

Updating the cost-effectiveness analysis of repeat screening for syphilis in pregnancy

A report for the UK National Screening Committee (UK NSC), prepared by the Sheffield Evidence Network for Screening Synthesis (SENSS)

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About the UK National Screening Committee

The UK National Screening Committee (UK NSC) advises ministers and the NHS in the 4 UK countries about all aspects of [population](#) and targeted screening and supports implementation of screening programmes.

Conditions are reviewed against [evidence review criteria](#) according to the UK NSC's [evidence review process](#).

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List of abbreviations

BASHH	The British Association for Sexual Health and HIV
BNF	British National Formulary
CLIA	Chemiluminescence immunoassay
CS	Congenital syphilis
COReC	The Care and Outcomes Research Centre
EIA	Enzyme immunoassay
ICER	Incremental cost-effectiveness ratio
IDPS	Infectious Diseases in Pregnancy Screening
IgG	Immunoglobulin G
IgM	Immunoglobulin M
ISHT	The Integrated Sexual Health Tariff
ISOSS	The Integrated Screening Outcomes Surveillance Service
IUFD	Intrauterine foetal demise
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK
NHS	National Health Service
NSC	National Screening Committee
ONS	The Office for National Statistics
PCR	Polymerase Chain Reaction
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
RPR	Rapid plasma reagin
SENS	Sheffield Evidence Network for Screening Synthesis
TPLA	<i>Treponema pallidum</i> latex agglutination
TPHA	<i>Treponema pallidum</i> haemagglutination
TPPA	<i>T. pallidum</i> particle agglutination assays
UKHSA	The UK Health Security Agency

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Plain English summary

Syphilis is a sexually transmitted infection with potentially serious health impacts if not detected and treated. Congenital syphilis is when a baby develops syphilis before birth. This happens when syphilis passes from the mother to the baby during pregnancy. It can lead to miscarriage or stillbirth. It can also mean the baby is born too early, dies at birth, or has serious health problems.

In the UK, all pregnant women are offered a syphilis test early in pregnancy. This is part of the NHS Infectious Diseases in Pregnancy Screening programme. This report asks whether all pregnant women should also have a second routine test. This second test would happen in the last 3 months of pregnancy, known as the third trimester.

The UK National Screening Committee last reviewed this question in 2020. Aquarius Population Health built a model for that review. It compared 2 options. The first option was the current policy: one routine test early in pregnancy. The second option was to test all pregnant women again in the third trimester. The model found that this extra test might prevent a small number of additional cases. It also found that it would add high costs. Overall, repeat screening for all pregnant women was unlikely to be good value for money in the UK at that time.

Evidence was limited in 2020. There was little direct UK data on how common syphilis was at the start of pregnancy. We did not know how often women got syphilis later in pregnancy after an early test showed they did not have it. There was also little data on pregnancy outcomes. Because of these evidence gaps, some parts of the model had to use assumptions. They also used expert advice and evidence from outside the UK.

New national data are now available from ISOSS. This is the Integrated Screening Outcomes Surveillance Service. ISOSS collects data on syphilis in pregnancy and congenital syphilis in England. Reported syphilis in pregnancy has also increased. NHS England and the UK Health Security Agency therefore asked for the analysis to be updated.

We rebuilt the 2020 model using the Aquarius report. We then updated it with the best evidence now available. We used ISOSS data to estimate how often syphilis is present at the start of pregnancy. We also looked at how often women get syphilis during pregnancy. We looked at serious outcomes linked to syphilis in pregnancy. These included congenital syphilis. They also included death before birth, death at birth, and early birth. We updated the model to match the current testing pathway. We also updated costs using current NHS and other standard sources. We then tested how the results changed when we changed key assumptions.

The updated analysis has 2 aims. The first aim is to see whether repeat screening for all pregnant women provides good value for money. The second is to assess how certain the result is. The model also looks at areas with higher infection rates and checks whether the answer changes in those areas. It also shows which factors have the biggest effect on whether a second routine test is worth the cost.

The main limitation is the lack of evidence on long-term effects. We do not know much about how congenital syphilis affects children as they grow up. Because of this, the model used data from children with other serious conditions. These included cerebral palsy and meningitis. The model also does not include the impact on the quality of life of mothers and carers. Evidence on this is very limited. A separate analysis included a reduction in mothers' quality of life. This had very little impact on the results.

Repeat screening would prevent some cases of congenital syphilis. However, the extra cost would be large compared with the expected health benefits.

Executive summary

Background

Syphilis is a systemic bacterial infection caused by *Treponema pallidum* subspecies pallidum. It is primarily transmitted sexually, though vertical transmission during pregnancy can cause congenital syphilis. While treatment with benzathine penicillin during pregnancy is highly effective, untreated maternal syphilis increases the risk of stillbirth and vertical transmission. Affected infants may be asymptomatic at birth or develop early symptoms. Infants born with congenital syphilis face poor health outcomes and lower life expectancy.

Currently, the UK National Screening Committee (UK NSC) recommends a single routine syphilis screen for women during the first trimester using a treponemal immunoassay, with a repeat screen only recommended for the small proportion deemed at high risk of infection. A 2020 cost-effectiveness evaluation commissioned by the UK NSC concluded that repeat screening in the third trimester was not cost-effective for all women. (1)

However, recent UK data reveals a higher prevalence of syphilis among pregnant women than previously estimated. This analysis updates the previous evaluation, rebuilding the 2020 model based on the Aquarius report and updating it with the best available evidence. Our analysis compares the cost-effectiveness of universal third trimester repeat screening against the current policy of a single routine screen for women not at high risk. Additionally, it explores regional variations and identifies the specific thresholds of key inputs (such as maternal prevalence, incident infection rates, screening costs, and long-term consequences of congenital syphilis) that would alter the policy recommendation.

Methods

A decision tree model retained the overall decision tree logic of the 2020 Aquarius model to support comparability, but updated the evidence sources for infection, outcomes, treatment and timing of diagnosis, and prioritising the most recent UK-specific evidence. The ISOSS data informed the modelled prevalence: the probability of a pregnant woman having syphilis at the start of pregnancy was estimated to be 0.084% in the base case analysis.

The analysis was conducted from a National Health Service (NHS) healthcare perspective for England using a life-time horizon, with an annual discount rate of 3.5%. The model followed an annual cohort of 618,753 women entering the antenatal screening pathway, defined using Infectious Diseases in Pregnancy Screening (IDPS) standards data. The cost-effectiveness metrics were compared against a decision threshold of £20,000 per QALY.

Results

In the base case analysis, repeat screening substantially increased the number of tests and treatments but resulted in small absolute reductions in adverse outcomes. Annually, repeat screening added 584,126 screens, preventing 0.2 neonatal deaths and 12.2 congenital syphilis cases, equivalent to approximately 47,900 additional screens per congenital syphilis case prevented.

While preventing these cases reduced long-term health costs (£0.71 million vs £1.88 million under single screening), the repeat strategy increased annual screening costs by £9.67 million (rising from £10.24 million to £19.9 million). Because only a fraction of the population benefited, repeat screening remained £9.14 million more costly overall.

Repeat screening generated 142 additional quality adjusted life years (QALYs), primarily benefiting infants born to women who acquired syphilis after a negative first screen. The resulting deterministic incremental cost-effectiveness ratio (ICER) was £64,219 per QALY, well above the £20,000 threshold. The probabilistic sensitivity analysis (PSA) yielded a similar mean ICER of £67,849 per QALY. The probability of cost-effectiveness reached 50% at a £70,000 per QALY threshold.

Key uncertainties and limitations

Uncertainties were explored through sensitivity and scenario analyses. The utility assigned to children with congenital syphilis was the largest driver of uncertainty; lower utility values reflect a more severe long-term health state, generating more QALYs per prevented case and improving the ICER. The second major driver was the percentage of infections after the early screen occurring before 28 weeks, with lower proportion occurring before 28 weeks (equivalently, more infections occurring after 28 weeks) reducing cost-effectiveness.

Regionally, London had the lowest ICER (£48,386 per QALY) due to having the highest syphilis prevalence (0.107%). For repeat screening to be cost-effective at the current £20,000 threshold, maternal prevalence would need to reach 0.214% (double the current prevalence in London). Applying a lifetime horizon with a 1.5% annual discount rate reduced the ICER to £32,290 per QALY, but none of the tested scenarios had an ICER below £20,000 per QALY.

The main limitation is the uncertainty surrounding the long-term consequences of congenital syphilis, which required using proxies based on cerebral palsy and meningitis. Additionally, the model does not fully capture wider quality of life impacts on mothers or carers, though existing evidence is limited and an exploratory analysis incorporating maternal disutility showed minimal effect on the ICER.

Conclusions

Universal repeat screening would prevent additional cases of congenital syphilis and other serious adverse outcomes. However, the absolute benefits remain small relative to the scale and economic cost of a nationwide programme. This does not mean repeat screening lacks clinical value, but it suggests that universal national repeat screening is unlikely to be cost-effective under current assumptions.

Introduction and approach

Background

Definition

Syphilis is a systemic bacterial infection caused by *Treponema pallidum* subspecies *pallidum*. It is transmitted primarily through sexual contact, but vertical transmission from a pregnant woman to her baby can occur during pregnancy and can result in congenital syphilis (CS). Untreated syphilis progresses through recognised clinical stages: primary, secondary, latent and tertiary. Primary syphilis typically presents with a painless chancre and regional lymphadenopathy. Secondary syphilis usually develops weeks to months later and may include rash, mucocutaneous lesions, fever, malaise and generalised lymphadenopathy. Latent syphilis is defined by serological evidence of infection in the absence of symptoms and is usually classified as early latent within 2 years of infection and late latent thereafter. Tertiary disease develops years later in a minority of untreated patients and may involve gummatous, cardiovascular or neurological complications. (2)

Congenital syphilis results from transplacental transmission of *T. pallidum* during pregnancy. Transmission can occur at any stage of maternal infection, although the risk is highest in early maternal syphilis. Untreated maternal infection is associated with miscarriage, stillbirth, intrauterine foetal demise, preterm birth, neonatal death and congenital infection in surviving infants. Affected infants may be asymptomatic at birth or present with signs in the neonatal period or early infancy. Recognised manifestations include hepatosplenomegaly, jaundice, rash, rhinitis, anaemia, thrombocytopenia, skeletal abnormalities and later neurological or auditory sequelae. (3)

Clinical and public health information for patients and professionals is available through the NHS infectious diseases in pregnancy screening (IDPS) programme, UK Health Security Agency (UKHSA), the British Association for Sexual Health and HIV (BASHH), and the UK National Screening Committee (UK NSC).

Epidemiology

Following the adoption of penicillin as the standard treatment for syphilis in 1947, syphilis incidence in the UK fell substantially, but diagnoses have increased again over recent decades. Current UKHSA surveillance shows that syphilis remains an important and increasing public health concern in England. In 2024 there were 13,030 syphilis diagnoses overall, including 9,535 early-stage diagnoses. Although most transmission occurs outside pregnancy, these broader epidemiological trends matter because increasing infection in the general population can translate into increased exposure during pregnancy.

For pregnancy specifically, the evidence base is stronger than it was at the time of the previous UK NSC review in 2020 because national surveillance is now available through the Integrated Screening Outcomes Surveillance Service (ISOSS), part of the NHS IDPS programme. ISOSS collects and reports data on pregnancies to women who screen positive for syphilis and on paediatric outcomes in England. The most recent published ISOSS syphilis outcomes report recorded 1,040 pregnancies to 1,027 women who screened positive for syphilis in 2022 to 2023, compared with 934 pregnancies in 2021 to 2022. (4)

The rate of congenital syphilis in England in 2022 was 0.014 cases per 1000 births. This is low by international standards and well below the World Health Organization elimination threshold of fewer than 50 cases per 100,000 live births, equivalent to 0.5 cases per 1,000 live births. Nevertheless, it represents a sevenfold increase over the seven-year period from 2015. Congenital syphilis continues to occur, and recent English surveillance indicates continuing concern about maternal infection acquired after an initial negative screen, delayed booking, or incomplete engagement with care. (5)

Testing

In the UK, syphilis screening in pregnancy forms part of the NHS IDPS programme alongside screening for HIV and hepatitis B. The UK NSC recommends systematic, population-based screening for all eligible pregnant women in every pregnancy. The purpose of screening is to identify infection early enough to allow timely assessment, treatment and neonatal management, thereby reducing the risk of vertical transmission and its consequences. (4)

Current IDPS laboratory guidance states that screening is performed using a treponemal immunoassay, usually an enzyme immunoassay (EIA) or chemiluminescence immunoassay (CLIA). A second treponemal assay is then used to confirm a positive screening result, and a rapid plasma reagin (RPR) titre is performed to assess infection activity. This detail is important because the confirmatory pathway has changed since the earlier Aquarius model: following withdrawal of the *T. pallidum* particle agglutination assays (TPPA) assay from UK practice, confirmatory testing now uses *Treponema pallidum* haemagglutination (TPHA), *Treponema pallidum* latex agglutination (TPLA), or an alternative EIA or CLIA different from the primary assay. (4)

A limitation of any serological screening strategy is that very recent infection may not yet be detectable, and women can also acquire syphilis after an initial negative result. Current programme guidance therefore emphasises that women should be advised about the availability of repeat testing at any stage of pregnancy and encouraged to report symptoms or risks of exposure. BASHH guidance similarly recommends repeat testing later in pregnancy when there is clinical suspicion or risk after an earlier negative result. (2)

Repeat testing is recommended where there is identified risk, new exposure, relevant symptoms, or other clinical concern. Programme guidance also makes clear that women can be offered testing at any time in pregnancy if risk changes after an earlier negative result. (4)

Women with confirmed positive results should be referred promptly to specialist sexual health services, with multidisciplinary communication between screening, sexual health, obstetric and neonatal teams. Current English management guidance sets out a pathway including specialist assessment, referral, birth planning, neonatal alerting and infant review after birth. (6)

Treatment

Syphilis is treatable and curable, with high treatment efficacy rates for the mother (7) and high success rates for preventing congenital syphilis when administered during pregnancy. (8) Benzathine penicillin G remains first line treatment for syphilis and is the only treatment in pregnancy with proven efficacy for preventing congenital syphilis. In general, early syphilis is treated with a single dose of benzathine penicillin, while late latent infection or infection of unknown duration requires weekly dosing for 3 weeks. BASHH pregnancy guidance further recommends that when treatment for early syphilis is initiated in the third trimester, a second dose of benzathine penicillin G should be given one week later, with careful neonatal assessment at birth. (2)

Management in pregnancy involves more than maternal treatment alone. National and professional guidance emphasises specialist assessment, follow up serology, birth planning and neonatal review. Infants at high risk of congenital syphilis should be assessed at birth and, where indicated, treated promptly with intravenous benzyl penicillin for 10 days, with subsequent clinical and serological follow up. (6)

Current UK NSC recommendation

The current UK NSC recommendation is that single antenatal screening for syphilis should be conducted at the first trimester. The UK NSC recommendation page states that its 2018 evidence review supported continued screening in early pregnancy because the benefits outweighed the harms and no evidence was found to oppose that recommendation. The same page also records that the Committee explored the cost-effectiveness of a repeat screening test later in pregnancy in 2020 and did not recommend it. (1)

Accordingly, the current policy position is that all eligible pregnant women should be offered routine screening for syphilis in the first trimester of pregnancy through the NHS IDPS programme, but that universal repeat screening later in pregnancy is not currently recommended.

A key part of the background to this recommendation is the Aquarius Population Health model commissioned by the UK NSC and published in 2020. That model was designed specifically to compare 2 antenatal strategies: current practice, defined as a single routine early screen, and a proposed alternative of universal repeat screening in the third trimester. (1)

The model was a decision tree and took the UK health system perspective. Its base case analysis used a short-term time horizon covering pregnancy and the initial weeks after delivery, while additional scenario analyses explored a lifetime horizon by incorporating long-term costs and utilities for congenital syphilis. Key outcomes included total costs, congenital syphilis cases prevented, other adverse pregnancy outcomes prevented, numbers needed to rescreen, and cost per QALY in the lifetime scenario.

The Aquarius model also made several important structural assumptions. It assumed that very few women at high risk actually received repeat testing in current practice, so repeat screening for high-risk women was not modelled. It distinguished between women screened before and after 28 weeks' gestation, reflecting the practical importance of late booking. It assumed that the repeat screen would occur at 28 weeks, aligned with routine antenatal blood tests, and that no new maternal infection would occur between that repeat screen and delivery. It also had to estimate several key parameters using limited UK data, expert opinion, and non-UK sources, including the incidence of syphilis during pregnancy and some pregnancy outcome probabilities. For example, the probability of incident infection during pregnancy was derived from a US study (9) and then scaled to UK prevalence, and lifetime costs for congenital syphilis were proxied using estimates for cerebral palsy because no direct UK congenital syphilis lifetime cost data were available.

In the base case, the model found only small clinical gains from universal repeat screening. For one year of screening in a UK cohort of 725,891 pregnant women, repeat screening was estimated to prevent 5.5 cases of congenital syphilis, 2 cases of preterm birth, 0.1 neonatal deaths and 0.3 cases of intrauterine foetal demise, but at an additional healthcare cost of about £9.9 million. This equated to about £1.8 million per case of congenital syphilis prevented, and about 124,000 women needing to be rescreened to prevent one case. In the lifetime scenario, the incremental cost-effectiveness ratio was estimated at £180,817 per QALY gained when healthcare costs alone were included, or £120,494 per QALY when health and social care costs were included. The Aquarius report therefore concluded that there was little evidence that universal repeat screening would be cost-effective in the then current UK setting, where prevalence and incidence of syphilis in pregnant women were low.

The Aquarius sensitivity analyses were also influential in shaping the recommendation. They showed that repeat screening remained more costly than single screening across the range of values tested, and that results were especially sensitive to the cost per screen, the specificity of the screening process, the proportion of women screened early enough to

be eligible for repeat testing, and the incidence of syphilis acquired during pregnancy. The model suggested that repeat screening might become more favourable only in settings with substantially higher incident infection during pregnancy than the UK average assumed at the time. It also highlighted possible harms not fully quantified in the model, especially overtreatment and anxiety resulting from false positive results. Based on these findings, the UK NSC did not recommend universal repeat screening in 2020, but instead retained single routine screening with targeted retesting where clinically indicated.

