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

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ABSTRACT

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

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

Setting UK antenatal screening programme.

Population Hypothetical cohort of pregnant women who access antenatal care and receive a syphilis screen in 1 year.

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

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

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

INTRODUCTION

Syphilis is a bacterial sexually transmitted infection (STI) caused by Treponema pallidum subspecies pallidum. The prevalence of syphilis in the UK is low, however, the number of new diagnoses has increased over the last decade. In women, the number of cases rose from 345 in 2009 to 550 in 2018.1

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

In the UK, routine antenatal screening for syphilis, hepatitis B and HIV is offered to all pregnant women at their first routine antenatal appointment, usually before 12 weeks gestation, or later, for the small proportion of women who first present in their second or third trimester. Women who decline screening are formally reoffered and screening coverage currently exceeds 99.6%. Blood samples are initially tested using an enzyme immunoassay (EIA) with a T. pallidum particle agglutination assay (TPPA) performed on the same specimen to confirm a positive result. Women with a positive TPPA result are referred to a sexual health clinic to assess whether they have an active infection which requires treatment or a previous infection not requiring treatment. It is possible that women who screen negative for syphilis become positive later in pregnancy, either because they become infected with syphilis, or because their infection was too recent for a detectable antibody response to have been mounted at the time of the first screen. Management guidelines, outside the national screening programme, recommend that women are offered repeat testing for syphilis in late pregnancy if they have been diagnosed and treated for syphilis in the first trimester, if they consider themselves to be at risk of infection, or have a single ‘high-risk’ exposure. Assessing women’s risk can be problematic and risk can change during pregnancy. Data on coverage of repeat testing or management is not routinely collected. In 2011–2013, the Surveillance of Antenatal Syphilis Screening (SASS) study was conducted to provide quantitative data on the performance of the screening pathway.

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

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

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

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

Model parameters
Data were sought using PubMed, Google Scholar, online searches, references within papers, from experts and laboratory contacts and by data request to Public Health Agencies.
Clinical parameters
Key clinical parameters were derived from published data and national surveillance data. Where data were only available from outside the UK, they were scaled to reflect UK pregnancy outcomes and syphilis prevalence. See Table 1 for clinical parameters and methods of estimation. Furthermore, data from a large meta-analysis18 were adjusted to the UK setting to estimate the probability of each pregnancy outcome (online supplemental tables S2–S5).

Cost parameters
Cost parameters are presented in Table 1. National Health Service (NHS) tariff costs or published costs from the UK were used where possible. Where no UK data were available, microcosting was used to calculate costs—informed by clinical guidelines, expert opinion and incorporating published NHS costs and tariffs where possible. To estimate the additional lifetime cost of CS, cost estimates from outside the UK were converted to pound sterling (£).19 Where necessary, costs were
Table 1  Clinical and cost parameters for model comparing single screening with universal repeat screening of syphilis in pregnancy in the UK

| Clinical parameters                                                                 | Baseline value | Low       | High       | Distribution | Note                                                                                                                                 |
|-------------------------------------------------------------------------------------|----------------|-----------|------------|--------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Total number of women in model (representing 1 year)                                 | 725 891        | –         | –          | –            | Based on number of deliveries in the UK in 2017/2018 and the screening uptake. See online supplemental table S6.                      |
| Probability of having syphilis at the start of pregnancy                             | 0.00035        | 0.00028   | 0.00042    | Beta         | Data derived from 2011 SASS data (England only (244/691,494)). Assume same risk in other UK countries.                            |
| Probability of becoming infected with syphilis during pregnancy                      | 0.000017       | 0.0000017 | 0.00012    | Beta         | Incidence was estimated using published incidence and prevalence data from USA scaled to reflect UK prevalence.13 32             |
| Probability of receiving syphilis screen before 28 weeks gestation                   | 0.947          | 0.936     | 0.984      | Beta         | Estimate based on gestational week at first antenatal attendance. See online supplemental table S7. The low value is in line with results from SASS study.13 The high value is in line with data from Northern Ireland which (from the UK countries) has the highest proportion of women attending before 28 weeks. |
| Probability of true positive result                                                  | 0.995          | 0.984     | 1.00       | Beta         | Based on the average test sensitivity of five EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK.28 29 |
| Probability of false negative result‡                                               | 0.005          | 0.016     | 0.00       | Beta         | Based on the average test sensitivity of five EIA assays used in the UK. High and low values are based on best and worst test performance of assays used in the UK.28 29 |
| Probability of true negative result                                                  | 0.998          | 0.999     | 0.99       | Beta         | Based on average test specificity of five EIA assays (99.8%) used in the UK. High and low are estimates.28 29                    |
| Probability of false positive result‡                                               | 0.002          | 0.001     | 0.01       | Beta         | Based on average test specificity of five EIA assays (99.8%) used in the UK. High and low are estimates.28 29                    |
| Cost parameters (£)                                                                  |                |           |            |              | Estimated using microcosting. Screening is performed at the same time as other antenatal blood tests — this would also be the case for repeat screening at 28 weeks gestation. See online supplemental table S8. |
| Syphilis screen                                                                      | 13.36          | 6.68      | 26.72      | Gamma        | Estimated using microcosting. Screening is performed at the same time as other antenatal blood tests — this would also be the case for repeat screening at 28 weeks gestation. See online supplemental table S8. |
| Management of women diagnosed with syphilis in pregnancy                             | 314.09         | 251.27    | 376.91     | Gamma        | Clinical management by sexual health clinician estimate based on London Integrated Sexual Health Tariff.33 See online supplemental table S9. |
| Intrauterine fetal demise (IUFD)*                                                    | 4356.80        | 3485.44   | 5228.16    | Gamma        | Estimate based on 2013/2014 published estimate from UK inflated to 2017/2018 costs.34                                              |
inflated to 2017/2018 prices using mid-year conversion rates.20

