Syphilis screening in pregnancy in the United Kingdom, 2010-2011: a national surveillance study

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Running head: Antenatal syphilis screening in the UK

Word count: 3506 words

Key words: Syphilis; Pregnancy; Surveillance; Epidemiology; Congenital infection

Abstract

Objective. To evaluate the national antenatal syphilis screening programme and provide evidence for improving screening and management strategies.

Design. National population-based surveillance.

Setting. United Kingdom (UK).

Population. All pregnant women screening positive for syphilis, 2010-2011.

Methods. Demographic, laboratory and treatment details for each pregnancy were collected from UK antenatal units (~210), along with follow up information on all infants born to women requiring syphilis treatment in pregnancy.

Main outcome measures. Proportion of women with newly or previously diagnosed syphilis among those with positive screening tests in pregnancy; proportion requiring treatment.

Results. Overall 77% (1425/1840) of reported pregnancies were confirmed syphilis screen-positive. Of these, 71% (1010/1425) were in women with previously diagnosed syphilis (155 requiring treatment), 26% (374/1425) with newly diagnosed syphilis (all requiring treatment) and 3% (41/1425) required treatment but the reason was unclear. Thus 40% (570/1425) required treatment overall; of these, 96% (516/537) were treated (missing data: 33/570), although for 18% (83/456), this was not until the third trimester (missing data: 60/537). Follow up of infants born to treated women was poor, with at least a third not followed. Six infants were diagnosed with congenital syphilis; two mothers were untreated, three had delayed treatment and one incomplete treatment (first trimester).

Discussion. Over two years, among pregnant women with confirmed positive syphilis screening results in the UK, a quarter had newly diagnosed infections and two fifths required treatment. Despite high uptake of treatment, antenatal syphilis management could be improved by earlier detection, earlier treatment, and stronger links between healthcare teams.

Tweetable abstract. 25% of pregnant women screening positive for syphilis in the UK were newly diagnosed and 40% needed treatment.

Surveillance of antenatal syphilis screening in the United Kingdom, 2010-2011

Introduction

Syphilis in pregnancy remains a global public health problem, with approximately 1.36 million women (range: 1.16-1.56 million) worldwide estimated to have active syphilis in pregnancy in 2008.[1] Untreated syphilis infection is commonly associated with adverse pregnancy outcomes including miscarriage, stillbirth, preterm birth, hydrops and polyhydramnios,[2] and can be transmitted to the fetus, leading to growth restriction, low birth weight, and long-term sequelae including hearing loss, neurological impairment and bone deformities.[3] Congenital syphilis is almost entirely preventable, and the World Health Organization called for global elimination (less than 50 cases per 100 000 live births) by 2015, through testing of ≥95% of pregnant women and treatment of ≥95% of those identified.[4] In cases of early (primary, secondary, early latent) syphilis in pregnancy, treatment with a single intramuscular injection of benzathine penicillin G (2.4MU) is recommended, if administered in the first or second trimester of pregnancy, or two doses if administered later.[5] Current British guidelines also advise re-treatment if there is uncertainty over the efficacy of past treatment.[6] For late latent syphilis in pregnancy, three doses of benzathine penicillin are recommended.[6]

In the United Kingdom (UK), new diagnoses of infectious syphilis in women more than doubled between 1999 and 2007, and anecdotally sexual health clinics reported around 10 cases of congenital infection annually.[7] Since a peak of around 500 in 2005, new diagnoses in women subsequently declined to 265 in 2012, although infections in men remain 10-fold higher, mainly due to ongoing transmission in men who have sex with men.[8]

Screening is routinely offered and recommended to all pregnant women in England,[9] with uptake over 97%;[10] in 2014, 0.14% of pregnant women (971/709,204) screened positive.[10] However, a positive screening test can indicate current or past syphilis infection, or may be a false positive result, sometimes indicating a history of endemic treponemal infection such as yaws or pinta. Women screening positive for syphilis therefore need referral to an appropriate specialist (e.g. a

genitourinary (GU) physician) for clinical assessment based on a detailed medical history, physical examination, and laboratory results. Although uptake of screening is high, concerns have been raised about the subsequent investigation, treatment and follow up of screen-positive women and their babies.[11]

The aim of this study was to evaluate the UK antenatal syphilis screening programme and provide evidence for improving screening and management strategies, by reviewing screen-positive pregnancies over a two-year period and assessing their management and outcome.

