,891)

[1]Additional lifetime health and social care costs for individuals born with CS (£651,387 per individual) - adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.

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Table S16. Clinical outcomes for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Strategy	Syphilis antenatal screens	Women treated for syphilis	False positive screens	Intrauterine fetal demise	Preterm deliveries	Neonatal deaths	Congenital syphilis
Existing: single screen	725,891	1,709	1,451	2,906.1	54,240	1,447	43.2
Alternative: repeat screen	1,411,696	3,163	2,823	2,904.3	54,226	1,446	4.2
Difference	685,805	1,455	1,371	-1.8	-13	-0.9	-39.0

Table S17. Cost outcomes for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£ 1,777,764,124	£ 9,697,904	£ 536,669	£ 1,767,529,551
Alternative: repeat screen	£ 1,787,402,601	£ 18,860,259	£ 993,521	£ 1,767,548,821
Difference	£ 9,638,476	£ 9,162,355	£ 456,852	£ 19,270

Table S18. Requirements to prevent one outcome for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Outcome	Cost	Women screened in third trimester	Women treated for syphilis – TP and FP	Additional false positives
Congenital syphilis	£247,284	17,595	37	35
IUFD	£5,332,625	379,431	805	759
Neonatal death	£11,063,507	787,200	1,670	1,574

TP, True positive; FP, False positive

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Table S19. Short and long-term cost outcomes for Scenario 3 (higher syphilis incidence in pregnancy)

Syphilis incidence (new infections between screens)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime health and social care costs
Probability (%)				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER
0.00003	(0.003)	Single	£1,777,506,256	2,904.6	54,229.9	1,446.6	13.2		
		Repeat	£1,787,361,768	2,904.1	54,226.5	1,446.4	3.4		
		Difference	£9,855,513	-0.5	-3.4	-0.2	-9.7	£1,011,791	£38,140
0.00004	(0.004)	Single	£1,777,534,908	2,904.8	54,231.0	1,446.7	16.5		
		Repeat	£1,787,366,305	2,904.1	54,226.4	1,446.4	3.5		
		Difference	£9,831,398	-0.6	-4.5	-0.3	-13.0	£756,892	£11,171
0.00005	(0.005)	Single	£1,777,563,560	2,904.9	54,232.1	1,446.8	19.8		
		Repeat	£1,787,370,842	2,904.2	54,226.4	1,446.4	3.6		
		Difference	£9,807,283	-0.8	-5.7	-0.4	-16.2	£603,983	Cost saving
0.00006	(0.006)	Single	£1,777,592,212	2,905.1	54,233.1	1,446.9	23.2		
		Repeat	£1,787,375,379	2,904.2	54,226.4	1,446.4	3.7		
		Difference	£9,783,167	-0.9	-6.8	-0.4	-19.5	£502,056	Cost saving
0.00007	(0.007)	Single	£1,777,620,864	2,905.2	54,234.2	1,446.9	26.5		
		Repeat	£1,787,379,916	2,904.2	54,226.4	1,446.4	3.8		
		Difference	£9,759,052	-1.1	-7.9	-0.5	-22.7	£429,258	Cost saving
0.00008	(0.008)	Single	£1,777,649,516	2,905.4	54,235.3	1,447.0	29.9		
		Repeat	£1,787,384,453	2,904.2	54,226.3	1,446.4	3.9		
		Difference	£9,734,937	-1.2	-9.0	-0.6	-26.0	£374,662	Cost saving

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Table S19. Continued from previous page.

Syphilis incidence (new infections between screens)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime health and social care costs
Probability (%)				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER
0.00009	(0.009)	Single	£1,777,678,168	2,905.6	54,236.4	1,447.1	33.2		
		Repeat	£1,787,388,990	2,904.2	54,226.3	1,446.4	4.0		
		Difference	£9,710,822	-1.4	-10.1	-0.7	-29.2	£332,201	Cost saving
0.0001	(0.01)	Single	£1,777,706,820	2,905.7	54,237.5	1,447.2	36.5		
		Repeat	£1,787,393,527	2,904.2	54,226.3	1,446.4	4.1		
		Difference	£9,686,707	-1.5	-11.2	-0.7	-32.5	£298,234	Cost saving
0.00011	(0.011)	Single	£1,777,735,472	2,905.9	54,238.6	1,447.3	39.9		
		Repeat	£1,787,398,064	2,904.3	54,226.3	1,446.5	4.1		
		Difference	£9,662,592	-1.7	-12.4	-0.8	-35.7	£270,443	Cost saving
0.00012	(0.012)	Single	£1,777,764,124	2,906.1	54,239.7	1,447.3	43.2		
		Repeat	£1,787,402,601	2,904.3	54,226.2	1,446.5	4.2		
		Difference	£9,638,476	-1.8	-13.5	-0.9	-39.0	£247,284	Cost saving

CS, congenital syphilis; ICER, IUFD, Intrauterine foetal demise; ICER, Incremental cost-effectiveness ratio. Lifetime costs and utilities were discounted at 3.5%.

[1]Lifetime health and social care costs adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.

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Table S20. Cost per screen needed to meet NICE ICER thresholds (Scenario 7)

Threshold of interest	Per screen cost required to achieve threshold	Incremental cost-effectiveness ratio (ICER)	Additional short-term cost (repeat screen vs. single screen)	Cost per CS case avoided (short-term cost)
Long-term health and social care costs and utilities				
£100k ICER threshold	£11.79	£99,877.04	£8,810,149	£1,596,738
£30k ICER threshold	£6.46	£29,884.61	£5,154,808	£934,250
£20k ICER threshold	£5.70	£19,904.45	£4,633,596	£839,786
Per screen cost half the baseline value (used in DSA)	£6.68	£32,773.60	£5,305,685	£961,594

CS, congenital syphilis; DSA, deterministic sensitivity analysis. ICERs were calculated using the additional lifetime health and social care cost of CS (£651,387) as used in Scenario 1 adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. Per screen cost was calculated to the nearest penny. Lifetime costs and utilities were discounted at 3.5%.

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, Title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2, Abstract
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5, Para 3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7, Line 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, Para 3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 7, Line 4
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, Para 2&3
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5, Para 3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, Para 3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 11, Line 10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

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	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 7, Para2 Supplementary material
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8/9 Table 1.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7 Final paragraph
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 6 Para 1 and Figure 1 & Figure S1.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Supplementary Table S1.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Sensitivity and Scenario analysis p10.
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 8/9 Table 1.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 8/9 Table 1.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

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		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 15.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 20

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Repeat screening for syphilis in pregnancy as an alternative screening strategy in the United Kingdom: a cost-effectiveness analysis

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Abstract

Objectives: To assess the cost-effectiveness of universal repeat screening for syphilis in late pregnancy, compared with the current strategy of single screening in early pregnancy with repeat screening offered only to high-risk women.

Design: A decision tree model was developed to assess the incremental costs and health benefits of the two screening strategies. The base case analysis considered short-term costs during pregnancy and the initial weeks after delivery. Deterministic and probabilistic sensitivity analyses and scenario analyses were conducted to assess the robustness of the results.

Setting: UK antenatal screening programme.

Population: Hypothetical cohort of pregnant women who access antenatal care and receive a syphilis screen in one year.

Primary and secondary outcome measures: The primary outcome was the cost to avoid one case of congenital syphilis (CS). Secondary outcomes were the cost to avoid one case of intrauterine fetal demise (IUFD) or neonatal death and the number of women needing to be screened/treated to avoid one case of CS, IUFD or neonatal death. The cost per quality-adjusted life year (QALY) gained was assessed in scenario analyses.

Results: Base case results indicated that for pregnant women in the UK (n=725,891), the repeat screening strategy would result in 5.5 fewer cases of CS (from 8.8 to 3.3), 0.1 fewer cases of neonatal death, and 0.3 fewer cases of IUFD annually compared to the single screening strategy. This equates to an additional £1.8 million per case of CS prevented. When lifetime horizon was considered, the incremental cost-effectiveness ratio (ICER) for the repeat screening strategy was £120,494.

Conclusions: Universal repeat screening for syphilis in pregnancy is unlikely to be cost-effective in the current UK setting where syphilis prevalence is low. Repeat screening may be cost-effective in countries with a higher syphilis incidence in pregnancy, particularly if the cost per screen is low.

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Strengths and limitations of this study

- This is the first health economic analysis to assess the cost-effectiveness of repeat screening strategy for syphilis in pregnancy compared to the single screen strategy within the UK setting.
- Experts provided input to inform the model inputs and validate the model structure and assumptions.
- Extensive sensitivity analyses were performed to assess uncertainty in the results.
- A lack of long-term data on the costs and utilities associated with congenital syphilis meant the focus of the analysis was on the short-term costs and health benefits, with the incremental cost-effectiveness ratio (ICER) being calculated in scenario analyses.

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Introduction

Syphilis is a bacterial sexually transmitted infection (STI) caused by *Treponema pallidum* subspecies *pallidum*. The prevalence of syphilis in the UK is low, however, the number of new diagnoses has increased over the last decade. In women, the number of cases rose from 345 in 2009 to 550 in 2018 [1].

Congenital syphilis (CS) occurs via vertical transmission of syphilis during pregnancy which can occur during any trimester and at any of the four stages of syphilis infection. The highest risk of transmission, however, occurs in primary syphilis when sores or chancres are present. Adverse pregnancy outcomes can include intrauterine fetal demise (IUFD), prematurity and neonatal death, with the risk being considerably higher in women with untreated syphilis than in pregnant women with no syphilis or in pregnant women who receive adequate treatment for syphilis following diagnosis at first trimester screening [2]. The risk of CS is difficult to quantify due to the small number of cases, the wide range of disease presentations and probable underdiagnosis. There is evidence, albeit limited, that the risk of CS is higher if women become infected whilst pregnant than if they have active syphilis at the time of conception [2,3]. In infants born with CS, the infection can cause reduced growth and development, neurological impairment, bone deformities, and hearing loss [4,5]. Infants treated with intravenous benzylpenicillin sodium in the first two months of life are reported to have a good short-term prognosis, but long-term outcomes have not been investigated in detail [6,7].

In the UK, routine antenatal screening for syphilis, hepatitis B and human immunodeficiency virus (HIV) is offered to all pregnant women at their first routine antenatal appointment, usually before 12 weeks gestation, or later, for the small proportion of women who first present in their second or third trimester [8,9]. Women who decline screening are formally re-offered and screening coverage currently exceeds 99.6% [9–11]. Blood samples are initially tested using an enzyme immunoassay (EIA) with a *T. pallidum* particle agglutination assay (TPPA) performed on the same specimen to confirm a positive result. Women with a positive TPPA result are referred to a sexual health clinic to assess whether they have an active infection which requires treatment or a previous infection not requiring treatment. It is possible that women who screen negative for syphilis become positive later in pregnancy, either because they become infected with syphilis, or because their infection was too recent for a detectable antibody response to have been mounted at the time of the first screen. Management guidelines, outside the national screening programme, recommend that women are offered repeat testing for syphilis in late pregnancy if they have been diagnosed and treated for syphilis in the first trimester, if they consider themselves to be at risk of infection, or have a single

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'high-risk' exposure [11,12]. Assessing women's risk can be problematic and risk can change during pregnancy. Data on coverage of repeat testing or management is not routinely collected. In 2011-13, the Surveillance of Antenatal Syphilis Screening (SASS) study was conducted to provide quantitative data on the performance of the screening pathway [13].