The reason for revisiting the question now is that the evidential context has changed. The earlier Aquarius analysis had to rely partly on limited UK pregnancy specific data and several structural assumptions that were necessary at the time. Since then, the IDPS and ISOSS have provided a stronger UK basis for estimating maternal prevalence, pregnancy outcomes and the timing of congenital syphilis diagnosis. Data from ISOSS shows that the prevalence of syphilis in pregnancy has risen in recent years (9), potentially increasing the cost-effectiveness of a repeat screen. In light of this, during the 2024 open call for topics, the UK NSC received a proposal to re-evaluate the cost-effectiveness of universal repeat screening and it subsequently commissioned SENSS to carry out this work. The SENSS protocol for the present update states that the current work reconstructs the 2020 Aquarius decision tree model from the published report and updates it using ISOSS and other contemporary evidence, rather than reusing the original proprietary model itself.

Objectives

The aim of this analysis is to advise the UK NSC on whether the UK should now offer an additional universal screen for syphilis in the third trimester of pregnancy. This is being addressed by reconstructing the 2020 Aquarius decision tree model from the published report and updating it using newly available epidemiological, clinical and cost evidence, with ISOSS data as the principal source for maternal and congenital syphilis epidemiology in England.

The specific objectives are to reconstruct the 2020 model and document any differences between the reconstructed model and the published 2020 results; update key epidemiological parameters, including prevalence of syphilis at the start of pregnancy and incidence during pregnancy; revise assumptions and inputs relating to test accuracy, treatment, pregnancy outcomes, congenital syphilis presentation and costs; examine decision uncertainty through deterministic sensitivity analysis, probabilistic sensitivity analysis and policy relevant scenarios; and identify the conditions under which universal repeat screening might become cost-effective, including whether conclusions differ in higher incidence regions or under alternative assumptions about key parameters.

This means the model addresses not only the headline question of whether universal third trimester repeat screening is cost-effective compared with the current policy of a single routine antenatal screen with targeted retesting, but also threshold and scenario questions

relevant to policy making. These include whether the conclusions differ by region, which parameters drive the results most strongly, and at what levels of maternal prevalence, incident infection, screening cost, or long-term consequences of congenital syphilis the policy conclusion would change.

Methods

Stakeholder engagement

Stakeholder engagement was undertaken at the beginning of the modelling process to inform the scope, structure, assumptions and data sources used in the updated cost-effectiveness analysis. A 2-hour online stakeholder workshop was held on Tuesday 28 October 2025. The workshop was coordinated by 3 members of the SENSS team and attended by 9 external stakeholders with expertise in antenatal screening, infectious diseases in pregnancy, syphilis surveillance, clinical care, public health, and screening policy.

The purpose of the workshop was to review the proposed update to the 2020 Aquarius model and to identify areas where stakeholder input was required to ensure that the updated analysis reflected current clinical practice, current surveillance data and relevant implementation considerations. The discussion covered the scope of the analysis; the availability, use and interpretation of ISOSS data; the classification of congenital syphilis cases; the current screening and confirmatory testing pathway; treatment assumptions; service capacity; the appropriate model perspective and time horizon; screening accuracy; costs and NHS inflation or tariff assumptions; life expectancy, utility and cost proxies for congenital syphilis; treatment mix; and penicillin allergy.

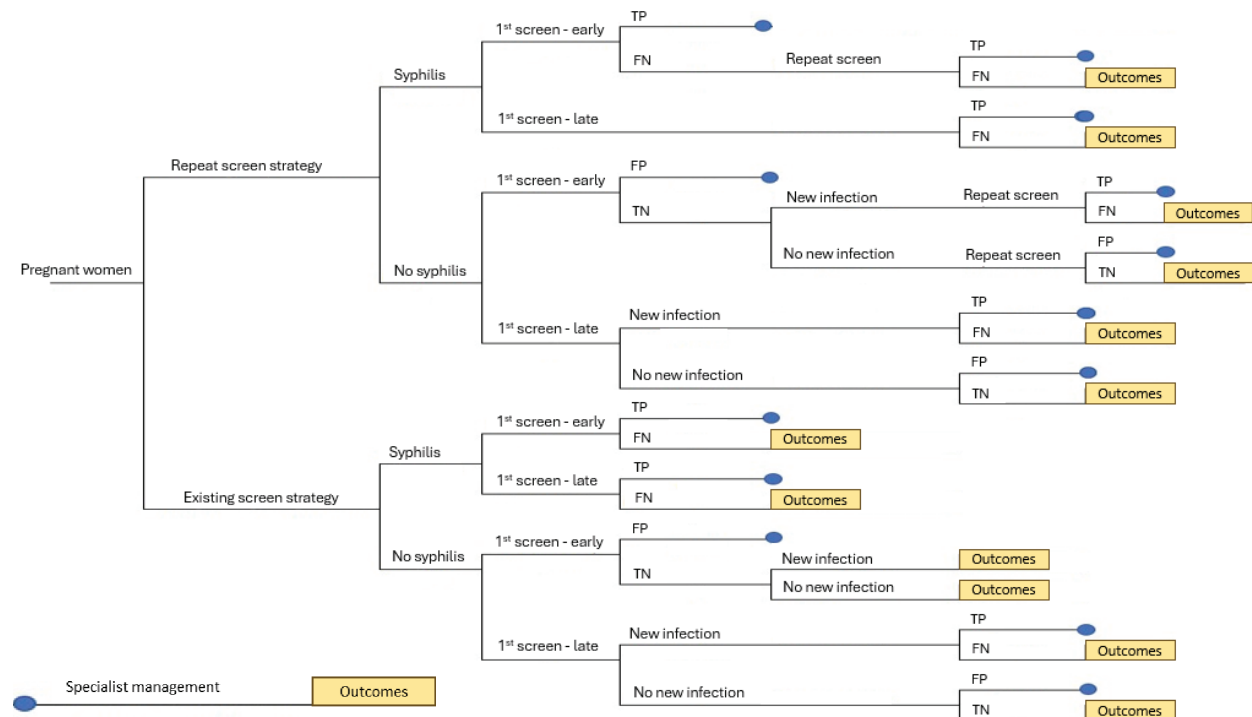
Stakeholder input informed several modelling decisions. ISOSS data for England were considered appropriate for use in the analysis. Confirmed and probable cases of congenital syphilis were included in the base case, with possible cases explored in scenario analysis. Stakeholders advised that delays due to service capacity did not need to be modelled explicitly, in light of updated 2023 guidance. They also supported the use of a long-term time horizon in the base case, provided that a short-term time horizon was also reported for comparison with the previous Aquarius analysis. Stakeholders advised that, in the absence of direct evidence on long-term outcomes for congenital syphilis, proxies from other childhood conditions were preferable to estimates derived from adult syphilis, and that uncertainty in these assumptions should be tested in sensitivity analysis. Stakeholder feedback also supported reviewing ISOSS data on treatment patterns and conducting threshold analysis, particularly because the incidence of syphilis in pregnancy may be underestimated if not all cases are detected. Alternative treatment costs were not included in the model because stage specific treatment data were unavailable and the proportions receiving alternative treatments were small.

Additional stakeholder advice was sought after the workshop where specific technical input was required. In particular, follow-up advice from UKHSA contacts informed consideration of costing assumptions, including the cost of repeat syphilis screening and related pathway costs. Further input was also sought on issues such as penicillin allergy and whether improved test accuracy data were available. This stakeholder engagement was used to refine the model structure, validate key assumptions, identify appropriate data sources, and define scenario and sensitivity analyses relevant to UK NSC decision making. Expert stakeholder comments on the draft model report and responses from the SENSS team are included in appendix 3.

Model structure and perspective

A decision tree model assessed the cost-effectiveness of universal third trimester repeat screening for syphilis in pregnancy compared with current practice of a single early antenatal screen. The model retained the overall decision tree logic of the 2020 Aquarius model to support comparability but updated the evidence sources for infection, diagnosis, treatment timing and outcomes. The updated model therefore addresses the same policy question as Aquarius, while using newer UK evidence. A schematic of the model structure is shown in Figure 1. A table of all parameter values is found in Appendix 2.

Figure 1 - Model decision tree structure



Abbreviations: TP - True Positive, FP - False Positive, TN - True Negative, FN - False Negative

Figure 1 shows the model decision tree structure with 2 separate branches, one for the existing screening strategy (single screen in early pregnancy) and another for the repeat screening strategy in the third trimester. The syphilis pathways in Figure 1 represent infections requiring treatment. Women with previously treated infections who do not

require further treatment (unless reinfected) will be grouped with women without syphilis, as their test result classifications for treatment purposes are equivalent. The model assumes that any woman capable of transmitting syphilis to her child requires treatment. Screen positive results proceed down a 'specialist management' pathway.

This analysis was undertaken to evaluate the cost-effectiveness of introducing universal third trimester repeat screening for syphilis in pregnancy, compared with current practice. It was not designed to evaluate the current antenatal syphilis screening programme itself, nor to assess whether the existing programme should continue. The current programme is treated as the comparator and remains outside the scope of the evaluation. The findings should therefore be interpreted only in relation to the potential addition of a universal repeat screen, and not as evidence for or against the value, effectiveness or continuation of the current screening programme.

In keeping with the Aquarius analysis, the comparator is a single early screen: repeat screening for high-risk women was not incorporated in the comparator for a number of reasons. Firstly, the way that risk is defined means that it is difficult to estimate the proportion of the population that are high-risk for modelling purposes. Secondly, while repeat screening is currently recommended for high-risk women, expert opinion suggests that the uptake for this is much lower than that for single screening. Thirdly, outcome data specifically for high-risk women is not available. If it were possible to do so, accounting for high-risk women in the model would reduce the cost effectiveness (in other words, increase the ICER) of universal repeat screening vs the current policy (unless this were offset by higher uptake among high-risk women with universal repeat screening).

The analysis was conducted from an NHS healthcare perspective for England. The model followed an annual cohort of 618,753 women entering the antenatal screening pathway, defined using IDPS standards data. This differs from the earlier Aquarius model, which used an annual UK cohort of 725,891 pregnant women based on births and screening uptake. The updated cohort definition is important because repeat screening is an antenatal screening intervention, and because intrauterine foetal demise is an outcome in the model. A births-based denominator risks misalignment with outcomes that occur before birth, whereas the antenatal screening cohort better represents the population to whom the intervention would be offered.

Congenital syphilis can reduce life expectancy and cause serious long-term health complications, leading to ongoing healthcare and treatment costs. These impacts would not be captured in a short-term analysis and would therefore underestimate the overall cost-effectiveness of repeat screening. In line with NICE guidance for economic evaluation (10), a lifetime time horizon was used in the base case analysis to incorporate both the long-term costs and health impacts of congenital syphilis.

This differs from the 2020 Aquarius base case, which focused on short-term costs and outcomes during pregnancy and the initial weeks after delivery, with lifetime costs and QALYs explored only in scenario analysis. Aquarius avoided lifetime costs and health utility in the base case because of uncertainty in long-term congenital syphilis evidence. Given the uncertainty surrounding the long-term estimates, we conducted a scenario analysis using a short-term time horizon, which facilitates comparison with the findings from the 2020 Aquarius model. This approach was endorsed by expert stakeholders. A discount rate of 3.5% per annum was used in the base case analysis, in keeping with NICE guidance (10), with a scenario analysis conducted using a discount rate of 1.5% per annum.

The base case analysis estimated lifetime costs, quality adjusted life years (QALYs), and cost-effectiveness, expressed as incremental cost-effectiveness ratios (ICERs), which were compared against a decision threshold of £20,000 per QALY, reflecting the NICE reference case threshold in place at the time the analysis was initiated in 2025.

Threshold analysis was used to identify the values that key parameters would need to reach for repeat screening to be considered cost-effective at a willingness to pay threshold of £20,000 per QALY.

Screening pathway and outcomes

Blood samples are tested using an EIA or a CLIA to detect IgG and IgM antibodies against *Treponema pallidum* and related treponemal infections. Samples with negative results require no further testing. Since the previous analysis, the screening pathway has changed; TPPA are no longer used to confirm positive results. A second treponemal test is still performed to confirm a positive result, but this is now a TPHA assay, or a TPLA assay or an EIA/CLIA that is different from the primary screening assay. In addition to the treponemal tests, a RPR titre is also performed to assess infection activity.

The model includes 4 adverse outcomes: intrauterine foetal demise, preterm birth, neonatal death and congenital syphilis. The probability of each outcome varies according to the modelled pathway, specifically, whether the woman has syphilis, the timing of infection during pregnancy, and whether (and when) the infection is diagnosed and treated (see Figure 1). This is clinically important because repeat screening has value only if it changes a woman's pathway from undiagnosed or untreated infection to diagnosed and treated infection before delivery.

The repeat screen can affect outcomes through 2 main routes. First, it can identify women who acquire syphilis after the initial screen. Second, it can identify women whose infection was present but not detectable or not identified at the first screen. Women already diagnosed at booking are not the main source of incremental benefit because they are already managed in both strategies. Women who first enter antenatal care late have less

opportunity to benefit from a scheduled repeat screen. Therefore, repeat screening generates costs across almost all women eligible for the second test, but generates health benefits only for women whose infection is acquired after, or missed at, the first screen and is then detected and treated because of the repeat screen.

Data sources and method updates

Clinical data

Key model inputs were updated using UK-specific evidence. Screening standards data from the IDPS was used to define the antenatal screening cohort and ascertain the number of women screening positive for syphilis. Data on the number of pregnant women entering the antenatal screening pathway in England and in each region were available from the financial years 2021/22 to 2024/2025, along with the number of pregnant women with screen positive results. In the base case analysis, we used data for England from 2024/25, the most recent screening year available, but also carried out regional analysis and explored the results from previous screening years and for 2021 to 2025 as a whole. 618,753 pregnant women in England started antenatal screening in 2024/25, of whom 1,183 screened positive for syphilis.

Ideally, the number of women attending screening over the screening year would be adjusted for the time at risk of infection, but as the screening uptake is very high (9) and the number of positive results only includes women who screened positive during pregnancy (not those diagnosed retrospectively, for example due to a congenital syphilis diagnosis for the child), the total count of women starting antenatal syphilis screening was suitable for the model cohort.

IDPS Standards data does not specify the number of newly diagnosed syphilis cases identified among pregnant women, but this was available from surveillance data of women with a screen positive result from ISOSS. 520 pregnant women required treatment for syphilis in 2024/25, of whom 406 were newly diagnosed and 112 had been previously diagnosed (the timing of diagnosis was not recorded for 2 cases). Of the 520 pregnant women who required treatment, 56 did not receive it, including 34 of those who were newly diagnosed with syphilis.

Our analysis is based on the assumption that all women diagnosed with syphilis and requiring treatment receive this in accordance with BASHH guidelines (2): accounting for the fact that this is not the case in practice would reduce the cost-effectiveness of repeat screening (in other words, it would increase the ICER), as additional screening costs would be incurred without the benefit of treatment.

94% of pregnant women receive their syphilis screen before 28 weeks gestation. The cost-effectiveness of repeat screening at 28 weeks gestation would be insensitive to the

proportion receiving their first screen after this (where the pathway for both strategies is the same), but we explored a scenario where all women received their first screen early, as this is in line with clinical guidance recommending that screening be offered at the booking appointment between 8-10 weeks (1).

The ISOSS data informed the modelled prevalence: the probability of a pregnant woman having syphilis at the start of pregnancy was estimated to be 0.084% in the base case analysis. This is over twice as high as the estimates (of 0.025% and 0.035%) in the 2020 Aquarius report, which had been derived from the Surveillance of Antenatal Syphilis Screening (SASS) study data for 2010/11. The incidence of syphilis was then estimated using the same method as in the Aquarius analysis, in which incidence is scaled using a ratio from Shiber et al. (9) The probability of a woman becoming infected with syphilis during pregnancy was estimated to be 0.0042% in the base case, compared with 0.0017% in the Aquarius analysis.

ISOSS data was also used to inform the timing of diagnoses for syphilis during pregnancy and the outcomes of the pregnancies for women infected with syphilis. With the exception of preterm birth, the adverse pregnancy outcomes were rare, so data from the previous 4 screening years (from 2021/22 to 2024/2025) were combined in order to calculate outcome probabilities from a larger sample. Of the 1,848 women requiring treatment for syphilis during pregnancy between 2021 and 2025 (including multigravida pregnancies), 1,438 were newly diagnosed and 1,315 of these received treatment.

The risk of adverse pregnancy outcomes for women without syphilis were updated using the latest available data from MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK), based on surveillance of perinatal deaths in 2023 (11). The probability of neonatal death was 0.163%, the probability of stillbirth was 0.322%, and the probability of preterm birth was 8%. As congenital syphilis is exclusively passed from the mother to the child during pregnancy or childbirth (12), the probability of congenital syphilis in children born to mothers without syphilis was set to 0%.

Congenital syphilis cases in live infants were categorised based on the criteria in Table 1. There were approximately three times as many possible cases of congenital syphilis as confirmed or probable cases. Based on our conversations with the UK NSC and stakeholders, confirmed and probable cases of congenital syphilis were included in the base case analysis, with a scenario analysis including possible cases as well.

Table 1 - Congenital syphilis case categories

Category	Possible	Probable	Confirmed
Criteria	All of the following: - The woman had untreated or inadequately treated syphilis at delivery - A reactive RPR in the infant's serum (or no serology results available for infant) - The infant has no features of probable or confirmed congenital syphilis	The woman had untreated or inadequately treated syphilis at delivery, a reactive RPR in the infant's serum and at least one of the following in the infant: - Any evidence of congenital syphilis on physical examination - Any evidence of congenital syphilis on radiographs of long bones - A positive cerebrospinal fluid RPR test - Infant's RPR titre fourfold or greater than that of mother (note a lower RPR titre does not exclude the diagnosis)	At least one of the following: <i>Treponema pallidum</i> identified by dark field microscopy, or positive syphilis PCR from: umbilical cord, placenta, neonatal nasal / pharyngeal discharge, body fluids or skin lesion swabs - Detection of <i>Treponema pallidum</i> specific IgM in the infant

Abbreviations: IgM - Immunoglobulin M, PCR - Polymerase Chain Reaction, RPR - Rapid plasma reagin

Updated pregnancy outcome probabilities for women diagnosed with syphilis early and late in pregnancy were calculated directly from the ISOSS data: these were then adjusted for women who required but did not receive treatment by calculating the risk of adverse outcomes associated with not receiving treatment using a metanalysis by Qin et al. (13). The same method was used as in the Aquarius analysis, with an exception: counterintuitively, the probability of vertical transmission in the analysis by Qin et al was higher for women with syphilis at the time of conception and who were treated in the third trimester than for women who did not receive treatment. Therefore, we used the higher probability for both groups, on the assumption that the risk of vertical transmission from untreated mothers with syphilis at the time of conception would be at least as high. Using the approach taken in the Aquarius analysis would reduce the cost-effectiveness of repeat screening (in other words, increase the ICER).