**Outcomes**

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

**Sensitivity and scenario analyses**

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

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

1. Lifetime time horizon with incremental cost-effectiveness ratio (ICER) in terms of cost per quality-adjusted life year (QALY) as the main outcome.
2. Incomplete uptake of the repeat screen—where the probability of having a second screen was 99.6%, in line with the current uptake of screening in England.
3. Increased syphilis incidence—varying incidence at 10 intervals between the baseline and the high value used in sensitivity analysis (0.012%).
4. No late presentation to antenatal care—all women are screened twice in the repeat screening strategy.
5. 100% sensitivity and specificity of the syphilis screening process.
6. 100% specificity of the repeat screen (ie, no false positives).
7. Examining the per screen cost required to meet the standard National Institute for Health and Care Excellence (NICE) cost-effectiveness threshold of £20 000–£30 000.21

In scenario analysis 1, the lifetime healthcare and social care costs for infants born with CS were considered. Since no data on the lifetime cost of CS were available, cerebral palsy (CP) was used as a proxy as it can also lead to a range of disabilities, vary hugely in severity, and may sometimes be a result of CS. The lifetime health and social care costs of CP were taken from a single Danish study22 adjusted to reflect UK life expectancy and gender split.

As EuroQol five-dimensions (EQ-5D) data have not been reported for CS or CP, a utility of 0.74 for infants with CS relative to a score of 1.00 for infants born with no CS was used, adapted from a 2006 study of new-born screening strategies where 0.74 was used for infants with ‘mild developmental delay’.23 These utility values were used in a similar health economic model from the USA16 and were used to calculate QALYs. In the absence of data on changes to utility for infants born with CS, it was assumed that the difference in utility between infants born with CS and infants with no CS remained constant through childhood and adulthood.

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

The life expectancy of infants with CS was estimated as 70 years, in line with the estimate for CP22 and in light of reports of CS diagnoses in a wide range of ages.24 The life expectancy of infants with no CS was estimated as 81 years based on current UK data.25 All costs and utilities were discounted at 3.5%, in line with NICE guidelines.26

RESULTS

Base case analysis

The base case results indicate that in 1 year of screening pregnant women in the UK (n=725 891), the repeat screening strategy would result in 5.5 fewer cases of CS, 2 fewer cases of preterm delivery, 0.1 fewer cases of neonatal death (ie, one less neonatal death every 10 years on average), and 0.3 fewer cases of IUFD compared with the single screening strategy (table 2).

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

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

Sensitivity and scenario analyses

The DSA results indicated that even accounting for parameter uncertainty, the total cost of the repeat screening strategy was always higher than the cost of the single screening strategy (see online supplemental figure S2 for Tornado diagram). Total costs were most sensitive to changes in the per screen cost, but also to changes in the specificity of the screening process, the proportion of women first attending antenatal care before their third trimester, syphilis incidence and the cost of syphilis treatment (online supplemental figure S2). In the DSA examining the impact of clinical and cost parameters on the number of CS cases, the model was most sensitive to syphilis incidence during pregnancy and the probability of CS in infants born to women infected with syphilis during pregnancy who did not receive treatment (ie, were undiagnosed; see online supplemental figure S3). In all iterations in the 1000 PSA Monte Carlo simulations, the repeat screening strategy cost more than the single screening strategy and resulted in fewer cases of CS. The incremental cost and incremental cases of CS prevented are shown in online supplemental figure S4.