Syphilis prevalence in pregnant women is low, the SASS study found that 0.04% (1/2800) of pregnant women required treatment for syphilis in 2010-2011, although the prevalence may have subsequently increased [13]. CS incidence is also low and below the WHO elimination threshold of ≤0.5/1000 [14]. However, between March 2016 and January 2017, four cases of CS occurred in the UK in women who screened negative for syphilis in pregnancy [15]. None of whom had a repeat screen during pregnancy, and confirmatory testing later showed that they had acquired syphilis whilst pregnant. These infections would likely have been diagnosed and treated if repeat screening in late pregnancy was offered to all pregnant women, an approach that has not been assessed in the UK. Two models assessed the cost-effectiveness of universal repeat screening in the US, where the prevalence of syphilis in pregnant women is higher than in the UK. One found that universal repeat screening was cost saving [16], whilst the other found that it cost $419,842 per CS case avoided [17].

To inform the UK National Screening Committee (UK NSC) and in response to an increase in syphilis diagnoses in the UK and the continued occurrence of CS cases each year, albeit very small numbers, the clinical and cost-effectiveness of universal screening in the first and third trimesters, as an alternative strategy to universal screening in the first trimester only, was assessed.

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Methods

Model structure

A decision tree model in TreeAge (TreeAge Pro 2019, R2. TreeAge Software, Williamstown, MA, USA) was developed to assess the incremental costs and health benefits of universal repeat screening for antenatal syphilis compared with universal screening in the first trimester only (**Figure 1**). For both screening strategies, the decision tree followed the true disease state of women and the population was split into women screened in the first/second trimester and women screened in the third trimester (i.e. late presenters who would miss the opportunity for repeat screening). Women with a positive result received treatment at a sexual health clinic plus any additional testing required. Each branch (with or without syphilis) ended with the same pregnancy outcomes: IUFD or no IUFD, the latter resulting in a preterm or term delivery and either neonatal death, an infant with CS, or an infant with no CS (online supplement **Figure S1**).

Figure 1. Overview of decision tree comparing single screening with universal repeat screening of syphilis in pregnancy

Footnote:
PW, pregnant women; FN, false negative result; FP, false positive result; TN, true negative result; TP, true positive result.
With reference to the timing of 1st syphilis screen, 'early' refers to 1st or 2nd trimester and 'late' refers to the third trimester.
Where branches split, the probabilities are shown in the top branch, with # indicating (1-probability).
Blue circle indicates referral to specialist management for treatment and the same seven pregnancy outcomes (as is shown in the topmost branch). Each branch ends with the same outcomes, but with different probabilities for each branch. Pregnancy outcomes are presented in **Figure S1** in online supplement.

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The model included pregnant women in the UK who accessed antenatal care and received a syphilis screen in 2018 (the latest available data at the time). Pregnant women who were not screened (0.04%) were not included, since any change to the screening strategy would have no impact on their outcomes. Costs were considered from the UK healthcare system perspective. Social care costs were not included in the short-term. To assess the overall impact of the two screening strategies, the costs for all pregnancy outcomes for all women screened were considered, not just costs for women with syphilis. The model threshold for early versus late first screen was 28 weeks gestation, i.e. the start of the third trimester. The time horizon for the base case analysis considered short-term costs during pregnancy and the perinatal period. Lifetime costs and utilities were not used in the base case analysis (but were considered in scenario analysis) as the data available on the long-term costs and utilities associated with CS were limited and include too much uncertainty to provide a robust result. See **Table S1** for base case model assumptions.

Model parameters

Data were sought using PubMed, Google Scholar, online searches, references within papers, from experts and laboratory contacts and by data request to Public Health Agencies.

Clinical parameters

Key clinical parameters were derived from published data and national surveillance data. Where data were only available from outside the UK, they were scaled to reflect UK pregnancy outcomes and syphilis prevalence. See **Table 1** for clinical parameters and methods of estimation. Furthermore, data from a large meta-analysis [18] were adjusted to the UK setting to estimate the probability of each pregnancy outcome (online supplement **Tables S2-S5**).

Cost parameters

Cost parameters are presented in **Table 1**. National Health Service (NHS) tariff costs or published costs from the UK were used where possible. Where no UK data were available, micro-costing was used to calculate costs - informed by clinical guidelines, expert opinion and incorporating published NHS costs and tariffs where possible. To estimate the additional lifetime cost of CS, cost estimates from outside the UK were converted to pound sterling (£) [19]. Where necessary, costs were inflated to 2017/18 prices using mid-year conversion rates [20].

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Table 1. Clinical and cost parameters for model comparing single screening with universal repeat screening of syphilis in pregnancy in the UK

	Baseline value	Low	High	Distribution	Note
Clinical parameters					
Total number of women in model (representing one-year)	725,891	-	-	-	Based on number of deliveries in the UK in 2017/2018 and the screening uptake. See **Table S6**.
Probability of having syphilis at the start of pregnancy	0.00035	0.00028	0.00042	Beta	Data derived from 2011 SASS data [13] (England only [244/691,494]). Assume same risk in other UK countries.
Probability of becoming infected with syphilis during pregnancy	0.000017	0.0000017	0.00012	Beta	Incidence was estimated using published incidence and prevalence data from United States scaled to reflect UK prevalence [13,21].
Probability of receiving syphilis screen before 28 weeks gestation	0.947	0.936	0.984	Beta	Estimate based on gestational week at first antenatal attendance. **Table S7** in online supplement. The low value is in line with results from SASS study [13]. The high value is in line with data from Northern Ireland which (from the UK countries) has the highest proportion of women attending before 28 weeks.
Probability of true positive result	0.995	0.984	1.00	Beta	Based on the average test sensitivity of five EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK [22,23].
Probability of false negative result[1]	0.005	0.016	0.00	Beta	Based on the average test sensitivity of five EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK [22,23].
Probability of true negative result	0.998	0.999	0.99	Beta	Based on average test specificity of five EIA assays (99.8%) used in the UK. High and low are estimates [22,23].
Probability of false positive result[1]	0.002	0.001	0.01	Beta	Based on average test specificity of five EIA assays (99.8%) used in the UK. High and low are estimates [22,23].
Cost parameters					
Syphilis screen	13.36	6.68	26.72	Gamma	Estimated using micro-costing. Screening is performed at the same time as other antenatal blood tests – this would also be the case for repeat screening at 28 weeks gestation. See **Table S8**.

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	Baseline value	Low	High	Distribution	Note
Management women diagnosed with syphilis in pregnancy	314.09	251.27	376.91	Gamma	Clinical management by sexual health clinician estimate based on London Integrated Sexual Health Tariff [24]. See **Table S9**.
Intrauterine fetal demise (IUFD)[2]	4,356.80	3,485.44	5228.16	Gamma	Estimate based on 2013/14 published estimate from UK inflated to 2017/2018 costs [25].
Preterm delivery	7,100.37	5,680.30	8,520.45	Gamma	Estimate based on UK costs for delivery at 32-33 weeks and 34-36 weeks gestation (inflated from 2010/11 costs) [26]. UK data on gestational age at delivery (**Table S10**) were then used to calculate the proportion of deliveries at 32-33 (28%) and 34-36 weeks (72%).
Term delivery (37+ weeks)	2,034.62	1,627.69	2,441.54	Gamma	Estimate based on published cost using inflated 2010/11 UK data [26].
Neonatal death[3]	5,805.80	4,644.64	6,966.96	Gamma	Estimated using cost of IUFD plus additional hospital costs. See **Table S11**.
CS testing and treatment	6,607.68	5,286.14	7,929.21	Gamma	Estimated using micro-costing. See **Table S12** and **Table S13**.
CS neonatal screen	245.25	196.20	294.30	Gamma	Screening test for neonates born to women treated for syphilis in pregnancy. Estimated using micro-costing. See **Table S14**.
CS lifetime healthcare cost	80,423.37	-	-	Gamma	Average additional lifetime healthcare costs attributable to CS based on cost estimate for cerebral palsy (estimate from 2000) [27].
CS lifetime health and social care cost	651,387.47	-	-	Gamma	Average additional lifetime health and social costs attributable to CS based on cost estimate for cerebral palsy (estimate from 2000) [27].

[1] These probabilities refer to the final diagnosis after all diagnostic testing plus discussion with sexual health consultant if diagnostic tests result is positive for treponemal antibodies. [2]IUFD refers to the death of a baby in the uterus at ≥20 weeks gestation i.e. stillbirth. [3]Neonatal death refers to the death of a baby within the first 28 days after birth. EIA: Enzyme immunoassay. CS, congenital syphilis. For costs, high and low values are +/- 20% of baseline values with exception of syphilis screening cost where high and low values are +/- 50%.

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Outcomes

The primary outcome was cost to avoid one case of CS. Secondary outcomes were: cost to avoid one case of IUFD or neonatal death; the number of women who need to be screened to avoid one case of CS, IUFD or neonatal death; and the number of women who need to be treated for syphilis to avoid one case of CS, IUFD or neonatal death.

Sensitivity and scenario analyses

A univariate deterministic sensitivity analysis (DSA) was run for all probabilities and costs to determine which parameters had the greatest impact on the outcome of the model. This was done by selecting a high and low value for each input and generating outcomes. A probabilistic sensitivity analysis (PSA) using Monte Carlo simulation (1000 iterations) was used to assess the robustness of the results and calculate 95% credibility intervals (CIs) for each output using the mean and standard deviation. A beta distribution was used for clinical probability inputs, and a gamma distribution for cost inputs (**Table 1**).

As well as the base case analysis, seven scenarios were assessed to observe how changes in model assumptions and certain parameters impacted the main outcomes:

1) Lifetime time horizon with incremental cost-effectiveness ratio (ICER) in terms of cost per QALY as the main outcome.
2) Incomplete uptake of the repeat screen – where the probability of having a second screen was 99.6%, in line with the current uptake of screening in England.
3) Increased syphilis incidence - varying incidence at 10 intervals between the baseline and the high value used in sensitivity analysis (0.012%).
4) No late presentation to antenatal care – all women are screened twice in the repeat screening strategy.
5) 100% sensitivity and specificity of the syphilis screening process.
6) 100% specificity of the repeat screen (i.e. no false positives).
7) Examining the per screen cost required to meet the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20,000-£30,000 [28].