The timing of diagnosis during pregnancy was recorded in the ISOSS data for 1,248 women requiring treatment: over 90% of these (1,157) were diagnosed before 28 weeks gestation, with 91 diagnosed later in pregnancy. These pregnancies resulted in 150 preterm births, 16 cases of IUFD or stillbirth, 6 neonatal deaths, and 29 cases of congenital syphilis. As the vast majority of women attending screening in their first or second trimester, most of the adverse pregnancy outcomes were to women diagnosed at less than 28 weeks gestation, with the exception of congenital syphilis: roughly half (15 out of 29) of the children with congenital syphilis were born to women diagnosed in the third trimester, reflecting the fact that congenital syphilis is more likely to be contracted later in pregnancy.

The calculated probabilities of vertical transmission for women diagnosed during pregnancy data were compared with published treatment success rates and evidence from the literature that the risk of vertical transmission is significantly higher in women treated in the third trimester than those treated earlier in pregnancy (14). Based on the ISOSS data, the probability of vertical transmission was estimated to be 1.21% for women treated prior to 28 weeks gestation versus 16.48% for women treated later in pregnancy. Taking a weighted average based on the relative frequencies of early and late diagnosis gives an overall probability of vertical transmission for treated women of 2.3%: this is consistent with evidence that penicillin treatment during pregnancy successfully prevents vertical transmission during pregnancy in approximately 98% of cases (4).

The probability of vertical transmission for untreated mothers infected after the first screen but prior to 28 weeks gestation could not be derived from the ISOSS data, as the number of children with congenital syphilis born to mothers with undiagnosed syphilis during pregnancy is unknown. We used the same value as in the Aquarius analysis: 50% of children born to untreated mothers infected during pregnancy (but prior to 28 weeks) would acquire congenital syphilis. This value was based on expert opinion and was varied in the sensitivity analysis. Higher values of 70-100% for women with primary or secondary syphilis at delivery can be found in the literature, but these derive from a 1999 review (37) that cites a 1975 paper as the original source; in the 1975 paper, the value is 50%. (38)

Lower values can also be found in a 2013 systematic review. Based on six case-control studies, the meta-analysis found that 15% of infants born to mothers with untreated syphilis had clinical evidence of congenital syphilis. (39) This value, adjusted to 16%, was used in a later WHO report. (40) Using a lower value for the vertical transmission probability would reduce the cost-effectiveness of repeat screening (in other words, increase the ICER). While the available evidence supports our 50% base case assumption with some evidence suggesting that the vertical transmission rate may be lower, we also examined higher values in scenario analyses to reflect the full range reported in the literature and the uncertainty surrounding this influential parameter.

In keeping with the model structure used in the Aquarius analysis, it was assumed that all infections during pregnancy after the first screen would occur prior to a repeat screen. Repeat screening is assumed to take place at 28 weeks gestation, to coincide with an existing blood test (if it occurred later, the cost per screen would be higher to account for additional staff time). Hence, the model assumes that all infections after the first screen occur prior to 28 weeks gestation.

The BASHH and CDC guidelines refer to treatment completion <30 days before delivery as a risk factor of congenital syphilis (2) (41), suggesting that infections acquired late in pregnancy can still cause congenital syphilis. The CDC recommendation of repeat screening at both 28 weeks and delivery for high-risk women also suggests that some infections occur after 28 weeks. The first screen usually takes place between 8-12 weeks

gestation and full-term pregnancy usually lasts 39–41 weeks, so the period between the first screen and 28 weeks gestation accounts for approximately 60% of the period between the first screen and delivery. A scenario analysis was therefore conducted assuming that 60% of infections after the first screen occurred prior to the repeat screen.

Ideally, the model would be informed by the accuracy of diagnostic tests in UK practice for different stages of syphilis, but data on this were unavailable. We therefore used the average sensitivity and specificity of EIA assays from the Aquarius analysis: in the base case, the probability of a true positive result was 99.5% and the probability of a true negative test result was 99.8%. We explored a scenario assuming test sensitivity and specificity of 100%, and another with 100% specificity for the repeat screen, on the assumption that women who received a true negative result at their first screen were less likely to receive a false negative result at their second screen if not infected with syphilis during pregnancy.

Length and quality of life data

Life expectancy was updated using the latest population and mortality data from the Office for National Statistics (ONS) 2024 life tables (15). Life expectancy is 83.3 years for women and 79.4 for men. As life expectancy is reported separately for males and females, a sex ratio derived from the ONS mid-year population estimates (16) was used to estimate an average life expectancy for children born without syphilis of 81.4 years.

In an Aquarius scenario analysis, a life expectancy of 70 years was assumed for children with congenital syphilis: 70 years was the maximum age in the study providing a proxy for lifetime costs (17), but this was due to the data cut. In the absence of a value for life expectancy with congenital syphilis in the literature, a value of 73.2 years was used in our base case analysis, based on an assumed life expectancy ratio of 0.9. This affects the QALYs accrued in the model and the ratio was varied in the sensitivity analysis. In a scenario considering alternative costs, the lifetime cost for congenital syphilis was also inflated based on the assumption of longer life expectancy.

A utility value of 0.74 was used for infants with congenital syphilis, in line with the Aquarius analysis and 2 previous cost-effectiveness analyses of syphilis screening (18), (19). This value was originally derived from a 2000 US study eliciting parental values for outcomes of occult bacteraemia (20) and is a slight modification of the mean utility for infants with minor brain damage as a result of meningitis. Ideally this would have been updated using a utility estimate specific to congenital syphilis, but targeted literature searching did not identify a more suitable lifetime estimate, nor did a 2024 systematic literature review by Miao et al. (21). Expert stakeholders confirmed that the proxy value used in the Aquarius model remains appropriate in the absence of data specific to congenital syphilis and the use of this value ensures alignment with previous economic evaluations in this area.

A scenario including maternal disutility associated with adverse pregnancy outcomes was included to explore the wider family impact. The standardised mean age of mothers in 2024 at the birth of their child from latest ONS birth data (22) was 31 years: this was subtracted from the projected average life expectancy of 88 years for females currently aged 31 from the ONS life expectancy calculator (23) to give an expected remaining years of life of 57 years. Utility weights for mothers experiencing adverse pregnancy outcomes were obtained from the systematic literature review by Miao et al. (21): these were 0.92 for IUFD/stillbirth, 0.76 for neonatal death and 0.88 for congenital syphilis. In the model, the utility decrements based on these weights were applied in the first year.

Cost data

The Aquarius analysis was costed using prices for the 2017/18 financial year. This current analysis is costed in 2024/25 prices, consistent with the latest screening year with available clinical data. Where prior costs were used, these were inflated to 2024/25 prices using the NHSCII pay & prices inflation indices from the Unit Costs of Health and Social Care 2024 Manual (24), the latest manual available from the Care and Outcomes Research Centre (CReC).

Detailed costing work accompanied by extensive stakeholder engagement informed the costing approach undertaken in the Aquarius analysis: we have verified this approach, updated the costs to reflect the current treatment pathway, prices and screening data, and searched for alternative cost sources. Stakeholder workshops and the BASHH guidance (2) were used to confirm the laboratory pathway, treatment assumptions and key uncertainties for scenario testing.

The Integrated Sexual Health Tariff (ISHT) was used to account for the cost of treating and managing women diagnosed with syphilis in the model (25). These tariffs reflect the care pathway and derive from time-driven activity-based costing from London pilot sites. Payment category C was used, which includes care involving multiple visits to a sexual health clinic. As in the Aquarius analysis, the tariff cost was uplifted using consultant staff time costs from CReC (formerly PSSRU) (26), to reflect the fact that patients would see a consultant doctor at some of the sessions. The latest STI Intervention C cost for the London ISHT is lower than the tariff cost used in the Aquarius analysis when converted to current prices (£388.37), reflecting changes in the pathway. Using the cost from the Aquarius analysis adjusted for inflation would reduce the cost-effectiveness of repeat screening relative to single screening, as more women would be treated and managed for syphilis in the repeat screen strategy. This cost was considered in a scenario exploring alternative costs.

The STI tariff cost includes the cost of referral to a sexual health clinic for women who receive treatment for syphilis, but not for women who test positive but do not require treatment. The cost per syphilis screen was therefore marginally increased to account for

this. In the latest data available, of the 618,753 pregnant women who started screening, 520 women required treatment for syphilis, compared with the 1,183 who tested positive. The proportion of women testing positive but not requiring treatment (0.107%) was therefore recalculated using the latest data. With this exception, the cost per syphilis screen in pregnancy (£16.55) was the same as that used in the Aquarius analysis after adjusting for inflation. The cost per syphilis screen from the Aquarius analysis (£16.52, after inflation) was considered in a scenario exploring alternative costs.

This cost did not include staff time costs associated with blood sample collection for syphilis screening, on the assumption that this would coincide with existing routine blood sample collection in pregnancy (if this were not the case, the incremental cost of repeat screening would be substantially higher). The cost per screen includes the cost of laboratory testing (£15.77), which in turn includes the cost of additional laboratory staff time, as testing for syphilis involves additional laboratory work. The cost of laboratory testing used was the same as in the Aquarius analysis, after adjusting for inflation. This was an average of the laboratory testing cost from the sexual health tariff (£20.40, with inflation) and a lower cost quoted by a laboratory manager (£11.13, with inflation). Given the sensitivity of the results to the overall cost per screen, a scenario was considered in which this cost was halved to £8.27.

The majority of women treated for syphilis in pregnancy receive benzathine penicillin, in accordance with BASHH guidelines (2). However, a proportion of women are allergic to penicillin, requiring penicillin desensitisation or alternative treatment. This was not captured in the Aquarius analysis as the numbers involved are small, but it has been modelled in other studies: 2 US cost-effective analyses (18), (19) assumed that 10% of women were allergic to penicillin. There is uncertainty around the proportion of women who are allergic to penicillin in the UK: a study of NHS general practices in 2013/14 found that 5.9% of patients in the UK have a penicillin allergy on their medical records (27), but as few as 10% of these may be truly allergic (28). Given this uncertainty and the small proportions involved, stakeholders agreed at consultation that penicillin desensitisation need not be included in the model, in line with the Aquarius analysis.

It was our intention to include syphilis treatments other than benzathine penicillin in the model, which were not accounted for in the Aquarius analysis. According to the latest ISOSS report, 2 out of 341 women (0.6%) received doxycycline for syphilis in pregnancy and 2 (0.6%) received ceftriaxone, with the treatment for one (0.3%) unspecified (9). However, the treatment regimens for doxycycline and ceftriaxone vary according to the stage of syphilis (29) and data on the proportions of pregnant women with each stage were unavailable. Given that doxycycline and ceftriaxone are more expensive than benzathine penicillin and more women would be treated with the repeat screen strategy, including the costs of these treatments and/or penicillin desensitisation would reduce the cost effectiveness of the repeat screen strategy. However, as the proportion receiving

alternative treatments or penicillin desensitisation are low, including either is unlikely to have a large effect on the total costs.

Modelling potential delays between a positive screening result and treatment initiation were considered. However, updated national guidance introduced in April 2023 reduced the maximum notification time for a positive test from 10 to 5 working days, with notifications now delivered virtually (30). These changes support maintaining the assumption made in the Aquarius analysis of no significant referral or treatment delays in the updated model.

The BASHH guidelines recommend the testing and treatment of the sexual partner should a pregnant woman test positive for syphilis (2). In line with the Aquarius analysis, this has not been included in the base case analysis due to data limitations on the uptake of partner testing and the proportion of partners testing positive. A scenario analysis was conducted with the assumption that sexual partners of women receiving a false positive test result incur testing and treatment costs. The model does not account for reinfection by sexual partners during pregnancy for partners who are not tested and treated: this in line with the Aquarius analysis, in which it is assumed that women who receive treatment for syphilis will not be reinfected. This overestimates the effectiveness of both the first and the repeat screens.

The results of the Aquarius analysis were sensitive to the inclusion of lifetime healthcare costs for children born with congenital syphilis. These lifetime costs were approximated using a 2009 Danish study on the cost of cerebral palsy (17), which estimated lifetime healthcare costs associated with cerebral palsy of €66,155 for men and €65,258 for women. These costs were adjusted in the Aquarius analysis to account for the differing life expectancy, sex ratio and discount rate in the UK. Ideally an estimate specifically for costs incurred by the NHS over the lifetime of children born with congenital syphilis would be used; we conducted literature searching to try to identify suitable values.

An evidence review had been carried out by Public Health England in 2019 to inform their Sexual and Reproductive Health Return on Investment Tool (31). This tool, along with the lifetime cost from the Aquarius analysis and costs derived from matching NHS Secondary Uses Service tariffs (32) with HES admitted patient care data (33), informed the costs attributed to congenital syphilis in UK Health Security Agency's (UKHSA) 2024 STI Prioritisation Framework (34). A mean cost for hospital spells including a primary diagnosis of congenital syphilis (£4,676) had been calculated for 2022/23. In the absence of a lifetime cost estimate, it was our intention to approximate a value using this cost (discounted over time) along with the average number of hospital spells over a patient's lifetime. However, after consulting with the health economist who worked on STI Prioritisation Framework, this cost was identified as a mean cost for a patient's first hospital spell, which might differ substantially from that for subsequent spells.

The value from the Aquarius analysis was therefore used for the lifetime healthcare cost for congenital syphilis (£99,443.12, with inflation). This cost was varied in the sensitivity analysis, and we considered the impact of inflating this to account for the longer life expectancy for infants with congenital syphilis used in our analysis.

In our base case analysis, the mean cost for the first hospital spell with congenital syphilis from the STI Prioritisation Framework (£5,234.57, after inflation) was used in preference to the total cost for testing and treating neonates with clinical signs of congenital syphilis (£8,170.36, after inflation). This was for two reasons: firstly, not all infants with congenital syphilis display signs at birth; the mean cost for the first hospital spell accounts for later presentations. Secondly, the cost in the Aquarius analysis was calculated using microcosting with a length of hospital stay of 10 days, which stakeholder feedback indicated was longer than expected. For validation, the cost from the Aquarius analysis was recalculated using a length of hospital stay of 6.06 days, the average length from the Hospital Episode Statistics (33). This gave a cost of £5,573.25, more similar to that from the STI Prioritisation Framework. The cost from the Aquarius analysis based on the longer length of stay was considered in a scenario exploring alternative costs.

The costs of implementing a repeat screening programme in the UK were not included in the model: accounting for implementation costs would increase the short-term costs associated with repeat screening, reducing its cost-effectiveness compared with the existing programme.

Model build and assumptions

The model was built in Microsoft Excel, with Visual Basic used for macros. The model was initially built using the information available in the Aquarius report and the results were compared with those reported as a means of verification. The model was also validated with reference to the TECH-VER verification checklist for health economic models. (36)

All models are simplifications of reality and therefore require simplifying assumptions to be made. Assumptions made in the model are listed below:

- The repeat screen would be performed at 28 weeks gestation to coincide with existing routine anaemia blood tests and it is assumed that there would be no additional staff time costs associated with the blood sample collection for syphilis screening.
- It is assumed 100% of infections during pregnancy after the first screen would occur prior to a repeat screen (i.e. before 28 weeks gestation)
- All women who are correctly diagnosed as having syphilis are referred to and treated in a sexual health clinic in accordance with BASHH guidelines. The proportion requiring penicillin desensitisation is assumed to be low.
- Pregnant women diagnosed with syphilis at their first screen would not receive nor require a repeat screen.

- Pregnant women first attending antenatal care after 28 weeks gestation will receive their first screen at that point and not receive a repeat screen. The uptake of the second screen in women who have the opportunity for a repeat screen is assumed to be 100%.
- It is assumed that very few women at high risk of syphilis infection receive repeat testing in current practice and so this is not included in the model.
- For the purpose of this analysis, pregnant women requiring treatment are those capable of transmitting syphilis to their children. Children cannot acquire congenital syphilis if the mother is categorised as not having syphilis.
- In a scenario with a microcosting approach for treatment of neonates with congenital syphilis, 40% of neonates are assumed to display signs at delivery, with the remaining 60% displaying signs in the days or weeks after delivery.
- 50% of children born to untreated mothers infected during pregnancy acquire congenital syphilis.
- Utility losses for the mother due to untreated syphilis with a false negative result or unnecessary anxiety with a false positive result are small compared with utility losses for the child due to adverse outcomes.
- The utility and lifetime healthcare costs associated with congenital syphilis are similar to those for minor brain damage as a result of meningitis and cerebral palsy, respectively.
- The accuracy of the test would be the same at both screens. 100% specificity for the repeat screen is considered in a scenario, based on the assumption that pregnant women receiving a true negative result at their first screen would be less likely to receive a false negative result at their second screen if not infected with syphilis during pregnancy.

Uncertainty analysis

Uncertainty analysis was planned as a core part of the evaluation because several important inputs remain uncertain. These include incidence of syphilis acquired during pregnancy, prevalence at booking, screening cost, testing pathway accuracy, probability of congenital syphilis following undiagnosed infection, and the long-term health and cost consequences of congenital syphilis.

This was necessary because the policy question is not only whether repeat screening is cost-effective in the national base case, but also whether it might become cost-effective under plausible alternative conditions, such as higher regional incidence, lower screening costs or greater long-term burden of congenital syphilis.

The sensitivity and scenario analyses were chosen after an appraisal of existing models, review of the 2020 Aquarius model, review of the updated evidence sources, and a

dedicated stakeholder discussion that had members with clinical, public health and screening expertise.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was used to vary uncertain parameters jointly where distributions could be specified. This provides a broader assessment of decision uncertainty than one-way analysis because the model result depends on combined uncertainty across several inputs.

The PSA estimated mean costs, QALYs, ICERs, and the probability that repeat screening is cost-effective at different willingness to pay thresholds. A cost-effectiveness acceptability curve was produced to show how the probability of cost-effectiveness changes across thresholds. The mean probabilistic results were based on 10,000 iterations.