When lifetime costs and utilities were considered (scenario 1), the health and social care cost per additional QALY gained for the repeat screening strategy (ICER) was £120 494. In DSA, the ICER was £32 716 and £205 600, when discounting of utilities was 0% and 6%, respectively (see online supplemental table S15). Even if

Patient and public involvement

There was no patient or public involvement (PPI) in the design of the evaluation. A report outlining the model was reviewed by the UK NSC which has PPI representation and was made available for public consultation.
When the probability of becoming infected with syphilis between screens was increased sevenfold to 0.00012 (scenario 3), repeat screening resulted in 39 fewer cases of CS compared with single screening, 0.9 fewer neonatal deaths, 13 fewer preterm deliveries, and 1.8 fewer cases of IUFDs while the repeat strategy cost an additional £9 638 476 (online supplemental tables S16 and S17). In this scenario, the cost per CS case prevented was £247 284 (online supplemental table S18). Online supplemental table S19 in the online supplement presents the cost per case of CS avoided and the ICER when the probability of becoming infected with syphilis between screens is higher than baseline (at 10 intervals between 0.00003 and 0.00012). As anticipated, with each increase in incidence of syphilis infection, the repeat screening strategy resulted in more CS cases prevented and a lower cost per CS case prevented. When lifetime healthcare and social-care costs were considered, the ICER was £11 171 (below the £20–£30k threshold used by NICE), when syphilis incidence in pregnancy was 0.004% and became cost saving at an incidence of 0.005% (1 in 100 000) or higher.

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

**DISCUSSION**

We report on the cost-effectiveness of repeat universal syphilis antenatal screening in the UK. Our results indicate that this screening strategy would not be cost effective in the current UK setting where the prevalence and incidence of syphilis among pregnant women is low. Although the repeat screening strategy is likely to result in fewer cases of CS the additional costs related to providing the second screen rather than treatment or delivery costs for women with syphilis. The PSE and DSA indicated costs for women with syphilis.

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

| Screening strategy | Syphilis antenatal screens | Women treated for syphilis | False positive maternal syphilis | Intrauterine fetal demise (all causes)* | Preterm deliveries (all causes)* | Neonatal deaths (all causes)* | Congenital syphilis cases |
|--------------------|---------------------------|---------------------------|-------------------------------|---------------------------------------|-------------------------------|----------------------------|--------------------------|
| Existing: single screen | 725 891                  | 1705                       | 1451                          | 2904.4                               | 54 228                        | 1446.5                    | 8.8                      |
| Estimate            | 725 891 to 725 891        | 1698 to 1737               | 1443 to 1482                  | 2890 to 2916                         | 53 905 to 54 282              | 1441 to 1457              | 8.7 to 8.9               |
| 95% CI              |                          |                           |                               |                                       |                               |                           |                          |
| Alternative: repeat screen | 1 411 696                | 3089                       | 2823                          | 2904.1                               | 54 226                        | 1446.4                    | 3.3                      |
| Estimate            | 1 411 456 to 1 411 503    | 3074 to 3150               | 2806 to 2883                  | 2889 to 2915                         | 53 903 to 54 280              | 1441 to 1457              | 3.3 to 3.3               |
| 95% CI              |                          |                           |                               |                                       |                               |                           |                          |
| Difference           | 685 805                  | 1384                       | 1372                          | −0.3                                 | −2                            | −0.1                      | −5.5                     |

*These adverse pregnancy outcomes are all-cause outcomes for all 725 891 women screened, including the small number with syphilis infection.
†95% confidence interval, calculated using probabilistic sensitivity analysis.

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

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

**Strengths and weaknesses**

This is the first health economic analysis to assess the costs and clinical benefits of a repeat screening strategy for syphilis compared with a single screen strategy within the UK setting. The input values in the model were based on the best available evidence from the published literature, (HRQoL) were considered (Scenario 1), the cost per QALY gained was £120 494 for the repeat screening strategy compared with the single screening strategy. This is well above the £20k–£30k cost per QALY threshold that NICE uses to assess interventions,21 and also exceeds the £100 000 threshold used to assess drugs/interventions for rare conditions (the threshold used when the intervention results in <10 additional QALYs to an individual in their lifetime).27 For this analysis, costs and utilities were discounted by 3.5%, in line with NICE guidelines for England.26 When no discounting of utilities was assessed in DSA, the cost per QALY gained was £32 716, just above the £30k threshold.

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UK-specific surveillance data, NHS tariffs and published costs, and with input from experts in the field where data were lacking. These inputs were rigorously tested in sensitivity and scenario analyses to add confidence to the results, despite limited data in some areas.

There were sparse UK data available on pregnancy outcomes in women treated for syphilis or in infants born with CS. There are no published EQ-5D scores for CS and a lack of evidence on changes to utility and health and social care costs over time for infants born with CS. We therefore used the additional lifetime cost of CP, estimated in a study from Denmark,22 as a proxy for the lifetime cost of CS. As such, the primary focus of the analysis was the short-term costs and CS cases avoided since it was difficult to have confidence in the estimate used for lifetime CS cost or utility.