In scenario analysis 1, the lifetime healthcare and social care costs for infants born with CS were considered. Since no data on the lifetime cost of CS were available, cerebral palsy (CP) was used as a proxy as it can also lead to a range of disabilities, vary hugely in severity, and may sometimes be a result of CS. The lifetime health and social care costs of CP were taken from a single Danish study [27] adjusted to reflect UK life expectancy and gender split.

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As EuroQol-5D (EQ-5D) data have not been reported for CS or CP, a utility of 0.74 for infants with CS relative to a score of 1.00 for infants born with no CS were used, adapted from a 2006 study of new-born screening strategies where 0.74 was used for infants with 'mild developmental delay' [29]. These utility values were used in a similar health economic model from the US [16] and were used to calculate quality adjusted life-years (QALY). In the absence of data on changes to utility for infants born with CS, it was assumed that the difference in utility between infants born with CS and infants with no CS remained constant through childhood and adulthood.

Parental HRQoL were not considered as this would add complexity to the model. There are no published data on many of the utility scores for each of the pregnancy outcomes, for maternal syphilis diagnosis or receiving a false negative result. These would need to be based on uncertain estimates or from expert opinion due to limited evidence on HRQoL.

The life expectancy of infants with CS was estimated as 70 years, in line with the estimate for CP [27] and in light of reports of CS diagnoses in a wide range of ages [30]. The life expectancy of infants with no CS was estimated as 81 years based on current UK data [31]. All costs and utilities were discounted at 3.5%, in line with NICE guidelines for England [32]. In DSA, discounting of utilities was varied from 0 to 6%.

Patient and public involvement

There was no patient or public involvement (PPI) in the design of the evaluation. A report outlining the model was reviewed by the UK NSC which has PPI representation and was made available for public consultation.

Results

Base case analysis

The base case results indicate that in one year of screening pregnant women in the UK (n=725,891), the repeat screening strategy would result in 5.5 fewer cases of CS, 2 fewer cases of preterm delivery, 0.1 fewer cases of neonatal death (i.e. one less neonatal death every 10 years on average), and 0.3 fewer cases of IUFD compared to the single screening strategy (**Table 2**).

The healthcare costs would be £9,886,863 higher for the repeat screening strategy (£1,777,469,008 vs. £1,787,355,870 respectively when total annual screening costs, treatment costs, and delivery costs for all pregnant women screened were considered) with most of this increase (£9,162,355) being a result of the additional screening costs (**Table 3**).

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Table 2. Base case clinical outcomes for model comparing universal repeat screening of syphilis in late pregnancy with single screening

Screening strategy	Syphilis antenatal screens	Women treated for syphilis	False positive maternal syphilis	Intrauterine fetal demise (all causes)[1]	Preterm deliveries (all causes)[1]	Neonatal deaths (all causes)[1]	Congenital syphilis cases
Existing: single screen							
Estimate	725,891	1,705	1,451	2,904.4	54,228	1,446.5	8.8
95% CI[2]	725,891-725,891	1,698-1,737	1,443-1,482	2,890-2,916	53,905-54,282	1,441-1,457	8.7-8.9
Alternative: repeat screen							
Estimate	1,411,696	3,089	2,823	2,904.1	54,226	1,446.4	3.3
95% CI[2]	1,411,456-1,411,503	3,074-3,150	2,806-2,883	2,889-2,915	53,903-54,280	1,441-1,457	3.3-3.3
Difference	685,805	1,384	1,372	-0.3	-2	-0.1	-5.5

[1] These adverse pregnancy outcomes are all-cause outcomes for all 725,891 women screened, including the small number with syphilis infection.

[2] 95% CI, confidence intervals calculated using probabilistic sensitivity analysis.

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Table 3. Base case short-term annual healthcare costs from model comparing universal repeat screening of syphilis in late pregnancy with single screening

Screening strategy	Total healthcare costs	Cost breakdown[1]		
		Antenatal syphilis screening	Syphilis treatment (in pregnant women found positive)	Perinatal costs (for all pregnancies)
Existing: single screen				
Estimate	£ 1,777,469,008	£ 9,697,904	£ 535,434	£ 1,767,235,670
Lower 95% CI	£ 1,769,393,140	£ 9,661,636	£ 532,820	£ 1,759,111,560
Upper 95% CI	£ 1,778,772,048	£ 9,822,870	£ 545,591	£ 1,768,490,710
Alternative: repeat screen				
Estimate	£ 1,787,355,870	£ 18,860,259	£ 970,254	£ 1,767,525,357
Lower 95% CI	£ 1,779,322,118	£ 18,786,836	£ 964,636	£ 1,759,402,583
Upper 95% CI	£ 1,788,703,813	£ 19,100,346	£ 989,342	£ 1,768,782,187
Cost difference	£ 9,886,863	£ 9,162,355	£ 434,820	£ 289,687

[1] Costs to the NHS in the UK for all 725,891 pregnant women screened. Costs are spilt into 1) antenatal screening costs, which includes sample collection and laboratory testing; 2) syphilis treatment within sexual health clinics; and 3) perinatal costs, which includes the costs of delivery and neonatal care for all infants.

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Table 4. Requirements to prevent one outcome – from model comparing universal repeat screening of syphilis in late pregnancy with single screening

Outcome	Cost	Women screened in third trimester	Women treated for syphilis – TP and FP	Additional false positives
Congenital syphilis	£ 1,791,880	124,294	251	249
Intrauterine fetal demise	£ 37,852,707	2,625,664	5,300	5,251
Neonatal death	£ 79,507,578	5,515,066	11,133	11,030

FP, false positive; TP, true positive for syphilis infection.

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The model calculated that 124,292 women would need to be rescreened in the third trimester to prevent one case of CS, 2.6 million to prevent one case of IUFD (i.e. one case prevented approximately every 3.6 years if every pregnant woman was rescreened), and 5.5 million to prevent one case of neonatal death (i.e. one case prevented approximately every 7.6 years if every pregnant woman was rescreened, **Table 4**). It would cost an additional £1,791,880 per case of CS prevented, £37,852,707 per case of IUFD prevented, and £79,507,578 per neonatal death prevented. An additional 251 women need to receive treatment for syphilis to prevent one case of CS (**Table 4**).

Sensitivity and scenario analyses

The DSA results indicated that even accounting for parameter uncertainty, the total cost of the repeat screening strategy was always higher than the cost of the single screening strategy (see **Figure S2** in online supplement for Tornado diagram). Total costs were most sensitive to changes in the per screen cost, but also to changes in the specificity of the screening process, the proportion of women first attending antenatal care before their third trimester, syphilis incidence, and the cost of syphilis treatment (**Figure S2**). In the DSA examining the impact of clinical and cost parameters on the number of CS cases, the model was most sensitive to syphilis incidence during pregnancy and the probability of CS in infants born to women infected with syphilis during pregnancy who did not receive treatment (i.e. were undiagnosed; see **Figure S3**). In all iterations in the 1,000 PSA Monte Carlo simulations, the repeat screening strategy cost more than the single screening strategy and resulted in fewer cases of CS. The incremental cost and incremental cases of CS prevented are shown online in online **Figure S4**.

When lifetime costs and utilities were considered (Scenario 1), the health and social care cost per additional QALY gained for the repeat screening strategy (ICER) was £120,494. In DSA, the ICER was £32,716 and £205,600, when discounting of utilities was 0% and 6% respectively (see **Table S15** in online supplement). Even if a lower discounting rate were considered by NICE in the future, it is unlikely that 0% discounting would be used.

In further scenario analyses, reducing the uptake of repeat testing to 99.6% (in line with current uptake of the first screen, Scenario 2), including all women who attended antenatal care before their third trimester (i.e. no late first screen, Scenario 4), including 100% sensitivity and specificity of the screening process (Scenario 5), or including no false positives in the second screen (Scenario 6) had very little impact on the model outcomes, reducing the base case cost per CS case avoided by <10% (data not shown).

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When the probability of becoming infected with syphilis between screens was increased seven-fold to 0.00012 (Scenario 3), repeat screening resulted in 39 fewer cases of CS compared to single screening, 0.9 fewer neonatal deaths, 13 fewer preterm deliveries, and 1.8 fewer cases of IUFDs whilst the repeat strategy cost an additional £9,638,476 (**Table S16** and **S17** in online supplement). In this scenario, the cost per CS case prevented was £247,284 (**Table S18**). **Table S19** in the online supplement presents the cost per case of CS avoided and the ICER when the probability of becoming infected with syphilis between screens is higher than baseline (at 10 intervals between 0.00003 and 0.00012). As anticipated, with each increase in incidence, the repeat screening strategy resulted in more CS cases prevented and a lower cost per CS case prevented. When lifetime healthcare and social-care costs were considered, the ICER was £11,171 (below the £20-£30k threshold used by NICE), when syphilis incidence in pregnancy was 0.004% and became cost saving at an incidence of 0.005% (1 in 100,000) or higher.

Scenario 7 examined the cost per screen needed to meet NICE ICER thresholds (at the current syphilis incidence) (see supplementary material **Table S20**). The per screen cost would need to decrease from £13.36 to £6.46 to take the ICER below £30k and £5.70 to take it below £20k when lifetime health and social care costs and utilities of CS were considered.

Discussion

We report on the cost-effectiveness of repeat universal syphilis antenatal screening in the UK. Our results indicate that this screening strategy would not be cost-effective in the current UK setting where the prevalence and incidence of syphilis among pregnant women is low. Although the repeat screening strategy is likely to result in fewer cases of CS, the number of cases prevented would be small, 5-6 a year, and would cost an additional £9.9 million, equivalent to £1.8 million per case prevented. Most of the increase in cost is a result of the additional costs related to providing the second screen rather than treatment or delivery costs for women with syphilis.

The PSA and DSA indicated that the model results are robust to changes in the inputs. When lifetime health and social-care costs and health-related quality of life were considered (Scenario 1), the cost per QALY gained was £120,494 for the repeat screening strategy compared to the single screening strategy. This is well above the £20k-30k cost per QALY threshold that NICE uses to assess interventions [28], and also exceeds the £100,000 threshold used to assess drugs/interventions for rare conditions (the threshold used when the intervention results in <10 additional QALYs to an individual in their lifetime) [33]. For this analysis, costs and utilities were discounted by 3.5%, in line

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with NICE guidelines for England [32]. When no discounting of utilities was assessed in DSA, the cost per QALY gained was £32,716, just above the £30k threshold.

Only two previous economic evaluations have assessed universal repeat syphilis screening in pregnancy compared to single screening in early pregnancy, both in the United States (US). Albright *et al.* reported that repeat third-trimester screening would prevent 60 CS cases per 4 million women costing $419,842 per case avoided, concluding that repeat screening was not cost-effective [17]. Hersh *et al.* found that repeat screening would prevent 41 CS cases per 3.9 million women and result in total cost savings of $52 million [16]. Neither study accounted for late presentation to antenatal care - syphilis prevalence and incidence were considerably higher than in the UK as were healthcare costs.

