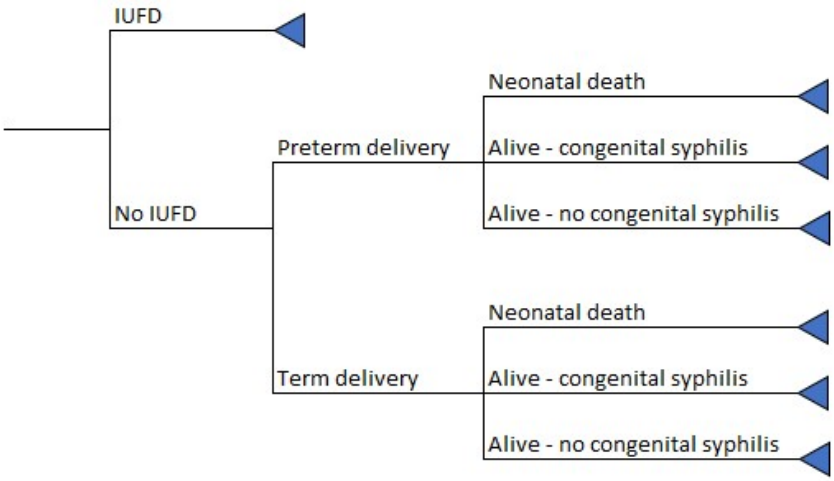
Online Supplement

Contents

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

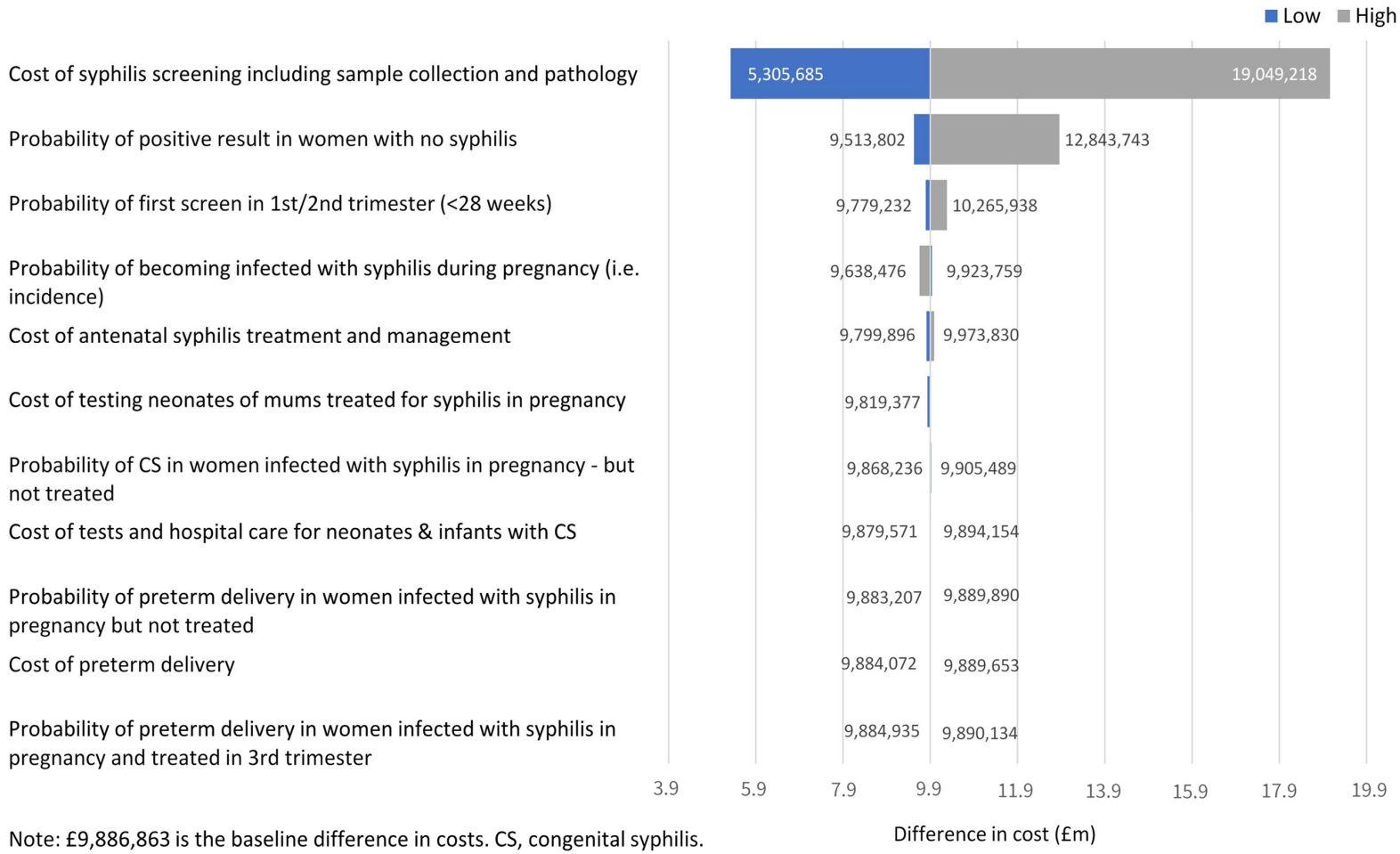


Footnote:

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

