Aquarius Population Health

Repeat screening for syphilis in pregnancy as an alternative screening strategy in the UK

- a cost-effectiveness analysis

Prepared for: UK National Screening Committee (UK NSC)

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About Aquarius: Aquarius Population Health is an independent Healthcare Consultancy based in London.

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Executive Summary

Objective

To assess whether it is clinically and cost effective to offer all pregnant women screening for syphilis in early pregnancy and again in the third trimester compared with the current strategy of single screening in early pregnancy with a repeat screen offered only to women at high risk.

Perspective

Short-term costs to the National Health Service (NHS) in the UK were considered. Total healthcare costs are presented and are broken down into antenatal screening costs; syphilis treatment costs (within sexual health clinics); and perinatal costs (all pregnancy outcomes, delivery and neonatal testing and care).

In additional analysis, the lifetime healthcare and social care costs for infants born with congenital syphilis are considered.

Methods

A decision tree model was developed to assess the incremental costs and health benefits of the two screening strategies.

Key outcomes: cost to avoid one case of congenital syphilis, intrauterine fetal demise (IUFD) and neonatal death. The number of women needing to be screened to avoid one case of congenital syphilis, IUFD or neonatal death and the number of women needing to be treated to avoid once case of congenital syphilis, intrauterine fetal demise or neonatal death.

Time horizon: The base-case analysis considered short-term costs during pregnancy and the initial weeks after delivery.

Experts from reference laboratories, NHS sexual health clinics, and NHS hospital antenatal and paediatric care advised on the model structure, clinical and cost parameters.

Clinical parameters used in the model 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.

Cost parameters were adapted from published literature, from NHS reference costs and tariffs, or where no data were found, costs were calculated using published tariffs, staff and consumables costs, published clinical guidelines and with input from clinical experts.

Deterministic and probabilistic sensitivity analyses were conducted to determine the robustness of the result. Scenario analyses explored a lifetime time horizon, the impact of structural assumptions and of higher syphilis incidence.

Results

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 congenital syphilis, 2 fewer cases of preterm delivery, 0.1 fewer cases of neonatal death and 0.3 fewer cases of IUFD compared to the single screening strategy. The healthcare costs would be £9.9 million (m) higher for the repeat screening strategy compared to the current strategy (£1,777m vs. £1,787m respectively when screening costs, treatment costs and delivery costs were considered) with most (£9.2m) of this increase being a result of the additional screening costs. This equates to £1.8m per case of congenital syphilis prevented.

The model calculated that 124,292 women would need to be rescreened in the third trimester to prevent one case of congenital syphilis, 2.6m women to prevent one case of IUFD, and 5.5m women to prevent one case of neonatal death.

The deterministic sensitivity analysis (DSA) found 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. The total costs were most sensitive to changes in the per screen cost. Total costs were also sensitive, but to a lesser extent, to changes in the specificity of the screening process, the proportion of women first attending antenatal care before their 3rd trimester, syphilis incidence and the cost of syphilis treatment.

In the one-way sensitivity analysis, 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).

When lifetime costs and utilities were considered, the cost per additional QALY gained for the repeat screening strategy was £180,817. If social care costs were also considered, the cost of gaining one QALY was £120,494.

Conclusion and Recommendation

Based on the results of this analysis, we would not recommend implementation of universal repeat screening for syphilis in pregnancy as there is no evidence that it would be cost-effective in the current UK setting where the prevalence and incidence of syphilis in pregnant women is low. Repeat screening could also have some potential harms, including overtreatment with antibiotics and unnecessary anxiety, which the model did not account for.

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Abbreviations

BPG	Benzathine penicillin G
CI	Confidence interval
CS	Congenital syphilis
DSA	Deterministic sensitivity analysis
EIA	Enzyme immunoassay
EQA	External quality assessment
EVPI	Expected value of perfect information
FN	False negative
FP	False positive
HRQoL	health-related quality of life
ICER	Incremental cost-effectiveness ratio
IDPS	Infectious Diseases in Pregnancy Screening
IQC	Internal quality control
IUFD	Intrauterine fetal demise
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PHE	Public Health England
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life-years
TN	True negative
TP	True positive
TPPA	*T. pallidum* particle agglutination assay
STI	Sexually transmitted infection
UK NSC	UK National Screening Committee
US	United States of America

Introduction

Syphilis burden in the UK

Syphilis is a sexually transmitted bacterial infection caused by *Treponema pallidum* subspecies *pallidum* which can be successfully treated with antibiotics. The burden of syphilis in the UK has remained low since penicillin became widely available. However, over the past two decades the number of new diagnoses has increased and the number of cases in women more than doubled between 1999 and 2007 [1,2]. Syphilis prevalence in pregnant women remains low. A study of syphilis screening in pregnancy in England found that one-in-2800 pregnant women required treatment for syphilis in the period 2010-2011 [3].

Syphilis disease stages

There are four stages of syphilis infection: primary, secondary, latent and tertiary (late). The first two stages are symptomatic with sores, referred to as chancres, developing on the genital or mouth region in primary syphilis which lasts 4-12 weeks, and rash or more general symptoms such as fever and sore throat developing in the secondary stage which lasts 3-4 months. In some cases, these symptoms can be mild and overlooked or go unnoticed.

Latent syphilis is typically asymptomatic, although there can be a relapse of symptoms in the early latent stage, which lasts up to 2 years. The late latent stage, which can last a lifetime, is generally non-symptomatic. In one-third of cases, latent syphilis develops into the tertiary stage around 10-13 years after the initial infection. This final stage can result in severe multi-organ damage, neurosyphilis and death [4].

Congenital syphilis (CS)

Vertical transmission of syphilis during pregnancy (trans-placental passage) can occur during any trimester and at any stage of infection - with the highest risk of transmission in primary syphilis. The risk of adverse pregnancy outcomes, including intrauterine fetal demise (IUFD), prematurity and neonatal death, is 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 [5]. There is evidence that the risk of congenital syphilis (CS) is higher in women who become infected with syphilis during pregnancy than in women who have active syphilis at the time of conception [6,7]. However, the probability of CS and other adverse pregnancy outcomes is difficult to measure and to quantify, in part, due to the very small number of CS cases.

In infants born with CS, the infection can cause reduced growth and development, and result in neurological impairment, bone deformities and hearing loss [8,9]. Benzyl penicillin sodium (intravenous) is used to treat CS in neonates. Treatment is given for ten days with 30 mg/kg doses given 12-hourly for the first seven days and 8-hourly for the subsequent three days [5,10]. Infants are likely to then have monitoring beyond the completion of treatment. Infants treated in the first two months of life have a good short-term prognosis, but the long-term prognosis for infants treated for CS at birth or treated later, due to delayed diagnosis, have not been reported [11,12]. Evidence indicates that most infants with CS develop signs by 5 weeks, however, there is a lack of data on the proportion of CS cases with late presentation (after 2 years) [5].

In the UK, the number of CS cases in recent years has remained low and is below the WHO threshold for elimination (<0.5/1000 live births). In the 5-year period Feb 2010 – Jan 2015, there were 17 confirmed cases of CS [13,14]. Where information on syphilis stage was available, 60% [6/10] of CS cases were born to women with primary syphilis, 30% [3/10] secondary syphilis and 10% [1/10] early latent syphilis. Of the 20 CS cases between February 2010 and January 2017, 11 had no record of the mother receiving antenatal screening [14].

There is a chance that women who screen negative for syphilis become positive later in pregnancy, either because they become infected during the pregnancy, or because their infection was too recent for a detectable antibody response to have been mounted at the time of the first screen. In March 2016 - January 2017 four cases of CS occurred in women who received a negative result when screened for syphilis in pregnancy – although the timing of the screening in pregnancy was not reported. None of these women had a repeat screen during pregnancy. Confirmatory testing later showed that they had acquired syphilis during pregnancy. In these four cases, two women had infants with confirmed CS and two had infants classified as probable CS cases [14].

Syphilis screening in pregnancy

In the UK, routine antenatal screening for hepatitis B, HIV and syphilis is offered and recommended to all pregnant women at their booking appointment (their first routine antenatal appointment with a midwife), usually near the end of their first trimester at 10-12 weeks' gestation. Women who initially decline screening are referred to a multi-disciplinary team who explain the benefits of the screening. The small proportion of women who first present to antenatal care in their second or third trimester are offered the routine screening at that appointment (See Appendix 2.)

Public Health England (PHE) screening performance thresholds for antenatal syphilis screening are currently set at ≥95% coverage for 'acceptable' and ≥99% for 'achievable' [15]. Screening coverage in the UK is high - at 99.6% in England [15] and 99.97% in Northern Ireland in 2016/17 [16].

At present, some women are offered a repeat test for syphilis in pregnancy. Current guidelines recommend that women are tested for syphilis following a single 'high risk' exposure, if they have symptoms indicating syphilis or consider themselves to be at risk of infection [17]. Assessing women's risk can be problematic and risk can change during pregnancy. Repeat screens are typically provided within a sexual health clinic and are not part of the Infectious Diseases in Pregnancy Screening (IDPS). The number of pregnant women receiving a repeat screen is thought to be very low, however, data on offer and uptake are not routinely monitored or reported.

Syphilis screening assay

Blood samples are initially tested using an enzyme immunoassay (EIA). This assay tests for antibodies against treponemal infections, including, but not exclusively, syphilis (*Treponema pallidum*). Samples from women with a non-syphilis treponemal infection will initially produce a positive result as will women with a previous syphilis infection. Syphilis serology can remain positive for many years after acute infection with or without treatment. Following a positive result, the same test is repeated using the same assay, and then a *T. pallidum* particle agglutination assay (TPPA) is performed on the same specimen to confirm the result. Women with a TPPA positive result are referred to a sexual health clinic for assessment – where they will be examined and have a sexual history taken to assess whether they have an active infection which requires treatment.

Management of syphilis in pregnant women

Women requiring treatment for syphilis are treated by the sexual health specialist and are retested later in pregnancy for syphilis as part of this clinical management.

Primary, secondary and early latent syphilis are treated with benzathine penicillin G (BPG) as a single muscular injection. Late latent syphilis is treated with the same dose weekly for 3 weeks with no more than 7 days between doses [5].

Universal repeat screening strategy

Due to the increase in syphilis diagnoses in sexual health clinics in the UK and the continued incidence of CS cases each year, albeit very small numbers, the UK NSC wish to assess the cost effectiveness of an alternative screening strategy.

Universal repeat screening is likely to identify women who are infected with syphilis during pregnancy, increasing the number of syphilis cases diagnosed and treated before birth thereby reducing the number of CS cases and adverse pregnancy outcomes associated with maternal syphilis.

The cost-effectiveness of this approach has not been evaluated in the UK. There have been two cost-effectiveness studies published from the US, with conflicting results – these are discussed in a later section.

Aim

The UK NSC wish to compare the clinical and cost-effectiveness of two syphilis antenatal screening strategies:

Strategy 1: **Current practice – single screen**

Universal screening in the first trimester only. Repeat screening is only offered to women at 'high risk' of infection.

Strategy 2: **Proposed alternative – repeat screen**

Universal screening in the first trimester plus universal repeat screening in the third trimester.

Perspective

Costs are considered from the UK health system perspective. The primary analysis was performed from a healthcare perspective and includes short-term healthcare costs to the NHS in England, Northern Ireland, Scotland and Wales. The costs are split into three areas since costs relating to syphilis screening are borne by the screening programme, costs relating to syphilis treatment by sexual health clinics and cost related to testing neonates, delivery and neonate care are borne by hospital trusts. To assess the overall impact of changing the screening strategy, the costs for all pregnancy outcomes for all women screened are considered, not just the costs for women with syphilis.

Life-time costs and utilities were not used in the base-case analysis since there were limited data on the long-term costs and utilities of CS which would result in a lot of uncertainty in the model. Life-time healthcare costs associated with CS are considered in additional analysis (Scenario analysis 1).

Population

The model includes pregnant women in the UK accessing antenatal care and receiving an initial syphilis screen. Women who are not screened for syphilis (0.04%) are not included in the model since any change to the screening strategy will have no impact on their pregnancy outcomes.

Outcomes

The total costs and benefits for each approach will be estimated plus the incremental costs and benefits. The following outcomes are considered:

1. Cost
    - total cost of screening strategies with a breakdown of costs
    - cost per case of congenital syphilis prevented
    - cost per IUFD prevented
    - cost per neonatal/infant death prevented
    - cost per preterm delivery prevented
    - cost per QALY gained (calculated in lifetime scenario analysis 1)

2. Health benefits
    - Total number of cases of
        - congenital syphilis
        - IUFD
        - neonatal/infant death
        - preterm delivery
    - Total number of women screened
    - Total number of women treated
    - Total number of false positives

3. The incremental number of women repeat screened in the third trimester to avoid one case of
    - congenital syphilis

- IUFD
- neonatal/infant death
- preterm delivery

4. The incremental number of women treated in the third trimester to avoid one case of
    - congenital syphilis
    - IUFD
    - neonatal/infant death
    - preterm delivery

Previous economic modelling

Only two economic evaluations assessing the impact of universal repeat screening have been undertaken. Both were carried out in the US and a summary of the studies can be found in Table 1 [18,19]. Albright *et al* [18] considered only short-term costs and estimated the cost to prevent one case of CS to be $419,842 if repeat screening were implemented. Hersh *et al* [19] took into account the lifetime healthcare costs related to CS and found that repeat screening was cost saving compared to single screening. As well as differences in pregnancy outcomes and healthcare costs between the US and the UK, these economic evaluations do not account for late presentation to antenatal care which is important, since late presentation (defined in our model as ≥28 weeks gestation) not only increases the risk of adverse pregnancy outcomes but also means there is no opportunity for a repeat screen.