Deterministic sensitivity analysis

One-way deterministic sensitivity analysis was used to vary individual parameters across plausible ranges. This was included to identify the inputs with greatest influence on the ICER and to explain why the model results changed.

The cost per screen was included because it is applied to nearly all women eligible for repeat screening. Even small changes in the unit cost can have a large effect when multiplied across the antenatal screening cohort. This was also a major driver in the Aquarius model. Aquarius found that at the lowest screening cost of £6.68, repeat screening still cost £5.3 million more than single screening; at the highest screening cost of £26.72, repeat screening cost £19.0 million more.

Incidence of syphilis acquired during pregnancy was included because it determines the number of women for whom a repeat screen can provide additional benefit. Repeat screening can only prevent additional congenital syphilis cases if women acquire infection after the first screen, or if early infection was not detectable or identified at the first screen. Aquarius found that the number of congenital syphilis cases was most sensitive to incidence during pregnancy and the probability of congenital syphilis among untreated women infected during pregnancy.

Test sensitivity and specificity were included because the value of repeat screening depends on detecting additional true infections while avoiding false positives. Specificity is particularly important in a low prevalence population because a small false positive rate can still lead to additional referrals, treatment, neonatal screening and anxiety when applied to a large cohort. Aquarius similarly found that total costs were sensitive to the probability of a positive result in women without syphilis.

The probability of congenital syphilis following untreated incident maternal infection was included because it determines how often a missed infection leads to the main long-term outcome in the model. Lifetime congenital syphilis costs, child health utility, child life expectancy and maternal disutility were included because the lifetime model depends on assumptions about the long-term burden of congenital syphilis.

Scenario analyses

Scenario analyses were used to examine structural assumptions and policy relevant alternatives that could not be fully explored by varying one parameter at a time.

A short-term time horizon was included to show how results change when long-term congenital syphilis consequences are excluded, and to support comparison with the Aquarius model, where the base case used a shorter time horizon. A lifetime horizon with alternative discounting (1.5% per annum) was included because most QALY gains occur over the child's lifetime. Lower discounting gives greater weight to future child health benefits.

Test accuracy scenarios were included to assess the effect of assuming perfect sensitivity and specificity, or perfect specificity for the repeat screen. These scenarios distinguish the value of detecting incident infection from the cost and harm of false positive results.

A parental disutility scenario was included because the base case focuses on the child's health outcomes and does not fully capture quality of life effects on parents or carers when a child has congenital syphilis. This is distinct from maternal health utility during pregnancy which is not included in the model.

A possible congenital syphilis scenario was included because congenital syphilis is rare and classification of confirmed versus possible cases can influence event counts. Alternative cost scenarios were included because screening cost is a major driver of the ICER and may differ depending on laboratory configuration, procurement, confirmatory testing and whether the repeat test can be integrated into existing 28 week blood tests. An 'all women screened early' scenario was included because women who enter antenatal care late have less opportunity to benefit from a scheduled repeat screen.

Screening year trend analysis

A screening year trend analysis was undertaken to test whether the cost-effectiveness conclusion was sensitive to the screening year used to inform the model epidemiology. For each year, the model used the number of pregnant women who started screening, the prevalence of syphilis at booking and the incidence of syphilis acquired during pregnancy estimated for that screening year. This was important because, if prevalence and incidence increase over time, repeat screening would be expected to identify more

infections that would otherwise be missed by single early screening, prevent more congenital syphilis cases and generate more QALYs. The analysis therefore examined whether the more recent screening years, with their year-specific prevalence and incidence estimates, produced more favourable cost-effectiveness results than earlier years.

The 2024 to 2025 screening year was used as the base case because it was the latest complete screening year available. The 2021 to 2022, 2022 to 2023, and 2023 to 2024 screening years were analysed separately to assess the trend over time. A combined 2021 to 2025 analysis was also included to show the average result across the full observation period. The combined estimate covers the full observation period, so its incremental costs and QALYs are larger in absolute terms than the annual estimates. The ICER remains directly interpretable because it is the ratio of incremental costs to incremental QALYs. The combined estimate is useful for describing the overall result across the period, but it does not replace the base case because it includes earlier years when the epidemiology was less favourable to repeat screening.

Regional and threshold analyses

Regional analyses were included because national average incidence may obscure local variation. The updated model used regional prevalence and incidence estimates to test whether conclusions changed in higher incidence regions or outbreak-like settings.

Threshold analysis was used to identify the values that key parameters would need to reach for repeat screening to be considered cost-effective at a willingness to pay threshold of £20,000 per QALY, reflecting the NICE reference case threshold in place at the time the analysis was initiated in 2025. These included cost per screen, prevalence at booking, incidence acquired during pregnancy, lifetime cost of congenital syphilis and utility loss associated with children born with congenital syphilis. This is important for UK NSC decision making because it outlines under which conditions the cost effectiveness of repeat screening would be reconsidered, and which indicators should be monitored if, for example, the epidemiology changes.

Results

Base case

Clinical outcomes

The clinical outcomes from screening are shown in Table 2. In the modelled cohort of 618,753 women, repeat screening substantially increased the number of tests and treatments but resulted in relatively small absolute reductions in adverse outcomes.

Table 2 – Annual clinical results under single and repeat screening

Outcome	Single screen only	Repeat screening	Difference
Syphilis antenatal screens	618,753	1,202,879	+584,126
Women treated for syphilis	1,755	2,950	+1,195
False positive screen results	1,239	2,405	+1,166
Congenital syphilis cases	23.1	10.9	-12.2
Preterm births	49,527	49,520	-6.8
Intrauterine foetal demise cases	1,999	1,997	-1.8
Neonatal deaths	1,010	1,010	-0.2

Each year repeat screening prevented approximately 12.2 cases of congenital syphilis, 6.8 preterm births, 1.8 intrauterine foetal demises and 0.2 neonatal deaths. The largest absolute effect was on congenital syphilis, which fell from 23.1 to 10.9 cases in the modelled cohort. Reductions in intrauterine foetal demise and neonatal death were smaller because these are rarer outcomes and occur only in a subset of pregnancies affected by untreated or late treated syphilis.

A useful way to interpret these results is to relate outcomes prevented to the additional screening activity required. Repeat screening added 584,126 antenatal syphilis screens and prevented 12.2 congenital syphilis cases, equivalent to approximately 47,900 additional screens per congenital syphilis case prevented. The number of additional screens required to prevent rarer severe outcomes was much higher: approximately 325,000 additional screens per intrauterine foetal demise prevented and almost 3 million additional screens per neonatal death prevented.

Repeat screening also increased the number of women treated for syphilis by 1,195 and generated 1,166 additional false positive screen results. This reflects the scale of applying an additional test across almost the whole eligible antenatal population. Although the tests are accurate, the low prevalence and incidence of syphilis mean that additional screening identifies relatively few pregnancies in which outcomes can be changed.

Compared with the 2020 Aquarius model, the updated model suggests greater clinical benefit from repeat screening. Aquarius estimated that 124,294 women would need to be rescreened to prevent one congenital syphilis case, whereas the updated model estimates approximately 47,900 additional screens per case prevented. This improvement is likely to reflect the higher incidence of syphilis in the updated model and the use of more current UK evidence. However, the overall pattern remains the same: repeat screening produces clearer reductions in congenital syphilis than in rarer outcomes such as intrauterine foetal

demise and neonatal death, and the number of additional screens required remains large relative to the absolute number of outcomes prevented.

Short-term costs

The short-term cost from screening is shown in Table 3. In the modelled cohort of 618,753 women, repeat screening increased short-term healthcare costs by £10.3 million compared with single screening. Most of this increase was due to the additional antenatal screening activity; 584,126 additional screens would be conducted, each incurring laboratory testing costs. Treatment and management costs also increased due to the 1,195 additional women testing positive and entering the syphilis management pathway. Perinatal costs were slightly higher under repeat screening, although the relative difference was very small because repeat screening affected outcomes in only a small proportion of pregnancies.

Table 3 – Short-term annual cost of screening

Screening strategy	Antenatal screening costs (£)	Treatment & management costs for women testing positive (£)	Perinatal costs for all pregnancies (£)	Total healthcare costs (£)
Single screen only	10,238,177	537,098	1,878,418,712	1,888,656,889
Repeat screening	19,903,401	902,726	1,879,067,734	1,898,971,135
Cost difference	+9,665,223	+365,628	+649,022	+10,314,246

Repeat screening increased antenatal annual screening costs by £9.67 million, from £10.24 million under single screening to £19.90 million under repeat screening. This accounted for more than 90% of the total short-term cost increase. The large increase reflects the scale of the programme: because only around 5% of women were assumed to have their first screen after 28 weeks gestation, almost all women in the repeat screening strategy were eligible for an additional 28 week screen.

Treatment and management costs increased by £0.37 million. Although the cost of managing a woman diagnosed with syphilis is higher than the cost of a single screen, the number of additional women treated was much smaller than the number of additional screens. Repeat screening added 584,126 screens but 1,195 additional women treated for syphilis. This means treatment and management costs contributed only a small proportion of the overall cost difference.

Perinatal costs increased by £0.65 million. This may appear counterintuitive because repeat screening reduced adverse outcomes, including congenital syphilis, preterm birth,

intrauterine foetal demise and neonatal death. However, perinatal costs are calculated across all pregnancies and include delivery, neonatal care, congenital syphilis testing for infants born to women testing positive, and treatment costs for infants with congenital syphilis. Repeat screening led to more women testing positive later in pregnancy, which increased neonatal assessment and screening activity. As repeat screening changed outcomes for only a small proportion of pregnancies, the reduction in adverse outcome costs was not large enough to offset these additional perinatal costs in the short-term analysis.

Overall, the short-term costs indicate that the economic impact of repeat screening is driven primarily by programme scale. The intervention is applied to nearly the whole eligible antenatal population, while only a small proportion of pregnancies experience a change in clinical outcome.

Long-term costs

The long-term cost from screening is shown in Table 4. Congenital syphilis is associated with long-term healthcare costs. Because repeat screening prevented additional congenital syphilis cases, it reduced long-term costs compared with single screening. Long-term costs were £1.88 million under single screening and £0.71 million under repeat screening, giving a long-term saving of approximately £1.18 million.

However, this saving only partly offset the additional short-term costs of repeat screening. Repeat screening increased short-term antenatal and postnatal costs by £10.31 million, mainly because of the additional screening activity. After including long-term congenital syphilis costs, the repeat screening strategy remained £9.14 million more costly overall than single screening.

Table 4 – Lifetime costs of screening

Screening strategy	Short-term costs, antenatal & postnatal (£)	Long-term costs (£)	Lifetime costs (£)
Single screen only	1,888,656,889	1,882,207	1,890,539,096
Repeat screening	1,898,971,135	706,999	1,899,678,134
Cost difference	+10,314,246	-1,175,208	+9,139,038

The lifetime analysis therefore reduces, but does not remove, the cost difference between strategies. The £1.18 million long-term saving offsets around 11% of the £10.31 million increase in short-term costs. This shows that avoided long-term congenital syphilis costs are important, but not large enough in the base case to outweigh the additional programme costs of universal repeat screening.

Health-related quality of life

The health-related quality of life outcomes from screening is shown in Table 5. These have been discounted at a rate of 3.5% per annum so that QALYs accrued in later years are valued less highly than those accrued in earlier years, reducing the total discounted QALYs. As syphilis is uncommon, most women in the model did not have syphilis at any point during pregnancy. Infants born to these women therefore accounted for more than 99.9% of total modelled QALYs in both screening strategies, and there was no difference between strategies for this group.

Table 5 - Discounted health-related quality of life outcomes from screening

Infant QALYs by cohort and strategy			Single screen only	Repeat screening	Difference
Women with syphilis at the time of conception	Attended 1st screen early	TP at 1st screen	13,399	13,399	0
		FN at 1st screen	59	60	+1
	Attended 1st screen late	TP	754	754	0
		FN	3	3	0
Women without syphilis at the time of conception	Attended 1st screen early	FP at 1st screen	32,397	32,397	0
		TN at 1st screen, then new infection	524	665	+141
		TN at 1st screen, with no new infection	16,165,256	16,165,256	0
	Attended 1st screen late	Infected during pregnancy	38	38	0
		Not infected during pregnancy	911,562	911,562	0
		Total QALYs		17,123,992	17,124,134

Abbreviations: FN - False Negative, FP - False Positive, QALYs - Quality Adjusted Life Years, TN - True Negative, TP - True Positive

Repeat screening generated 142 additional QALYs in total. Almost all of this benefit, 141 QALYs, came from infants born to women who were negative at the first screen and then acquired syphilis during pregnancy. This is the main pathway through which repeat screening adds value: these women would not be identified by a single early screen, but could be detected and treated if a repeat screen were offered later in pregnancy.

By contrast, there was no difference between strategies for infants born to women who were correctly diagnosed with syphilis at the first screen, because these women enter the treatment pathway in both strategies. There was also no difference for women whose first screen occurred after 28 weeks, because they had already passed the point at which a scheduled repeat screen would be offered.

The only other QALY gain was among women with syphilis at conception who attended their first screen early but received an initial false negative result. The gain in this group was small, at 1 QALY, because the screening tests are highly sensitive and relatively few infections are missed at the first screen. Overall, the QALY results show that the benefit of universal repeat screening is concentrated almost entirely in infections acquired after an initial negative screen, rather than in women already infected and detected at booking. This concentration of benefit helps explain why repeat screening can be clinically beneficial but still have a high ICER: the additional screening cost is applied to almost the whole eligible antenatal population, while the QALY gain is generated by a very small subgroup.

Cost-effectiveness results

The total costs of the repeat screening strategy are higher than for single screening due to the additional costs of screening and treatment. While not affecting the outcome of the vast majority of pregnancies, the reduction in adverse pregnancy outcomes due to repeat screening results in additional QALYs over the infant's lifetime. The deterministic base case analysis used a lifetime time horizon so that the long-term consequences of preventing adverse pregnancy outcomes could be included.

In the base case deterministic model results (Table 6), repeat screening increased lifetime costs by £9.14 million and generated 142 additional QALYs. The resulting incremental cost-effectiveness ratio (ICER) was £64,219 per QALY, which is above the decision threshold of £20,000 per QALY considered in this report.

Table 6 - Deterministic base case cost-effectiveness results

Screening strategy	Lifetime costs (short + long-term) (£)	Total QALYs
Single screen only	1,890,539,096	17,123,992
Repeat screening	1,899,678,134	17,124,134
Difference	9,139,038	142
ICER (£/QALY)	64,219	

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

The base case ICER of £64,219 per QALY is more favourable than the Aquarius lifetime ICERs of £180,817 per QALY using healthcare costs alone and £120,494 per QALY including health and social care costs.

Overall, the updated model suggests that while repeat screening remains cost increasing, it would now be more clinically beneficial and economically favourable than in the Aquarius analysis. However, the ICER remains above the stated threshold, suggesting that while the cost-effectiveness of the repeat screening for syphilis during pregnancy has improved (due to, for example, the increased prevalence of syphilis), repeat screening would still not be considered cost-effective compared with single screening at conventional decision thresholds.

Uncertainty analysis

Probabilistic sensitivity analysis

The PSA produced results (Table 7) very close to the deterministic base case. Mean probabilistic lifetime costs were £1,889,840,546 for single screening and £1,899,033,118 for repeat screening. Mean total QALYs were 17,123,969 and 17,124,105, respectively. This gave an incremental cost of £9,192,572, incremental QALYs of 135, and a mean probabilistic ICER of £67,849 per QALY.

Table 7 - Mean probabilistic cost-effectiveness results from 10,000 iterations

Screening strategy	Lifetime costs (short + long-term) (£)	Total QALYs
Single screen only	1,889,840,546	17,123,969
Repeat screening	1,899,033,118	17,124,105
Difference	9,192,572	135
ICER (£/QALY)	67,849	

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

This close agreement between the deterministic and probabilistic results indicates that the main conclusion is not an artefact of one central parameter value. When uncertainty is varied jointly across the model, repeat screening remains more effective but still not cost-effective at conventional thresholds.

The PSA also helps interpret the direction of uncertainty. The repeat screening strategy consistently occupies the area of higher cost and higher QALYs: it is not clinically ineffective, but the additional QALYs are too small relative to the additional cost. This is similar to the Aquarius probabilistic analysis, which found that repeat screening was always more costly while preventing more congenital syphilis cases.

Figure 2 - Probabilistic sensitivity analysis cost-effectiveness plane

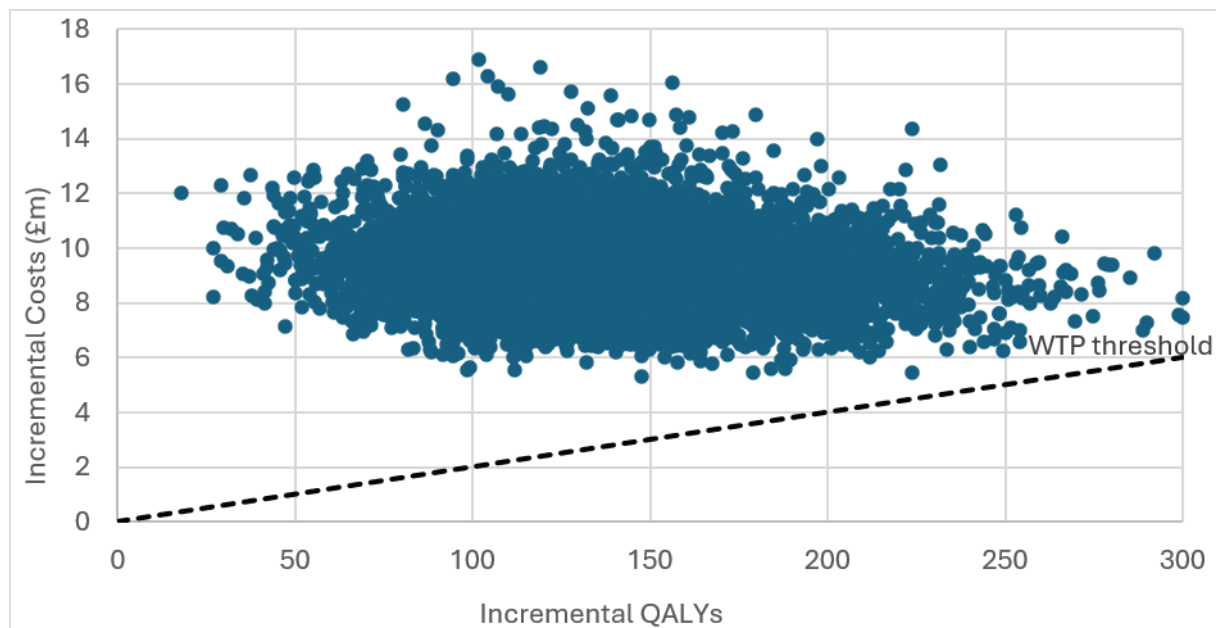


Figure 2 plots the incremental costs and incremental QALYs from the PSA iterations. The cloud of points sits entirely in the north-east quadrant, meaning that repeat screening is more effective and more costly than single screening. This is an important distinction: the model is not suggesting that repeat screening is clinically ineffective. Rather, it suggests that the additional health benefit is generally too small relative to the additional cost.