It is important to note that changes to the screening strategy would not change the number of adverse pregnancy outcomes in women who decline screening, in women who present late to antenatal care and have one screen but no opportunity for a repeat screen, or in women who first present at the time of delivery, thereby missing the opportunity for any antenatal screening or treatment. For this reason, and because treatment for syphilis is not universally effective at preventing adverse pregnancy outcomes, it is likely that there would continue to be a very small number of infants born with CS each year irrespective of changes made to the screening strategy.

Strengths and weaknesses

This is the first health economic analysis to assess the costs and clinical benefits of a repeat screening strategy for syphilis compared to a single screen strategy within the UK setting. The input values in the model were based on the best available evidence from the published literature, UK-specific surveillance data, NHS tariffs and published costs, and with input from experts in the field were data were lacking. These inputs were rigorously tested in sensitivity and scenario analyses to add confidence to the results, despite limited data in some areas.

There were sparse UK data available on pregnancy outcomes in women treated for syphilis or in infants born with CS. There are no published EQ-5D scores for CS and a lack of evidence on changes to utility and health and social care costs over time for infants born with CS. We therefore used the additional lifetime cost of CP, estimated in a study from Denmark [27], as a proxy for the lifetime cost of CS. As such, the primary focus of the analysis was the short-term costs and CS cases avoided since it was difficult to have confidence in the estimate used for lifetime CS cost or utility.

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The model assumed that women could not become infected with syphilis between the repeat screen and delivery. As the incidence estimate relates to the full duration of pregnancy, this assumption would overestimate the number of women diagnosed at the repeat screen and treated, therefore overestimating the benefits of the repeat screen strategy. However, the number of women who become infected with syphilis is small and thus this would likely have little impact on the overall results. Since we do not know what repeat screening coverage would be, the model assumed 100% coverage, since all women in the model had already agreed to a first screen. This is optimistic since it assumes continued engagement with antenatal services. However, scenario analysis 2 showed that even when uptake was <100% it would be unlikely to have much impact on the cost per CS case avoided.

It was also assumed that all women and neonates diagnosed with syphilis receive the appropriate full course of treatment and all infants born to women diagnosed with syphilis in pregnancy receive syphilis testing at birth. However, the SASS study [13] found that in 2010-11, not all women diagnosed with syphilis received complete treatment and inadequate paediatric follow-up was identified as an issue. Lack of treatment in these women and neonates is likely to make the repeat screening even less cost-effective.

Since there are no published estimates of the diagnostic accuracy (DA) of the syphilis screening process, accounting for the diagnostic accuracy of laboratory assays and the diagnosis decision making by clinicians, average sensitivity and specificity of EIA assays used in UK laboratories were used [23]. The DA values used here are considerably higher than those used in the US models [16,17], where a different testing algorithm is used [22] and would, if anything, bias repeat screening results towards being more cost-effective.

Implications for clinicians and policymakers

The number of CS cases was most sensitivity to changes in the syphilis incidence between screens. It may be cost-effective to repeat screen for a period of time where there is a known syphilis outbreak or if there are multiple cases of CS in a short period within the same geographical area in women who tested negative for syphilis at the first screen - as this would indicate a much higher syphilis incidence in pregnancy in that area.

Our model focused on the UK but is relevant to other European countries with similar syphilis prevalence and healthcare costs. Our analyses, using UK cost estimates, suggest that a universal second screen in late pregnancy could become cost-effective if the incidence of syphilis in pregnancy

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were to increase (to 5 per 100,000 pregnant women), indicating that in countries that have far higher syphilis prevalence than the UK, a second screen could be cost saving. For example, recent estimates suggest that the prevalence of syphilis in the WHO African region is more than 10-fold higher than in the WHO European Region [34]. In such a high prevalence setting, combined with lower local healthcare costs, a second syphilis screen in late pregnancy could be cost-effective.

There could be some negative impact associated with repeat screening. A false positive result may lead to additional costs, unnecessary anxiety for mothers and their families, impact the mother's relationships, possibly even damage their confidence in the screening programme, as well as lead to overtreatment. It is vital to minimise unnecessary use of antibiotics where possible given growing concerns around antimicrobial resistance and because there is some evidence that antibiotic use in pregnancy increases the risk of childhood epilepsy, obesity, and asthma [35].

Alternative approaches to reduce the number of CS cases and other adverse pregnancy outcomes could be more cost-effective and should be explored. These include better targeting of high-risk individuals and sexual health promotion in pregnancy. Furthermore, of the 20 CS cases in the UK since 2010, 11 had no record of the mother receiving antenatal screening. It remains unknown whether this was because testing was refused or due to very late/no first antenatal attendance [15]. This highlights the need to ensure timely screening in pregnancy, particularly in women who present late who are already at increased risk of adverse pregnancy outcomes. Education for pregnant women around sexual health and STI prevention might be cost-effective and could be considered.

Unanswered questions and future research

Our model had a single disease focus. At present however, pregnant women are screened for syphilis, HIV and hepatitis B. It would be useful to assess the potential cost-effectiveness of a repeat screen for all three infections since treatment for these infections during late pregnancy and/or at birth would reduce the risk of vertical transmission. Screening for all three infections may yield more benefits in terms of clinical outcomes and may make this strategy more cost-effective.

Furthermore, data collection including gestational week of first screen, coverage of repeat screen in high-risk women, pregnancy outcome for women treated for syphilis, stage of infection in women diagnosed with syphilis, and cost estimation for lifetime costs of being born with CS, would help inform future evaluations of screening strategies.

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Conclusions

The results of this health economic analysis indicate that implementing universal repeat screening for syphilis in pregnancy is unlikely to be cost-effective in the current UK setting where the prevalence and incidence of syphilis in pregnant women is low. Repeat screening could be considered in areas with a high syphilis incidence in pregnancy and may then be cost-effective, particularly if the cost per screen were low.

If syphilis prevalence continues to increase, the cost-effectiveness of the repeat screening strategy should be re-examined, highlighting the importance of continued monitoring of syphilis in pregnant women, screening uptake, CS cases and long-term follow-up.

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Author contributions: The model structure was developed by SH, with input from GW, FS and JM. The final model structure was informed by input from JM, HB, MT, IA, KT and EA. SH developed the model parameters with input from MT, IA, GW, HB, FS, JM and KT. SH drafted the paper. All authors contributed to the interpretation of the results and contributed to the contents of the paper. All authors have approved the final submitted version.

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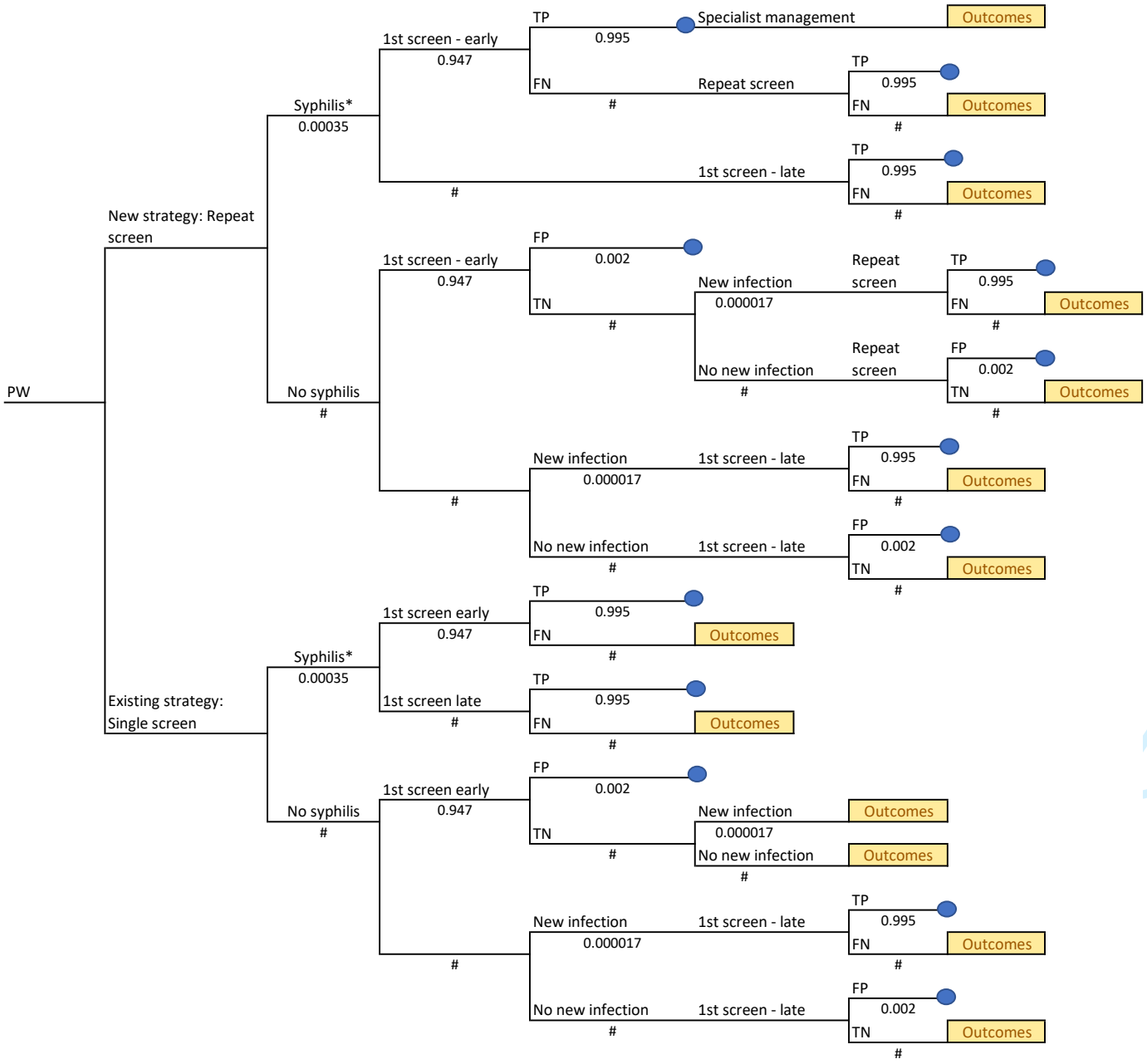
PW
New strategy: Repeat screen
Existing strategy: Single screen
Syphilis*
0.00035
No syphilis
#
1st screen - early
0.947
1st screen late
1st screen early
TP
0.995
FN
FP
0.002
TN
Specialist management
Repeat screen
New infection
0.000017
No new infection
1st screen - late
Outcomes