Table 1. Summary data for two US economic evaluations of single vs. repeat syphilis screening in pregnancy

Study	**Albright *et al*** [18]	**Hersh *et al*** [19]
Publication year	2015	2018
Setting	US	US
Time horizon	Neonatal	Lifetime
Type of model	Decision tree	Decision tree
Cohort number	4 million	3.9 million
Syphilis incidence in pregnancy	0.012%	0.012%
Total annual cost difference (repeat vs. single)	$26m additional	$52m cost saving
Cost to prevent one case of CS	$419,842 additional	$1,268,293 cost saving
CS cases prevented / year	60	41
Numbers rescreened to prevent one case CS	65,790	Not reported
Cost per QALY	-	$14,098 cost saving
Estimated cost of CS	Neonatal care only: $12,610	Delayed treatment[1]: $1,481,426 Prompt treatment[1]: $818,405

[1] Assume these are life-time costs. m, million

Methods

Developing a decision tree

The two US studies [18,19] and a preliminary model developed internally by PHE were used as a starting point to develop a draft decision tree.

Syphilis experts were invited to comment on the draft decision tree and to discuss the screening and treatment guidelines, data availability, tree structure, and outcomes at a workshop hosted by Aquarius. There was consensus around a number of important changes made to the decision tree structure. Informed by the discussions at the workshop, the overall tree structure was finalised and agreed upon (see Figure 1).

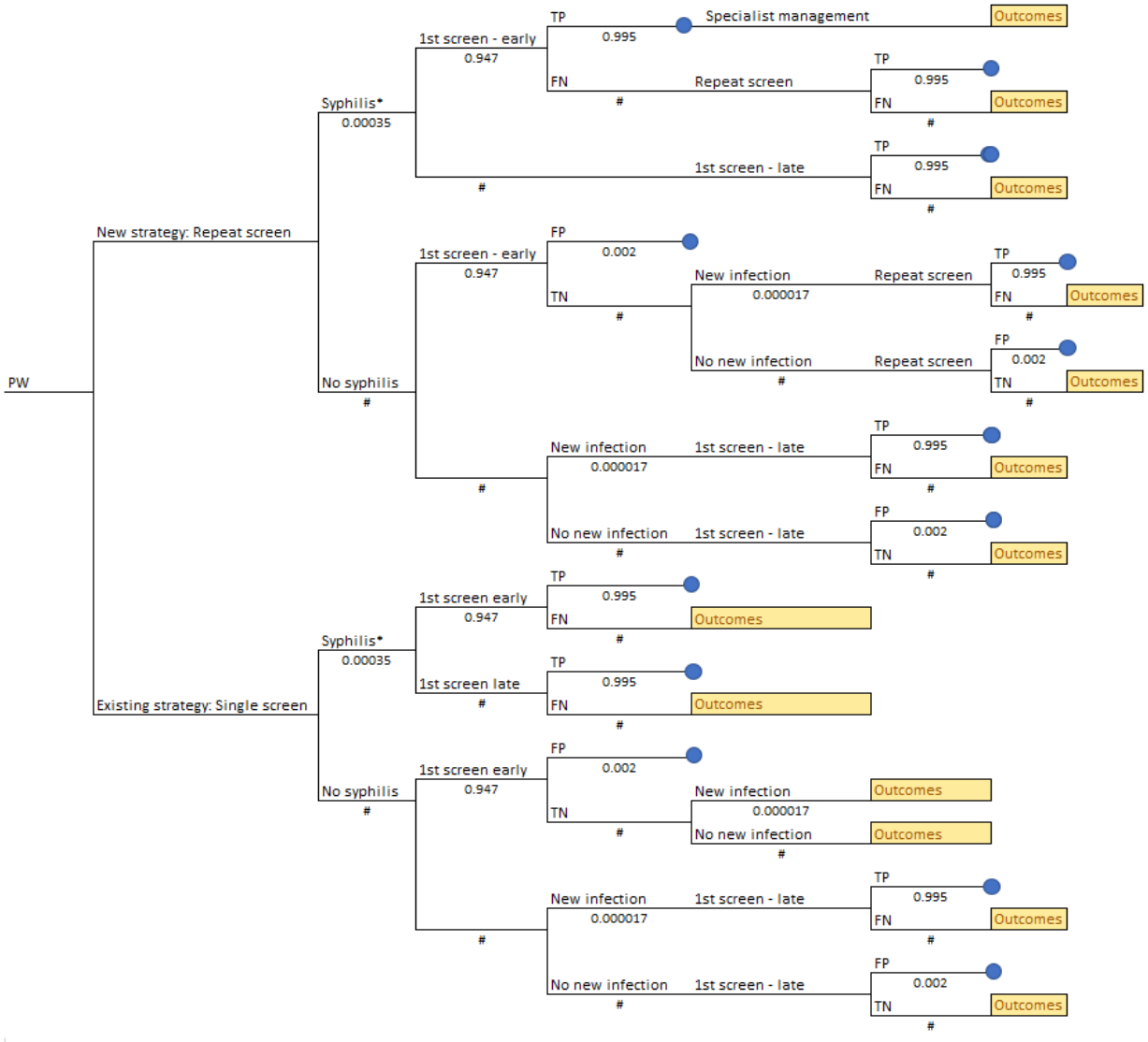
Decision tree structure

At present, the national screening guidelines recommend that women at high risk of becoming infected are offered a repeat screen, however, in practice, few women receive repeat screening. There are no available data on the number of high vs. low risk women, the incidence of syphilis in these two groups or the number of women offered or receiving a repeat screen during pregnancy. Therefore, due to the small numbers involved, lack of data and on the advice of the project advisors, repeat screening for high risk women was not included in the model for current care.

The decision tree is presented in Figure 1 and Figure 2. The alternative repeat screening strategy is shown in the top half and the current single screen strategy in the lower half. The pathway follows the true disease state of women and then defines the population by women who are screened in the first/second trimester and women screened in their third trimester (due to late first attendance in antenatal care). Women with a positive result receive treatment at a sexual health clinic plus any repeat testing required.

As with the models used in Albright *et al* and Hersh *et al*, each branch ends with the same pregnancy outcomes, IUFD, then either a pre-term or term delivery resulting in either neonatal death, an infant with CS or an infant with no CS (Figure 2).

Figure 1. Overview of Decision Tree



PW, pregnant women; FN, false negative result; FP, false positive result; TN, true negative result; TP, true positive result.

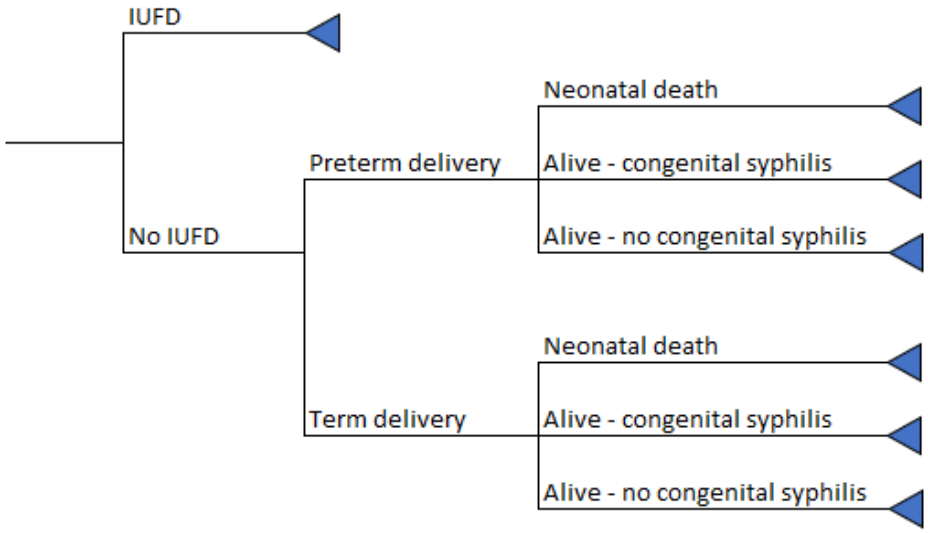
With reference to the timing of 1st syphilis screen, 'early' refers to 1st or 2nd trimester and 'late' refers to the third trimester.

Where branches split, the probabilities are shown in the top branch, with # indicating (1-probability).

Each branch ends with the same outcomes, shown in Figure 2, with different probabilities for each branch.

Blue circle indicates referral to specialist management for treatment and the same seven pregnancy outcomes (as is shown in the topmost branch).

Figure 2. Decision Tree Pregnancy Outcomes



Footnote:
IUFD, intrauterine fetal demise; pre-term refers to <37 weeks gestation. The blue triangle indicates the branch end point.

Building the cost-effectiveness model

The decision tree model was built in TreeAge (TreeAge Pro 2019, R2. TreeAge Software, Williamstown, MA.). The parameters used in the economic model are presented in Table 2, Table 3 and Table 4.

Data collection approach

To inform the model structure and parameters, data was sought from peer reviewed research using PubMed and Google Scholar and using references cited by relevant papers. Published data including surveillance reports, clinical guidelines, and screening protocols were sought online via Google and other search engines and recommended by the advisors involved.

Data on the total number of pregnancies and/or deliveries, timing of first antenatal attendance and delivery and uptake of syphilis screening were requested directly from health surveillance units in the four UK countries.

Cost data were sought by searching online for published prices, estimates or tariffs, asking laboratory managers (known contacts) and the advisors. Where no costing data were available, micro-costing was used to estimate the costs. These calculations were informed by clinical guidelines and expert opinions and used published NHS tariffs where available.

Clinical parameters

Syphilis prevalence

The prevalence of syphilis at the start of the model was informed using published data from the Surveillance of Antenatal Syphilis Screening (SASS) study, a national surveillance study which collected information on syphilis positive pregnancies from all NHS maternity units in the UK in 2010-2011 [3]. The study reported 244 syphilis screen positive women from 961,494 women screened in 2011, giving a prevalence of 25/100,000 (0.025%).

GUMCAD data (surveillance data from sexual health clinics in England), were not used to inform the parameters because the prevalence of syphilis in STI clinic attendees differs considerably from the prevalence in pregnant women - the 2014-2018 GUMCAD data [20] indicate that syphilis prevalence was 2/100,000 (0.002%) in women of all ages.

Syphilis incidence

No data on syphilis incidence in pregnancy were available from the UK. In the two previous health economic models from the US [18,19], the probability of syphilis incidence in pregnancy was estimated as 0.000121. This estimate was based on the final 9-years of data (years 2000-2009) from a US based study of syphilis in pregnancy, Shiber *et al* [21]. This US based study reported seroconversions over a 17-year time period in women with a high risk of syphilis infection based on their geographical area (i.e. they lived in a high prevalence area). The prevalence of syphilis infection in these women was 0.244% (i.e. probability of 0.00244), considerably higher than the prevalence in pregnant women in the UK, 0.035%, estimated using data from the SASS study [3].

To estimate the probability of syphilis infection during pregnancy, the syphilis incidence from Shiber *et al* [21] was scaled to reflect the difference in prevalence between pregnant women in the study and pregnant women in the UK (Table 2).

Table 2. Clinical parameter inputs

Parameter	Baseline value	Low	High	Distribution	Note
Total number of women in model (representing one-year)	725,891	-	-	-	Based on number of deliveries in the UK in 2017/2018 and estimated screening uptake. See Appendix 1.
Probability of having syphilis at the start of pregnancy	0.00035	0.00028	0.00042	Beta	Data derived from 2011 SASS data [3] (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	Estimated using published data from US scaled to reflect UK prevalence [3,21].
Probability of receiving syphilis screen <28 weeks gestation	0.947	0.936	0.984	Beta	Estimate based on gestational week at first antenatal attendance. Appendix 2. Low is in line with results from SASS study [3]. High 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.
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.
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.
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.

[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.

Accuracy of syphilis screening

It is very difficult to assess the sensitivity and specificity of the full screening process, taking into account the assay performance and the clinician's decision as to whether treatment for syphilis is required for women with a positive result for antibodies. There is no 'gold standard' assay for syphilis, and no audits or published studies from the UK on the sensitivity and specificity of the screening process or its positive predictive value (PPV). Anecdotally, blood tests in pregnant women produce more false positive results than in other groups.

In the absence of published data on the accuracy of the screening process, the probability of a positive result in women with active syphilis (i.e. sensitivity) and the probability of a negative result in women with no syphilis (i.e. specificity) were based on the average test performance of EIA assays used in the UK and the same estimate is used for the first screen and the repeat screen. High and low values are based on best and worst test performance of assays used in the UK (Table 2). This means that the model assumes that the majority of women with treponemal antibodies but who do not require treatment for syphilis (i.e. women who previously had an infection, have a non-syphilis treponemal infection or have an incorrect assay result) are correctly informed that they are negative for active syphilis and do not require treatment. Nevertheless, the cost for the additional assessment needed for these women is taken into account in the average cost per screen (Appendix 5).