Methods

The Surveillance of Antenatal Syphilis Screening (SASS) study was a comprehensive national surveillance study through which information on all syphilis-positive pregnancies was requested from designated respondents in all maternity units in the UK. It was modelled on the National Study of HIV in Pregnancy and Childhood,[12] and for 80% of units the respondent was the same individual. Study respondents were contacted every three months and asked to report all pregnancies in women attending for antenatal care in 2010-2011 with a positive syphilis screening test. Basic demographic, pregnancy and laboratory data were collected using a standard form. Respondents were asked to report whether screen-positive cases were classified as newly diagnosed or previously diagnosed syphilis infection (with or without history of adequate treatment), or false positive[9] (e.g due to other treponemal infections, non-specific reactivity, or test errors), and to provide treatment details if it was required. Information on other positive screening tests in pregnancy (e.g. HIV, hepatitis B virus) was also collected. For pregnancies where treatment was required, outcome information was requested soon after the estimated date of delivery (EDD), along with details of the paediatrician responsible for infant follow-up; paediatricians were contacted between 2011 and 2013, when infants were at least 6 months old, to identify cases of congenital syphilis. Duplicate reports were matched using maternal dates of birth and other identifiers (EDD, ethnicity, etc), as no

93 names were collected. A parallel paediatric study of congenital syphilis cases diagnosed between
94 2010 and 2015 was carried out through the British Paediatric Surveillance Unit (BPSU) of the Royal
95 College of Paediatrics and Child Health (www.rcpch.ac.uk/what-we-do/bpsu/current-
96 studies/congenital-syphilis/congenital-syphilis). Cases of congenital syphilis reported through the
97 two studies were matched using mothers' and babies' dates of birth and other identifiers, in order to
98 ascertain any cases missed by either study.

99 Maternal country of birth was grouped by United Nations region
100 (http://unstats.un.org/unsd/methods/m49/m49regin.htm). Hospitals were grouped by UK country
101 and English region using the National Health Service (NHS) Strategic Health Authorities in place at
102 the time of the study. Setting of previous syphilis diagnosis (if relevant) was recorded as "Antenatal"
103 (i.e. in a previous pregnancy) or "Other / Not known". If date of booking for antenatal care (i.e. first
104 antenatal appointment) was missing, the earliest syphilis test date was used as a proxy. Gestation at
105 antenatal booking was calculated from booking date and EDD in most cases; where EDD was missing,
106 it was estimated from delivery date and gestation at birth (*n*=59). The interval between antenatal
107 booking and treatment was calculated from treatment date and booking date, or first test date if
108 booking date was missing. Time since arrival in the UK for women born abroad was calculated as the
109 difference between year of arrival and year of booking.

110 Data were managed in Access 2010 (Microsoft Corp., Redmond, Washington, USA) and analysed
111 using Stata version 12.1 (Stata Corp. LP, College Station, Texas, USA). Categorical variables were
112 compared using χ^2 tests or Fisher's exact tests, and medians using Kruskal-Wallis tests. Analyses
113 relate to pregnancies and some women (<3%) had more than one pregnancy reported during the
114 study period. Preterm birth and low birthweight rates for the general population were obtained
115 from Office for National Statistics data for the whole of England and Wales,[13] and comparisons made
116 using the one-sample test of proportions.

117

Results

Response rates

Ninety-eight percent of reporting cards were returned (total 1662/1697; on average 208/212 per reporting period). There were 2162 reports of syphilis screen-positive pregnancies, of which 223 were excluded (Figure 1), leaving 1939 reports. Of these, 92% (1781/1939) were from England, 4% (84/1939) from Scotland, 3% (51/1939) from Northern Ireland, and 1% (23/1939) from Wales.

Syphilis classification / diagnosis and baseline characteristics

There was insufficient information to classify 5% of screen-positive pregnancies (99/1939) (Figure 1), mostly because they were lost to follow up (48/99), or resulted in miscarriage or termination (28/99), and no further details were available. Among 1840 classified pregnancies, 77% (1425) were confirmed positives (i.e. newly or previously diagnosed syphilis infection), the remainder being reported as "false positives" (Figure 1). Among confirmed positives, 26% (374/1425) of women were newly diagnosed with syphilis, and 71% (1010/1425) had a previous syphilis diagnosis; 3% (41/1425) were reported to require treatment but whether this was for a previously or newly diagnosed infection was unclear (Figure 1).