The PSA points cluster around an incremental QALY gain of roughly 100 to 200 QALYs and an incremental cost of around £8 million to £12 million, with a small number of more extreme iterations. All points lie above the cost-effectiveness threshold line of £20,000/QALY shown on the figure. This means that, even when the model generates more favourable health gains, the additional costs remain too high for repeat screening to be judged cost-effective at this threshold. The deterministic ICER of £64,219 per QALY and the mean probabilistic ICER of £67,849 per QALY are therefore both consistent with the overall location of the PSA cloud.

Figure 3 - Cost-effectiveness acceptability curve for repeat screening compared with single screening at different thresholds

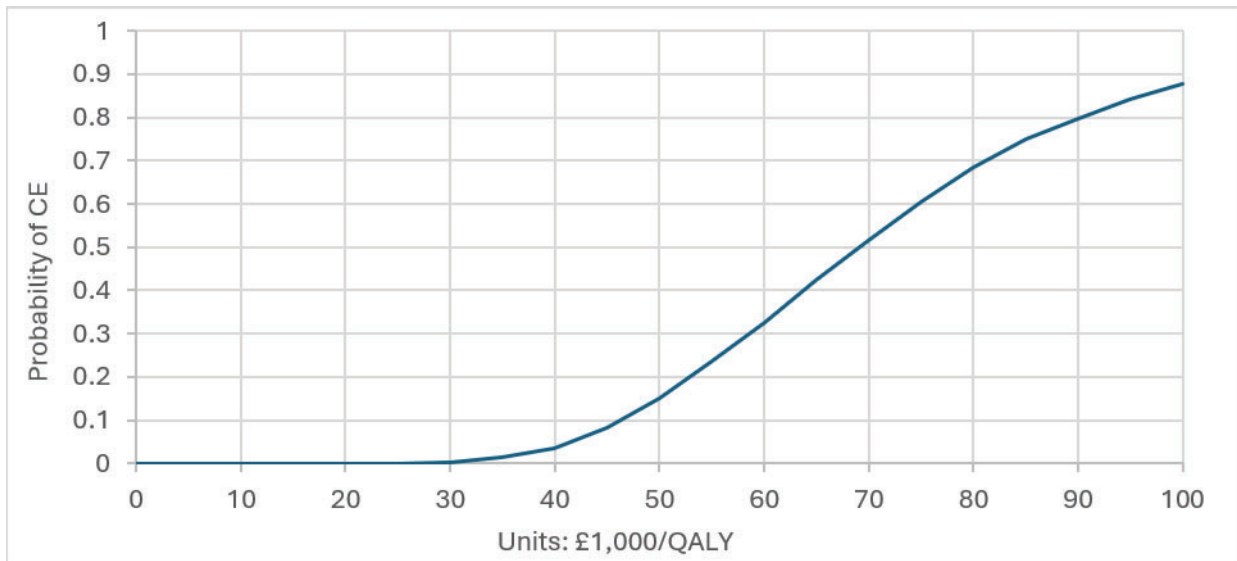


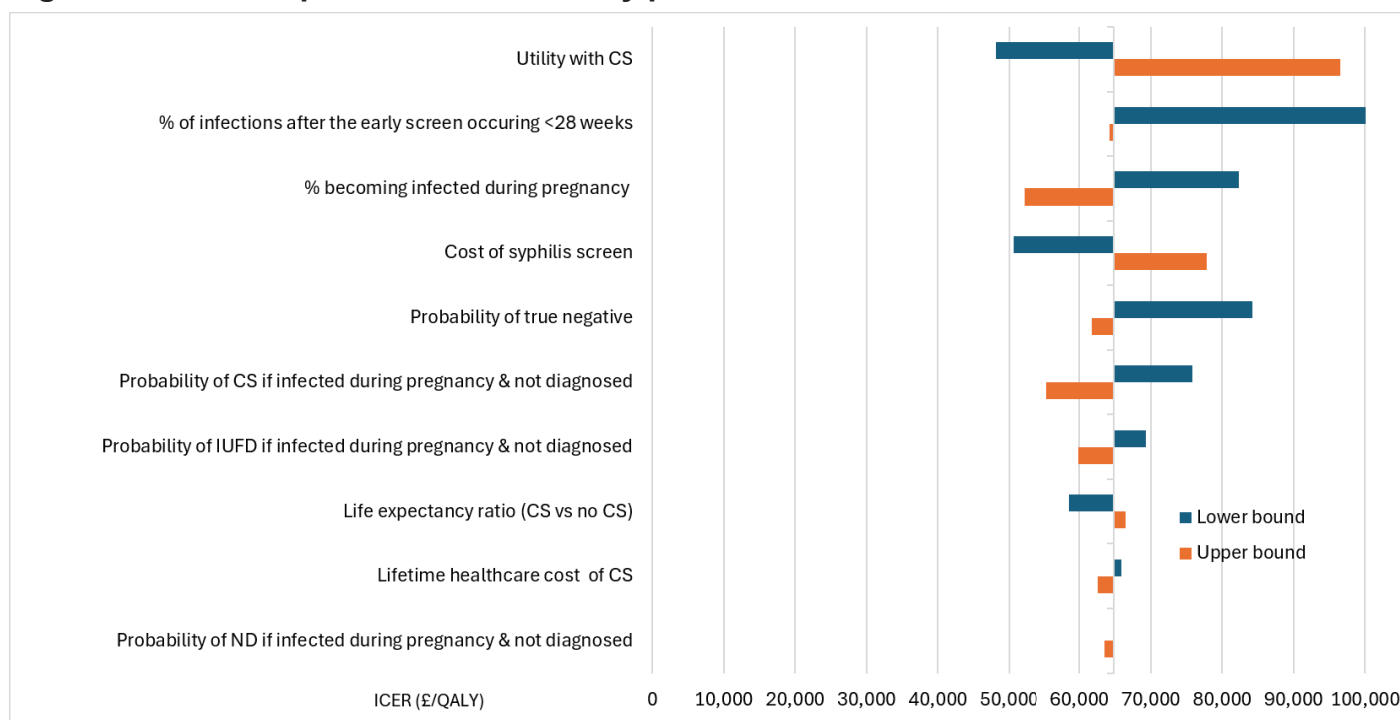
Figure 3 summarises the same uncertainty in a different way by showing the probability that repeat screening is cost-effective at different willingness to pay thresholds. The probability is close to zero at low thresholds and remains very low around the conventional threshold used in the report context. It then increases gradually as the threshold rises, reaching approximately 50% at about £70,000 per QALY and 88% at £100,000 per QALY.

This shape reinforces the interpretation from the cost-effectiveness plane. Repeat screening is not dominated because it produces additional QALYs. However, decision uncertainty is centred at a relatively high willingness to pay value. In practical terms, a decision maker would need to be willing to pay substantially more per QALY than the £20,000 threshold used in this report before repeat screening would have a high probability of being judged cost-effective.

Deterministic sensitivity analysis

One-way deterministic sensitivity analysis was used to vary individual parameters across plausible ranges. The results were then compared against a conventional ICER threshold of £20,000 per QALY.

Figure 4 - Tornado plot: effect of one-way parameter variation on the ICER



Abbreviations: CS - congenital syphilis, ICER - Incremental cost-effectiveness ratio, IUFD - Intrauterine foetal demise, ND – Neonatal Death

The tornado plot in Figure 4 shows that the utility assigned to children with congenital syphilis is the largest driver of uncertainty. When the utility value is lower, congenital syphilis represents a more severe long-term health state and each prevented case generates more QALYs, improving the ICER. When the utility value is higher, congenital syphilis is assumed to have a smaller effect on quality of life and the ICER worsens. This is why the longest bar belongs to utility with congenital syphilis: the model values repeat screening mainly through the long-term child health consequences that are avoided.

The second major driver was the percentage of infections after the early screen occurring before 28 weeks, with a lower proportion occurring before 28 weeks (equivalently, more infections occurring after 28 weeks) reducing cost-effectiveness. The third driver was the percentage of women becoming infected during pregnancy. This is directly linked to the pathway through which repeat screening adds value. Women who acquire infection after an initial negative screen cannot be detected by a single booking screen, but they can be identified by a later repeat screen. Increasing this parameter therefore increases the number of women for whom repeat screening can change diagnosis and treatment, which improves cost-effectiveness. Decreasing it has the opposite effect, because the same programme cost is spread across fewer preventable cases.

The cost of the syphilis screen is also influential because of the number of additional screens conducted with repeat screening. Repeat screening adds 584,126 screens, so even small changes in unit cost have a large effect on total programme costs. This is why the screening cost appears above many clinical outcome parameters in the tornado plot.

The finding is not that the test is expensive in isolation, but that even a relatively small per screen cost becomes important when applied to nearly the whole eligible antenatal population.

Test specificity, represented in the tornado plot by the probability of a true negative result, is also important in this low prevalence setting. Lower specificity increases false positive results, follow up activity, treatment and infant assessment without generating corresponding health gains. Higher specificity reduces those downstream costs. This explains why the true negative parameter is a larger driver than some severe clinical outcomes: false positives are individually less severe, but they occur in a much larger denominator.

The remaining influential parameters are mainly those that determine the consequences of missed incident infection: the probability of congenital syphilis, the probability of intrauterine foetal demise, life expectancy with congenital syphilis, lifetime healthcare cost of congenital syphilis, and neonatal death. These parameters affect the ICER because they define the benefit of detecting and treating infection before delivery. Their bars are shorter than the leading parameters, which suggests that the base case conclusion is not dependent on a single adverse outcome probability alone.

Overall, the tornado plot (Figure 4) tells a coherent story. Repeat screening becomes more favourable when congenital syphilis is assumed to have greater lifetime health consequences, when more women acquire syphilis during pregnancy, when screening costs are lower, and when false positive results are minimised. It becomes less favourable when congenital syphilis is assumed to have less lifetime impact, incidence during pregnancy is lower, screening costs are higher, or specificity is lower. The deterministic sensitivity analysis did not result in ICERs below the conventional threshold of £20,000 per QALY.

Scenario analyses

The results tables for all the scenario analyses are included in Appendix 1 (Appendix Tables 1-16). The scenario analyses show a clear ordering in terms of impact on the ICER. The largest improvement came from applying a lifetime horizon with a 1.5% annual discount rate, which reduced the ICER to £32,290 per QALY. This is because future child health benefits and avoided long-term costs are discounted less heavily, so the long-term consequences of preventing congenital syphilis carry more weight.

The next most favourable scenario was using upper bounds for syphilis incidence and prevalence. Incremental costs were £8,593,411, incremental QALYs were 205, and the ICER was £41,994 per QALY. This improves cost-effectiveness because repeat screening is only beneficial for infections acquired after, or missed at, the first screen. Higher incidence and prevalence increase the number of women entering the part of the model

where repeat screening can make a difference, increasing the number of preventable congenital syphilis cases.

The third most favourable scenario was using lower bounds for health utility and life expectancy with congenital syphilis. Incremental costs were £9,139,038, incremental QALYs increased to 201, and the ICER fell to £45,483 per QALY. This is more favourable because congenital syphilis is assumed to have more severe and longer lasting consequences, so each prevented case generates larger lifetime QALY gains.

The test accuracy scenarios had a smaller effect. Assuming 100% sensitivity and specificity produced an ICER of £59,333 per QALY, while assuming 100% specificity for the repeat screen produced an ICER of £59,226 per QALY. These scenarios reduce false positives, unnecessary follow up and missed infections, but the base case test accuracy is already high. They also do not substantially change the number of preventable infections. The main constraint remains structural: repeat screening adds 584,126 screens, but only a small proportion of women can benefit.

The remaining scenarios had little effect or were less favourable. Maternal disutility, defined here as maternal quality of life loss from having a child born with congenital syphilis rather than direct maternal health loss during pregnancy, produced an ICER of £63,508 per QALY. This was only slightly more favourable than the base case because incremental QALYs increased only from 142 to 144. Although parental disutility increases the QALY loss associated with each congenital syphilis case, repeat screening prevents only a limited number of cases, so the additional QALY gain is modest. Costs remained at £9.14 million.

The 'all women screened early' scenario, assuming 100% uptake of the initial screen, produced an ICER of £64,219 per QALY, again very close to the base case, because repeat screening still mainly detects infections acquired after the first screen and, as we are considering repeat screening at 28 weeks gestation, the pathway for women receiving their first screen later than 28 weeks gestation is the same for both strategies in the base case analysis. Alternative cost sources produced an ICER of £64,506 per QALY, effectively unchanged.

The scenario with a lower probability of congenital syphilis (based on the Qin study) for children born to untreated women with syphilis at the time of conception produced an ICER of £64,506 per QALY: this was only slightly higher than the base case, as the vast majority of women with syphilis at the time of conception are diagnosed at the first screen.

Including possible congenital syphilis cases (as defined in Table 1), rather than confirmed cases only, was less favourable, producing an ICER of £68,152 per QALY. Incremental QALYs fell from 142 to 135, while costs increased slightly from £9.14 million to £9.23

million, suggesting that the broader case definition did not increase the incremental benefit of repeat screening.

Overall, the ordering shows that the ICER is driven mainly by assumptions about how future child health benefits are valued, screening cost and the timing of infections relative to 28 weeks, the severity and duration of congenital syphilis consequences, and syphilis incidence during pregnancy. Test accuracy, alternative costs, and first screen uptake shift the ICER only modestly. None of the tested scenarios bring repeat screening within the £20,000 cost-effectiveness threshold.

Regional analyses

The regional analysis results are in Table 8. The analysis is based on data on the number of pregnant women requiring treatment for syphilis in 2024-25, the latest screening year with full data available. Regional ICERs varied substantially, reflecting differences in prevalence and incidence.

Table 8 - Cost-effectiveness of repeat screening in different regions of England (2024-2025)

Region	Prevalence	Incidence	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
England	0.084%	0.0042%	9,139,038	142	64,219
East of England	0.074%	0.0036%	1,081,457	15	74,551
London	0.107%	0.0053%	1,774,022	37	48,386
Midlands	0.086%	0.0043%	1,690,264	27	62,387
North East & Yorkshire	0.099%	0.0049%	1,286,713	24	53,436
North West	0.094%	0.0046%	1,148,907	20	56,737
South East	0.056%	0.0028%	1,326,336	13	100,939
South West	0.045%	0.0022%	831,837	7	126,531

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

London had the most favourable regional ICER (£48,386 per QALY) because prevalence and incidence were highest. The South West had the least favourable ICER (£126,531 per QALY) because prevalence and incidence were lowest. No region had an ICER at or below £20,000 per QALY. The same conclusion was reached when data from the previous 3 screening years were considered.

Table 9 shows the economics outcomes (ICERs) for repeat screening across the years in observation. The ICERs generally became more favourable over time in England overall and in several regions, consistent with rising prevalence and incidence. This pattern was most marked in London, where the ICER fell from £101,902 per QALY in 2021 to 2022 to £48,386 per QALY in 2024 to 2025. However, trends were not uniform across regions. For example, the North West showed a less consistent pattern, while the South East and

South West had less favourable ICERs in 2024 to 2025 than in 2023 to 2024, despite remaining more favourable than in some earlier years.

When data were pooled across 2021 to 2025, ICERs were generally less favourable than those based on 2024 to 2025 alone. This is expected where prevalence and incidence have increased over time, because pooling includes earlier years with lower infection rates. However, even using the most favourable single-year estimates, all regional ICERs remained above £20,000 per QALY.

Table 9 - Cost-effectiveness of repeat screening in different regions of England: comparison across the years in observation

Region	ICER (£/QALY)				
	2021-2022	2022-2023	2023-2024	2024-2025	2021-2025
England	90,984	76,487	64,880	64,219	73,041
East of England	109,139	82,838	82,960	74,551	85,944
London	101,902	76,756	52,500	48,386	65,233
Midlands	83,456	59,854	55,039	62,387	64,028
North East & Yorkshire	63,895	61,776	53,331	53,436	57,852
North West	57,943	61,029	71,262	56,737	61,324
South East	146,459	109,582	91,487	100,939	109,435
South West	183,740	207,839	95,115	126,531	142,223

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

These results show that epidemiology is important to cost-effectiveness, but that regional variation observed over the past 4 screening years is not sufficient to make universal repeat screening cost-effective at the £20,000 per QALY threshold. London was consistently the most favourable region in the latest analysis, but its 2024 to 2025 ICER remained £48,386 per QALY. The regional results therefore support continued surveillance and outbreak responsive planning, rather than immediate routine regional implementation.

Screening year trend analysis

Table 10 shows the cost-effectiveness results by screening year after updating the model with the prevalence at booking and incidence during pregnancy. The 2024 to 2025 base case had the lowest ICER, at £64,219 per QALY. The least favourable single-year result was 2021 to 2022, with an ICER of £90,984 per QALY. The combined 2021 to 2025 estimate was £73,041 per QALY. All estimates remained above the £20,000 per QALY threshold.

Table 10 - Cost-effectiveness of universal repeat screening by screening year

Screening year	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
2021 to 2022	9,688,274	106	90,984

Screening year	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
2022 to 2023	9,504,508	124	76,487
2023 to 2024	8,611,679	133	64,880
2024 to 2025 (base case)	9,139,038	142	64,219
2021 to 2025 combined	36,943,450	506	73,041

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

The trend over time was in the expected direction. From 2021 to 2022 to 2024 to 2025, incremental QALYs increased from 106 to 142. Over the same period, the ICER fell from £90,984 to £64,219 per QALY. This is a reduction of £26,765 per QALY, or approximately 29%. The more recent prevalence and incidence data therefore make repeat screening more favourable than the earliest screening year in the analysis. The improvement was driven mainly by greater health gain rather than by a large reduction in incremental cost.