The specificity of the second screen may be higher than the first screen. Women with a negative first screen and a positive second screen in later pregnancy will be much easier to interpret clinically. In particular, women with primary infection are more likely to have clinical signs and may have a risk of recent infection, informing the clinician's decision as to whether treatment is required. Scenario 5 presents the results of the model where the screening process has 100% accuracy (sensitivity and specificity) and Scenario 6 presents the results of the model where the second screen has 100% specificity (i.e. no false positives). Scenarios 5 and 6 assume that women positive for antibodies who do not require treatment are correctly identified as false positive by the attending clinician and are therefore do not incur any treatment costs.

Pregnancy outcomes

The probabilities for each of the pregnancy outcomes are presented in Table 3. A full explanation of how these were calculated is outlined in Appendix 4. In brief, data from a large meta-analysis [22] were adjusted to the UK setting. No data on the risk of the different

pregnancy outcomes were available for women who become infected with syphilis during pregnancy. These probabilities were estimated based on expert opinion.

In women with syphilis at the time of conception treated before 28 weeks gestation, the risk of passing on the infection to their infant was 1%. In women who became infected during pregnancy, the chance of passing on the infection was 1% in women treated after 28 weeks and 50% in women receiving no treatment (Appendix Table 4.3).

Table 3. Pregnancy outcomes - parameter inputs

Parameter	Baseline value	Low	High	Note
Pregnant women with no syphilis				
IUFD	0.004	0.003	0.005	See Appendix 4.
Preterm delivery	0.075	0.058	0.097	See Appendix 4.
Neonatal death	0.002	0.001	0.003	See Appendix 4.
Congenital syphilis	0.000	-	-	Assumption
Pregnant women with syphilis diagnosed and treated <28 weeks				
IUFD	0.005	0.002	0.012	See Appendix 4.
Preterm delivery	0.079	0.042	0.143	See Appendix 4.
Neonatal death	0.003	0.001	0.014	See Appendix 4.
Congenital syphilis	0.011	0.008	0.016	See Appendix 4.
Pregnant women with syphilis diagnosed and treated ≥28 weeks				
IUFD	0.023	0.018	0.028	See Appendix 4.
Preterm delivery	0.183	0.119	0.275	See Appendix 4.
Neonatal death	0.013	0.005	0.032	See Appendix 4.
Congenital syphilis	0.038[1]	0.029	0.047	See Appendix 4.
Pregnant women with syphilis not diagnosed/treated				
IUFD	0.028	0.023	0.033	See Appendix 4.
Preterm delivery	0.241	0.188	0.305	See Appendix 4.
Neonatal death	0.014	0.009	0.022	See Appendix 4.
Congenital syphilis	0.034[1]	0.026	0.042	See Appendix 4.
Pregnant women infected with syphilis during 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/treated				
IUFD	0.028	0.023	0.033	Assumed to have same risk as women with syphilis not diagnosed/treated.
Preterm delivery	0.241	0.188	0.305	
Neonatal death	0.014	0.009	0.022	
Congenital syphilis	0.500	0.250	0.750	Estimate based on expert opinion.

Low and high values are based on the 95% confidence intervals from the meta-analysis Qin *et al.* [22] adjusted to the UK setting in the same way as the baseline values (See Appendix 4).

[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. These estimates are from a meta-analysis which used data from 15 and 33 studies respectively and both and have wide confidence intervals.

Table 4. Cost parameter inputs

Cost	Baseline (£)	Low (£)	High (£)	Distribution	Note
Syphilis screen	13.36	6.68	26.72	Gamma	Estimated using micro-costing. See Appendix 5.
Management women diagnosed with syphilis in pregnancy	314.09	251.27	376.91	Gamma	Clinical management by sexual health clinician estimate based on NHS tariff [23]. See Appendix 6.
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 [24].
Pre-term 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) [25]. UK data on gestational age at delivery (Appendix 3) 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 2010/11 UK data inflated to 2017/18 costs [25].
Neonatal death	5,805.80	4,644.64	6,966.96	Gamma	Estimated using cost of IUFD plus additional hospital costs. See Appendix 10.
CS testing and treatment	6,607.68	5,286.14	7,929.21	Gamma	Estimated using micro-costing. See Appendix 8 and Appendix 9.
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 Appendix 7.
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) [26].
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) [26].

CS, congenital syphilis. High and low values are +/- 20% of baseline values with exception of syphilis screening cost where high and low values are +/- 50%.

Cost data

Where possible, published costs from the UK or NHS tariff costs were used. In some cases, no published data or tariffs were available, therefore micro-costing was used. These estimates were developed using treatment guidelines and expert advice and all estimates were validated by an expert in the field such as a paediatrician or sexual health consultant.

Where cost estimates from outside the UK were used, costs were converted to pound sterling (£) [27]. Where necessary, costs were inflated to 2017/18 prices using mid-year conversion rates [28].

Cost of antenatal syphilis screening

The cost per screen was calculated using a micro-costing approach (Appendix 5). This took into account the cost of consumables used for taking the blood sample and laboratory tests but did not include the nurse time to take the blood sample since blood tests for other infections such as HIV are taken during the booking appointment, so screening for syphilis would not increase the time of the appointment. The per screen cost also includes the cost of a repeat screen due to inconclusive test results in a small proportion of women, input from the multi-disciplinary team for women requiring additional input due to initial reluctance to screen and the cost of a 30-minute appointment at a sexual health clinic for a small proportion (0.06%) of women who receive a positive antibody result but who do not then require treatment either because they have another treponemal infection or because they had syphilis in the past which was treated – women who would be categorised as ‘no syphilis’ in the model.

The cost of the repeat screen was assumed to be the same as the cost as the first screen – since in both cases, samples would be taken at a routine antenatal appointment when other screening tests are performed.

Cost of treatment for women diagnosed with syphilis in pregnancy

The cost of treatment and management of women diagnosed with syphilis in pregnancy was calculated using micro-costing (Appendix 6). This cost would be the same for women diagnosed with syphilis during their first screen as for women diagnosed at the repeat screen.

The STI Intervention C NHS tariff from the London Integrated Sexual Health Tariff 2017/18 was used, however it was adjusted to reflect that a consultant would conduct the treatment sessions as opposed to a doctor/nurse mix [23].

Cost of delivery and obstetric outcomes

The additional cost of neonatal death was calculated by combining the additional cost of IUFD [24], with the NHS tariff cost for 3 nights in a neonatal intensive care unit [29]. See Appendix 10.

Cost of syphilis testing and treatment in neonates

The cost of testing and treating neonates with CS was calculated using the clinical guidelines and input from a senior hospital paediatrician see Appendix 8 and Appendix 9. For neonates without CS, born to women who were treated for syphilis in pregnancy, the cost of neonate screening was calculated using micro-costing, see Appendix 7.

Lifetime costs and utilities

No data were available on the lifetime cost of CS. Instead, the life-time cost of cerebral palsy was used as a proxy, since cerebral palsy can also lead to a range of disabilities and vary hugely in severity – and in some cases may be a result of CS.

In additional analyses, the lifetime health and social care costs of cerebral palsy from a single study from Europe (Denmark) were used (Kruse *et al* [26]). The study calculated the additional lifetime healthcare costs for cerebral palsy which included primary health care, hospitals and pharmaceuticals. It also calculated the social care costs which included: specialised schooling and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services, not all of which would typically be included in the UK definition of personal social services (PSS)[1]. The Kruse *et al* data were adjusted for use in this model to reflect a 3.5% discount rate, and UK life expectancy and gender split.

Health effects

No studies were found which reported the EQ-5D[2] for CS or cerebral palsy, the preferred measure of health-related quality of life (HRQoL) for the National Institute for Health and Care Excellence (NICE). Instead, a utility of 0.74 was used for infants with CS compared to a utility of 1.00 in infants born with no CS, a value used in Hersh *et al*. [19] and adapted from a 2006 study of new-born screening strategies where 0.74 was used for infants with a 'mild developmental delay' [30]. Quality adjusted life-years (QALY) were calculated using these utilities values. The parent's HRQoL were not considered, nor were HRQoL for the other pregnancy outcomes.

[1] https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness#ftn.footnote_14
[2] https://euroqol.org/

The life expectancy of infants with CS was assumed to be 70, in line with the estimate for cerebral palsy [26], and in light of reports of CS diagnoses in a wide range of ages [31]. The life expectancy of infants with no CS was estimated as 81 years. All costs and utilities had a 3.5% discount rate.

Definitions

The model categorises women into groups, defined below:

No syphilis	• women with no syphilis antibodies • women with syphilis antibodies who have previously received complete treatment (since in the absence of other risk factors, women with a previous diagnosis not requiring treatment would have the same management and risks as women with no syphilis antibodies) • women with other treponemal infections
Syphilis	• women with a previous syphilis diagnosis who require treatment (either due to incomplete or undocumented treatment) • women with active syphilis infection
Pre-term delivery	delivery at ≤36 weeks gestation
Term delivery	delivery at 37+ weeks gestation
1st screen early	syphilis screen in first or second pregnancy trimester
1st screen late	syphilis screen in the third trimester – due to late first attendance in antenatal care
False positive	A positive diagnosis of a woman in the 'no syphilis' group after the screening process which may or may not include confirmatory diagnostics tests and discussion with a clinician and results in unnecessary treatment for syphilis.
False negative	A negative diagnosis for a woman in the 'syphilis' group after the screening process which may or may not include confirmatory tests and discussion with a clinician and results in no treatment for syphilis where treatment is required.

Timing of screen

In the model, the threshold for early versus late first screen is 28 weeks gestation. In clinical practice, presenting for first antenatal visit after 20 weeks would be viewed as a late presentation. However, published data on risk of adverse events with early versus late presentation tends to use 28 weeks as the cut-off. Furthermore, the second screening test would likely take place at the 28-week appointment when blood tests are already taken for

other routine monitoring, so anyone receiving the first screening prior to this would have the opportunity to have the repeat screen at that 28-week attendance.

Assumptions

Table 5. Assumptions applied to screening strategies and rationale

- 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 [5]. Uptake of treatment in diagnosed women is thought to be high. No published data were found to support or refute this.
- 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) [5].
- There is no loss to follow-up.
  - Inclusion of loss to follow-up in the model would add unnecessary complexity to the model. Lack of data on loss to follow-up.
- 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.

- Pre-term 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 this late in pregnancy. Timing of repeat screen based on expert advice – and is hypothetical as repeat screening is not current practice.
- In the current care pathway, no women undergo a repeat screen.
  - Following expert advice that few high-risk women currently receive repeat screening. Lack of data around uptake of repeat screening and pregnancy outcomes for low risk vs. high risk women.

Omissions

Syphilis stage

There is evidence that the stage of syphilis infection changes the risk of vertical transmission and other adverse pregnancy outcomes. The model does not account for differences in infection stage (i.e. primary syphilis vs. late syphilis) since data about prevalence of different stages and their impact on outcome were not available. It does however account for the increased risk of CS in women who become infected with syphilis during pregnancy and who would therefore have primary syphilis.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction is the flu like reaction to penicillin treatment for syphilis experienced by approximately 40% of women treated for syphilis. In pregnant women, the Jarisch-Herxheimer reaction can also cause uterine contractions for up to 24 hours [5]. Although the reaction is common in the UK, the symptoms are not clinically significant in the vast majority of cases, do not incur additional costs and there is no evidence of increased risk of adverse pregnancy outcomes. For these reasons, the model does not include the Jarisch-Herxheimer reaction. This decision was supported by the clinical experts.

The Jarisch-Herxheimer reaction was not considered in the Hersh model [19]. While the Albright model [18] included the additional cost of a 24-hour maternal hospitalisation in 45% of women receiving treatment for syphilis, the reaction did not alter the risk of adverse pregnancy outcome in the base case model.

Point-of-care testing for syphilis

Including a point of care (POC) syphilis test at delivery in the model was considered. One use of the POC test would be in women who miss antenatal screening – these women would fall outside the model and the screening programme since they have missed the opportunity for preventing the adverse pregnancy outcomes associated with syphilis. As such, POC was not considered in the model.

Delayed presentation of congenital syphilis

Diagnosing CS at delivery or within months of delivery is likely to be beneficial in the longer term compared to a delayed diagnosis. Due to a lack of data on the ratio of early vs late diagnosis, and the cost and health impacts this would have, this was not considered in the model.

Sensitivity analysis and scenario analysis

Univariate deterministic sensitivity analysis (DSA) on all probabilities and costs was used to determine which parameters had the greatest impact on the outcome of the model when altered.

Probabilistic sensitivity analysis (PSA) using Monte Carlo simulation (running 1000 simulations) was used to assess the robustness of the results and calculated the 95% confidence intervals (CIs) for each output using the mean and standard deviation. For clinical probability inputs, the β (beta) distribution was used[3]. For cost inputs, the γ (gamma) distribution was used[4]. The distributions were calculated using study data where possible.

[3] Beta distribution is typically used to represent uncertainty in clinical probabilities as it is a continuous distribution on a zero-one interval [32].

[4] Gamma distribution is typically used to represent uncertainty in cost parameters as it is a continuous, skewed distribution which is always positive [32].

Seven different scenarios were assessed to observe how changes in the model assumptions and some of the parameters impacted the main outcomes (Table 6). The lifetime healthcare and social care costs for infants born with CS were also considered.