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

It was also assumed that all women and neonates diagnosed with syphilis receive the appropriate full course of treatment and all infants born to women diagnosed with syphilis in pregnancy receive syphilis testing at birth. However, the SASS study13 found that in 2010–2011, not all women diagnosed with syphilis received complete treatment and inadequate paediatric follow-up was identified as an issue. Lack of treatment in these women and neonates is likely to make the repeat screening even less cost-effective.

Since there are no published estimates of the diagnostic accuracy (DA) of the syphilis screening process, accounting for the DA of laboratory assays and the diagnosis decision making by clinicians, average sensitivity and specificity of EIA assays used in UK laboratories were used.26 The DA values used here are considerably higher than those used in the US models.16 17 where a different testing algorithm is used29 and would, if anything, bias repeat screening results towards being more cost-effective.

Implications for clinicians and policy-makers

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

Our model focused on the UK but is relevant to other European countries with similar syphilis prevalence and healthcare costs. Our analyses, using UK cost estimates, suggest that a universal second screen in late pregnancy could become cost-effective if the incidence of syphilis in pregnancy were to increase (to 5 per 100 000 pregnant women), indicating that in countries that have far higher syphilis prevalence than the UK, a second screen could be cost saving. For example, recent estimates suggest that the prevalence of syphilis in the WHO African region is more than 10-fold higher than in the WHO European Region.30 In such a high prevalence setting, combined with lower local healthcare costs, a second syphilis screen in late pregnancy could be cost-effective.

There could be some negative impact associated with repeat screening. A false positive result may lead to additional costs, unnecessary anxiety for mothers and their families, impact the mother’s relationships, possibly even damage their confidence in the screening programme, as well as lead to overtreatment. It is vital to minimise unnecessary use of antibiotics where possible given growing concerns around antimicrobial resistance and because there is some evidence that antibiotic use in pregnancy increases the risk of childhood epilepsy, obesity and asthma.31

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

Unanswered questions and future research

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

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

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

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

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

- IUFD
- Preterm delivery
  - Neonatal death
  - Alive - congenital syphilis
  - Alive - no congenital syphilis
- Term delivery
  - Neonatal death
  - Alive - congenital syphilis
  - Alive - no congenital syphilis

Footnote:
IUFD, intrauterine fetal demise; preterm refers to <37 weeks gestation. The blue triangle indicates the branch end point.
This diagram complements Figure 1 in the main body of the paper. The probability of each of these outcomes occurring for each branch of the tree is presented in Table S2.
Figure S2. Tornado diagram – one-way deterministic sensitivity analysis of total costs - parameters with least impact removed

- Cost of syphilis screening including sample collection and pathology
  - Low: £5,305,685
  - High: £19,049,218
- Probability of positive result in women with no syphilis
  - Low: £9,513,802
  - High: £12,843,743
- Probability of first screen in 1st/2nd trimester (<28 weeks)
  - Low: £9,779,232
  - High: £10,265,938
- Probability of becoming infected with syphilis during pregnancy (i.e. incidence)
  - Low: £9,638,476
  - High: £9,923,759
- Cost of antenatal syphilis treatment and management
  - Low: £9,799,896
  - High: £9,973,830
- Cost of testing neonates of mums treated for syphilis in pregnancy
  - Low: £9,819,377
- Probability of CS in women infected with syphilis in pregnancy - but not treated
  - Low: £9,868,236
  - High: £9,905,489
- Cost of tests and hospital care for neonates & infants with CS
  - Low: £9,879,571
  - High: £9,894,154
- Probability of preterm delivery in women infected with syphilis in pregnancy but not treated
  - Low: £9,883,207
  - High: £9,889,890
- Cost of preterm delivery
  - Low: £9,884,072
  - High: £9,889,653
- Probability of preterm delivery in women infected with syphilis in pregnancy and treated in 3rd trimester
  - Low: £9,884,935
  - High: £9,890,134

Note: £9,886,863 is the baseline difference in costs. CS, congenital syphilis.
Figure S3. Tornado diagram - one-way deterministic sensitivity analysis of CS cases - parameters with least impact removed

Low

High

- Probability of becoming infected with syphilis in pregnancy (i.e. incidence)
- Probability of CS in women infected with syphilis in pregnancy no treatment
- Probability of having first screen in first/second trimester (<28 weeks)
- Probability of positive result in women with active syphilis
- Probability of CS in women infected with syphilis in pregnancy treated in 3rd trimester
- Probability of IUFD in women infected with syphilis in pregnancy receiving no treatment
- Probability of positive result in women with no syphilis
- Probability of CS in women with syphilis but no treatment
- Probability of CS in women with syphilis screened >28 weeks
- Probability of having syphilis infection at first screen
- Probability of IUFD in women infected with syphilis in pregnancy treated in 3rd trimester
- Probability of IUFD in women with syphilis screened after 28 weeks
- Probability of IUFD in women with syphilis but no treatment

Note: 5.5 is the baseline difference in congenital syphilis (CS) cases.
Figure S4. Incremental cost versus additional cases of CS prevented