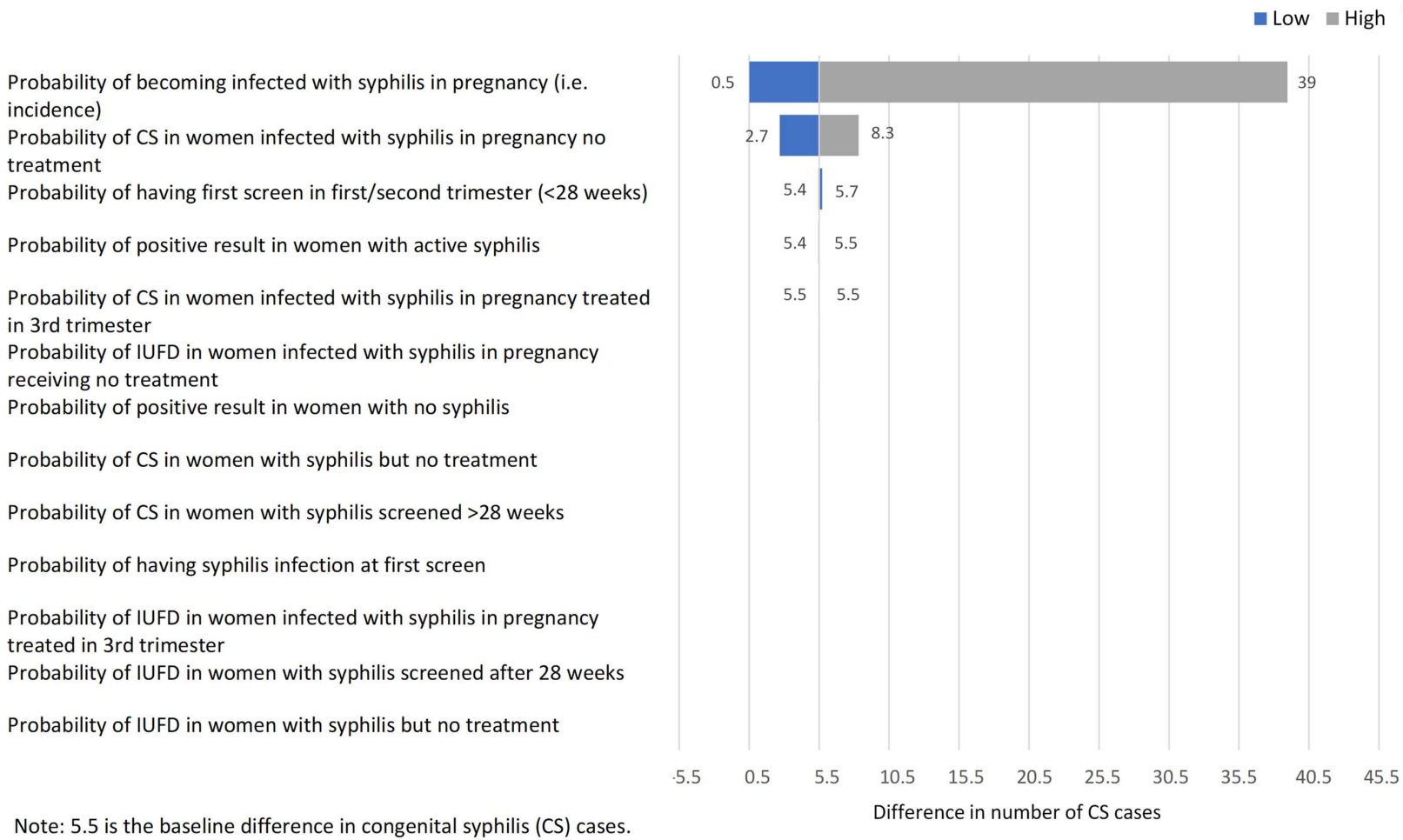
This diagram complements **Figure 1** in the main body of the paper. The probability of each of these outcomes occurring for each branch of the tree is presented in **Table S2**.