Table 6. Scenarios assessed

	Scenario assessed
1	Lifetime time horizon
2	Accounts for incomplete uptake of the repeat screen. The decision tree was altered to include additional branches to allow the possibility of women who had received the early first screen to miss the second screen (Appendix 14). The probability of having a second screen was estimated as 0.996, in line with the current uptake of first screening in England.
3a	Syphilis incidence was increased to probability 0.00012 (0.012%), the high value used in sensitivity analysis.
3b	To inform regions which have a higher incidence of syphilis in pregnancy, this scenario presents short-term and lifetime costs (ICERs) for higher syphilis incidence at 10 intervals between the baseline probability and the high probability used in sensitivity analysis (0.00012).
4	All women attended their first antenatal care in the first or second trimester, thereby allowing them to have a repeat screen in the repeat screen scenario.
5	100% sensitivity and specificity of the syphilis screening procedure.
6	100% specificity of the repeat screen.
7	Examining the per screen cost required to meet NICE cost-effectiveness thresholds.

Results

Base case results

The base case results are presented in Table 7. Using the base case assumptions, the repeat screening strategy compared to the single screen strategy resulted in 5.5 fewer cases of CS per year, two fewer cases of preterm delivery, 0.1 fewer cases of neonatal death (i.e. one less death every 10 years on average) and 0.3 fewer cases of IUFD (Table 7).

The repeat screening strategy resulted in an additional 1,384 women diagnosed as having syphilis, of whom 13 were women with an active syphilis infection who required treatment, with the remaining 1,372 women being false positives (Table 7).

The short-term annual healthcare costs are presented in Table 8. The estimated cost of screening all 725,891 women was £10m for the single screening strategy and £19m for the repeat strategy – a 95% increase. The costs associated with treatment of syphilis in pregnant women diagnosed as a result of the screening, a cost borne by sexual health clinics, was £535,434 for the current strategy and £970,254 for the repeat strategy – an 81% increase. Perinatal costs increase by 0.02% from £1767.2m in the single screen strategy to £1767.5m in the repeat strategy. These costs, borne by hospital trusts, include all the costs associated with IUFD, preterm and term delivery for all infants, plus the testing and treatment of infants with CS.

Requirements to prevent one case of each of the adverse pregnancy outcomes are presented in Table 9. In the base case, which included a total of 725,891 women and represented one-year in the screening programme, 124,292 women would need to be rescreened to prevent one case of congenital syphilis; 2.6m women would need to be rescreened to prevent one case of IUFD (i.e. one case prevented roughly every 3.6 years if every pregnant woman was rescreened); and 5.5m to prevent one case of neonatal death (i.e. one case prevented roughly every 7.6 years if every pregnant woman was rescreened). 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 would receive treatment for syphilis to prevent one case of CS, but 249 of these would be false positives (Table 9).

Table 7. Base case clinical outcomes

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
Existing: single screen							
Estimate	725,891	1,705	1,451	2,904.4	54,228	1,446.5	8.8
95% CI (from PSA)[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 (from PSA)[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 in the model, including the small number with syphilis infection.

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

Table 8. Base case short-term annual healthcare costs

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 in the model. 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.

Table 9. Requirements to prevent one outcome

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.

One-way sensitivity analysis – impact on total costs

The results of the DSA are presented in Figure 3. Parameters with no or minimal impact on the total cost when altered are not included in Figure 3. All results are presented as a table in Appendix 12. Figure 4 presents the same data as Figure 3, excluding the two parameters which have the most impact - to improve resolution of the remaining parameters.

For every parameter in the model, the cost of the repeat screening strategy was always higher than the cost of the single screening strategy regardless of whether the parameter was at its highest or lowest estimated value.

The total costs were most sensitive to changes in the cost of screening pregnant women. At the lowest estimated cost per screen (£6.68), the repeat screening strategy cost £5.3m more than the single screen strategy (£4.6m less than the difference in costs in the base case) equating to £961,594 per CS case avoided. When long-term healthcare costs were considered, this equated to £93,096 per QALY, and £32,774 when social care costs were also considered (see Appendix 21 and Scenario 7). Caution is required when interpreting these results as the data on lifetime estimates are limited.

At the highest estimated cost per screen (£26.72), the repeat screening strategy cost £19m more than the single screen (£9.2m more than the difference in costs in the base case), equating to £3.5m per CS case avoided.

The total costs were also sensitive to the probability of a positive result in women with no syphilis (the chance of a false positive screening result). At the lowest estimated specificity (95%), the repeat screening strategy cost £9.5m more than the single screen strategy and at the highest estimated specificity (100%), the repeat screening strategy cost £3.0m more than the single screen strategy.

The total costs were somewhat sensitive to the proportion of women attending their first screen early vs. late; syphilis incidence during pregnancy; and the cost of syphilis treatment. For each of these parameters, the difference in cost between the strategies was £9.9m plus or minus less than £500,000.

Figure 3. Tornado diagram – one-way deterministic sensitivity analysis of total costs

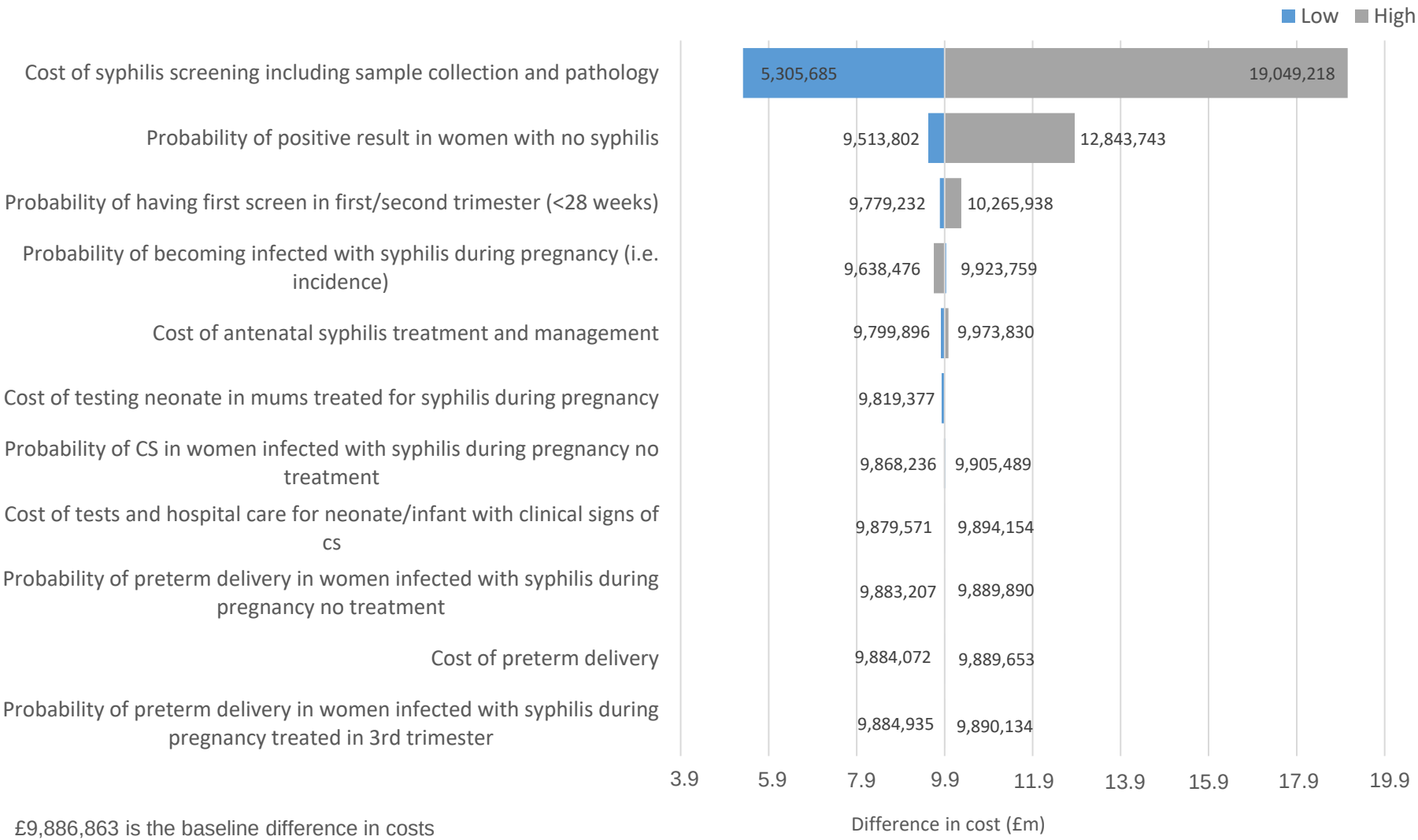
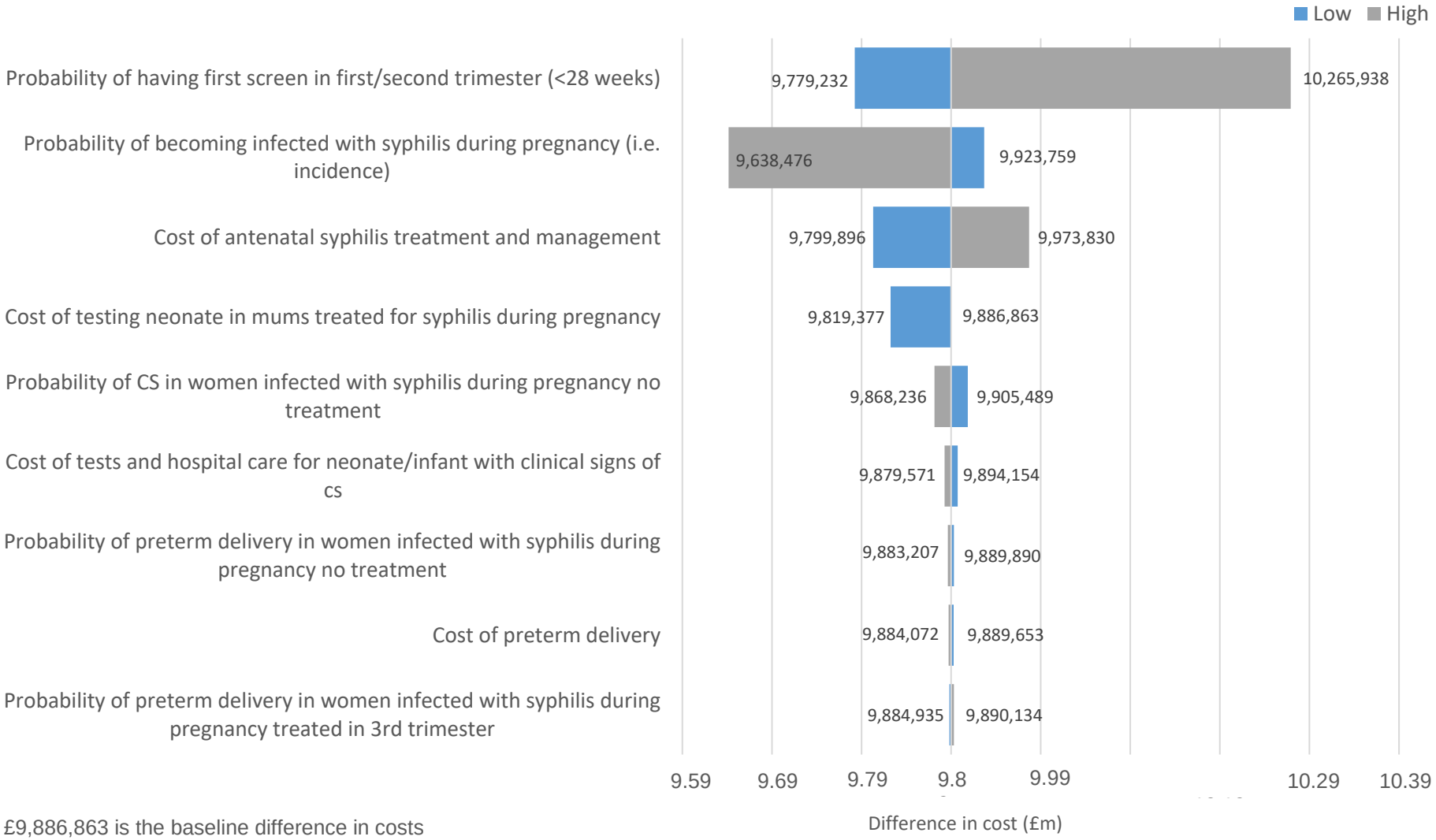


Figure 4. Tornado diagram – one-way deterministic sensitivity analysis of total costs – parameters with most or least impact removed