Online Supplement

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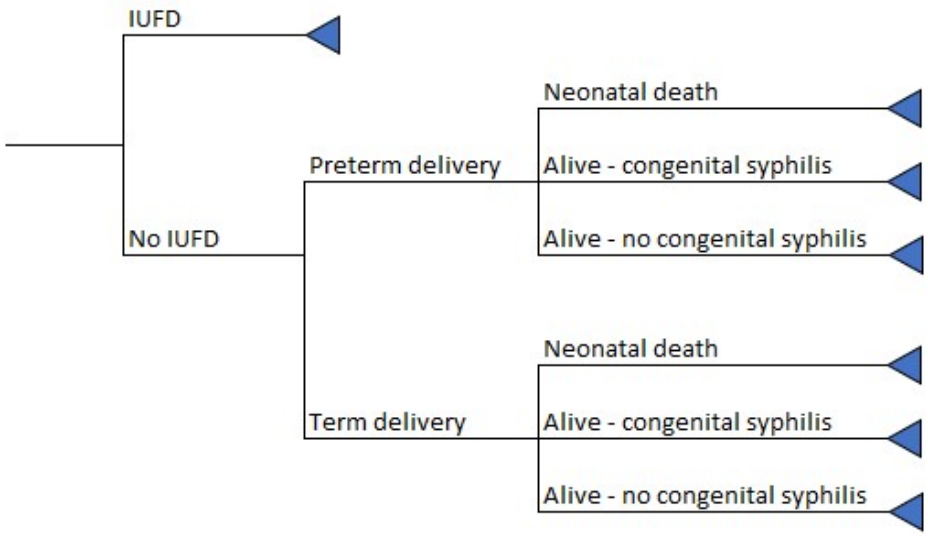
Figure S1. Pregnancy outcomes used in the decision tree comparing universal repeat screening of syphilis in late pregnancy with single screening



Footnote:

IUFD, intrauterine fetal demise; preterm refers to <37 weeks gestation. The blue triangle indicates the branch end point.

This diagram complements **Figure 1** in the main body of the paper. The probability of each of these outcomes occurring for each branch of the tree is presented in **Table S2**.

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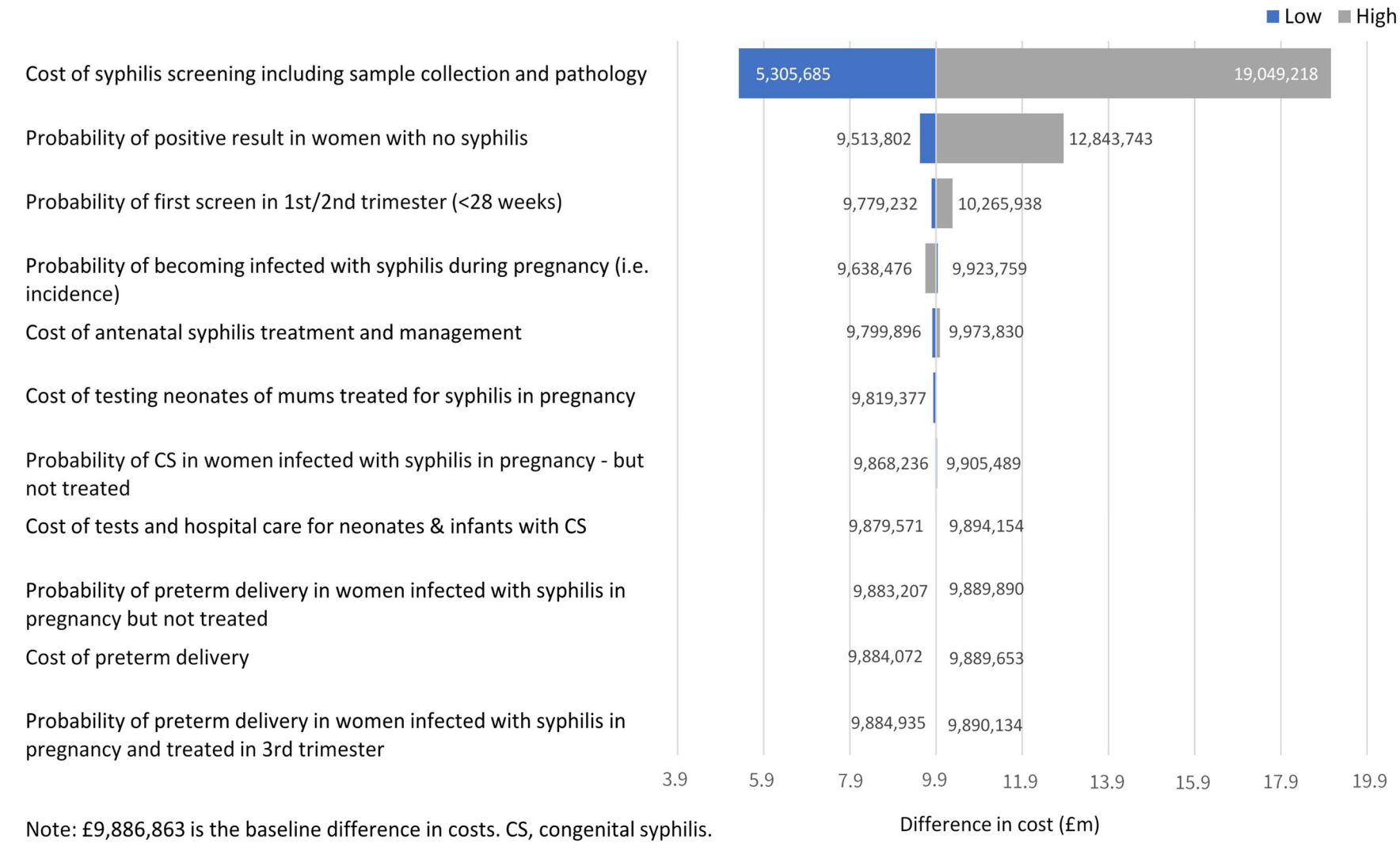
Figure S2. Tornado diagram – one-way deterministic sensitivity analysis of total costs - parameters with least impact removed



Note: £9,886,863 is the baseline difference in costs. CS, congenital syphilis.

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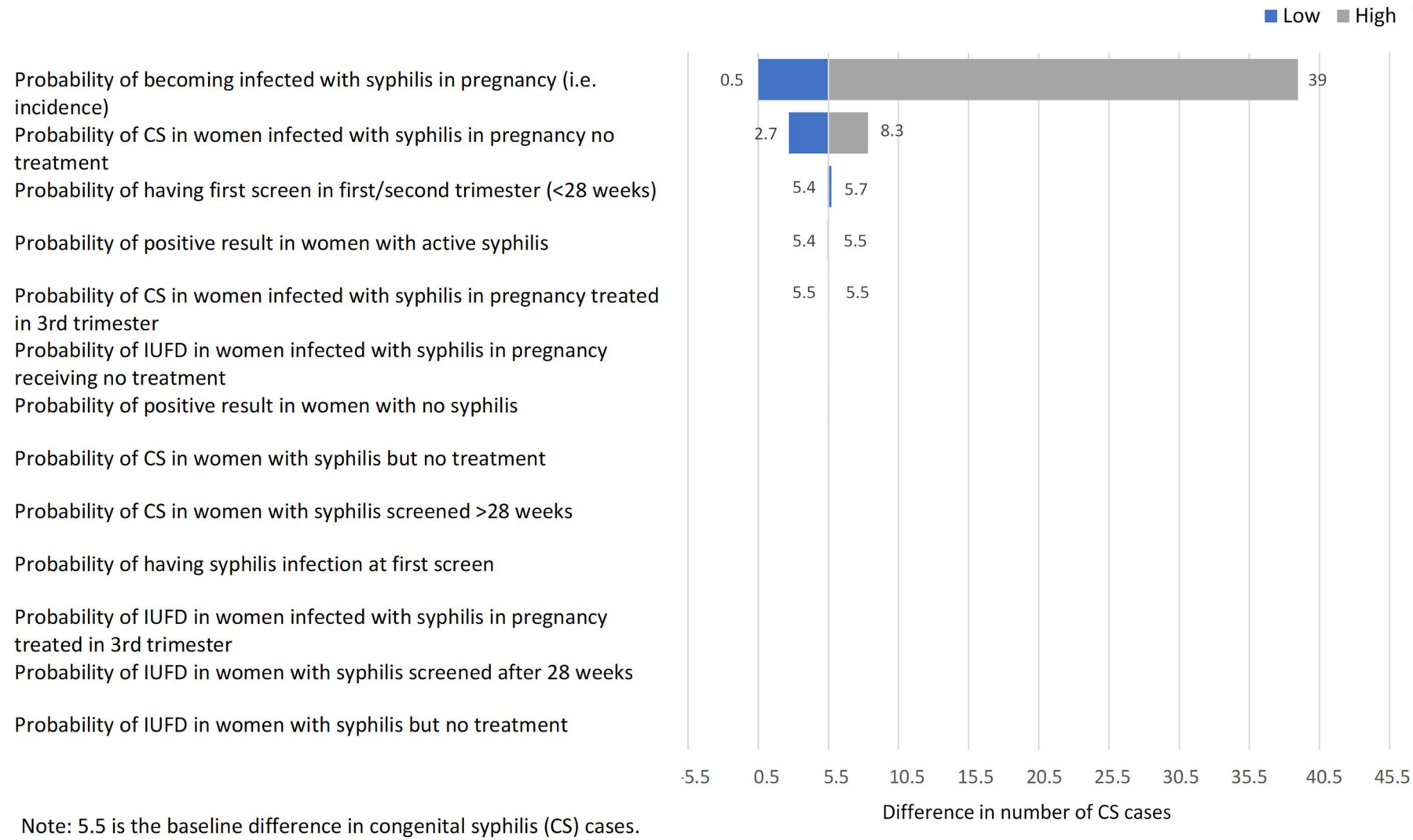
Figure S3. Tornado diagram - one-way deterministic sensitivity analysis of CS cases - parameters with least impact removed



Note: 5.5 is the baseline difference in congenital syphilis (CS) cases.