Incremental costs fell from £9.69 million in 2021 to 2022 to £8.61 million in 2023 to 2024, before rising to £9.14 million in 2024 to 2025. In contrast, incremental QALYs increased by 36 over the same period. This pattern is consistent with the model structure: higher prevalence at booking and higher incidence during pregnancy increases the number of women in pathways where repeat screening can affect diagnosis, treatment and pregnancy outcomes. As more infections are acquired during pregnancy or first become detectable later in pregnancy, the same repeat screening pathway prevents more congenital syphilis and generates more lifetime QALYs.

The 2023 to 2024 and 2024 to 2025 estimates were similar, with ICERs of £65,880 and £64,219 per QALY, respectively. Although incremental costs were lower in 2023 to 2024, the 2024 to 2025 base case generated more QALYs. This explains why the latest screening year remained slightly more favourable overall. The combined 2021 to 2025 ICER of £73,041 per QALY sits between the earlier and later single-year estimates, as expected when earlier, less favourable prevalence and incidence estimates are included alongside more recent data.

Threshold analysis

Threshold analysis was used to identify how far key model inputs would need to change for repeat screening to reach an ICER of £20,000 per QALY. These results are shown in Table 11, and they provide context for interpreting both the national base case and the regional analyses.

Table 11 - Threshold analysis results

Parameter	Base case value	Value resulting in ICER of £20,000/QALY	% of base case value
Cost of syphilis screen (£)	16.55	5.77	35%
Syphilis incidence (prevalence fixed at 0.084%)	0.0042%	0.0106%	255%
Syphilis prevalence	0.084%	0.214%	254%
Probability of vertical transmission if infected during pregnancy & not diagnosed	0.5	N/A: a probability of 1 resulted in an ICER of £33,641/QALY	N/A
Utility with congenital syphilis	0.74	-0.237	-32%
Lifetime healthcare cost of congenital syphilis (£)	99,443	631,927	635%

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, N/A - not applicable, QALYs - Quality Adjusted Life Years

The thresholds indicate that repeat screening is not close to cost-effective in the base case. The cost per screen would need to fall substantially, from £16.55 to approximately £5.77. Incidence during pregnancy would need to more than double, from 0.0042% to 0.0106%. This incidence threshold is around 2.5 times the England base case estimate and around twice the latest London estimate of 0.0053%, the highest regional incidence in the analysis. Lifetime healthcare costs of congenital syphilis would need to increase more than 6 times the base case value, or the utility assigned to congenital syphilis would need to fall to -0.237, implying a health state worse than death.

The congenital syphilis probability threshold is particularly important. Even if the probability of congenital syphilis following untreated incident infection was increased from 0.5 to 1.0, the ICER remained £33,641 per QALY, above the £20,000 per QALY threshold. This indicates that solely increasing the risk of vertical transmission in those infected during pregnancy and not diagnosed is not sufficient to make repeat screening cost-effective under otherwise base case assumptions; the result would require substantial change in one or more of the major drivers, particularly incidence during pregnancy, screening cost, or the long-term burden of congenital syphilis.

Discussion

Overview

Universal repeat screening prevented additional adverse outcomes, particularly congenital syphilis, but the absolute benefit was small relative to the scale of the programme. In the base case, repeat screening prevented 12.2 cases of congenital syphilis, 6.8 preterm births, 1.8 intrauterine foetal demises and 0.2 neonatal deaths in a cohort of 618,753 women. Achieving these gains required 584,126 additional antenatal syphilis screens,

1,195 additional women treated for syphilis and 1,166 additional false positive screen results. The central finding is therefore not that repeat screening is ineffective, but that the additional clinical benefit is concentrated in a small subgroup of pregnancies while the costs and testing activity are spread across almost the whole eligible antenatal population.

The ICER of £64,219 per QALY reflects the relationship between the large number of additional screens and the relatively small number of additional adverse outcomes prevented. The model is not showing that repeat screening has no clinical benefit. It is showing that, under current national base case assumptions, the clinical benefit is not large enough to justify the cost of applying the intervention to the whole eligible antenatal population. It is important to emphasise that this analysis does not call into question the current antenatal syphilis screening programme. The existing programme was used as the comparator and was not itself evaluated. The findings should therefore be interpreted only in relation to the potential addition of a universal repeat screen, and not as an assessment of the current screening programme.

The updated analysis is more favourable to repeat screening than the 2020 Aquarius analysis, both clinically and economically. Aquarius estimated that repeat screening would prevent 5.5 congenital syphilis cases in a UK cohort of 725,891 women, whereas the updated model estimates 12.2 cases prevented in a smaller England cohort of 618,753 women. The updated base case ICER of £64,219 per QALY is also substantially lower than the Aquarius lifetime ICERs of £180,817 per QALY from a healthcare perspective and £120,494 per QALY when health and social care costs were included. However, the direction of the policy conclusion is unchanged: updated data make repeat screening look more favourable than before, but not favourable enough to bring universal repeat screening within conventional cost-effectiveness thresholds.

The results are explained by a narrow clinical pathway through which repeat screening can add benefit. The repeat screen only changes outcomes where infection is acquired after booking, or was present but missed or not yet detectable at booking, and where the repeat screen leads to diagnosis and treatment in time to reduce foetal or neonatal harm. This is reflected in the QALY results: almost all the incremental benefit, 141 of 142 additional QALYs, came from infants born to women who were negative at the first screen and then acquired syphilis during pregnancy. By contrast, there was no difference for women diagnosed at the first screen or for women whose first screen occurred too late to receive a scheduled repeat screen. The repeat screen is therefore clinically effective in the subgroup where it changes diagnosis and treatment, but that subgroup is small relative to the total screened population.

It also explains why preterm birth, IUFD and neonatal death change less than congenital syphilis. These outcomes are severe, but only a small proportion of them are attributable to syphilis infections that would be detected by repeat screening. The model therefore

estimates only 6.8 fewer preterm births, 1.8 fewer IUIDs and 0.2 fewer neonatal deaths, despite a much larger reduction in congenital syphilis.

The cost results are generated mainly by screening volume. Repeat screening increases short-term costs by £10.31 million. Avoided long-term congenital syphilis costs reduce costs by £1.18 million, leaving a net lifetime incremental cost of £9.14 million. The long-term savings therefore offset only part of the immediate screening cost. The QALY gain is generated mainly through avoided congenital syphilis. Repeat screening generates 142 additional QALYs, largely by preventing 12.2 congenital syphilis cases. This equates to approximately 11.6 QALYs per congenital syphilis case prevented on average. The model is therefore giving high value to the prevention of serious long-term child health consequences, which is appropriate given that the programme is primarily intended to prevent congenital syphilis and its lifelong impacts in children. This also explains why the lifetime horizon matters. The short-term time horizon produced an ICER of £73,477 per QALY, while the base case lifetime analysis produced £64,219 per QALY. When the discount rate was reduced to 1.5%, the ICER fell to £32,290 per QALY. The intervention becomes more favourable when future child health benefits are given more weight. However, this also highlights why uncertainty in lifetime congenital syphilis outcomes is important. The more the analysis depends on future benefits, the more dependent it becomes on assumptions about child utility, life expectancy and lifetime costs. This is reflected in the results of the sensitivity analyses.

The sensitivity analyses show that the model's findings are driven by parameters that affect either the number of preventable congenital syphilis cases or the value of preventing each case. The health utility of children with congenital syphilis was the most influential parameter in the deterministic sensitivity analysis. This is expected because QALY gains accumulate over a lifetime. Incidence during pregnancy was also highly influential because it determines how many women acquire infection after the first screen and can therefore benefit from repeat screening. Cost per screen was also influential because the unit cost is multiplied across 584,126 additional screens.

The scenario analyses reinforce this interpretation. When congenital syphilis was assumed to have more severe and longer lasting consequences, the ICER improved to £45,483 per QALY because each prevented case generated more lifetime QALYs. When incidence and prevalence were increased, the ICER also improved, to £41,944 per QALY, because more women entered the part of the model where repeat screening could change outcomes. However, neither scenario brought the ICER close to £20,000 per QALY, showing that more favourable assumptions about disease burden or epidemiology improve the result but do not, on their own, change the overall conclusion.

Taken together, these results show that the model is not highly sensitive to every plausible change. It is most sensitive to incidence, screening cost, and the lifetime health loss

associated with congenital syphilis. It is less sensitive to test accuracy improvements, possible case inclusion, and early screening assumptions.

A further implication is that the model findings are driven less by syphilis prevalence at booking than by infections acquired or first detectable after the booking screen. In the base case QALY results, almost all the incremental QALY gain came from infants born to women who were negative at the first screen and then acquired syphilis during pregnancy. This suggests that future surveillance should focus not only on the number of women requiring treatment at booking, but also on evidence of infection acquired later in pregnancy, repeat testing activity, and cases occurring after an earlier negative screen. These indicators are more directly linked to the pathway through which universal repeat screening generates benefit.

The regional analysis confirms that epidemiology is important. London had the most favourable ICER at £48,386 per QALY, with prevalence of 0.107% and incidence of 0.0053%. The South West had the least favourable ICER at £126,531 per QALY, with prevalence of 0.045% and incidence of 0.0022%.

This pattern is exactly what would be expected from the model structure. Higher incidence regions have more infections that can be detected by repeat screening, so the same intervention produces more QALYs. Lower incidence regions have fewer preventable infections, so the cost per QALY is higher. However, no region reached £20,000 per QALY, so current regional variation alone does not support routine regional implementation of repeat screening.

The threshold analysis shows that the base case result is not close to the £20,000 per QALY threshold. The cost per screen would need to fall substantially, from £16.55 to around £5.77, or incidence during pregnancy would need to more than double, from 0.0042% to 0.0106%, for repeat screening to reach the threshold under otherwise unchanged base case assumptions. The lifetime healthcare cost of congenital syphilis or the assumed utility loss associated with congenital syphilis would also need to be much more severe than in the base case. Particularly important is the finding that even setting the probability of congenital syphilis after untreated incident infection to 1.0 only reduced the ICER to £33,641 per QALY. This indicates that the conclusion is not dependent on this single uncertain parameter: other changes would be needed before universal repeat screening became cost-effective.

Overall, the updated model reaches the same broad policy conclusion as Aquarius, but on a more current evidence base. It estimates larger clinical benefits and a substantially lower ICER than Aquarius, reflecting updated epidemiology, ISOSS-informed inputs and the use of a lifetime horizon in the base case. However, the core economic finding remains unchanged: repeat screening prevents adverse outcomes, but the cost of screening the eligible population remains large relative to the number of additional outcomes prevented.

Strengths

A major strength of this update is that it preserves comparability with the 2020 Aquarius model while updating the evidence inputs most likely to affect the decision. The model retains the same broad policy question and decision tree logic, but updates infection, diagnosis, treatment timing and outcome inputs using newer UK evidence and current pathway assumptions.

A second strength is the use of current UK evidence. ISOSS informs prevalence, incidence, timing of diagnosis, pregnancy outcomes, and congenital syphilis presentation. IDPS data define the antenatal screening cohort, and the model reflects current clinical and laboratory pathways.

A further strength is the detailed exploration of uncertainty. Deterministic sensitivity analysis, probabilistic sensitivity analysis, scenario analysis, regional analysis and threshold analysis were used to test the robustness of the conclusion and identify when the result might change. These analyses were consistent with the model logic: repeat screening became more favourable when incidence rose, screening cost fell, future child health benefits were given greater weight, or congenital syphilis was assumed to have more severe lifetime consequences.

Limitations

The most important limitation is uncertainty in the long-term consequences of congenital syphilis. The QALY gains depend on assumptions about quality of life, life expectancy, and long-term health and social care costs for children with congenital syphilis. Direct UK evidence is limited, and previous modelling used cerebral palsy as a proxy. Aquarius also noted that no UK estimate of lifetime congenital syphilis cost was available and that the lifetime cost estimate did not account for differences between early and delayed presentation.

The model does not fully capture wider quality of life effects for mothers, parents or carers. Earlier maternal diagnosis may provide short-term health benefit and may reduce anxiety or uncertainty, but these effects were not included because high quality pregnancy-specific utility values were not available and the likely incremental QALY gain over the pregnancy period is small compared with the lifetime child health effects. Including maternal utility would be expected to make repeat screening slightly more favourable but is unlikely to change the overall conclusion unless the benefits are substantially larger than currently evidenced.

A parental disutility scenario was included to explore wider family impact, but it had little effect on the ICER because repeat screening prevents a small absolute number of congenital syphilis cases. Modelling these wider effects more fully would require evidence

on maternal health states, timing of diagnosis, symptom development, treatment pathways and longer-term family quality of life impacts. Given the limited evidence base, these impacts are best treated as exploratory rather than core drivers of the base case results.

There is also a conceptual limitation around whose health benefits are included. The screening programme is primarily concerned with preventing congenital syphilis, but diagnosing maternal syphilis also has public health benefits. It may trigger partner notification, reduce onward transmission, identify reinfection risk, and connect women to sexual health services. These benefits are difficult to include in a pregnancy focused decision tree and may fall outside the immediate remit of antenatal screening, but they are relevant to policy context.

Another limitation is uncertainty around the cost assigned to each repeat syphilis screen. The analysis followed the costing approach used in the Aquarius report, which was developed using stakeholder feedback and microcosting to estimate the wider cost of screening. We did not identify better quality published sources for all relevant costs. The base case cost of £16.55 was therefore intended to reflect a wider screening pathway cost, rather than only the direct purchase or laboratory cost of the test itself.

Stakeholder feedback during this update highlighted uncertainty about what should be included in the cost of a repeat screen. A repeat screen at 28 weeks may be added to a consultation and blood taking appointment that is already taking place, but it may still involve additional pathway costs, including staff time, sample handling, administration, reporting, follow up of reactive results and overheads. Feedback from one stakeholder suggested that the direct laboratory or purchase cost of a repeat syphilis test may be around £5 to £6. However, this appears likely to reflect the cost of the test itself, rather than the full cost of delivering repeat screening within the antenatal pathway. It was not possible before submission to verify the exact elements included in this estimate or to update the analysis on a consistent basis.

The analysis therefore retained the base case cost of £16.55 (adjusted for inflation), which is more consistent with the wider pathway-based costing approach used by the previous analysis conducted by Aquarius. This is important because the cost per screen is applied to a large number of women and was a key driver of the ICER. The threshold analysis showed that the overall cost per screen would need to fall from £16.55 to £5.77 for repeat screening to reach £20,000 per QALY. Therefore, the £5 to £6 estimate should not be interpreted as a like-for-like replacement for the base case cost unless it can be shown to capture all relevant incremental pathway costs. However, if the true marginal cost of adding syphilis testing to existing 28 week blood tests were substantially lower than assumed in the base case, the cost-effectiveness of universal repeat screening could be more favourable than estimated.

The model assumes that all infections during pregnancy after the first screen would occur prior to a repeat screen, which likely overestimates the cost-effectiveness of repeat screening, especially given the assumption that the repeat screen occurs at 28 weeks gestation. Infection after 28 weeks gestation is biologically plausible and the CDC recommendation of repeat screening at both 28 weeks and at delivery for high-risk women suggests that some infections occur after 28 weeks (41). If so, a smaller proportion of infections during pregnancy would be detected by repeat screening at 28 weeks than is modelled.

The costs of implementing a universal repeat screening programme in the UK were not included in the model: accounting for implementation costs would increase the short-term costs associated with repeat screening, resulting in a less favourable cost-effectiveness estimate for universal repeat screening.

The model necessarily simplifies test performance. In practice, sensitivity and specificity are not fixed properties of a single assay alone; they depend on disease stage, timing of infection, confirmatory algorithms, clinical history, previous treatment and interpretation of serology. The model's stage-dependent assumptions improve on the previous fixed approach, but cannot fully reproduce the complexity of real-world syphilis diagnosis.

The timing of repeat screening is also uncertain. A 28 week screen is attractive because it aligns with routine antenatal blood tests, but it creates a trade-off. Earlier repeat screening gives more time for treatment to reduce foetal risk, while later repeat screening captures more infections acquired after booking. The model cannot fully capture the continuum of infection timing, seroconversion, treatment timing and foetal exposure.

The comparator is another limitation. The model compares universal repeat screening with current practice, but current practice includes targeted repeat testing for women with identified risk, new exposure, symptoms or clinical concern. The extent to which this happens consistently in practice is uncertain. If targeted retesting is more effective than assumed, the incremental benefit of universal repeat screening would be smaller. If targeted retesting misses many women at risk because risk is not disclosed, recognised, or stable over pregnancy, the incremental benefit of universal repeat screening would be larger.

The analysis assumes that all screen positive women and relevant infants complete the recommended care pathway. In practice, referral, maternal treatment, partner management and infant follow up may not always be completed. Any shortfall in these steps would reduce the benefit achieved by detecting additional infections through repeat screening, and would therefore make universal repeat screening appear less cost-effective than in the base case model.

The analysis does not fully capture harms from false positive results or overtreatment. In the base case, repeat screening generated 1,166 additional false positive screen results, so even small harms per false positive could matter when applied across the whole programme. These harms may include anxiety, stigma, relationship effects, unnecessary antibiotic exposure, additional appointments and reduced confidence in screening. The model includes some downstream costs associated with positive results, but it does not assign a QALY loss to false positive results or overtreatment. This may make repeat screening appear slightly more favourable than it would be if these non-cost harms were fully quantified.

The model also simplifies reinfection and partner management. Women diagnosed and treated for syphilis during pregnancy may be reinfected if partners are not tested and treated. Conversely, repeat screening may generate additional benefit by triggering partner notification and preventing reinfection or onward transmission. A static decision tree focused on pregnancy outcomes cannot fully capture these transmission dynamics.

A further limitation is the treatment of preterm birth, neonatal death, intrauterine foetal demise and congenital syphilis as separable outcomes within a decision tree structure. In reality, these outcomes are biologically and clinically related. Preterm birth may affect neonatal mortality risk; intrauterine foetal demise and stillbirth may include undiagnosed congenital infection; and congenital syphilis may present across a spectrum from asymptomatic infection to severe neonatal disease.