This figure is an output from the Probabilistic Sensitivity Analysis (PSA) and shows the impact of parameter uncertainty on the cost per additional case of CS prevented in universal repeat screening of syphilis in late pregnancy versus single screening.
Table S1. Assumptions applied to screening strategies and rationale

| Assumption                                                                 | Note                                                                                                                                                                                                 | Note                                                                                                                                                  |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| All women found positive for syphilis, at their first or repeat screen,   | As per clinical guidelines [1]. Uptake of treatment in diagnosed women is thought to be high. No published data were found to support or refute this assumption. |                                                                                                                                                       |
| are referred to care within a sexual health clinic and are successfully    |                                                                                                                                                                                                     |                                                                                                                                                       |
| treated within that setting.                                               |                                                                                                                                                                                                     |                                                                                                                                                       |
| The clinical management of women who are diagnosed with syphilis at their  | Recommendation from experts. This is hypothetical, as repeat screening is not current practice.                                                                                                   |                                                                                                                                                       |
| 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.  |                                                                                                                                                                                                     |                                                                                                                                                       |
| Infants born with CS display signs of CS, 40% at birth and 60% some weeks/  | Based on expert opinion and evidence indicating that most infants with CS develop signs by 5 weeks. Lack of data on the proportion of CS cases with late presentation (after two years) [1]. |                                                                                                                                                       |
| months after delivery and are tested and treated accordingly.             |                                                                                                                                                                                                     |                                                                                                                                                       |
| There is no loss to follow-up, i.e. all women who are identified as       | Inclusion of loss to follow-up in the model would add unnecessary complexity to the model. Also, there is lack of data on loss to follow-up in this setting. |                                                                                                                                                       |
| needing treatment receive it.                                              |                                                                                                                                                                                                     |                                                                                                                                                       |
| There is 100% uptake of repeat screening in women who were initially      | Assessed in Scenario Analysis 2.                                                                                                                                                                    |                                                                                                                                                       |
| screened.                                                                 |                                                                                                                                                                                                     |                                                                                                                                                       |
| 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    | Recommendation from experts. This is hypothetical, as repeat screening is not current practice.                                                                                                   |                                                                                                                                                       |
| screen at that point and therefore miss the opportunity for a repeat test. |                                                                                                                                                                                                     |                                                                                                                                                       |
| Preterm vs. term delivery impacts costs but the model assumes it has no    | Lack of data around correlation between timing of delivery and pregnancy outcome.                                                                                                                  |                                                                                                                                                       |
| impact on the risk of pregnancy outcomes (neonatal death or congenital    |                                                                                                                                                                                                     |                                                                                                                                                       |
| syphilis).                                                                 |                                                                                                                                                                                                     |                                                                                                                                                       |
| The repeat screen would be performed at 28 weeks gestation to coincide    | No data could be found on the incidence of syphilis or the impact of a new syphilis infection that late in pregnancy. Timing of repeat screen based on expert advice – and is hypothetical as repeat screening is not current practice. |                                                                                                                                                       |
| with existing routine anaemia blood tests. It was assumed that no new     |                                                                                                                                                                                                     |                                                                                                                                                       |
| syphilis infection could occur between this screen and delivery.           |                                                                                                                                                                                                     |                                                                                                                                                       |
| No women undergo a repeat screen in the current care pathway (i.e. the    | Following expert advice that few high-risk women receive repeat screening at present. Lack of data around uptake of repeat screening and pregnancy outcomes for low risk vs. high risk women. |                                                                                                                                                       |
| single screening strategy).                                               |                                                                                                                                                                                                     |                                                                                                                                                       |
| Parameter                                      | Baseline value | Low    | High   | Note                          |
|-----------------------------------------------|----------------|--------|--------|-------------------------------|
| Pregnant women with no syphilis               |                |        |        |                               |
| IUFD                                          | 0.004          | 0.003  | 0.005  | Tables S3-S5                 |
| Preterm delivery                              | 0.075          | 0.058  | 0.097  | Tables S3-S5                 |
| Neonatal death                                | 0.002          | 0.001  | 0.003  | Tables S3-S5                 |
| Congenital syphilis                           | 0.000          | -      | -      | Assumption                   |
| Pregnant women with syphilis diagnosed and treated <28 weeks |                |        |        |                               |
| IUFD                                          | 0.005          | 0.002  | 0.012  | Tables S3-S5                 |
| Preterm delivery                              | 0.079          | 0.042  | 0.143  | Tables S3-S5                 |
| Neonatal death                                | 0.003          | 0.001  | 0.014  | Tables S3-S5                 |
| Congenital syphilis                           | 0.011          | 0.008  | 0.016  | Tables S3-S5                 |
| Pregnant women with syphilis diagnosed and treated ≥28 weeks |                |        |        |                               |
| IUFD                                          | 0.023          | 0.018  | 0.028  | Tables S3-S5                 |
| Preterm delivery                              | 0.183          | 0.119  | 0.275  | Tables S3-S5                 |
| Neonatal death                                | 0.013          | 0.005  | 0.032  | Tables S3-S5                 |
| Congenital syphilis                           | 0.038<sup>1</sup> | 0.029  | 0.047  | Tables S3-S5                 |
| Pregnant women with syphilis not diagnosed or treated |                |        |        |                               |
| IUFD                                          | 0.028          | 0.023  | 0.033  | Tables S3-S5                 |
| Preterm delivery                              | 0.241          | 0.188  | 0.305  | Tables S3-S5                 |
| Neonatal death                                | 0.014          | 0.009  | 0.022  | Tables S3-S5                 |
| Congenital syphilis                           | 0.034<sup>1</sup> | 0.026  | 0.042  | Tables S3-S5                 |
| Pregnant women infected with syphilis in pregnancy and diagnosed and treated in 3<sup>rd</sup> trimester |                |        |        |                               |
| IUFD                                          | 0.006          | 0.002  | 0.013  | Assumed to have same risk as women diagnosed and treated for syphilis infection in 1<sup>st</sup> trimester. |
| Preterm delivery                              | 0.071          | 0.038  | 0.127  |                               |
| Neonatal death                                | 0.003          | 0.001  | 0.015  |                               |
| Congenital syphilis                           | 0.010          | 0.007  | 0.014  |                               |
| Pregnant women infected with syphilis during pregnancy not diagnosed or treated |                |        |        |                               |
| IUFD                                          | 0.028          | 0.023  | 0.033  | Assumed to have same risk as women with syphilis not diagnosed or treated. Estimate based on expert opinion. |
| Preterm delivery                              | 0.241          | 0.188  | 0.305  |                               |
| Neonatal death                                | 0.014          | 0.009  | 0.022  |                               |
| Congenital syphilis                           | 0.500          | 0.250  | 0.750  |                               |