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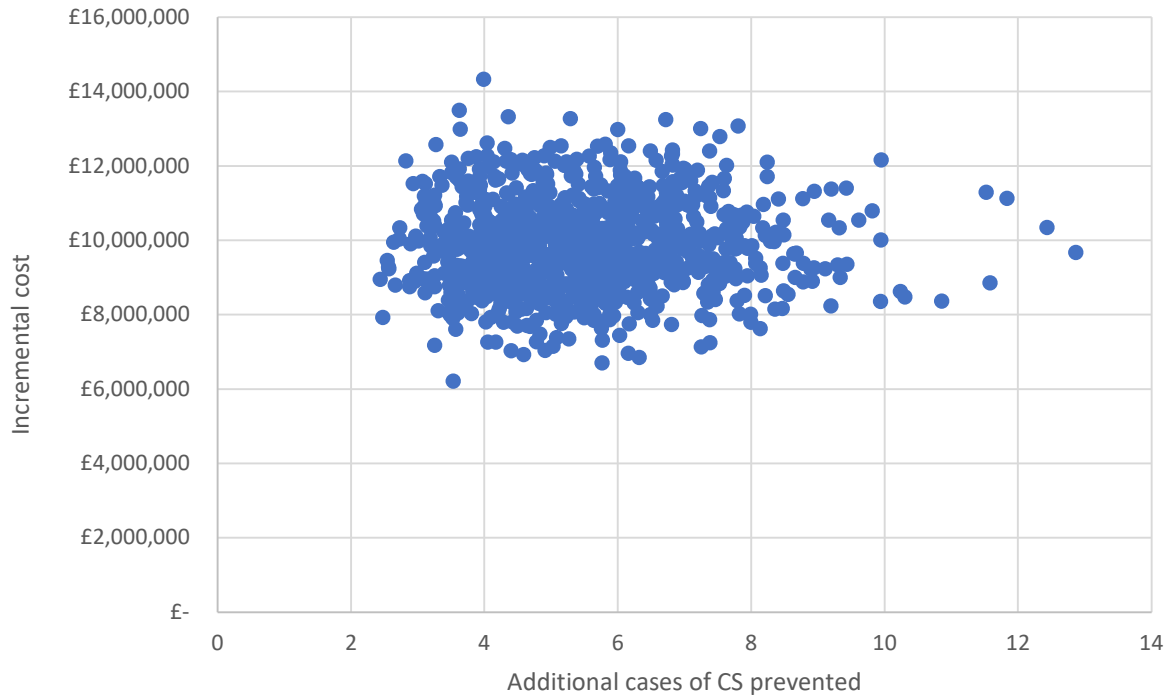
Figure S4. Incremental cost versus additional cases of CS prevented



This figure is an output from the Probabilistic Sensitivity Analysis (PSA) and shows the impact of parameter uncertainty on the cost per additional case of CS prevented in universal repeat screening of syphilis in late pregnancy versus single screening.

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Table S1. Assumptions applied to screening strategies and rationale

Assumption	Note
All women found positive for syphilis, at their first or repeat screen, are referred to care within a sexual health clinic and are successfully treated within that setting.	As per clinical guidelines [1]. Uptake of treatment in diagnosed women is thought to be high. No published data were found to support or refute this assumption.
The clinical management of women who are diagnosed with syphilis at their first screen includes repeat testing of syphilis and as such they do not receive a repeat screen as part of the IDPS in either screening strategy.	Recommendation from experts. This is hypothetical, as repeat screening is not current practice.
Infants born with CS display signs of CS, 40% at birth and 60% some weeks/months after delivery and are tested and treated accordingly.	Based on expert opinion and evidence indicating that most infants with CS develop signs by 5 weeks. Lack of data on the proportion of CS cases with late presentation (after two years) [1].
There is no loss to follow-up, i.e. all women who are identified as needing treatment receive it.	Inclusion of loss to follow-up in the model would add unnecessary complexity to the model. Also, there is lack of data on loss to follow-up in this setting.
There is 100% uptake of repeat screening in women who were initially screened.	Assessed in Scenario Analysis 2.
The model inputs are not correlated.	To avoid over complexity in the model and due to lack of evidence around correlation.
Pregnant women who attend first antenatal care late receive their first screen at that point and therefore miss the opportunity for a repeat test.	Recommendation from experts. This is hypothetical, as repeat screening is not current practice.
Preterm vs. term delivery impacts costs but the model assumes it has no impact on the risk of pregnancy outcomes (neonatal death or congenital syphilis).	Lack of data around correlation between timing of delivery and pregnancy outcome.
The repeat screen would be performed at 28 weeks gestation to coincide with existing routine anaemia blood tests. It was assumed that no new syphilis infection could occur between this screen and delivery.	No data could be found on the incidence of syphilis or the impact of a new syphilis infection that late in pregnancy. Timing of repeat screen based on expert advice – and is hypothetical as repeat screening is not current practice.
No women undergo a repeat screen in the current care pathway (i.e. the single screening strategy).	Following expert advice that few high-risk women receive repeat screening at present. Lack of data around uptake of repeat screening and pregnancy outcomes for low risk vs. high risk women.

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Table S2. Pregnancy outcomes - parameter inputs for decision tree comparing universal repeat screening of syphilis in late pregnancy with single screening

Parameter	Baseline value	Low	High	Note
Pregnant women with no syphilis				
IUFD	0.004	0.003	0.005	**Tables S3-S5**
Preterm delivery	0.075	0.058	0.097	**Tables S3-S5**
Neonatal death	0.002	0.001	0.003	**Tables S3-S5**
Congenital syphilis	0.000	-	-	Assumption
Pregnant women with syphilis diagnosed and treated <28 weeks				
IUFD	0.005	0.002	0.012	**Tables S3-S5**
Preterm delivery	0.079	0.042	0.143	**Tables S3-S5**
Neonatal death	0.003	0.001	0.014	**Tables S3-S5**
Congenital syphilis	0.011	0.008	0.016	**Tables S3-S5**
Pregnant women with syphilis diagnosed and treated ≥28 weeks				
IUFD	0.023	0.018	0.028	**Tables S3-S5**
Preterm delivery	0.183	0.119	0.275	**Tables S3-S5**
Neonatal death	0.013	0.005	0.032	**Tables S3-S5**
Congenital syphilis	0.038[1]	0.029	0.047	**Tables S3-S5**
Pregnant women with syphilis not diagnosed or treated				
IUFD	0.028	0.023	0.033	**Tables S3-S5**
Preterm delivery	0.241	0.188	0.305	**Tables S3-S5**
Neonatal death	0.014	0.009	0.022	**Tables S3-S5**
Congenital syphilis	0.034[1]	0.026	0.042	**Tables S3-S5**
Pregnant women infected with syphilis in pregnancy and diagnosed and treated in 3rd trimester				
IUFD	0.006	0.002	0.013	Assumed to have same risk as women diagnosed and treated for syphilis infection in 1st trimester.
Preterm delivery	0.071	0.038	0.127	
Neonatal death	0.003	0.001	0.015	
Congenital syphilis	0.010	0.007	0.014	
Pregnant women infected with syphilis during pregnancy not diagnosed or treated				
IUFD	0.028	0.023	0.033	Assumed to have same risk as women with syphilis not diagnosed or treated. Estimate based on expert opinion.
Preterm delivery	0.241	0.188	0.305	
Neonatal death	0.014	0.009	0.022	
Congenital syphilis	0.500	0.250	0.750	

IUFD, intrauterine foetal demise. Low and high values are based on the 95% confidence intervals (CIs) from the meta-analysis Qin *et al.* [2] adjusted to the UK setting in the same way as the baseline values (See **Tables S3-S5**).

[1]The probability of congenital syphilis in women with syphilis is higher in women treated at ≥28 weeks gestation than in women receiving no treatment. This is because estimates are from a meta-

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analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.

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Table S3. Pregnancy outcome data taken from published large meta-analysis of international studies [2]

Pregnancy outcome	Women with no syphilis	Syphilis infection at time of conception					New syphilis infection during pregnancy	
		a	b	c	d	e	f	g
		First screen + treatment 1st trimester	First screen + treatment 2nd trimester	First screen + treatment 1/2nd trimester	First screen + treatment 3rd trimester	No treatment	Repeat screen + treatment 3rd trimester	No treatment
Congenital syphilis	0.0%	10.4%	17.6%	12.1%	40.6%	36.0%	10.4%	50%
Preterm delivery	7.2%	6.8%	10.1%	7.6%	17.6%	23.2%	6.8%	23.2%
IUFD (stillbirth)	3.7%	5.3%	4.2%	5.0%	21.3%	26.4%	5.3%	26.4%
Neonatal death	2.0%	3.8%	3.0%	3.6%	15.1%	16.2%	3.8%	16.2%

These data are from a systematic review and meta-analysis which measured pregnancy outcomes in women with and without syphilis (Qin *et al.* [2]). Each estimate is an average calculated by combining data from 2-33 different studies.

The risk of neonatal death was reported for the whole of pregnancy but was not calculated separately for treatment in each pregnancy trimester. For the model, the risk of intrauterine fetal demise (IUFD) in each trimester compared to the overall risk in pregnancy was used to estimate the risk of neonatal death in each trimester compared to the overall risk in pregnancy.

Column c, the risk of pregnancy outcomes if syphilis is diagnosed and treated in the 1st or 2nd trimester, was calculated using data from the 1st and 2nd trimesters (column a and b) and using UK data to calculate the proportion of women first attending antenatal care in their 1st or 2nd trimester (75.9% and 24.1% respectively). For example, the risk of congenital syphilis (CS) was calculated as follows: (0.759*0.104) + (0.241*0.176) = 0.121.

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Column e: no treatment group due to a false negative test result. The probability of CS in women with syphilis is higher in women treated in 3rd trimester (column d) than in women receiving no treatment (column e). This is because estimates are from a meta-analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.

Column f: women infected with syphilis during pregnancy but diagnosed and treated at their repeat screen (in third trimester) are assumed to have the same risk of adverse pregnancy outcomes as women who are diagnosed and treated in their first pregnancy trimester (column a) (from expert opinion).

Column g: the risk of preterm delivery, IUFD and neonatal death is assumed to be the same as for women who have syphilis at conception but who are not treated in pregnancy (column e). However, the risk of CS is estimated as 50%, since the risk is known to be high in primary infection (from expert opinion).

The risk of adverse pregnancy outcomes in women with no syphilis in the meta-analysis data (Qin *et al*) [2] were considerably higher than the numbers seen in pregnant women in the UK. The risk of CS in women with syphilis was also considerably higher in the meta-analysis results than seen in the UK [3,4]. Therefore, these inputs were adjusted to the UK settings (See **Table S4**).

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Table S4. Comparing the risk of adverse pregnancy outcomes in meta-analysis with risk observed in the UK in order to scale meta-analysis data

Pregnancy outcome	Meta-analysis data [2] A	UK data [n/N] B	UK vs. meta-analysis C	UK data reference
Women with no syphilis				
Preterm delivery	7.2%	7.485% [57,079/762,594]	104.0%	**Table S10**
IUFD (stillbirth)	3.7%	0.393% [3.93/1000] [1]	10.6%	[5]
Neonatal death	2.0%	0.172% [1.72/1000] [1]	8.6%	[5]
Women with syphilis				
Congenital syphilis (any trimester)	13.7%	1.28% [3.4/266][2]	9.4%	[3,4]

[1]The most recent data on pregnancy outcomes from the UK were from 2016 when the total number of pregnancies in the UK was 780,043 [5]. Pregnancy outcomes reported from the UK as a whole are used for the no syphilis group.

[2] Based on the numbers in our model, we would expect at total of 266 women in 2017/18 to have syphilis in pregnancy i.e. 254 women at the start of pregnancy [0.00035*725,891] plus 12 women infected during pregnancy [0.000017*725,637].