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



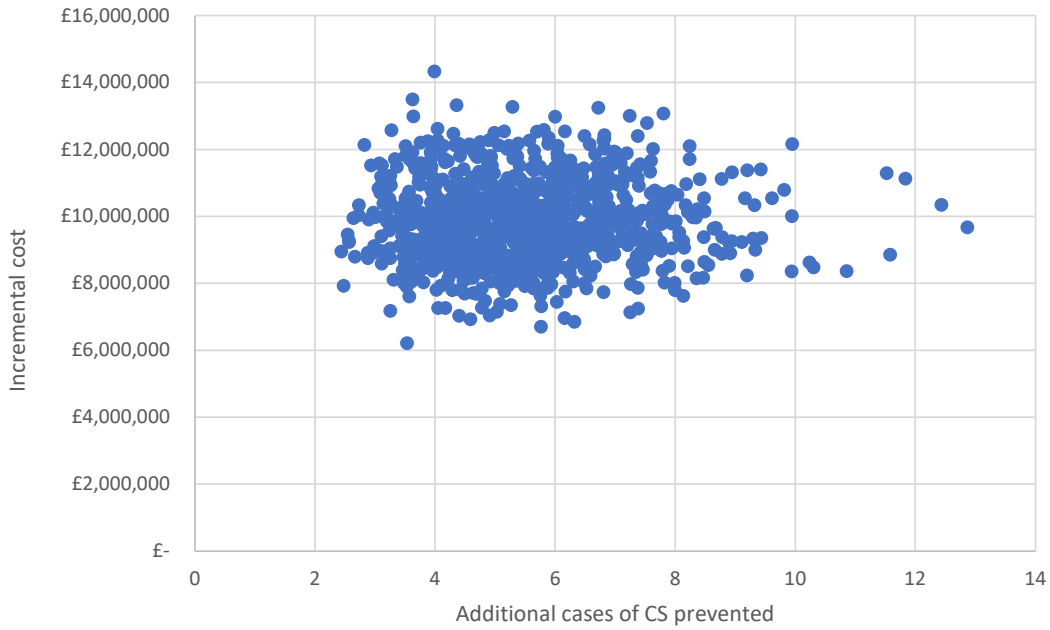
Note: £9,886,863 is the baseline difference in costs. CS, congenital syphilis.

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



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

Figure S4. Incremental cost versus additional cases of CS prevented



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

Table S1. Assumptions applied to screening strategies and rationale

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table S8. Calculating the cost per antenatal syphilis screen

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

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

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

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

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

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

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

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

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

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

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

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

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

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Table S12 Continued from previous page.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TP, True positive; FP, False positive

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

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

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Table S19. Continued from previous page.

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

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

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

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

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

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

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