£9,886,863 is the baseline difference in costs

One-way sensitivity analysis – impact on CS cases

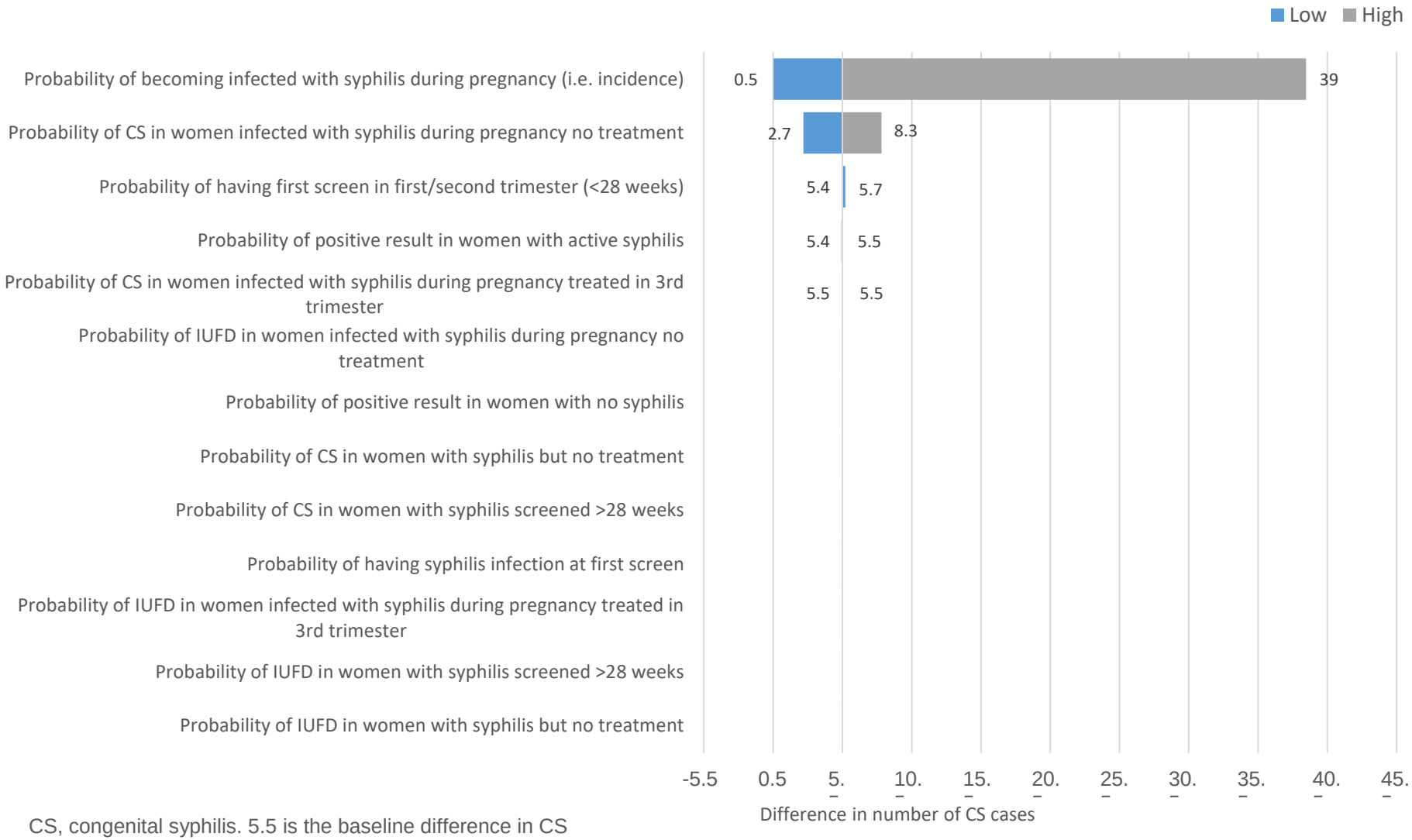
The results of the one-way (deterministic) sensitivity analysis, examining the impact of the parameters on the number of CS cases, are presented in Figure 5. Parameters which, when altered, did not impact the number CS cases, are not included in the tornado plot. The complete results are presented as a table in Appendix 13.

Examining the impact of changing parameter values on the number of infants born with CS, the model was most sensitive to 1) the syphilis incidence during pregnancy and 2) the probability of CS in women infected with syphilis during pregnancy who did not receive treatment (Figure 5).

At the highest incidence estimate (0.012%), the repeat screening strategy resulted in 39 fewer cases of CS compared to the single screen strategy (4.2 cases vs. 43 for repeat and single screening respectively). At the lowest value (0.00017%), the repeat screening strategy resulted in 0.6 fewer cases of CS compared to single screening (3.2 cases vs. 3.7 cases respectively).

For the probability of CS in women infected with syphilis during pregnancy who received no treatment, at the highest estimate (75%), the repeat screening strategy resulted in 8 fewer cases of CS compared to single screening (3.3 vs. 12 respectively) and at the lowest value (25%), the repeat screening resulted in 2.7 fewer cases of CS (6.0 vs. 3.3 respectively).

Figure 5. Tornado diagram - one-way deterministic sensitivity analysis - CS cases

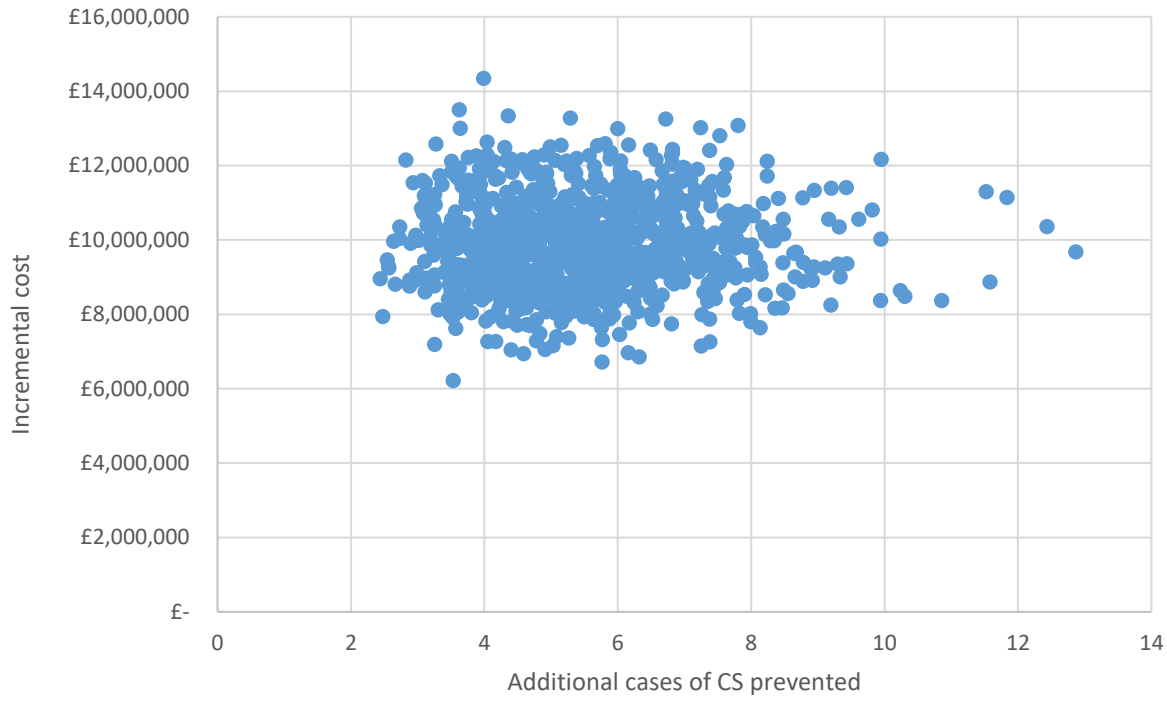


CS, congenital syphilis. 5.5 is the baseline difference in CS cases

Probabilistic sensitivity analysis (PSA)

Using Monte Carlo Simulation for PSA, in all 1000 simulations, the repeat screening strategy always cost more than the single screening strategy and always resulted in fewer cases of CS (the 95% CIs did not overlap). The incremental cost and incremental cases of CS prevented are shown in Figure 6.

Figure 6. Incremental cost vs. additional cases of CS prevented



Scenario analyses

Scenario 1: Lifetime time horizon

Using a utility of 0.74 for someone with CS at birth and a utility of 1.00 for someone without CS and discounting by 3.5% for a lifetime (70 and 81 years respectively), the total lifetime QALYs were 19.40 for someone with CS at birth and 26.98 for someone without CS – a difference of 7.58 QALYs. Using these total lifetime QALYs to calculate the difference in total QALYs between screening strategies, the repeat screening strategy resulted in 52.2 additional QALYs compared to the single screening strategy (see Appendix 11).

Based on an additional lifetime healthcare cost of £80,423 for each infant born with CS, and the difference in total QALYs between screening strategies, the cost per QALY gained was £180,817. When lifetime healthcare and social care costs were considered (£651,387 per infant born with CS), the cost per QALY gained reduced to £120,494 (Table 10).

Table 10. Long-term health care and social care costs

	Short-term costs [Antenatal + postnatal]	Long-term costs	Lifetime costs [short + long-term]	Total QALYs
Health care costs				
Existing: single screen	£1,777,469,008	£710,438	£1,778,179,446	19,464,817
Alternative: repeat screen	£1,787,355,870	£266,694	£1,787,622,565	19,464,869
Difference	£9,886,863	-£443,743	£9,443,119	52.2
ICER				£180,817
Health and social care costs[1]				
Existing: single screen	£1,777,469,008	£5,754,176	£1,783,223,184	19,464,817
Alternative: 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%.

[1]Lifetime health and social care costs adapted from a study of lifetime costs of cerebral palsy in Denmark [26]. 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.

Scenario 2: Incomplete uptake of repeat screen

The outcomes presented in Appendix 15 indicate that 99.6% uptake of repeat testing (in line with current uptake of first screen in England) had very little impact on the model outcomes. In this scenario, the repeat screening strategy cost £9.6m more than the existing screen strategy and resulted in 5.3 few cases of CS, 0.3 fewer cases of IUFD, 2 fewer cases of preterm delivery and 0.1 fewer neonatal deaths. In this scenario, the cost per CS case prevented is £1,791,880.

Scenario 3: High syphilis incidence in pregnancy

Appendix 16 shows the outcomes of the model when the probability of becoming infected with syphilis between screens is 0.00012, the same probability used in the two US models [18,19]. The repeat screening resulted in 39 fewer cases of CS compared to single screening (43.2 vs. 4.2 respectively), 0.9 fewer neonatal deaths, 13 fewer preterm deliveries and 1.8 fewer cases of IUFDs whilst the repeat strategy cost an additional £9.6m. In this scenario, the cost per CS case prevented is £247,284.

Appendix 17 shows the cost-per case of CS avoided and ICERs when the probability of becoming infected with syphilis between screens is four times higher than baseline, at 10 intervals from 0.00003 to 0.00012. With each increase in incidence, the repeat screening strategy results in a higher number of CS cases prevented, and a lower cost per CS case prevented. When lifetime healthcare costs are considered, the ICER is £26,683 (below the £20-30k threshold used by NICE), when the probability is 0.00009 (0.009%). When lifetime healthcare and social-care costs are considered, the ICER is £11,171 (below the threshold) when the probability is 0.00004 (0.004%). Caution is needed when interpreting these results as the data on lifetime estimates are limited.

Scenario 4: No late first screen

The data presented in Appendix 18 show that when all women attended antenatal care before their third trimester, the overall costs and pregnancy outcomes changed but the cost to prevent one case of CS, IUFD or neonatal death was unchanged.

Scenario 5: 100% sensitivity and specificity of screening

The data presented in Appendix 19 show that when there was 100% sensitivity and specificity of the screening process, there was very little impact on the model outcomes. The overall cost to avoid one case of CS reduced to £1,643,384 and no women were given unnecessary treatment.

Scenario 6: 100% specificity in the repeat screen

The data presented in Appendix 20 show that if there were no false positives in the second screen, the repeat screening strategy would cost £9.1m more than the existing strategy and result in 5.5 fewer cases of CS. The overall cost to avoid one case of CS would be £1,653,202.

Scenario 7: Cost per screen needed to meet the NICE ICER thresholds

The cost per screen at which the overall ICER reached NICE cost-effective thresholds calculated considering long-term healthcare costs and, separately, considering long-term health and social care costs using the same lifetime estimates from Scenario 1. Data are presented in Appendix 21. When lifetime healthcare costs of CS are considered, the per screen cost would need to be £1.87 to take the ICER below £30k and £1.11 to take it below £20k. If health and social care costs of CS are considered the per screen cost would need to be £6.46 to take it below £30k and £5.70 to take it below £20k. Caution is required when interpreting these results as the data on lifetime estimates are limited.

Discussion

Key findings

The results of this health economic analysis indicate that a repeat antenatal screening strategy for syphilis 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 would result in fewer cases of CS, the number of cases prevented would be small, approximately 5.5 per year. The repeat screening strategy would cost £9.9m more, equating to £1,791,880 per CS case prevented. Most of the increase in cost is a result of the additional costs related to providing the second screen – with a small proportion due to additional treatment and perinatal costs.

When lifetime costs and benefits were considered, for the repeat screening strategy, the cost per QALY gained was £180,817 when only healthcare costs were considered, and £120,494 when health and social care costs were considered. These are well above the £20k-30k cost per QALY threshold that NICE use to assess interventions. Since April 2017, NICE have recommended a higher threshold of £100k-£300k for drugs used to treat rare conditions - defined as conditions affecting less than 5 people in 10,000. This higher QALY threshold is dependent on the number of QALYs gained by an individual in their lifetime, with the £100k threshold used for treatments that deliver <10 additional QALYs and up to a £300k threshold for treatments that deliver >30 additional QALYs [33]. To our knowledge, this rare disease threshold has not been used to assess different screening strategies and its focus is on the use of specialised treatments for rare conditions rather than screening for rare diseases which can be treated with inexpensive drugs, as is the case with syphilis. It is not clear whether CS would be categorised as a rare condition for these purposes since the low incidence is due to prevention interventions, including treatment, and not because it is naturally rare. Either way, the difference in lifetime QALYs between CS and no CS is 7.58, which means the £100k threshold would be used, and as such, the £120k cost per QALY would be above this.