No data on the risk of the different pregnancy outcomes during each trimester were available from the UK. Therefore, the difference in overall risk in pregnancy between the UK and the metanalysis data was used to adjust data from the meta-analysis to calculate the risk of outcomes in each trimester for women in the UK. The calculated risks, used in the model, are presented in **Table S5** and an example of how they were calculated is included in the **Table S5** footnotes.

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Table S5. Pregnancy outcome data used in the model – adjusted from published large meta-analysis of international studies [2] to reflect UK risks

Pregnancy outcome	Women with no syphilis	Syphilis infection at time of conception					Becomes infected during pregnancy	
		First screen + treatment 1st trimester	First screen + treatment 2nd trimester	First screen + treatment 1/2nd trimester	First screen + treatment 3rd trimester	No treatment	Repeat screen + treatment 3rd trimester	No treatment
Congenital syphilis	0.0%	0.97%	1.65%	1.14%	3.80%	3.37%	0.97%	50.0%
Preterm delivery	7.48%	7.07%	10.50%	7.90%	18.03%	24.12%	7.07%	24.12%
IUFD (stillbirth)	0.39%	0.56%	0.45%	0.53%	2.26%	2.80%	0.56%	2.80%
Neonatal death	0.17%	0.32%	0.26%	0.31%	1.30%	1.39%	0.32%	1.39%

These numbers were calculated using data from a meta-analysis (**Table S3**) adjusted by the difference in the (overall) risk of pregnancy outcomes between the UK and the meta-analysis (**Table S4**, column C).

For example, the risk of congenital syphilis (CS) in women treated for syphilis in the 1st/2nd trimester (1.14%) was calculated as follows: (0.121*0.094) = 0.0114 i.e. the risk of CS in the 1st/2nd trimester from the meta-analysis (**Table S3**, column C) multiplied by the proportional in of risk of CS in pregnancy in the UK vs. the meta-analysis (**Table S4**, column C).

The published 95% confidence intervals were adjusted in the same way to calculate the low and high values used in the sensitivity analysis.

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Table S6. Overall number of women screened for syphilis in pregnancy, 2017/18

Country	Total number of deliveries	Estimated number screened	Reference
England	626,203	623,698	[36]
Northern Ireland	23,045	23,038	[38]
Scotland	51,197	50,992	[39]
Wales	28,361	28,248	[40]
UK total	728,806	725,976	

In England, Wales and Scotland, these data exclude women giving birth at home or in non-NHS hospitals.

Screening uptake in 2017/2018 for England, Wales and Scotland was estimated as 99.6% i.e. the same as uptake in England in 2016/2017 [15].

The uptake of screening in 2017/2018 for Northern Ireland was 99.97%, based on data collected by Public Health Agency Northern Ireland 2017/2018.

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Table S7. Gestational week at first antenatal care attendance – by UK country

UK country	<12 weeks		12-28 weeks		≥28 weeks		No data	With data available	Total	Reference
	n	%	n	%	n	%				
England	299,634	70.1%	103,137	24.1%	24,935	5.8%	~200,000	427,706	-	[6]
Northern Ireland	15,069	65.4%	7,607	33.0%	365	1.6%	4	23,041	23,045	[7]
Scotland	42,840	84.2%	5,876	11.5%	2,165	4.3%	316	50,881	51,197	[8]
Wales	22,878	82.2%	4,226	15.2%	745	2.7%	512	27,849	28,361	[9]
UK total	380,421	71.8%	120,846	22.8%	28,210	5.3%		529,477		

All data are for year 2017/18. The SASS study [3] found that in women screening positive for syphilis, 6.4% (81/1271) had their first antenatal attendance at 27 weeks or later. These data were used to calculate pregnancy outcomes and the percentage of women receiving a first syphilis screen before 28 weeks gestation (94.7% i.e. 501,267/529,477).

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Table S8. Calculating the cost per antenatal syphilis screen

Activity	Cost per item (£)	Proportion with cost	Average cost/person (£)	Notes
Blood sample collection	0.23	1.00	0.23	Includes only equipment costs. Syphilis screening is performed at the same time as other antenatal screening tests – and therefore does not incur additional staff time.
Laboratory testing (higher cost)	16.50	0.50	8.25	Price quoted in London Sexual Health full STI screen tariff [10].
Laboratory testing (lower cost)	9.00	0.50	4.50	Price quoted by laboratory manager in Leeds. This is the price charged per screen. It covers consumables, internal quality control (IQC), external quality assessment (EQA), laboratory staff time, and overheads. It accounts for the ratio of negative (which require only one test), positive (which require confirmatory work) test results.
Input from multi-disciplinary team	37.50	0.002	0.08	Estimate 1/500 women require 30 minutes input from the MDT based on expert opinion.
Reference laboratory testing	40.00	0.003	0.10	Estimate 1/400 samples sent to reference laboratory for confirmatory testing based on England's central reference lab receiving ~1300 samples/year (personal communication with laboratory manager).
Repeat test blood collection	3.86	0.01	0.04	1/100 women require a repeat test due to inconclusive test results. This cost is taken from London Sexual Health full STI screen tariff [10].
Laboratory testing (higher cost)	16.50	0.005	0.08	Repeat test due to inconclusive test result from first assay.
Laboratory testing (lower cost)	9.00	0.005	0.05	Repeat test due to inconclusive test result from first assay.
Referral to sexual health clinic	56.60	0.0006	0.04	Women with positive result for antibodies are referred to Sexual Health Clinic for sexual history and risk assessment. Cost based on a 30-minute appointment with a consultant plus 5 mins of receptionist time (staff costs taken from PSSRU 2017/18 [11]). Proportion taken from SASS study [3] which found 607/961,494 women had positive antibody result but did not then require treatment.
Total			**13.36**	

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Footnote: A 50:50 split between the higher and lower costs for laboratory tests was used. The cost of a repeat screen was assumed to be the same as the cost of a first screen since in both cases, samples would be taken at a routine antenatal appointment when other blood tests are performed, i.e. HIV and hepatitis B screening at first screen and routine anaemia blood tests at 28 weeks gestation.

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Table S9. Calculating the cost of treatment and management of women diagnosed with syphilis in pregnancy

Activity	Cost per woman (£)	Notes
STI Intervention C - Management of reactive treponemal serology	262.34	Cost taken from the London Integrated Sexual Health Tariff 2017/18 which includes 5 visits to clinic for treatment with penicillin regimen appropriate for the stage of infection [1,10]. In pregnant women diagnosed in the first trimester, all 5 visits would occur before delivery, in women diagnosed in final trimester, 3/5 visits would occur before delivery and 2 after delivery (personal communication with senior sexual health consultant).
Additional cost at 1st visit	16.50	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Additional cost at 2nd visit	8.25	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Additional cost at 5th visit	27.00	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [11].
Total	**314.09**	

There would be no change to the staff grade (from the tariff) at the 3rd or 4th visit, when the patient would be seen by a nurse.

This cost was calculated based on expert opinion from a senior consultant in sexual health.

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Table S10. Gestational week at delivery (used for calculating delivery costs and estimating pregnancy outcomes)

Country	≤33 weeks		34-36 weeks		>36 weeks		No data	With data available	Total	Ref	Notes
	n	%	n	%	n	%					
England	13,846	2.1%	35,533	5.4%	607,972	92.5%		657,351	-	[19]	2014 data
Northern Ireland	470	2.0%	1,385	6.0%	21,190	92.0%	0	23,045	23,045	[7]	2017/18 data
Scotland	868	1.7%	2,444	4.9%	46,791	93.4%	207	50,103	50,310	[8]	2017/18 data
Wales	723	2.3%	1,810	5.6%	29,562	92.1%	141	32,095	32,236	[20]	2017 data
UK total	15,907	2.1%	41,172	5.4%	705,515	92.5%		762,594			

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Table S11. Calculating the average healthcare costs associated with a neonatal death

Activity	Resource/ Activity	Quantity	Cost per unit	Total cost	Ref	Notes:
Cost of IUFD	-	-	-	£4,356.80	[12]	
Hospital stay	Day	3	£483.00	£1,449.00	[1,13]	Based on NHS tariff for Paediatric Major Infections with CC Score 0 - HRG code PW16E.
Total cost				**£5,805.80**		

The cost of neonatal death is calculated using the cost of intrauterine fetal demise (IUFD), which includes the cost of post-mortem, parental counselling and a subsequent pregnancy, plus an additional 3-days in a paediatric intensive care unit for the neonate. Three days hospital stay is an estimate based on expert opinion.

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Table S12. Calculating the cost of testing for syphilis in neonates with clinical signs of congenital syphilis (CS)

Activity	Number		Resource type	Resource/ Activity	Quantity /minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
	At birth	After birth							
Clinical assessment for signs of CS	1		Staff time	Consultant paediatrician	30	108.00	54.00	[11]	
Review of syphilis test results		8	Staff time	Consultant paediatrician	10 per review	108.00	144.00	[11]	
RPR/VDRL blood test	1	4	Staff time	Blood taken by nurse (band 6)	10 per test	45.00	37.50	[11]	Test at birth, 1, 3, 6 and 12 months.
IgM EIA blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	Test at birth, 1 and 3 months.
Syphilis blood tests (as above)	2	6	Diagnostics	Laboratory tests	5 (3 combined + 2 single)	12.75	63.75		Same cost if both tests are performed or only RPR/VDRL blood test performed.
Blood tests: full blood count, liver function, electrolytes	1		Staff time	Blood taken by nurse	10	45.00	7.50	[11]	
Blood tests (as above)	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
Lumbar puncture (white blood cell, protein, RPR, TPPA)	1		Staff time	Paediatric registrar	45	43.00	32.25	[11]	
Blood tests (as above)	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
X-ray of long bones	1		Staff time	Consultant Radiographer	30	93.00	46.50	[11]	Based on cost of Band 8c Radiographer

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Table S12 Continued from previous page.

Activity	Number At birth	Number After birth	Resource type	Resource/ Activity	Quantity /minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
Chest x-ray	1		Staff time	Consultant Radiographer	30	93.00	46.50	[11]	Based on cost of Band 8c Radiographer
X-ray film	1		Diagnostics	Diagnostic tests	2	25.00	50.00	[14]	
Ophthalmic assessment	1		Staff time	Consultant Ophthalmologist	30	108.00	54.00	[11]	
Audiology review	1		Staff time	Audiologist (Associate specialist)	10	105.00	17.50	[11]	
Sample taken for microscopy/PCR	1		Staff time	Nurse (band 6)	10	45.00	7.50	[11]	
Dark ground microscopy and PCR for *T. pallidum*	1		Diagnostics	Laboratory tests	1	20.00	20.00		Estimate
Results review and liaison with sexual health team	1		Staff time	Consultant paediatrician	60	108.00	108.00	[11]	
Total cost							**751.50**		

RPR/VDRL, rapid plasma reagent/venereal disease research lab test. Detailed testing protocol was obtained from Clinical Guidelines [1] and expert opinion.