The model includes women whose first syphilis screen occurs after 28 weeks' gestation. For these women, the repeat screening strategy does not provide an additional testing opportunity, because the planned 28 week repeat screen has already been missed. Their pathway is therefore the same under both strategies, and the results show no difference in outcomes for infants born to women who attended too late to receive a repeat screen. This matters because the benefit of universal repeat screening depends on women being in antenatal care early enough to receive both tests, and on positive results leading to timely referral and treatment before delivery. Repeat screening is therefore less able to prevent congenital syphilis cases where the main issue is no antenatal screening, very late presentation, delays in referral or treatment, incomplete treatment, or loss to follow up. This is not an omission from the model; it reflects a limit of what a routine repeat screening policy can achieve when cases are driven by delayed or incomplete engagement with the antenatal care pathway.

The updated model uses regional scenarios, but regional analysis is limited by the rarity and stochastic nature of congenital syphilis. A small number of cases in a region may reflect a true increase in incidence, but may also reflect random variation, local case ascertainment, or clusters that do not persist. Local or time limited repeat screening may be more plausible in outbreak settings than a national universal programme, but

implementation of repeat testing strategy should be based on sustained evidence of higher incidence, not isolated events.

The analysis is also limited by the use of a decision tree rather than a dynamic transmission model. A decision tree is appropriate for a screening decision over pregnancy because it is transparent, interpretable and comparable with previous work. However, it cannot capture population level transmission effects, feedback from partner treatment and future infections prevented.

Implications for UK NSC decision making

The results do not suggest that repeat screening has no value. In the base case, universal repeat screening prevented an additional 12.2 cases of congenital syphilis and generated 142 additional QALYs. However, this required 584,126 additional antenatal syphilis screens and increased lifetime costs by £9.14 million, giving an ICER of £64,219 per QALY. The policy relevant interpretation is therefore not that repeat screening is ineffective, but that universal national repeat screening is unlikely to be the most efficient use of NHS resources under current average risk assumptions.

The QALY results show that almost all the benefit of repeat screening came from infants born to women who were negative at the first screen and then acquired syphilis during pregnancy. This suggests that future monitoring should focus on evidence of infection acquired or first detectable after the booking screen, including incident maternal infection during pregnancy, repeat testing after an initial negative screen, congenital syphilis cases following earlier negative screening, and regional changes in incidence. The threshold analysis provides a useful benchmark: under otherwise base case assumptions, incidence during pregnancy would need to rise from 0.0042% to 0.0106% for repeat screening to reach £20,000 per QALY.

Improving targeted retesting under current practice may be a higher value alternative to universal repeat screening. Current policy already supports testing at any point in pregnancy where risk changes, symptoms arise, or clinical concern exists. This aligns with the model findings, because repeat screening only adds benefit for women whose infection is acquired after, missed at, or not yet detectable at the first screen. The key question is therefore whether targeted retesting is being implemented reliably in practice. Strengthening risk assessment, clinical prompts, sexual health and maternity communication, partner notification and rapid re-entry into testing may capture some of the benefit of repeat screening without applying an additional test to the whole antenatal population.

Outbreak responsive or regional repeat screening may be more plausible than a permanent national universal policy, but the regional results do not currently support routine regional implementation. London had the most favourable regional ICER at

£48,386 per QALY, while the South West had the least favourable ICER at £126,531 per QALY, and no region reached £20,000 per QALY. The incidence threshold of 0.0106% is around 2.5 times the current England estimate and around twice the current London estimate of 0.0053%. Regional implementation would therefore only be expected to become cost-effective in areas with sustained incidence substantially above that currently observed in any region, rather than in response to short-term fluctuation or isolated congenital syphilis cases.

The model also highlights where better evidence would help to reduce model uncertainty. The highest value evidence gaps are those that determine either the number of preventable cases or the value of preventing each case: incidence during pregnancy, the relationship between maternal infection timing and foetal outcome, the true incremental cost of adding syphilis testing to existing 28 week blood tests, the lifetime costs and utilities associated with congenital syphilis, and the effectiveness of targeted retesting in current practice.

Conclusion

The updated model provides a more current and UK-specific assessment of universal repeat screening for syphilis in pregnancy than the 2020 Aquarius analysis. It finds that repeat screening would prevent additional cases of congenital syphilis and other serious outcomes, but that the absolute benefit remains small relative to the scale and cost of a universal repeat screening programme. In the base case, repeat screening prevented 12.2 congenital syphilis cases and generated 142 additional QALYs, but required 584,126 additional antenatal syphilis screens and increased lifetime costs by £9.14 million, producing an ICER of £64,219 per QALY.

The analysis therefore does not show that repeat screening has no clinical value. Rather, it shows that universal national repeat screening is unlikely to be cost-effective under current base case assumptions. The conclusion could change with increased incidence during pregnancy, if the true marginal cost of adding syphilis testing to existing 28 week blood tests were lower than assumed, or if the long-term health burden of congenital syphilis were greater than represented in the base case. As such, and given the observed trend of increasing syphilis incidence over recent years, it may be prudent to construct a living or standing model for syphilis screening in pregnancy that can be easily updated with future evidence. At present, the findings support continued surveillance, improved targeted retesting and outbreak responsive planning rather than the introduction of universal national repeat screening.

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Appendix 1

Scenario results summary

The scenario analyses test structural and policy relevant alternatives rather than changing one parameter at a time. They therefore help interpret how the model behaves under different plausible versions of the decision problem. Across all scenarios shown in the Appendix, repeat screening remained more costly and more effective than single screening. None of the scenarios reduced the ICER to the conventional £20,000 per QALY threshold used in the report context, although some made repeat screening more favourable than the base case.

Appendix Table 1 - Scenario summary: Overall pattern of scenario analysis results

Scenario	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	Interpretation
Base case	9,139,038	142	64,219	Reference result
Mean PSA	9,192,572	135	67,849	Confirms base case conclusion under joint uncertainty
Lifetime horizon, 1.5% discount rate	8,325,393	258	32,290	Second most favourable scenario because future child health benefits carry more weight
Lower utility and life expectancy with congenital syphilis	9,139,038	201	45,483	More favourable because congenital syphilis is assumed to have greater lifetime burden
Upper incidence and prevalence	8,593,411	205	41,994	More favourable because more pregnancies can benefit from repeat screening
100% sensitivity and specificity	8,439,086	142	59,333	Moderate improvement from removing test errors
100% specificity for repeat screen	8,428,455	142	59,226	Moderate improvement from reducing false positives
Maternal disutilities included	9,139,038	144	63,508	Very small improvement because few cases are prevented
Alternative cost sources	9,115,860	142	64,506	Effectively unchanged
All women screened early	9,653,359	150	64,219	Effectively unchanged in ICER terms
Possible congenital syphilis cases included	9,230,799	135	68,152	Less favourable than the base case
Short-term time horizon	10,314,246	142	72,477	Less favourable because long-term avoided congenital syphilis costs are excluded

Scenario	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)	Interpretation
Cost per screen halved	£4,306,426	142	30,261	Most favourable scenario. Favourable since 584,126 additional screens are conducted with the repeat screen strategy than with single screening, so reducing the cost per screen leads to a greater reduction in the total costs for repeat screening
Vertical transmission of 100% if infected between the first and second screens & not diagnosed	£7,901,746	235	33,641	Favourable since repeat screening reduces the number of women infected during pregnancy that are undiagnosed, and in this scenario all livebirths to these women incur the significant lifetime costs and utility decrement associated with congenital syphilis
Vertical transmission of 16.5% if infected between the first and second screens & not diagnosed	£9,968,023	80	124,154	Less favourable since repeat screening reduces the proportion of women infected during pregnancy that are undiagnosed, and in this scenario are lower proportion of livebirths to these women incur the lifetime costs and utility decrement associated with congenital syphilis
60% of infections after the first screen occur prior to 28 weeks gestation	£9,632,706	86	112,092	Less favourable since infections occurring after 28 weeks would not be detected by repeat screening (unless repeat screening were to occur later in pregnancy: this would increase the cost per screen and hence also increase the ICER)
Including partner testing costs for false positive diagnoses	9,674,908	142	67,907	Moderately less favourable than the base case, since repeat screening leads to additional false positive diagnoses and so additional testing for partners

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, PSA - Probabilistic sensitivity analysis, QALYs - Quality Adjusted Life Years

The scenario summary outlined in Appendix Table 1 shows 3 broad patterns. First, scenarios that increase the value of preventing congenital syphilis produce the greatest improvement in cost-effectiveness. Halving the cost of screening produced the lowest ICER. The 1.5% discount-rate scenario is another clear example because future child health benefits are discounted less heavily. The lower utility and life expectancy scenario is also favourable because congenital syphilis is assumed to be more severe over the child's lifetime. Second, scenarios that increase the number of pregnancies in which repeat screening can make a difference, such as higher incidence and prevalence, also

improve the ICER. Third, scenarios that only alter downstream details, such as alternative cost sources, maternal disutility, or all women being screened early, have relatively little effect on the main conclusion.

Joint parameter variation: congenital syphilis burden and epidemiology

The scenario outlined in Appendix Table 2 assumes more severe long-term consequences of congenital syphilis by using lower values for utility and for life expectancy. Lifetime costs remain the same as the deterministic base case, but incremental QALYs increase from 142 to 201. The ICER falls to £45,483 per QALY. This demonstrates that the model is sensitive to how congenital syphilis is valued over the child's lifetime. However, even this more severe assumption does not bring repeat screening within the conventional £20,000 per QALY threshold.

Appendix Table 2 - Scenario analysis: lower bounds for utility and life expectancy with congenital syphilis

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,656,889	1,882,207	1,890,539,096	17,123,898
Repeat screening	1,898,971,135	706,999	1,899,678,134	17,124,099
Difference	10,314,246	-1,175,208	9,139,038	201
ICER (£/QALY)	45,483			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

The scenario outlined in Appendix Table 3 uses higher values for syphilis prevalence and incidence. It increases the number of women entering pathways in which repeat screening can prevent congenital syphilis or other adverse outcomes. Incremental QALYs increase to 205 and the ICER improves to £41,994 per QALY. This is directionally important because it shows that rising syphilis in pregnancy would make repeat screening more attractive. The result also shows that the levels tested are not sufficient, on their own, to make universal repeat screening cost-effective.

Appendix Table 3 - Scenario analysis: upper bounds for syphilis incidence and prevalence

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,782,122	2,549,329	1,891,331,451	17,123,890

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Repeat screening	1,899,067,548	857,314	1,899,924,862	17,124,095
Difference	10,285,426	-1,692,015	8,593,411	205
ICER (£/QALY)	41,994			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Time horizon and discounting

The short-term time horizon outlined in Appendix Table 4 excludes long-term congenital syphilis costs. This makes repeat screening less favourable because the model still captures the immediate additional screening and management costs but no longer captures the future cost offsets associated with preventing congenital syphilis. Incremental costs are £10.31 million and the ICER rises to £72,477 per QALY.

Appendix Table 4 - Scenario analysis: short-term time horizon.

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Total QALYs
Single screen only	1,888,656,889	17,123,992
Repeat screening	1,898,971,135	17,124,134
Difference	10,314,246	142
ICER (£/QALY)	72,477	

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

The 1.5% discount rate scenario outlined in Appendix Table 5 is the second most favourable scenario considered. Incremental costs fall to £8.33 million and incremental QALYs increase to 258, reducing the ICER to £32,290 per QALY. This result is consistent with the model logic: most of the health benefit of preventing congenital syphilis accrues over the child's lifetime, so reducing the discount rate gives greater weight to those future benefits. The scenario therefore highlights the importance of the lifetime horizon and the uncertainty around long-term child outcomes.

Appendix Table 5 - Scenario analysis: lifetime horizon with 1.5% annual discount rate.

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,656,889	3,185,338	1,891,842,226	29,374,931

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Repeat screening	1,898,971,135	1,196,484	1,900,167,619	29,375,189
Difference	10,314,246	-1,988,853	8,325,393	258
ICER (£/QALY)	32,290			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Test accuracy scenarios

Assuming perfect sensitivity and specificity as outlined in Appendix Table 6 reduces the ICER to £59,333 per QALY. The improvement occurs because missed infections and false positive results are removed from the model. The effect is only moderate because the base case test accuracy is already high. The main constraint remains that only a small number of pregnancies can benefit from universal repeat screening.

Appendix Table 6 - Scenario analysis: 100% sensitivity and specificity

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,887,900,566	1,840,193	1,889,740,759	17,124,000
Repeat screening	1,897,523,133	656,713	1,898,179,846	17,124,143
Difference	9,622,567	-1,183,481	8,439,086	142
ICER (£/QALY)	59,333			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Assuming 100% specificity for the repeat screen as outlined in Appendix Table 7 produces a very similar ICER of £59,226 per QALY. This scenario reduces false positive results and the costs associated with follow up, treatment pathways and infant assessment. It does not substantially increase QALYs because it does not increase by a large amount the number of true infections detected and treated in time to change outcomes.

Appendix Table 7 - Scenario analysis: 100% specificity for the repeat screen

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,656,889	1,882,207	1,890,539,096	17,123,992

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Repeat screening	1,898,260,551	706,999	1,898,967,551	17,124,134
Difference	9,603,663	-1,175,208	8,428,455	142
ICER (£/QALY)	59,226			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Additional health state and case definition scenarios

Including maternal disutility as outlined in Appendix Table 8 changes the QALY result only slightly. Incremental QALYs increase to 144 and the ICER falls marginally to £63,508 per QALY. This does not mean that parental or maternal impacts are unimportant. It means that, within the values tested, the number of additional congenital syphilis cases prevented is too small for this additional utility component to change the cost-effectiveness result.

Appendix Table 8 - Scenario analysis: maternal disutility included

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,656,889	1,882,207	1,890,539,096	17,123,587
Repeat screening	1,898,971,135	706,999	1,899,678,134	17,123,731
Difference	10,314,246	-1,175,208	9,139,038	144
ICER (£/QALY)	63,508			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Including possible congenital syphilis cases as outlined in Appendix Table 9 is less favourable than the base case. Incremental costs increase to £9.23 million and incremental QALYs fall to 135, producing an ICER of £68,152 per QALY. This is because the probability of vertical transmission if infected during pregnancy & not diagnosed is fixed in the model (at 0.5), while the probability if diagnosed is calculated using the ISOSS data: broadening the congenital syphilis case definition therefore increases the calculated probability of vertical transmission if infected during pregnancy & diagnosed relative to undiagnosed, and hence does not translate into proportionally greater incremental benefit from repeat screening.

Appendix Table 9 - Scenario analysis: possible congenital syphilis cases included

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,712,587	3,918,800	1,892,631,387	17,123,835
Repeat screening	1,899,029,275	2,832,910	1,901,862,186	17,123,971
Difference	10,316,689	-1,085,890	9,230,799	135
ICER (£/QALY)	68,152			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Cost and screening timing scenarios

Using alternative cost sources as outlined in Appendix Table 10 produces an ICER of £64,506 per QALY, which is very close to the deterministic base case result. This suggests that this particular alternative costing approach does not alter the conclusion. The broader model context still indicates that screening cost is important, but this scenario does not reduce incremental costs enough to change the interpretation of the results.

Appendix Table 10 - Scenario analysis: alternative cost sources

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,816,478	1,969,171	1,890,785,649	17,123,992
Repeat screening	1,899,161,844	739,665	1,899,901,509	17,124,134
Difference	10,345,366	-1,229,506	9,115,860	142
ICER (£/QALY)	64,506			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Assuming all women are screened early as outlined in Appendix Table 11 produces an ICER of £64,219 per QALY, effectively unchanged from the deterministic base case. This is informative because it shows that the key incremental benefit pathway is not primarily late first screening. Instead, the main QALY gain comes from infections acquired after an initial negative screen, which are only detectable through later testing.

Appendix Table 11 - Scenario analysis: all women screened early

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,660,226	1,943,724	1,890,603,950	17,123,984
Repeat screening	1,899,554,930	702,378	1,900,257,309	17,124,134
Difference	10,894,705	-1,241,346	9,653,359	150
ICER (£/QALY)	64,219			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Halving the cost per screen to £8.27 reduces the short-term costs for both screening strategies, but with a greater reduction for repeat screening, as 584,126 additional screens are conducted with repeat screen than with single screening. Halving the cost per screen therefore results in a significantly reduced ICER to £30,261/QALY.

Appendix Table 12 - Scenario analysis: cost per screen halved

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,883,537,800	1,882,207	1,885,420,008	17,123,992
Repeat screening	1,889,019,434	706,999	1,889,726,434	17,124,134
Difference	5,481,634	-1,175,208	4,306,426	142
ICER (£/QALY)	30,261			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Probability of vertical transmission scenarios

Altering the vertical transmission probability for untreated mothers infected during pregnancy (but prior to 28 weeks) leads to significant changes to the results, as outlined in Appendix Tables 13 & 14. This is because the lifetime costs and utility decrement associated with congenital syphilis are significant and repeat screening reduces the number of women infected during pregnancy who are undiagnosed. Using a higher or lower value for the vertical transmission probability increases or reduces the cost-effectiveness of repeat screening, respectively. This is largely due to the difference in the total QALYs and long-term costs for the single-screen strategy in these scenarios compared with that in the base case.

Appendix Table 13 - Scenario analysis: vertical transmission probability for women infected during pregnancy of 100%

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,690,189	3,099,842	1,891,790,032	17,123,898
Repeat screening	1,898,971,498	720,280	1,899,691,778	17,124,133
Difference	10,281,308	-2,379,562	7,901,746	235
ICER (£/QALY)	33,641			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Appendix Table 14 - Scenario analysis: vertical transmission probability for women infected during pregnancy of 16.5%

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,634,577	1,066,392	1,889,700,969	17,124,054
Repeat screening	1,898,970,891	698,101	1,899,668,992	17,124,135
Difference	10,336,314	-368,291	9,968,023	80
ICER (£/QALY)	124,154			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

Probability of infection occurring prior to 28 weeks' gestations

Altering the proportion of infection after the first screen that occur prior to 28 weeks gestation has a significant impact on the results, as outlined in in Appendix Tables 15 & 16. This is because infections occurring after 28 weeks would not be detected by repeat screening (unless repeat screening were to occur later in pregnancy). Using a proportion of 60% reduces the cost-effectiveness of repeat screening. This is largely due to a decrease in the total QALYs and increase in the long-term costs for the repeat-screen strategy compared with that in the base case.