The results of the sensitivity analyses show that the baseline results were stable. The PSA showed that the repeat screening strategy cost more and resulted in fewer cases of CS in 100% of simulations. In DSA, the total cost was most sensitive to changes in the cost per screen but even when the per screen cost was halved to £6.68, the cost per case of CS prevented remained high, (at £961,594), and the repeat screening strategy was unlikely to be cost effective - with an ICER of £93k when long-term healthcare costs and utilities were considered, or £33k when long-term health and social care costs were considered (Scenario

7). Caution is needed when interpreting these results as the data on lifetime estimates are limited.

In further sensitivity analysis, the number of CS cases was most sensitive to changes in the syphilis incidence between screens, which was explored in Scenario analysis 3. This showed that it may be cost effective to introduce repeat screening in areas where 1 in 25,000 (0.004%) or more women become infected with syphilis during pregnancy, after their first screen, a much higher incidence than the estimated average for pregnant women in the UK. This threshold should be viewed with caution, bearing in mind that the lifetime costs are based on limited data and that current guidelines already recommend a repeat screen in women with a known risk of infection. It is unlikely that areas of the UK have such a high incidence and it may be difficult to estimate the local incidence because not all cases of syphilis infection during pregnancy will result in CS and not all cases of CS will be identified or be as a result of a new infection in the mother during pregnancy.

It is not appropriate to use individual cases of CS as an indication that the cost-effectiveness threshold has been reached in a specific region – even if it can be confirmed that the mother had a negative syphilis screen in early pregnancy and became infected during pregnancy. This is because the number of CS cases in the UK is extremely low and stochastic. A single case of CS in a region does not mean that this region has a regularly higher incidence than elsewhere; even when the incidence in a region has been very low or even zero one year, there is still a chance there could be incident cases the following year if pregnant women become infected with syphilis.

It may be worth considering repeat screening for a short period of time within a region where there is a known syphilis outbreak or where there are multiple cases of CS in a short period within the same geographical area in women who were syphilis negative at first screen.

The prevalence of syphilis at first screen would provide a more practical threshold to monitor and respond to with repeat screening but further work would be needed to understand the relationship between prevalence and incidence of syphilis in pregnancy, and even in areas of low prevalence there could be circumstances when there is a higher incidence for a short period of time.

Any additional clinical benefits of the repeat screening strategy, such as a reduction in other adverse pregnancy outcomes, were small, with two fewer cases of preterm delivery, 0.1 fewer cases of neonatal death and 0.3 fewer cases of IUFD per year in the base case. Partner notification was not considered in the model but since the repeat screening strategy

meant more syphilis cases were diagnosed, it could lead to more of the sexual partners diagnosed and treated.

Repeat screening could also have some negative impacts or harms. There was a higher number of false positive results from the model (an additional 1,372 in repeat screening). This is likely to be an overestimate in both strategies, since in the base case, there were 1,705 women treated for syphilis in the single screen strategy, which is considerably higher than the reported number of women receiving treatment for syphilis each year (570 in 2010/11) [3]. This means that the difference in costs associated with syphilis treatment between the strategies may also be an overestimate. However, these costs make up just 4% of the difference in costs between strategies and in Scenario 5, when screening was 100% accurate and there are no false positives, the cost per CS case avoided remained high, at £1.6m.

The specificity of the screening process is likely to be better in the second screen than in the first because the clinician will already have information from the first screen as a reference. This means that there are likely to be fewer false positives at the second screen than at the first screen. Nevertheless, screening twice will result in additional false positives compared with screening once. As well as additional costs, a false positive result may also lead to unnecessary anxiety for mothers and their families, impact the mother's relationships, and possibly even damage their confidence in the screening programme. The negative impact of overtreatment was not quantified as part of the model. There is some evidence that use of antibiotics in pregnancy can increase the risk of childhood epilepsy, obesity, and asthma [34] and it is vital to minimise unnecessary use of antibiotics where possible given growing concerns around antimicrobial resistance.

It is important to note that any change to the screening programme would have no impact on the number of adverse pregnancy outcomes in women who refuse screening, women who first attend antenatal care late and have a first screen but miss the opportunity for a repeat screen, or women who attend very late in pregnancy and miss the opportunity for any screening. For this reason, and because treatment for syphilis is not 100% effective at preventing adverse pregnancy outcomes, there are likely to continue to be a small number of infants born with CS even if any changes to the screening strategy were made.

Strengths

This is the first health economic analysis to assess the cost and clinical benefits of a repeat screening strategy for syphilis compared to a single screen strategy within the UK setting. Clinical parameters were taken from published literature, UK specific surveillance data, and

with input from experts in the field. Many of the cost parameters were calculated using NHS clinical guidelines, NHS tariffs and published costs and were validated by experts working within public health, and/or the UK health system.

Limitations

Model assumptions

A model by definition is a simplification of reality and as such requires some assumptions to be made about the data and clinical practice. One such assumption is that women cannot become infected with syphilis between the repeat screen and delivery. The incidence estimate relates to the full duration of pregnancy, so this assumption should not affect the number of women becoming infected, but rather, will overestimate the number who would be diagnosed at the repeat screen and treated, therefore overestimating the benefits of the repeat screen strategy (although the number of women becoming infected with syphilis is small and therefore this would probably not have a huge impact on the overall results). In reality, women could become infected with syphilis at any stage of pregnancy. If universal repeat screening were to be implemented at any point in the future, then the decision of when to offer the repeat screen would need to be made based on clinical evidence and practical considerations such as coinciding with a routine antenatal appointment to maximise acceptability and uptake. When choosing the best time to perform the repeat screen in pregnancy, there would be a trade-off between the benefits of delaying the screen as late as possible, to maximise the chance that a new infection would be picked up, and the benefits of screening as early as possible to maximise the benefits of treating the infection swiftly, thereby reducing the risk of adverse pregnancy outcomes.

The model assumes that, since everyone has already accepted a first screen, there is 100% uptake of the second screen (in women who have the opportunity for a repeat screen). This may be optimistic, but even if uptake of the second screen were less than complete, it would be unlikely to affect the main results. In scenario 2 (Appendix 15), when uptake was reduced to 99.6%, in line with current uptake of the first screening, the cost per screen remained high at £1.8m.

The model also assumes that all women and neonates who are diagnosed positive for syphilis receive treatment. Great lengths are taken by antenatal teams to follow-up any women with a positive result, but the SASS study found that not all women who were diagnosed as having syphilis received complete treatment and identified paediatric follow-up as an issue [3]. Without further data on treatment completion rates and loss-to-follow up it is difficult to estimate what level of loss-to-follow up there is and in some cases loss to follow

up might be due to women moving abroad and receiving treatment elsewhere or women moving to private healthcare providers – which was not assessed. Lack of treatment in women and neonates found positive for syphilis is likely to make the repeat screening even less cost effective.

Data limitations

The small number of CS cases means that few data were available from the UK on pregnancy outcomes in women treated for syphilis or in infants born with CS. For life-time costs, it was necessary to use an estimate from elsewhere in Europe, since no estimate of the life-time cost of CS was available from the UK. We assumed that the life-time cost of CS was comparable to the lifetime cost of CP and the estimate did not account for any difference in cost between early presentation and delayed presentation of CS or consider utilities for other pregnancy outcomes or for the mother. It is difficult to have confidence in the estimate used – and for this reason the main focus of the analysis was on the short-term costs and health benefits. Research to estimate the life-time health and social care costs of CS in the UK would be useful for future economic analyses in this area.

Generalisability

This analysis was specific to the UK, using costs calculated using NHS tariffs, staff costs and laboratory costs as well as scaling pregnancy outcomes and syphilis incidence to reflect the UK setting. The cost of screening itself was calculated using micro-costing but a large proportion of this was the cost of the laboratory service - where an average of two costs identified was used. Sensitivity analysis indicates that small changes in this cost has a large impact the total cost of the screening programme. Laboratory costs will vary between regions and we could assume that in some areas, cost savings might be made due to economies of scale. Any savings made on the cost per test would have a large impact on the overall programme costs and the cost-effectiveness. Any change in the screening strategy would require additional staff training, education, communications and changes to clinical guidelines – which would increase the cost of the repeat screening strategy. Although the cost of these was not included in the model, the cost of continued professional development and training are included in the PSSRU staff costs [28] which were used to calculate many of the cost parameters.

Policy and research implications for preventing CS

The expected value of perfect information (EVPI) was not calculated since the cost per CS case prevented was high and the cost per QALY well above the £20-30k threshold in all sensitivity analyses conducted. Alternative approaches to reducing the number of adverse

pregnancy outcomes including CS cases could provide a more cost-effective approach and should be explored.

It is worth noting that even with a universal repeat screening strategy, some women do not access antenatal care until late in pregnancy missing the opportunity for a repeat screen. Late attendance rates in the UK are similar to those reported from elsewhere in Western Europe and the US [35]. Late attendees are disproportionately disadvantaged and vulnerable women and are more likely to have adverse pregnancy outcomes. Whilst these women will have the opportunity for treatment before delivery if diagnosed with syphilis, women who present for the first time in the last few weeks of pregnancy or at delivery, do not necessarily have time to receive a screening result or treatment if diagnosed. In 2017/18, in England, 5,697 women first attended antenatal care at 39 weeks gestation or later, representing 1.3% of pregnancies [36]. Very late presentation can be due to women arriving in the UK during pregnancy, many of whom will have attended antenatal care elsewhere before arrival. Reasons for genuine late presentation include language barriers, unresolved immigration issues and failures of the health system [37].

Without additional evidence on the effectiveness of treatment in late pregnancy to prevent CS and neonates born with CS it is difficult to know the benefit of ensuring treatment during pregnancy in women diagnosed in late pregnancy compared to treating the infant at birth if they have CS.

Of the 20 CS cases in the UK since 2010, 11 had no record of the mother receiving antenatal screening. It is not known whether this was because testing was refused or because of very late/no first antenatal attendance, or arrival in the UK midway through pregnancy [14]. This highlights the need for effort to be made to ensure timely screening in pregnancy, particularly in women first attending antenatal care later in pregnancy, who are already at increased risk of other adverse pregnancy outcomes. It may be worth exploring the cost-effectiveness of an organised targeted screening programme using point of care testing in later attenders. Such a programme could include testing for HIV and Hepatitis B, which may improve cost-effectiveness.

This model had a single disease focus, considering only syphilis. At present screening for HIV, hepatitis B and syphilis is performed in early pregnancy. Assessing whether a repeat screen for all three infections is cost-effective would be useful, because as with syphilis, women could become infected after the initial screen and treatment during pregnancy would reduce the risk of vertical transmission. Screening for all three may result in higher benefits in terms of clinical outcomes and this may make it more cost-effective.

Data collection in some specific areas would help to inform future evaluations of screening strategies. For example, gestational week of first screen, offer and uptake 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. Education around sexual health and STI prevention targeted at pregnant women might also provide a cost-effective intervention and could be considered.

Recommendation

Based on the results of this health economic analysis, implementation of universal repeat screening for syphilis in pregnancy is not recommended as there is little evidence that it would 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 be cost effective – particularly if the cost per screen is low. Interventions to ensure 100% uptake of screening in early pregnancy in all pregnant women plus education about sexual health and STI prevention should also be considered.

Were syphilis prevalence among sexual health clinic attendees to continue to increase, it is likely that syphilis incidence in pregnant women would also increase. If that were the case, there would be reason to re-examine the cost-effectiveness of the repeat screening strategy. This highlights the importance of continued monitoring of syphilis in pregnant women, uptake of screening and the number of CS cases each year.

Appendices

Appendix 1. 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.

Appendix 2. Gestational week at first antenatal attendance (for estimating pregnancy outcomes)

Country	<12 weeks		12-28 weeks		≥28 weeks		No data	With data available	Total	Ref	Notes
	n	%	n	%	n	%					
England	299,634	70.1%	103,137	24.1%	24,935	5.8%	~200,000	427,706	-	[36]	2017/18 data
Northern Ireland	15,069	65.4%	7,607	33.0%	365	1.6%	4	23,041	23,045	[41]	2017/18 data
Scotland	42,840	84.2%	5,876	11.5%	2,165	4.3%	316	50,881	51,197	[42]	2017/18 data
Wales	22,878	82.2%	4,226	15.2%	745	2.7%	512	27,849	28,361	[43]	2017/18 data
UK total	380,421	71.8%	120,846	22.8%	28,210	5.3%		529,477			

The SASS study [3] found that in women screen positive for syphilis, 6.4% (81/1271) had their first antenatal attendance at 27 weeks or later.

Appendix 3. Gestational week at delivery (for calculating delivery costs and estimating 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	-	[44]	2014 data
Northern Ireland	470	2.0%	1,385	6.0%	21,190	92.0%	0	23,045	23,045	[41]	2017/18 data
Scotland	868	1.7%	2,444	4.9%	46,791	93.4%	207	50,103	50,310	[42]	2017/18 data
Wales	723	2.3%	1,810	5.6%	29,562	92.1%	141	32,095	32,236	[40]	2017 data
UK total	15,907	2.1%	41,172	5.4%	705,515	92.5%		762,594			

Appendix 4. Calculating pregnancy outcomes for the UK setting.