Over half of the 1425 confirmed positive pregnancies were in European-born women (Table 1), of whom 39% (268/687) were born in Eastern Europe. Most women had previously been pregnant (Table 1), 88% (927/1058) of whom had previous live or still births. About 6% (81/1271) had their first antenatal appointment in the third trimester (at 27 weeks gestation or later), and 9% were reported to have screened positive for HIV, hepatitis B, and/or hepatitis C virus in pregnancy (Table 1). In about 5% of confirmed positive pregnancies (76/1425), respondents spontaneously reported that women did not attend antenatal or genitourinary medicine (GUM) appointments, had poor adherence to syphilis treatment, and/or had complex or adverse social circumstances (e.g. drug or alcohol use, immigration or housing problems, domestic violence, prison); often these factors were

reported as reasons for problems with referral or follow up, or to explain why information was not available.

There was wide variation by region in the proportion of false positives (23% overall, Figure 1), from less than 10% in about half of UK countries or regions, to 32% in London (270/849) and 56% in Scotland (46/82). Few false positives were reported as due to other treponemal infections (*n*<15).

Previously diagnosed syphilis infection

Among 1010 pregnancies in women with previously diagnosed syphilis, 31% (313/1010) overall and 36% (290/816) of those with previous pregnancies were reported to have been diagnosed during an earlier pregnancy, a median of three years prior to the current booking (interquartile range (IQR): 2, 5 years; *n*=283 overall). Most women with previously diagnosed syphilis (85%, 855/1010) were reported not to require treatment in the current pregnancy; however, treatment was advised for 15% (Figure 1), mainly because of inadequate documentation of previous treatment (other reasons included: previous treatment incomplete, loss to follow-up or miscarriage before treatment could be offered in a previous pregnancy, and possible reinfection and/or positive EIA IgM test in the current pregnancy). Among women with previously diagnosed syphilis, 79% (711/898) were referred to a GUM clinic for assessment (information missing for 112/1010). Among 187 women who were not referred, possible reasons included miscarriage or termination (*n*=9), loss to follow up or lack of engagement with care (*n*=7) and multiple care providers (*n*=7). However, for most, no reason was given for lack of referral.

Newly diagnosed syphilis infection

All 374 women with newly diagnosed syphilis required treatment in pregnancy, and virtually all were referred to a GU physician (two women were not referred owing to difficult circumstances). Syphilis disease stage was reported for 73% (273/374) of these women: 14% (39/273) were reported to have

primary, 4% (12/273) secondary, 14% (38/273) early latent, 66% (181/273) late latent, and 1% (3/273) late symptomatic/tertiary infection.

Treatment

Overall, 40% of confirmed positive pregnancies (570/1425) were in women who required treatment for syphilis in pregnancy (Figure 1); 96% were reported to have received treatment but 21 women were not treated (Table 2). Most treated women (89%) were prescribed benzathine penicillin, and median gestation at treatment initiation was 17.4 weeks (IQR: 14.2, 23.8 weeks; *n*=456). Treatment occurred in the third trimester in 18% of pregnancies (Table 2), and was more likely to be delayed in women born in European countries outside the UK (26%, 32/124) than in UK-born women (12%, 15/130, *p*=0.006). Median time since arrival in the UK among women born abroad was significantly shorter for those treated in the third trimester than for those treated in the first or second trimester (1 year, IQR: 0, 3 years, *n*=35, versus 3 years, IQR: 1, 7 years, *n*=113, *p*<0.001), but year of arrival was poorly reported (see Table 1). Among women treated in the third trimester, first antenatal appointment occurred at a median of 22.4 weeks (IQR: 13.0, 31.0 weeks, *n*=82), a median of 9.6 weeks prior to treatment initiation (IQR: 2.7, 19.0 weeks).

Among women receiving benzathine penicillin, 73% received at least three doses (Table 2), most of whom had late latent infection (66%, 209/318) or unreported disease stage (19%, 61/318). Eighty-eight percent of women with late latent syphilis (209/238) received three doses of benzathine penicillin, and 10 of 11 women with early syphilis treated in the third trimester received two or more doses. Among women with early syphilis infection who received benzathine penicillin before the third trimester, 81% (54/67) received more than one dose, even though guidelines suggest that one dose is sufficient. Seven of these were specifically reported to require additional doses (e.g. due to reinfection or treatment failure); half of the remainder (23/47) were classified as having early latent syphilis, which may be difficult to distinguish from late latent infection.

An additional five women were reported as having been treated during pregnancy although they did not require it (e.g. as a precaution due to late presentation or at patient request).

According to routine data sources, 691,494 women were screened for syphilis antenatally in 2011 in England[14]; in our study, 851 women had confirmed syphilis and 244 of these required treatment during pregnancy (figures restricted to pregnancies in England in 2011). In other words, for each woman requiring treatment who was identified through the screening programme, approximately 2800 women were screened for syphilis.