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Table S13. Calculating the cost of treating neonates with congenital syphilis (CS)

Activity	N	Resource type	Resource/ Activity	Unit	Cost per unit (£)	Cost per neonate (£)	Reference	Notes
Neonates with signs of CS at delivery (40%)								
Treatment for CS	23	Medication	Penicillin (dose 30mg/kg)	105mg dose	3.00 /600mg vial	12.08	[1,15,16]	Dose calculated using average birthweight of 3.5kg.
Treatment for CS	23	Medication	Glucose 5% or sodium chloride 0.9%	Infusion bag	2.14	49.22	[1,15,16]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	721.00	7,210.00	[1,13,17]	Based on NHS tariff for Neonatal Diagnoses with CC Score 0 - HRG code PB04D.
Neonates with signs of CS days/weeks after delivery (60%)								
Treatment for CS	30	Medication	Penicillin (dose 30mg/kg)	123.75mg dose	3.00 /600mg vial	18.56	[1,15,16]	Dose calculated using average weight at 1 month of 4.125kg.
Treatment for CS	30	Medication	Glucose 5% or sodium chloride 0.9%	Infusion bag	2.14	64.20	[1,15,16]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	483.00	4,830.00	[1,13,17]	Based on NHS tariff for Paediatric Major Infections with CC Score 0 - HRG code PW16E.
Total cost of treating neonates with CS (based on 40%/60% split)						5,856.18		
Total cost of testing and treating neonates with clinical signs of CS						6,607.68		

CS, congenital syphilis. Clinical guidelines recommend that treatment is given every 12 hours (for infants ≤7 days of age) and every 8 hours (for infants >7 days of age) for a total of 10 days with treatment typically starting on the day of delivery.

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Table S14. Calculating the cost of neonate screening in infants born to mothers treated for syphilis in pregnancy

Activity	Number		Resource type	Resource/ Activity	Quantity/ minutes	Cost per unit/hour (£)	Cost per neonate (£)	Ref	Notes
	At birth	After birth							
Clinical assessment for signs of CS	1		Staff time	Consultant paediatrician	30	108.00	54.00	[11]	
Review of test results		6	Staff time	Consultant paediatrician	10 per review	108.00	108.00	[11]	
RPR/VDRL blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	Tests every three months until RPR is negative (this usually occurs by six months). Cost based on band 6 nurse.
IgM EIA blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[11]	
Syphilis blood tests (as above)	2	4	Diagnostics	Laboratory tests	3 sets of tests	12.75	38.25	[10]	Based on average combined cost for tests.
Total cost							**£245.25**		

CS, congenital syphilis; IgM EIA, immunoglobulin M enzyme immunoassay; RPR/VDRL, rapid plasma reagent/venereal disease research lab test.

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Table S15. Long-term health care and social care costs associated with congenital syphilis (CS) – results of the model comparing universal repeat screening of syphilis in late pregnancy with single screening

	Short-term costs [Antenatal + postnatal]	Long-term costs[1]	Lifetime costs [short + long-term]	Total QALYs
Single screen	£1,777,469,008	£5,754,176	£1,783,223,184	19,464,817
Universal repeat screen	£1,787,355,870	£2,160,086	£1,789,515,957	19,464,869
Difference	£9,886,863	-£3,594,090	£6,292,773	52.2
ICER				£120,494
DSA: No discounting of utilities				
Single screen	£1,777,469,008	£5,754,176	£1,783,223,184	58,444,492
Universal repeat screen	£1,787,355,870	£2,160,086	£1,789,515,957	58,444,684
Difference	£9,886,863	-£3,594,090	£6,292,773	192.3
ICER				£32,716
DSA: 6% discounting of utilities				
Single screen	£1,777,469,008	£5,754,176	£1,783,223,184	11,948,666
Universal repeat screen	£1,787,355,870	£2,160,086	£1,789,515,957	11,948,686
Difference	£9,886,863	-£3,594,090	£6,292,773	30.6
ICER				£205,600

DSA, deterministic sensitivity analysis; ICER, Incremental cost-effectiveness ratio. Lifetime costs and utilities were discounted at 3.5% unless otherwise stated. Data presented are for all women screened for syphilis in one year (n=725,891).

[1]Additional lifetime health and social care costs for individuals born with CS (£651,387 per individual) - adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.

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Table S16. Clinical outcomes for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Strategy	Syphilis antenatal screens	Women treated for syphilis	False positive screens	Intrauterine fetal demise	Preterm deliveries	Neonatal deaths	Congenital syphilis
Existing: single screen	725,891	1,709	1,451	2,906.1	54,240	1,447	43.2
Alternative: repeat screen	1,411,696	3,163	2,823	2,904.3	54,226	1,446	4.2
Difference	685,805	1,455	1,371	-1.8	-13	-0.9	-39.0

Table S17. Cost outcomes for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£ 1,777,764,124	£ 9,697,904	£ 536,669	£ 1,767,529,551
Alternative: repeat screen	£ 1,787,402,601	£ 18,860,259	£ 993,521	£ 1,767,548,821
Difference	£ 9,638,476	£ 9,162,355	£ 456,852	£ 19,270

Table S18. Requirements to prevent one outcome for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

Outcome	Cost	Women screened in third trimester	Women treated for syphilis – TP and FP	Additional false positives
Congenital syphilis	£247,284	17,595	37	35
IUFD	£5,332,625	379,431	805	759
Neonatal death	£11,063,507	787,200	1,670	1,574

TP, True positive; FP, False positive

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Table S19. Short and long-term cost outcomes for Scenario 3 (higher syphilis incidence in pregnancy)

Syphilis incidence (new infections between screens)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime health and social care costs
Probability (%)				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER
0.00003	(0.003)	Single	£1,777,506,256	2,904.6	54,229.9	1,446.6	13.2		
		Repeat	£1,787,361,768	2,904.1	54,226.5	1,446.4	3.4		
		Difference	£9,855,513	-0.5	-3.4	-0.2	-9.7	£1,011,791	£38,140
0.00004	(0.004)	Single	£1,777,534,908	2,904.8	54,231.0	1,446.7	16.5		
		Repeat	£1,787,366,305	2,904.1	54,226.4	1,446.4	3.5		
		Difference	£9,831,398	-0.6	-4.5	-0.3	-13.0	£756,892	£11,171
0.00005	(0.005)	Single	£1,777,563,560	2,904.9	54,232.1	1,446.8	19.8		
		Repeat	£1,787,370,842	2,904.2	54,226.4	1,446.4	3.6		
		Difference	£9,807,283	-0.8	-5.7	-0.4	-16.2	£603,983	Cost saving
0.00006	(0.006)	Single	£1,777,592,212	2,905.1	54,233.1	1,446.9	23.2		
		Repeat	£1,787,375,379	2,904.2	54,226.4	1,446.4	3.7		
		Difference	£9,783,167	-0.9	-6.8	-0.4	-19.5	£502,056	Cost saving
0.00007	(0.007)	Single	£1,777,620,864	2,905.2	54,234.2	1,446.9	26.5		
		Repeat	£1,787,379,916	2,904.2	54,226.4	1,446.4	3.8		
		Difference	£9,759,052	-1.1	-7.9	-0.5	-22.7	£429,258	Cost saving
0.00008	(0.008)	Single	£1,777,649,516	2,905.4	54,235.3	1,447.0	29.9		
		Repeat	£1,787,384,453	2,904.2	54,226.3	1,446.4	3.9		
		Difference	£9,734,937	-1.2	-9.0	-0.6	-26.0	£374,662	Cost saving

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Table S19. Continued from previous page.

Syphilis incidence (new infections between screens)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime health and social care costs
Probability (%)				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER
0.00009	(0.009)	Single	£1,777,678,168	2,905.6	54,236.4	1,447.1	33.2		
		Repeat	£1,787,388,990	2,904.2	54,226.3	1,446.4	4.0		
		Difference	£9,710,822	-1.4	-10.1	-0.7	-29.2	£332,201	Cost saving
0.0001	(0.01)	Single	£1,777,706,820	2,905.7	54,237.5	1,447.2	36.5		
		Repeat	£1,787,393,527	2,904.2	54,226.3	1,446.4	4.1		
		Difference	£9,686,707	-1.5	-11.2	-0.7	-32.5	£298,234	Cost saving
0.00011	(0.011)	Single	£1,777,735,472	2,905.9	54,238.6	1,447.3	39.9		
		Repeat	£1,787,398,064	2,904.3	54,226.3	1,446.5	4.1		
		Difference	£9,662,592	-1.7	-12.4	-0.8	-35.7	£270,443	Cost saving
0.00012	(0.012)	Single	£1,777,764,124	2,906.1	54,239.7	1,447.3	43.2		
		Repeat	£1,787,402,601	2,904.3	54,226.2	1,446.5	4.2		
		Difference	£9,638,476	-1.8	-13.5	-0.9	-39.0	£247,284	Cost saving

CS, congenital syphilis; ICER, IUFD, Intrauterine foetal demise; ICER, Incremental cost-effectiveness ratio. Lifetime costs and utilities were discounted at 3.5%.

[1]Lifetime health and social care costs adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.

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Table S20. Cost per screen needed to meet NICE ICER thresholds (Scenario 7)

Threshold of interest	Per screen cost required to achieve threshold	Incremental cost-effectiveness ratio (ICER)	Additional short-term cost (repeat screen vs. single screen)	Cost per CS case avoided (short-term cost)
Long-term health and social care costs and utilities				
£100k ICER threshold	£11.79	£99,877.04	£8,810,149	£1,596,738
£30k ICER threshold	£6.46	£29,884.61	£5,154,808	£934,250
£20k ICER threshold	£5.70	£19,904.45	£4,633,596	£839,786
Per screen cost half the baseline value (used in DSA)	£6.68	£32,773.60	£5,305,685	£961,594

CS, congenital syphilis; DSA, deterministic sensitivity analysis. ICERs were calculated using the additional lifetime health and social care cost of CS (£651,387) as used in Scenario 1 adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. Per screen cost was calculated to the nearest penny. Lifetime costs and utilities were discounted at 3.5%.

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1, Title
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 2, Abstract
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Page 5, Para 3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 7, Line 1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 5, Para 3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 7, Line 4
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 5, Para 2&3
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 5, Para 3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 5, Para 3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 10, Lines 1-4
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	

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	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Page 7, Para2 Supplementary material
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 8/9 Table 1.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 7 Final paragraph
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 6 Para 1 and Figure 1 & Figure S1.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Supplementary Table S1.
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Sensitivity and Scenario analysis p10.
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 8/9 Table 1.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 8/9 Table 1.
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

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		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 15.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Discussion
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 20
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 20

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

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