Pregnancy outcome	Women with no syphilis	Syphilis infection at time of conception					Becomes infected during pregnancy	
		a First screen + treatment 1st trimester	b First screen + treatment 2nd trimester	c First screen + treatment 1/2nd trimester	d First screen + treatment 3rd trimester	e No treatment	f Repeat screen + treatment 3rd trimester	g 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%

Table. 4.1. Pregnancy outcome data from published meta-analysis of international studies

These data are from systematic review and meta-analysis which measured pregnancy outcomes in women with and without syphilis (Qin *et al.* [22]). Each estimate is an average taken from between 2 and 33 different international studies. The risk of neonatal death was reported for the whole of pregnancy but not separately for each pregnancy trimester of treatment. For the model, the risk for each trimester was calculated by using IUFD to scale the difference in risk for each trimester.

Column c is calculated using the 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 from Appendix 2). For example, CS was calculated as follows: (0.759*0.104) + (0.241*0.176) = 0.121.

Column e: no treatment group due to a false negative test result.

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

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

These risk of adverse pregnancy outcome in the no syphilis group in the meta-analysis data (Qin *et al*) were considerably higher than observed in pregnant women in the UK (Table 4.2). The risk of CS in women with syphilis was also considerably higher in the meta-analysis than observed in the UK [3,13].

Table. 4.2. Comparing pregnancy outcome data from international studies and the UK

Pregnancy outcome	International data	UK data	UK/International	Reference
Women with no syphilis				
Preterm delivery	7.2%	7.485% [57,079/762,594]	104.0%	See Appendix 3
IUFD (stillbirth)	3.7%	0.393% [3.93/1000] [1]	10.6%	[45]
Neonatal death	2.0%	0.172% [1.72/1000] [1]	8.6%	[45]
Women with syphilis				
Congenital syphilis (any trimester)	13.7%	1.28% [3.4/266][2]	9.4%	[3,13]

[1]The most recent data on pregnancy outcomes were available for 2016 when the total number of pregnancies in the UK was 780,043 [45]. These are used here to represent the 'no syphilis' population.

[2] Based on 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 additional women infected during pregnancy [0.000017*725,637]. The ratio between the UK and

international data was used to adjust data from the meta-analysis to reflect risk for UK setting both for women with no syphilis and for women with syphilis treated in different trimesters (Table 4.3). For example, CS in women treated in 1st/2nd trimester was calculated as follows: (0.121*0.094) = 0.0114 and women treated in 3rd trimester was calculated as follows: (0.406*0.094) = 0.038. The published 95% confidence intervals were adjusted in the same way for low and high values used in the sensitivity analysis.

Table 4.3. Adjusted pregnancy outcome data used in the model

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%

Appendix 5. Cost of syphilis screening in pregnancy

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.
Laboratory testing (higher cost)	16.50	0.50	8.25	Price quoted in London Sexual Health full STI screen tariff [23].
Laboratory testing (lower cost)	9.00	0.50	4.50	Price quoted by laboratory manager. This is the price charged per screen. It covers consumables, internal quality control (IQC), external quality assessment (EQA), laboratory staff time, and overheads and accounts for the proportion of tests which are negative (which require only one test) and positive (which require confirmatory work).
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 [23].
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 [28]). 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**

A 50:50 split between the higher and lower costs for laboratory tests was used.

Appendix 6. Cost of treatment and management of women diagnosed with syphilis in pregnancy

Activity	Cost per woman (£)	Notes
STI Intervention C tariff	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 [5,23]. 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 [28].
Additional cost at 2nd visit	8.25	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [28].
Additional cost at 5th visit	27.00	Additional cost due to patient being seen by consultant doctor instead of by doctor/nurse mix [28].
Total	**314.09**	

There is no change to staff level at the 3rd or 4th visit when the patient would be seen by a nurse.

Appendix 7. Cost of neonate screening in infants born to mothers treated for syphilis during 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	[28]	
Review of test results		6	Staff time	Consultant paediatrician	10 per review	108.00	108.00	[28]	
RPR/VDRL blood test	1	2	Staff time	Blood taken by nurse	10 per test	45.00	22.50	[28]	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	[28]	
Syphilis blood tests (as above)	2	4	Diagnostics	Laboratory tests	3 sets of tests	12.75	38.25	[23]	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.

Appendix 8. Cost of testing for syphilis in neonates with clinical signs of 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	[28]	
Review of syphilis test results		8	Staff time	Consultant paediatrician	10 per review	108.00	144.00	[28]	
RPR/VDRL blood test	1	4	Staff time	Blood taken by nurse (band 6)	10 per test	45.00	37.50	[28]	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	[28]	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	[28]	
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	[28]	
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	[28]	Based on cost of Band 8c Radiographer

Continued on follow 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	[28]	Based on cost of Band 8c Radiographer
X-ray film	1		Diagnostics	Diagnostic tests	2	25.00	50.00	[46]	
Ophthalmic assessment	1		Staff time	Consultant Ophthalmologist	30	108.00	54.00	[28]	
Audiology review	1		Staff time	Audiologist (Associate specialist)	10	105.00	17.50	[28]	
Sample taken for microscopy/PCR	1		Staff time	Nurse (band 6)	10	45.00	7.50	[28]	
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	[28]	
Total cost							**751.50**		

RPR/VDRL, rapid plasma reagent/venereal disease research lab test.

Detailed testing protocol was obtained from Clinical Guidelines [5] and expert opinion.

Appendix 9. Cost of treating neonates with congenital syphilis

Activity	N	Resource type	Resource/ Activity	Unit	Cost per unit (£)	Cost per neonate (£)	Ref	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	[5,47,48]	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	[5,47,48]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	721.00	7,210.00	[5,29,49]	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	[5,47,48]	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	[5,47,48]	Standard sized infusion bags are used with the surplus discarded.
Hospital stay	10	Tariff cost	Hospital stay	Days	483.00	4,830.00	[5,29,49]	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.

Appendix 10. Cost estimate for neonatal death.

Activity	Resource / Activity	Quantity	Cost per unit	Total cost	Ref	Notes:
Cost of IUFD	-	-	-	£4,356.80	[24]	
Hospital stay	Day	3	£483.00	£1,449.00	[5,29]	Based on NHS tariff for Paediatric Major Infections with CC Score 0 - HRG code PW16E. Three days is estimate based on expert opinion.
Total cost				**£5,805.80**		

The cost of neonatal death is calculated as 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.

Appendix 11. Calculating the total QALYs for the two screening strategies

Strategy	No congenital syphilis		Congenital syphilis		Total QALYs
	Number of infants	Lifetime QALYs	Number of infants	Lifetime QALYs	
Existing: single screen	721,531	19,464,646	8.8	171	19,464,817
Alternative: repeat screen	721,537	19,464,805	3.3	64	19,464,869
Difference					52.2

The number of infants was calculated as the total number of women in the model minus the number of IUFDs, neonatal deaths and infants with CS.

Lifetime QALYs were calculated based on life expectancy of 70 years for babies born with CS and 81 for babies born with no-CS.

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Appendix 12. One-way sensitivity analysis - Total costs

Variable Description	Total cost estimate for single screen strategy (£)		Total cost estimate for repeat screen strategy (£)		Cost difference (£)		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Cost of syphilis screening including sample collection and pathology	1,772,620,056	1,787,166,912	1,777,925,741	1,806,216,129	5,305,685	19,049,218	-4,581,178	9,162,355
Probability of positive result in women with no syphilis	1,777,064,245	1,780,707,109	1,786,578,048	1,793,550,852	9,513,802	12,843,743	-373,060	2,956,880
Probability of having first screen in first/second trimester (<28 weeks)	1,777,463,449	1,777,470,660	1,787,242,681	1,787,736,599	9,779,232	10,265,938	-107,631	379,076
Probability of becoming infected with syphilis during pregnancy (i.e. incidence)	1,777,425,170	1,777,764,124	1,787,348,929	1,787,402,601	9,923,759	9,638,476	36,896	-248,386
Cost of antenatal syphilis treatment and management	1,777,361,918	1,777,576,098	1,787,161,813	1,787,549,928	9,799,896	9,973,830	-86,967	86,967
Cost of testing neonate in mums treated for syphilis during pregnancy	1,777,386,089	1,777,469,008	1,787,205,466	1,787,355,870	9,819,377	9,886,863	-67,486	0
Probability of CS in women infected with syphilis during pregnancy no treatment	1,777,450,283	1,777,487,733	1,787,355,772	1,787,355,969	9,905,489	9,868,236	18,626	-18,626
Cost of tests and hospital care for neonate/infant with clinical signs of cs	1,777,457,334	1,777,480,682	1,787,351,488	1,787,360,253	9,894,154	9,879,571	7,292	-7,292
Probability of preterm delivery in women infected with syphilis during pregnancy no treatment	1,777,465,964	1,777,472,683	1,787,355,854	1,787,355,890	9,889,890	9,883,207	3,027	-3,656
Cost of preterm delivery	1,700,460,816	1,854,477,742	1,710,350,469	1,864,361,814	9,889,653	9,884,072	2,791	-2,791
Probability of preterm delivery in women infected with syphilis during pregnancy treated in 3rd trimester	1,777,468,900	1,777,469,191	1,787,353,835	1,787,359,325	9,884,935	9,890,134	-1,928	3,271
Cost of term delivery	1,505,331,241	2,049,600,087	1,515,217,197	2,059,487,856	9,885,957	9,887,769	-906	906
Probability of positive result in women with active syphilis	1,777,468,419	1,777,470,303	1,787,354,736	1,787,358,355	9,886,317	9,888,052	-546	1,190

Variable Description	Total cost estimate for single screen strategy (£)		Total cost estimate for repeat screen strategy (£)		Cost difference (£)		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Probability of having syphilis infection at first screen	1,777,433,615	1,777,504,401	1,787,321,102	1,787,390,639	9,887,487	9,886,238	624	-624
Probability of preterm delivery in women with syphilis screened >28 weeks	1,777,464,764	1,777,475,108	1,787,351,248	1,787,362,516	9,886,484	9,887,408	-379	545
Probability of neonatal death in women infected with syphilis during pregnancy treated in 3rd trimester	1,777,469,001	1,777,469,051	1,787,355,735	1,787,356,683	9,886,734	9,887,632	-128	769
Probability of neonatal death in women infected with syphilis during pregnancy no treatment	1,777,468,679	1,777,469,534	1,787,355,869	1,787,355,873	9,887,190	9,886,339	327	-524
Probability of preterm delivery in women with syphilis but no treatment	1,777,468,676	1,777,469,408	1,787,355,851	1,787,355,894	9,887,175	9,886,485	312	-377
Probability of IUFD in women with no syphilis	1,776,068,445	1,778,869,570	1,785,955,644	1,788,756,097	9,887,198	9,886,527	336	-336
Probability of neonatal death in women with no syphilis	1,773,273,382	1,781,664,633	1,783,160,580	1,791,551,161	9,887,198	9,886,528	335	-335
Probability of CS in women infected with syphilis during pregnancy treated in 3rd trimester	1,777,468,995	1,777,469,024	1,787,355,638	1,787,356,180	9,886,643	9,887,156	-220	293
Cost of IUFD (i.e. stillbirth)	1,774,938,256	1,779,999,759	1,784,825,347	1,789,886,394	9,887,090	9,886,635	228	-228
Cost of neonatal death	1,775,789,382	1,779,148,634	1,785,676,389	1,789,035,352	9,887,007	9,886,718	144	-144
Probability of IUFD in women infected with syphilis during pregnancy no treatment	1,777,468,875	1,777,469,141	1,787,355,870	1,787,355,871	9,886,995	9,886,730	132	-132
Probability of IUFD in women infected with syphilis during pregnancy treated in 3rd trimester	1,777,469,004	1,777,469,015	1,787,355,790	1,787,356,011	9,886,787	9,886,996	-76	133

Variable Description	Total cost estimate for single screen strategy (£)		Total cost estimate for repeat screen strategy (£)		Cost difference (£)		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Probability of neonatal death in women with syphilis screened >28 weeks	1,777,468,426	1,777,470,391	1,787,355,236	1,787,357,377	9,886,811	9,886,986	-52	124
Probability of CS in women with syphilis but no treatment	1,777,468,915	1,777,469,073	1,787,355,865	1,787,355,874	9,886,950	9,886,801	88	-62
Probability of CS in women with syphilis screened >28 weeks	1,777,468,258	1,777,469,757	1,787,355,054	1,787,356,687	9,886,796	9,886,930	-67	67
Probability of neonatal death in women with syphilis but no treatment	1,777,468,972	1,777,469,065	1,787,355,868	1,787,355,874	9,886,896	9,886,809	34	-54
Probability of IUFD in women with syphilis screened >28 weeks	1,777,468,952	1,777,469,064	1,787,355,809	1,787,355,931	9,886,858	9,886,868	-5	5
Probability of IUFD in women with syphilis but no treatment	1,777,469,003	1,777,469,013	1,787,355,870	1,787,355,871	9,886,867	9,886,858	5	-5
Probability of preterm delivery in women with no syphilis	1,715,229,804	1,858,013,859	1,725,116,667	1,867,900,722	9,886,863	9,886,863	0	0
Probability of neonatal death in women with syphilis screened <28 weeks	1,777,466,359	1,777,483,577	1,787,353,221	1,787,370,440	9,886,863	9,886,863	0	0
Probability of preterm delivery in women with syphilis screened <28 weeks	1,777,424,362	1,777,546,233	1,787,311,225	1,787,433,096	9,886,863	9,886,863	0	0
Probability of CS in women with syphilis screened <28 weeks	1,777,464,461	1,777,476,585	1,787,351,324	1,787,363,448	9,886,863	9,886,863	0	0
Probability of IUFD in women with syphilis screened <28 weeks	1,777,467,866	1,777,471,672	1,787,354,729	1,787,358,535	9,886,863	9,886,863	0	0