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

<sup>1</sup>The probability of congenital syphilis in women with syphilis is higher in women treated at ≥28 weeks gestation than in women receiving no treatment. This is because estimates are from a meta-
analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.
These data are from a systematic review and meta-analysis which measured pregnancy outcomes in women with and without syphilis (Qin et al. [2]). Each estimate is an average calculated by combining data from 2-33 different studies.

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

Column c, the risk of pregnancy outcomes if syphilis is diagnosed and treated in the 1st or 2nd trimester, was calculated using data from the 1st and 2nd trimesters (column a and b) and using UK data to calculate the proportion of women first attending antenatal care in their 1st or 2nd trimester (75.9% and 24.1% respectively). For example, the risk of congenital syphilis (CS) was calculated as follows: (0.759*0.104) + (0.241*0.176) = 0.121.
Column e: no treatment group due to a false negative test result. The probability of CS in women with syphilis is higher in women treated in 3rd trimester (column d) than in women receiving no treatment (column e). This is because estimates are from a meta-analysis which combined data from 15 and 33 studies respectively to estimate risk and both estimates have wide, overlapping confidence intervals.

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

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

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

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

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

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

No data on the risk of the different pregnancy outcomes during each trimester were available from the UK. Therefore, the difference in overall risk in pregnancy between the UK and the meta-analysis data was used to adjust data from the meta-analysis to calculate the risk of outcomes in each trimester for women in the UK. The calculated risks, used in the model, are presented in Table S5 and an example of how they were calculated is included in the Table S5 footnotes.
Table S5. Pregnancy outcome data used in the model – adjusted from published large meta-analysis of international studies [2] to reflect UK risks

| Pregnancy outcome | Women with no syphilis | Syphilis infection at time of conception | Becomes infected during pregnancy |
|-------------------|------------------------|------------------------------------------|----------------------------------|
|                   | First screen + treatment 1st trimester | First screen + treatment 2nd trimester | First screen + treatment 1/2nd trimester | First screen + treatment 3rd trimester | No treatment | Repeat screen + treatment 3rd trimester | No treatment |
| Congenital syphilis | 0.0% | 0.97% | 1.65% | 1.14% | 3.0% | 3.3% | 0.97% | 50.0% |
| Preterm delivery | 7.48% | 7.07% | 10.50% | 7.90% | 18.03% | 24.12% | 7.07% | 24.12% |
| IUFD (stillbirth) | 0.39% | 0.56% | 0.45% | 0.53% | 2.26% | 2.80% | 0.56% | 2.80% |
| Neonatal death | 0.17% | 0.32% | 0.26% | 0.31% | 1.30% | 1.39% | 0.32% | 1.39% |

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

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

The published 95% confidence intervals were adjusted in the same way to calculate the low and high values used in the sensitivity analysis.
Table S6. Overall number of women screened for syphilis in pregnancy, 2017/18