Appendix Table 15 - Scenario analysis: 60% of infections after the first screen occur prior to 28 weeks gestation

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
Single screen only	1,888,656,889	1,882,207	1,890,539,096	17,123,992
Repeat screening	1,898,995,700	1,176,102	1,900,171,802	17,124,078
Difference	10,338,812	-706,105	9,632,706	86

Screening strategy	Short-term costs (antenatal + postnatal) [£]	Long-term costs [£]	Lifetime costs (short + long-term) [£]	Total QALYs
ICER (£/QALY)	112,092			

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio, QALYs - Quality Adjusted Life Years

There will be an interaction effect between the vertical transmission probability for untreated women infected during pregnancy and the proportion of infections after the first screen that occur prior to 28 weeks gestation. As there is uncertainty around both of these values, joint parameter variation was conducted, with the resulting incremental cost-effectiveness ratios shown in Appendix Table 16.

Appendix Table 16 - Scenario analysis: ICERs when varying the vertical transmission probability for untreated women infected during pregnancy & the proportion of infections after the first screen that occur prior to 28 weeks gestation

ICER for repeat screening vs single screen only (£/QALY)		Proportion of infections after the first screen that occur prior to 28 weeks gestation				
		60%	70%	80%	90%	100%
Transmission probability for untreated women infected during pregnancy and the proportion of infections	16.5%	209,820	178,346	157,122	138,273	124,154 (scenario 14)
	50%	112,092 (scenario 15)	92,065	82,960	72,241	64,219 (base case)
	70%	87,046	72,735	63,102	54,577	48,200
	90%	69,919	58,031	50,032	42,956	37,664
	100%	63,374	52,415	44,605	38,519	33,641 (scenario 13)

Abbreviations: ICER - Incremental Cost-Effectiveness Ratio

Appendix 2

The parameters used in the model are listed in Appendix Tables 17 and 18. For the parameters varied independently in the sensitivity analysis (Appendix Table 17), the upper and lower bounds of the parameters varied in the deterministic sensitivity analysis are given, along with the probabilistic distribution used for these in the PSA.

Appendix Table 17 – Model parameters varied independently

Parameter name	Base case value	Lower bound	Upper bound	PSA Distribution
% with syphilis at the start of pregnancy	0.084%	0.067%	0.101%	Beta
% becoming infected during pregnancy	0.0042%	0.0033%	0.0050%	Beta
% receiving syphilis screen <28 weeks	94.7%	93.6%	98.4%	Beta

Probability of true positive	0.995	0.984	1	Beta
Probability of true negative	0.998	0.99	0.999	Beta
Probability of PT if no syphilis	0.080	0.064	0.096	Beta
Probability of IUFD if no syphilis	0.003	0.003	0.004	Beta
Probability of ND if no syphilis	0.002	0.001	0.002	Beta
Probability of CS if diagnosed <28 weeks	0.012	0.010	0.015	Beta
Probability of PT if diagnosed <28 weeks	0.108	0.086	0.130	Beta
Probability of IUFD if diagnosed <28 weeks	0.009	0.007	0.010	Beta
Probability of ND if diagnosed <28 weeks	0.004	0.003	0.005	Beta
Probability of CS if diagnosed ≥28 weeks	0.165	0.132	0.198	Beta
Probability of PT if diagnosed ≥28 weeks	0.275	0.220	0.330	Beta
Probability of IUFD if diagnosed ≥28 weeks	0.063	0.050	0.075	Beta
Probability of ND if diagnosed ≥28 weeks	0.010	0.008	0.013	Beta
Probability of CS if with syphilis not diagnosed	0.165	0.132	0.198	Beta
Probability of PT if with syphilis not diagnosed	0.362	0.290	0.435	Beta
Probability of IUFD if with syphilis not diagnosed	0.077	0.062	0.093	Beta
Probability of ND if with syphilis not diagnosed	0.011	0.009	0.013	Beta
Probability of CS if infected during pregnancy & diagnosed	0.012	0.010	0.015	Beta
Probability of PT if infected during pregnancy & diagnosed	0.108	0.086	0.130	Beta
Probability of IUFD if infected during pregnancy & diagnosed	0.009	0.007	0.010	Beta
Probability of ND if infected during pregnancy & diagnosed	0.004	0.003	0.005	Beta
Probability of CS if infected during pregnancy & not diagnosed	0.500	0.400	0.600	Beta
Probability of PT if infected during pregnancy & not diagnosed	0.362	0.290	0.435	Beta
Probability of IUFD if infected during pregnancy & not diagnosed	0.077	0.062	0.093	Beta
Probability of ND if infected during pregnancy & not diagnosed	0.011	0.009	0.013	Beta
Utility with CS	0.740	0.592	0.888	Beta
Life expectancy ratio (CS vs no CS)	0.9	0.720	1.000	Beta
% of infections after the early screen occurring <28 weeks	100%	60%	100%	Beta
Cost of syphilis screen	16.55	13.237	19.86	Gamma
Cost of management of women diagnosed with syphilis in pregnancy	363.23	290.59	435.88	Gamma

Cost of intrauterine foetal demise	5,387.16	4,309.73	6,464.60	Gamma
Cost of pre-term birth	8,779.57	7,023.66	10,535.49	Gamma
Cost of term birth (37+ weeks)	2,515.80	2012.64	3018.96	Gamma
Cost of neonatal death	7,178.84	5743.08	8614.61	Gamma
Cost of CS testing and treatment	5,234.57	4187.66	6281.49	Gamma
Cost of CS neonatal screen	303.25	242.60	363.90	Gamma
Lifetime healthcare cost of CS	99,443.12	79,554.50	119,331.75	Gamma
Lifetime healthcare & social cost of CS	805,437.59	644,350.07	966,525.11	Gamma

Abbreviations: CS - congenital syphilis, FN - False Negative, FP - False Positive, IUFD - Intrauterine foetal demise, PSA - Probabilistic sensitivity analysis, PT – Preterm, ND – Neonatal Death, TN - True Negative, TP - True Positive

Appendix Table 18 – Model parameters not varied independently

Parameter name	Base case value	Lower bound	Upper bound	PSA Distribution
Model cohort size	618,753	N/A	N/A	Fixed
% Screening uptake	100%	N/A	N/A	Fixed
Life expectancy (no CS)	81.4	N/A	N/A	Fixed
Probability of CS if no syphilis	0.0	N/A	N/A	Fixed
Life expectancy (CS)	73.2	N/A	N/A	Fixed
Probability of false negative	0.005	0.016	0.000	Dependent
Probability of false positive	0.002	0.010	0.001	Dependent

Abbreviations: CS - congenital syphilis, N/A - not applicable

Appendix 3

Appendix 3 contains feedback from the expert stakeholders on a draft version of the model report and responses from the SENSS team, who undertook the modelling work. Updates were made to the model and report following these stakeholder comments.

Comments on the draft report were received from:

- Dr Helen Fifer, Consultant Microbiologist, UKHSA and Advisor to IDPS
- Dr Katy Sinka, Consultant Epidemiologist, Head of STI section, UKHSA
- Professor Hermione Lyall, Consultant Paediatrician Imperial College Healthcare NHS Trust
- Professor Margaret Kingston, Consultant Genitourinary Medicine, Manchester University NHS Foundation Trust
- Sarah Dermont, IDPS, NHS England
- Justin Penner, Paediatric infectious diseases consultant, St Mary's Hospital, London

Assumptions regarding additional treatment and false positive results

Stakeholder comment

The statement that: "Repeat screening also increased the number of women treated for syphilis by 1,195 and generated 1,166 additional false positive screen results" does not appear intuitive and would benefit from further explanation.

In practice, most women undergoing repeat screening will already have had a negative screening result earlier in pregnancy. This prior result provides important clinical context when interpreting a subsequent reactive result. False positive results identified at the first screen will largely have been resolved through confirmatory testing and will not simply recur as new diagnostic dilemmas at the third-trimester screen.

Consequently, we would not expect more than 1,000 additional women to be treated for syphilis solely as a result of false positive findings generated by repeat screening. The clinical pathway for interpreting serological results in women with a documented recent negative screen is considerably more straightforward than the model narrative implies.

That said, the report estimates that these additional treatments contribute only approximately £0.43 million to overall costs, meaning that even if these assumptions were revised, the impact on the overall economic conclusions may be relatively modest.

SENSS response

Thank you for raising this point. The model estimates for the numbers of additional women treated and additional false positive screens result from the cohort size, prevalence, incidence, and screen accuracy inputs in the model. Unfortunately screen accuracy data by stage of screening was not available. The specificity of the screen is very high in the model base case (99.8%), but given the clinical context that you mention, we explored a scenario with 100% specificity for the repeat screen (i.e. with the assumption that there would be no additional false positives screen results due to repeat screening). If positive reactive results at the repeat screen are less likely to be interpreted as such when there has been a negative result earlier in pregnancy, this would have implications for the overall sensitivity of the repeat screen as well. Given that the cost per adverse outcome due to untreated infection is much higher than the cost per screen, increasing the specificity and reducing the sensitivity of the repeat screen is likely to reduce the cost-effectiveness of repeat screening overall.

Assumed cost per repeat screen

Stakeholder comment

Our greater concern relates to the assumed screening cost of £16.55 per repeat test.

This figure appears substantially higher than current operational costs observed in practice. For example, the North East pilot is reportedly delivering repeat syphilis screening at approximately £5 per screen. While this may represent laboratory costs alone, it raises an important question regarding the basis of the £16.55 estimate and the extent to which additional costs have been incorporated.

The report itself acknowledges uncertainty around this parameter within the limitations section. Given that the cost-effectiveness findings are highly sensitive to screening costs, obtaining robust contemporary data on the true marginal cost of adding syphilis testing to existing 28-week antenatal blood testing pathways appears essential if the conclusions are to be challenged or refined.

Indeed, if substantially lower screening costs were used, universal repeat screening may move much closer to being cost-effective.

SENSS response

We agree that obtaining robust contemporary data on the true marginal cost of adding syphilis testing to existing 28-week antenatal pathway would refine the model results. A more robust cost estimate was not identified at the time of the analysis, but a request has been made to see whether contemporary data for this is now available. We have also written in the report that it may be prudent to construct a living or standing model for syphilis screening in pregnancy that can be easily updated with future evidence, as the conclusion of the analysis could change if the true marginal cost were lower than assumed. The cost per screen was varied in the sensitivity analysis and in the threshold analysis, but given the sensitivity of the results to this value, we have added a scenario analysis in which the cost is halved.

Impact of increasing syphilis incidence

Stakeholder comment

We note that the sensitivity analyses identify increasing incidence during pregnancy as another important factor that improves cost-effectiveness.

The report states that:

"Incidence during pregnancy would need to more than double, from 0.0042% to 0.0107%. This incidence threshold is around 2.5 times the England base case estimate and around twice the latest London estimate of 0.0053%, the highest regional incidence in the analysis."

It would be helpful if the team could translate these percentages into absolute numbers of maternal and congenital syphilis cases. Given that syphilis diagnoses in women have been

increasing and that congenital syphilis cases have risen in parallel, understanding the practical implications of these thresholds would assist interpretation.

Whilst the threshold incidence may initially appear high, it is not difficult to envisage continued epidemiological trends moving in that direction. Understanding the scale of increase required in real-world terms would therefore be valuable.

SENSS response

Based on a cohort size of 618,753 pregnant women, an incidence of 0.0042% is equivalent to approximately 26 new infections occurring between the first screen and the repeat screen per year, while an incidence of 0.0106% is equivalent to approximately 66 new infections between the first and repeat screens per year. This would therefore be equivalent to an increase of approximately 40 new infections between the first and repeat screens per year.

Interaction between incidence and screening costs

Stakeholder comment

Importantly, the sensitivity analyses appear to consider individual parameters in isolation. However, the real-world situation is likely to involve simultaneous changes in both incidence and screening costs.

We would therefore be interested to see whether the team could construct a two-way sensitivity analysis, presented either as a table or graphical heat map, showing combinations of:

- syphilis incidence during pregnancy; and
- repeat screening cost per woman,

that would result in the intervention becoming cost-effective.

This would help address the central policy question. The increasing burden of syphilis is the reason this strategy has been revisited, and if current economic assumptions do not support immediate implementation of universal repeat screening, it would be useful to understand how close we may be to a threshold where that position changes.

Such an analysis would allow decision-makers to determine whether repeat screening should be considered a strategy that can be ruled out entirely, or whether it remains a realistic future option should incidence continue to rise or delivery costs fall. Additionally, an indication of whether this would then allow implementation if the threshold was reached, without the need for a repeat review exercise, would be helpful.

SENSS response

Syphilis incidence during pregnancy and the cost per screen are varied simultaneously in the probabilistic sensitivity analysis, along with other model parameters that could change in a real-world situation. We have carried out two-way sensitivity analysis in addition to this only where the association between two parameters is much greater than that with the other model parameters and where this would compound the impact on the cost-effectiveness results; for example, a scenario is considered with using the upper bounds for both incidence and prevalence, as there is a strong positive correlation between these parameters and an increase in either would increase the cost-effectiveness of repeat screening. There is a slight association between incidence and the cost per screen, as both are positively correlated with the prevalence of the syphilis: for example, a higher prevalence is associated with a higher incidence and a marginally higher cost per screen. Two-way variation (in which the incidence and the cost per screen are jointly increased or decreased) would therefore lessen the impact on the model results compared with individual variation. We appreciate that both these and other parameters may change in future. We therefore have written in the report that it may be prudent to construct a living or standing model for syphilis screening in pregnancy that can be easily updated with future evidence, as the conclusion of the analysis could change with increased incidence during pregnancy or if the true marginal cost were lower than assumed.

Future epidemiological trends

Stakeholder comment

There is a clear epidemiologic curve for syphilis infections with infections increasing exponentially year on year, this is also well documented worldwide especially in other high income countries. Is there a way to analyse this in terms of future projected trend in syphilis diagnoses? In only 3 cycles of data between 2021-2022 v 2024-2025 the ICER has more than halved in London for example and thus considering the projected epi curve one would certainly expect an ICER <20,000 in the coming 3 year cycle

SENSS response

We have not identified evidence of prolonged exponential increases in syphilis infections in pregnancy, but you are welcome to submit this during the consultation period. Recent modelling studies for syphilis cases in pregnancy have used techniques (such as joinpoint regression) that allow trends to change significantly over time.

It is important to distinguish between syphilis infections in pregnancy and in the general population: we have not modelled the latter in this project. Syphilis infections in pregnancy do not necessarily increase exponentially year on year: pregnant women are unlikely to become infected by other (recently) pregnant women, nor would an increase in the wider

population necessarily result in an exponential increase in infections in pregnancy (e.g. if the increase were concentrated in MSM).

The calculated prevalence for England from the ISOSS data does not show constant proportional growth over time; e.g. the increase was lower over the most recent year in England and in all but two regions, with three regions showing a decrease in prevalence. An exponential curve would therefore not provide a good fit to the data.

Polynomial curves provide a better fit: the best-fitting curves suggest that prevalence for England would peak then decline in the near future. However, with only four years' worth of data, there are few time points to use for a projection, so we do not think it would be appropriate to analyse the data in this way to inform decision-making.

Decision-making on the introduction of screening should be based on the most recent available data for that year. However, given the trend of increasing syphilis incidence over recent years, we conclude that it may be prudent to construct a living or standing model that can be easily updated with future evidence.

Comment on assumption: “40% of infants born with congenital syphilis would display signs at delivery, with the remaining 60% displaying signs in the days or weeks after delivery.”

Stakeholder comment

This is incorrect. Untreated congenital syphilis in children often doesn't show signs or symptoms until well after the 2nd year of life

SENSS response

The proportions in the text are only for neonates and are only used in a scenario analysis when testing costs are estimated using the micro-costing approach. In the base case, a cost estimate derived from Hospital Episode Statistics Admitted Patient Care (HES APC) data is used. We have clarified this in the text. Treatment costs for those diagnosed later in life are currently included in the average long-term healthcare cost for congenital syphilis.

Comment on assumption: “50% of children born to untreated mothers infected during pregnancy are assumed to acquire congenital syphilis.”

Stakeholder comment

This is incorrect. 90-100% of primary and secondary cases of maternal syphilis result in vertical transmission and 30-40% of early latent infections. Since we are speaking of new infections after initial negative screening none of these will be late latent infections and the

vast majority will be primary/secondary cases. 50% makes the assumption that almost all will be early latent. This is also hard to differentiate as symptomatic disease in pregnancy very commonly underrecognized

SENSS response

Thank you for your comment and for sending the examples in the literature. The percentages that you mention have been widely quoted. The original source for these percentages is a 1975 paper by Nicolas Fiumara, in which 50% pregnancies to untreated mothers with early lesion (primary or secondary) syphilis are expected to result in congenital syphilis, 40% with early latent syphilis and 10% with late latent syphilis.¹

We therefore think that 50% is an appropriate value for primary and secondary cases which, as you say, will make up the vast majority of new infections after initial screening and before repeat screening at 28 weeks' gestation.

We have however conducted scenario analyses with values of 70%, 90% and 100%, as well as lower figure: a 2013 systematic review and meta-analysis on untreated maternal syphilis estimated that 15% of children born to untreated pregnant women with syphilis displayed clinical evidence of congenital syphilis.² This figure was adjusted to 16% in 2013 WHO report.³

Comment on long-term costs

Stakeholder comment

There are also both short term and longterm consequences for the mother undiagnosed with syphilis and thus untreated when missed in pregnancy. Do these health costs not need to be considered as well? Healthcare accrual cost is not just secondary to the baby but also the mother

SENSS response

This has been discussed with the UK NSC and is deemed to fall outside of the scope of this project. The purpose of repeat screening for syphilis during pregnancy would be to prevent congenital syphilis. We include a scenario involving maternal disutilities associated with adverse outcomes for the child, but accounting for consequences unrelated to the primary beneficiary would be inconsistent with modelling for other UK NSC screening programmes.

References for appendix 3

1. Fiumara NJ. Syphilis in newborn children. Clin Obstet Gynecol. 1975 Mar;18(1):183-9. doi: 10.1097/00003081-197503000-00016. PMID: 1091383.

2. Gomez GB, Kamb ML, Newman LM, Mark J, Broutet N, Hawkes SJ. Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis. *Bull World Health Organ*. 2013 Mar 1;91(3):217-26. doi: 10.2471/BLT.12.107623. PMID: 23476094.
3. World Health Organization, Centers for Disease Control and Prevention. Investment case for eliminating mother-to-child transmission of syphilis: promoting better maternal and child health and stronger health systems.