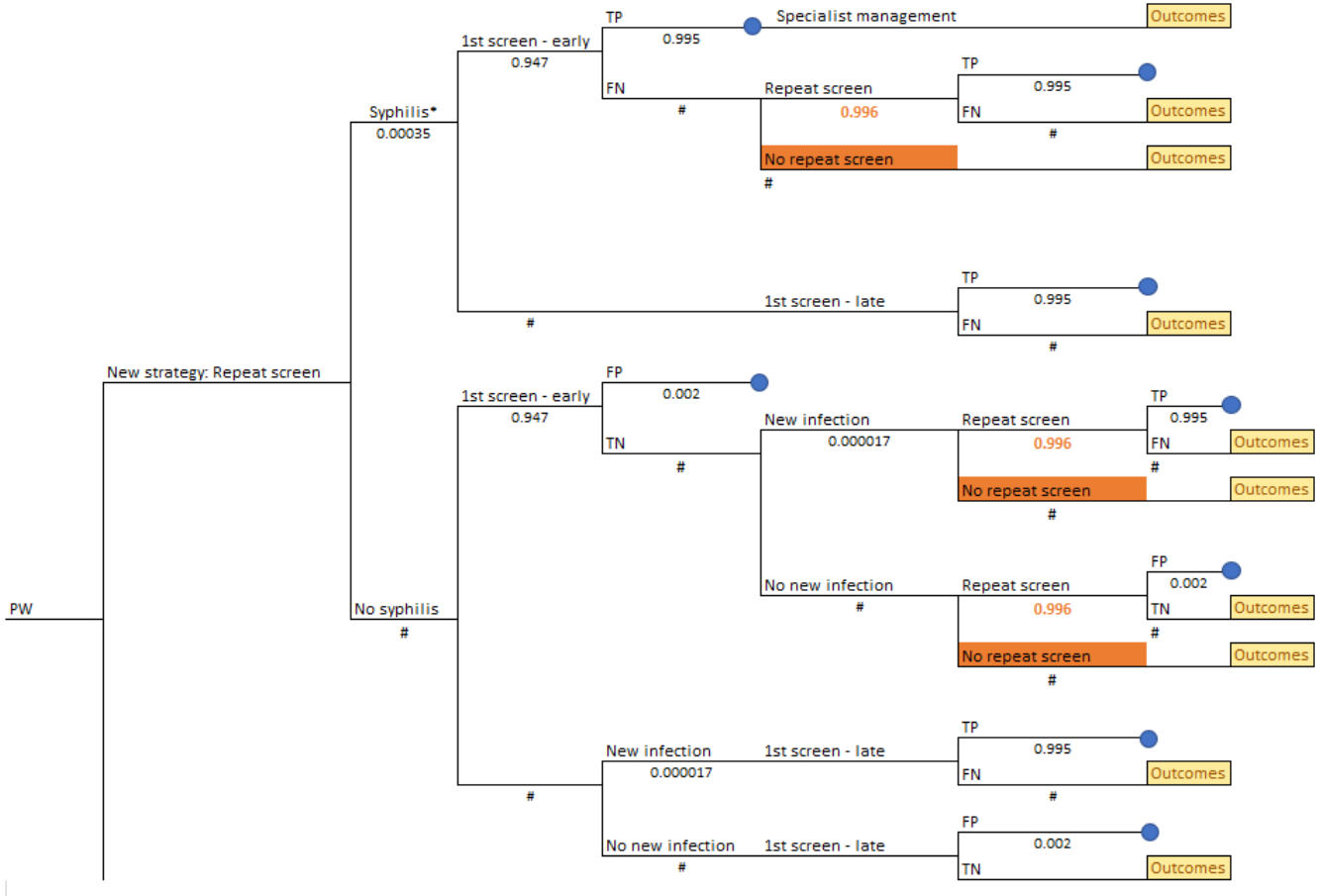
Appendix 13. One-way sensitivity analysis - Congenital syphilis cases

Variable Description	Estimate for total number of CS - single screen strategy		Estimate for total number of CS - repeat screen strategy		Difference between strategies		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Probability of becoming infected with syphilis during pregnancy (i.e. incidence)	3.7	43.2	3.2	4.2	0.55	38.98	-5.0	33.5
Probability of CS in women infected with syphilis during pregnancy no treatment	6.0	11.7	3.3	3.3	2.70	8.34	-2.8	2.8
Probability of having first screen in first/second trimester (<28 weeks)	8.8	8.8	3.1	3.4	5.73	5.45	0.2	-0.1
Probability of positive result in women with active syphilis	8.8	8.9	3.3	3.4	5.55	5.45	0.0	-0.1
Probability of CS in women infected with syphilis during pregnancy treated in 3rd trimester	8.8	8.8	3.3	3.4	5.55	5.47	0.0	0.0
Probability of IUFD in women infected with syphilis during pregnancy no treatment	8.8	8.9	3.3	3.3	5.49	5.55	0.0	0.0
Probability of positive result in women with no syphilis	8.8	8.8	3.3	3.3	5.47	5.52	0.0	0.0
Probability of CS in women with syphilis but no treatment	8.8	8.8	3.3	3.3	5.50	5.53	0.0	0.0
Probability of CS in women with syphilis screened >28 weeks	8.7	9.0	3.2	3.4	5.53	5.51	0.0	0.0
Probability of having syphilis infection at first screen	8.2	9.5	2.7	3.9	5.52	5.52	0.0	0.0
Probability of IUFD in women infected with syphilis during pregnancy treated in 3rd trimester	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0

Variable Description	Estimate for total number of CS - single screen strategy		Estimate for total number of CS - repeat screen strategy		Difference between strategies		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Probability of IUFD in women with syphilis screened >28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of IUFD in women with syphilis but no treatment	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of CS in women with syphilis screened <28 weeks	8.1	10.0	2.6	4.5	5.52	5.52	0.0	0.0
Probability of IUFD in women with no syphilis	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of IUFD in women with syphilis screened <28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women infected with syphilis during pregnancy no treatment	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women infected with syphilis during pregnancy treated in 3rd trimester	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women with no syphilis	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women with syphilis but no treatment	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women with syphilis screened <28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of neonatal death in women with syphilis screened >28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of preterm delivery in women infected with syphilis during pregnancy no treatment	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0

Variable Description	Estimate for total number of CS - single screen strategy		Estimate for total number of CS - repeat screen strategy		Difference between strategies		Difference from average cost difference between strategies	
	Low	High	Low	High	Low	High	Low	High
Probability of preterm delivery in women infected with syphilis during pregnancy treated in 3rd trimester	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of preterm delivery in women with no syphilis	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of preterm delivery in women with syphilis but no treatment	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of preterm delivery in women with syphilis screened <28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0
Probability of preterm delivery in women with syphilis screened >28 weeks	8.8	8.8	3.3	3.3	5.52	5.52	0.0	0.0

Appendix 14. Scenario 2 – Loss to follow up <100% repeat screening in women with early first screen - Adjustments to decision tree



Additional branches are shown in orange. For each of the new branches (shown in orange), the probabilities for the different pregnancy outcomes are the same as the branch above i.e. women not treated either because they are false negative or true negative.

The (lower) current strategy single screen branches are unaffected and therefore not included in this diagram.

Appendix 15. Scenario 2 – Loss to follow up <100% repeat screening in women with early first screen

Table 15.1. Clinical outcomes

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	1,705	1,451	2,904.4	54,228	1,446.5	8.8
Alternative: repeat screen	1,388,379	3,042	2,776	2,904.1	54,227	1,446.4	3.5
Difference	662,488	1,337	1,325	-0.3	-2	-0.1	-5.3

Table 15.2. Cost outcomes

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£ 1,777,469,008	£ 9,697,904	£ 535,434	£ 1,767,235,670
Alternative: repeat screen	£ 1,787,019,717	£ 18,548,739	£ 955,470	£ 1,767,515,508
Difference	£ 9,550,709	£ 8,850,835	£ 420,037	£ 279,838

Table 15.3. Requirements to prevent one outcome

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
IUFD	£ 37,852,707	2,625,664	5,300	5,251
Neonatal death	£ 79,507,578	5,515,066	11,133	11,030

TP, True positive; FP, False positive

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Appendix 16. Scenario 3 – higher risk of syphilis infection in pregnancy

Table 16.1. Clinical outcomes

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 16.2. Cost outcomes

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 16.3. Requirements to prevent one outcome

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

Appendix 17. Scenario 3 - short and long-term costs outcomes for higher syphilis incidence in pregnancy

Syphilis incidence (new infections between screens) Probability (%)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime healthcare costs	Lifetime health and social care costs
				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER	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	£98,563	£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	£71,627	£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	£55,455	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	£44,668	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	£36,962	Cost saving

Table continued on next page. See footnotes on next page.

Appendix 17 continued.

Syphilis incidence (new infections between screens) Probability (%)		Screening Strategy	Short-term costs	Pregnancy outcomes				Short-term cost per CS case prevented	Lifetime healthcare costs	Lifetime health and social care costs
				IUFD	Preterm	Neonatal death	Congenital syphilis		ICER	ICER
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	£31,181	Cost saving
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	£26,683	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	£23,085	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	£20,141	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	£17,687	Cost saving

CS, congenital syphilis; ICER, IUFD, Intrauterine fetal 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 [26]. 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.

Appendix 18. Scenario 4 - 100% early first screen

Table 18.1. Clinical outcomes

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	1,704	1,451	2,904.1	54,227	1,446.4	8.8
Alternative: repeat screen	1,450,078	3,166	2,900	2,903.9	54,225	1,446.3	3.0
Difference	724,187	1,462	1,448	-0.3	-2	-0.1	-5.8

Table 18.2. Cost outcomes

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£1,777,461,045	£9,697,904	£535,230	£1,767,227,912
Alternative: repeat screen	£1,787,901,238	£19,373,041	£994,386	£1,767,533,811
Difference	£10,440,193	£9,675,137	£459,156	£305,900

Table 18.3. Requirements to prevent one outcome

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
IUFD	£37,852,707	2,625,664	5,300	5,251
Neonatal death	£79,507,578	5,515,066	11,133	11,030

TP, True positive; FP, False positive

Appendix 19. Scenario 5 - 100% assay sensitivity and specificity

Table 19.1. Clinical outcomes

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	255	0	2,904.3	54,228	1,446.5	8.8
Alternative: repeat screen	1,413,069	266	0	2,904.1	54,226	1,446.4	3.3
Difference	687,178	12	0	-0.3	-2	-0.1	-5.6

Table 19.2. Cost outcomes

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£ 1,776,658,894	£ 9,697,904	£ 80,004	£ 1,766,880,986
Alternative: repeat screen	£ 1,785,798,323	£ 18,878,604	£ 83,673	£ 1,766,836,046
Difference	£ 9,139,429	£ 9,180,700	£ 3,669	-£ 44,940

Table 19.3. Requirements to prevent one outcome

Outcome	Cost	Women screened in third trimester	Women treated for syphilis	Additional false positives
Congenital syphilis	£ 1,643,384	123,563	2	0
IUFD	£ 35,561,339	2,673,797	45	0
Neonatal death	£ 73,625,962	5,535,811	94	0

TP, True positive; FP, False positive

Appendix 20. Scenario 6 - 100% specificity in the second screen

Table 20.1. Clinical outcomes

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	1,705	1,451	2,904.4	54,228	1,446.5	8.8
Alternative: repeat screen	1,411,696	1,718	1,451	2,904.1	54,226	1,446.4	3.3
Difference	685,805	13	0	-0.3	-2	-0.1	-5.5

Table 20.2. Cost outcomes

Cost	Total	Antenatal screening	Syphilis treatment (in pregnant women)	Perinatal costs
Existing: single screen	£1,777,469,008	£9,697,904	£535,434	£1,767,235,670
Alternative: repeat screen	£1,786,590,704	£18,860,259	£539,453	£1,767,190,992
Difference	£9,121,696	£9,162,355	£4,020	-£44,678

Table 20.3. Requirements to prevent one outcome

Outcome	Cost	Women screened in third trimester	Women treated for syphilis - TP	Additional false positives
Congenital syphilis	£1,653,202	124,294	2	0
IUFD	£34,923,201	2,625,664	49	0
Neonatal death	£73,354,309	5,515,066	103	0

TP, True positive; FP, False positive

Appendix 21. Scenario 7 – Cost per screen needed to meet the NICE ICER thresholds

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 care costs				
£100k ICER threshold	£7.20	£99,924.94	£5,662,304	£1,026,227
£30k ICER threshold	£1.87	£29,932.51	£2,006,963	£363,739
£20k ICER threshold	£1.11	£19,952.35	£1,485,751	£269,275
Per screen cost half the baseline value (used in DSA)	£6.68	£93,096.41	£5,305,685	£961,594
Long-term health and social care costs				
£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 cost of CS as used in Scenario 1 adapted from a study of lifetime costs of cerebral palsy in Denmark [26] (healthcare: £80,423; health and social care: £651,387). Per screen cost was calculated to the nearest pence. Lifetime costs and utilities were discounted at 3.5%.

NICE typically use a £20k-£30k threshold to assess interventions. There is a higher £100k threshold for rare conditions [33].

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