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

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

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

The uptake of screening in 2017/2018 for Northern Ireland was 99.97%, based on data collected by Public Health Agency Northern Ireland 2017/2018.
Table S7. Gestational week at first antenatal care attendance – by UK country

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

All data are for year 2017/18. The SASS study [3] found that in women screening positive for syphilis, 6.4% (81/1271) had their first antenatal attendance at 27 weeks or later. These data were used to calculate pregnancy outcomes and the percentage of women receiving a first syphilis screen before 28 weeks gestation (94.7% i.e. 501,267/529,477).
Table S8. Calculating the cost per antenatal syphilis screen

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

Total 13.36
Footnote: A 50:50 split between the higher and lower costs for laboratory tests was used. The cost of a repeat screen was assumed to be the same as the cost of a first screen since in both cases, samples would be taken at a routine antenatal appointment when other blood tests are performed, i.e. HIV and hepatitis B screening at first screen and routine anaemia blood tests at 28 weeks gestation.
Table S9. Calculating the cost of treatment and management of women diagnosed with syphilis in pregnancy

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

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

This cost was calculated based on expert opinion from a senior consultant in sexual health.
Table S10. Gestational week at delivery (used for calculating delivery costs and estimating pregnancy outcomes)

| Country      | ≤33 weeks | 34-36 weeks | >36 weeks | No data | With data available | Total | Ref      | Notes          |
|--------------|-----------|-------------|-----------|---------|---------------------|-------|----------|----------------|
|              | n         | %           | n         | %       |                     |       |          |                |
| England      | 13,846    | 2.1%        | 35,533    | 5.4%    | 607,972             | 92.5% | 657,351  | [19] 2014 data |
| Northern Ireland | 470     | 2.0%        | 1,385     | 6.0%    | 21,190              | 92.0% | 0        | 23,045 [7] 2017/18 data |
| Scotland     | 868       | 1.7%        | 2,444     | 4.9%    | 46,791              | 93.4% | 207      | 50,310 [8] 2017/18 data |
| Wales        | 723       | 2.3%        | 1,810     | 5.6%    | 29,562              | 92.1% | 141      | 32,236 [20] 2017 data |
| UK total     | 15,907    | 2.1%        | 41,172    | 5.4%    | 705,515             | 92.5% | 762,594  |                |
Table S11. Calculating the average healthcare costs associated with a neonatal death

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

The cost of neonatal death is calculated using the cost of intrauterine fetal demise (IUFD), which includes the cost of post-mortem, parental counselling and a subsequent pregnancy, plus an additional 3-days in a paediatric intensive care unit for the neonate. Three days hospital stay is an estimate based on expert opinion.
Table S12. Calculating the cost of testing for syphilis in neonates with clinical signs of congenital syphilis (CS)

| Activity                                      | Number At birth | Resource type | Resource/Activity       | Quantity /minutes | Cost per unit/hour (£) | Cost per neonate (£) | Ref | Notes                                                                 |
|-----------------------------------------------|-----------------|---------------|-------------------------|-------------------|------------------------|----------------------|-----|------------------------------------------------------------------------|
| Clinical assessment for signs of CS           | 1               | Staff time    | Consultant paediatrician| 30                | 108.00                 | 54.00                | [11]          |                                                                         |
| Review of syphilis test results               | 8               | Staff time    | Consultant paediatrician| 10 per review     | 108.00                 | 144.00               | [11]          |                                                                         |
| RPR/VDRL blood test                          | 1               | Staff time    | Blood taken by nurse (band 6)| 10 per test     | 45.00                  | 37.50                | [11]          | Test at birth, 1, 3, 6 and 12 months.                                    |
| IgM EIA blood test                           | 1               | Staff time    | Blood taken by nurse    | 10 per test       | 45.00                  | 22.50                | [11]          | Test at birth, 1 and 3 months.                                           |
| Syphilis blood tests (as above)              | 2               | Diagnostics   | Laboratory tests        | 5 (3 combined + 2 single)| 12.75                 | 63.75                |                                                             | Same cost if both tests are performed or only RPR/VDRL blood test performed. |
| Blood tests: full blood count, liver function, electrolytes | 1               | Staff time    | Blood taken by nurse    | 10                | 45.00                  | 7.50                 | [11]          |                                                                         |
| Blood tests (as above)                       | 1               | Diagnostics   | Laboratory tests        | 1                 | 20.00                  | 20.00                | Estimate      |                                                                         |
| Lumbar puncture (white blood cell, protein, RPR, TPPA) | 1               | Staff time    | Paediatric registrar    | 45                | 43.00                  | 32.25                | [11]          |                                                                         |
| Blood tests (as above)                       | 1               | Diagnostics   | Laboratory tests        | 1                 | 20.00                  | 20.00                | Estimate      |                                                                         |
| X-ray of long bones                          | 1               | Staff time    | Consultant Radiographer | 30                | 93.00                  | 46.50                | [11]          | Based on cost of Band 8c Radiographer                                  |
Table S12 Continued from previous page.

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

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

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

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

CS, congenital syphilis. Clinical guidelines recommend that treatment is given every 12 hours (for infants ≤7 days of age) and every 8 hours (for infants >7 days of age) for a total of 10 days with treatment typically starting on the day of delivery.
Table S14. Calculating the cost of neonate screening in infants born to mothers treated for syphilis in pregnancy

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

CS, congenital syphilis; IgM EIA, immunoglobulin M enzyme immunoassay; RPR/VDRL, rapid plasma reagent/venereal disease research lab test.
Table S15. Long-term health care and social care costs associated with congenital syphilis (CS) – results of the model comparing universal repeat screening of syphilis in late pregnancy with single screening

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

DSA: No discounting of utilities

|                        | Short-term costs [Antenatal + postnatal] | Long-term costs \(^1\) | Lifetime costs [short + long-term] | Total QALYs |
|------------------------|-----------------------------------------|------------------------|-----------------------------------|-------------|
| Single screen          | £1,777,469,008                          | £5,754,176             | £1,783,223,184                    | 58,444,492  |
| Universal repeat screen| £1,787,355,870                          | £2,160,086             | £1,789,515,957                    | 58,444,684  |
| Difference             | £9,886,863                              | -£3,594,090            | £6,292,773                        | 192.3       |
| ICER                   |                                         |                       |                                   | £32,716     |

DSA: 6% discounting of utilities

|                        | Short-term costs [Antenatal + postnatal] | Long-term costs \(^1\) | Lifetime costs [short + long-term] | Total QALYs |
|------------------------|-----------------------------------------|------------------------|-----------------------------------|-------------|
| Single screen          | £1,777,469,008                          | £5,754,176             | £1,783,223,184                    | 11,948,666  |
| Universal repeat screen| £1,787,355,870                          | £2,160,086             | £1,789,515,957                    | 11,948,686  |
| Difference             | £9,886,863                              | -£3,594,090            | £6,292,773                        | 30.6        |
| ICER                   |                                         |                       |                                   | £205,600    |

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

\(^1\)Additional lifetime health and social care costs for individuals born with CS (£651,387 per individual) - adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.
Table S16. Clinical outcomes for Scenario 3 (0.00012 probability of syphilis infection in pregnancy)

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

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

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

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

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

TP, True positive; FP, False positive
Table S19. Short and long-term cost outcomes for Scenario 3 (higher syphilis incidence in pregnancy)

| Syphilis incidence (new infections between screens) | Screening Strategy | Short-term costs | Pregnancy outcomes | Short-term cost per CS case prevented | Lifetime health and social care costs |
|-----------------------------------------------------|--------------------|------------------|--------------------|---------------------------------------|---------------------------------------|
|                                                     | Probability (%)    | Short-term costs | ICUFD | Preterm | Neonatal death | Congenital syphilis |                             | ICER |                             |
|                                                     |                    |                  |       |         |               |                   |                             |                  |
| 0.00003 (0.003)                                     | Single             | £1,777,506,256   | 2,904.6 | 54,229.9 | 1,446.6 | 13.2 |                             | £1,011,791 | £38,140 |
|                                                     | 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  |                             |                  |                  |
| 0.00004 (0.004)                                     | Single             | £1,777,534,908   | 2,904.8 | 54,231.0 | 1,446.7 | 16.5 |                             | £756,892 | £11,171 |
|                                                     | 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 |                             |                  |                  |
| 0.00005 (0.005)                                     | Single             | £1,777,563,560   | 2,904.9 | 54,232.1 | 1,446.8 | 19.8 |                             | £603,983 | Cost saving |
|                                                     | 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 |                             |                  |                  |
| 0.00006 (0.006)                                     | Single             | £1,777,592,212   | 2,905.1 | 54,233.1 | 1,446.9 | 23.2 |                             | £502,056 | Cost saving |
|                                                     | 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 |                             |                  |                  |
| 0.00007 (0.007)                                     | Single             | £1,777,620,864   | 2,905.2 | 54,234.2 | 1,446.9 | 26.5 |                             | £429,258 | Cost saving |
|                                                     | 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 |                             |                  |                  |
| 0.00008 (0.008)                                     | Single             | £1,777,649,516   | 2,905.4 | 54,235.3 | 1,447.0 | 29.9 |                             | £374,662 | Cost saving |
|                                                     | 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 |                             |                  |                  |

Table continued over the page.
Table S19. Continued from previous page.

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

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

\(^1\)Lifetime health and social care costs adapted from a study of lifetime costs of cerebral palsy in Denmark [18]. The social care costs include specialised schooling, and after school care, support to parents, residential institutions, supervised workshops, day centre, and other adult support services.
Table S20. Cost per screen needed to meet NICE ICER thresholds (Scenario 7)

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

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