Pregnancy outcomes among women requiring treatment

Outcome details were sought for all 570 pregnancies in women reported to require treatment (Figure S1). There were 10 stillbirths; no evidence of congenital syphilis was found at post-mortem in five, including three where other causes were identified (e.g. congenital anomalies); for the other five no further details were available.

Deliveries occurred between July 2010 and March 2012. Among the 477 pregnancies with information on delivery (including five twin births) (Figure S1), 10% were delivered by elective caesarean section (45/454), 21% (97/454) by emergency caesarean section, and 69% (312/454) vaginally. For singleton live births, the preterm delivery rate (<37 weeks gestation) was 8% (32/419; 95% confidence interval (CI), 5-11%), similar to that in the general population (6.2% in England in 2005, *t*-test p=0.22)[13]. Median birth weight was 3.3 kg (IQR: 3.0, 3.6 kg), and 10% of infants weighed <2.5 kg (41/431, 95% CI: 7%-13%), significantly higher than the general population (6.1% in England in 2005, *t*-test p=0.004)[13].

For 26% (125/482) of live born infants (including the five sets of twins), paediatric follow up forms were not returned. Furthermore, where forms were received, 18% (64/357) of infants were lost to follow up (e.g. moved away, failed to attend appointments, family declined follow up, etc), and another 15% (53/357) had no paediatric follow up, 20 reportedly because the mother had been

adequately treated. Among infants whose mothers had newly diagnosed syphilis in pregnancy, 15% (36/240) were lost to follow up and 8% (19/240) were reported not to have been followed up.

Six infants born to women who required treatment in pregnancy were diagnosed with congenital syphilis: four of the mothers received incomplete and/or delayed treatment (one received partial treatment in the first trimester, and three were treated in the third trimester only), but two were untreated; four of the six infants were preterm. One additional infant, whose mother was reported to this study as previously diagnosed and adequately treated (therefore not followed up further) was subsequently reported to the BPSU study as having congenital syphilis, likely as a result of maternal reinfection.

Discussion

Main findings

Over 1900 pregnancies in women screening positive for syphilis in pregnancy in 2010-2011 were reported in this UK study. Among the 1425 pregnancies with confirmed syphilis, about a quarter were in women with newly diagnosed infection, and over two thirds (71%) had a previous syphilis diagnosis; of the latter, most were seen by a GU physician, and about 15% were reported to have required treatment in pregnancy. Our findings suggested that among women with a previous syphilis diagnosis, about a third had been diagnosed in a previous pregnancy, reflecting the high uptake of antenatal screening over previous years.[15] About 40% of confirmed syphilis-positive pregnancies were in women requiring treatment, two thirds due to a newly diagnosed infection, and 96% were treated. Most women with late latent syphilis infection (88%) received three doses of benzathine penicillin, in line with UK guidelines.

Strengths and limitations

This study was the first national evaluation of the antenatal syphilis screening programme in the UK. High response rates were achieved, and the number of pregnancies reported corresponded closely with the number expected for 2010-2011 based on routine data (~1000/year).[10, 14] Despite good case ascertainment, miscarriages and pregnancy terminations in syphilis-positive women were probably under-ascertained, as the study only included women accessing antenatal care. In order to avoid missing cases, we invited respondents to report all syphilis screen-positive pregnancies including false positives; these accounted for almost a quarter of reports, with wide variation across the country, partly due to an incident involving IgM test kits used in some laboratories.[16] We were also aware of differential reporting of false positive results by unit, with some respondents providing these figures and others not, an issue that may also arise in routine data sources.

Interpretation

This study suggested that for every case of syphilis identified and treated, about 2800 women were screened. Although this number may seem high, antenatal syphilis screening combined with treatment has been shown to be cost-effective even in low-to-moderate prevalence settings [17] and its high uptake (>97%) suggests that it is acceptable to pregnant women. Furthermore, the UK antenatal syphilis screening programme was reviewed in 2013, with a recommendation that screening should continue in light of ongoing transmission among women of reproductive age, and the balance of benefits to harm.[18]

We identified 570 women requiring treatment for syphilis in pregnancy over two years (~285/year), at least two thirds with undiagnosed infection who would likely have remained untreated in the absence of screening, with a risk of onward transmission to their babies and sexual partners. In a previous survey among GU physicians, 139 similar cases were identified over three years (1994-1997, ~46/year), with 70% response rate (lower than in our study).[19] Although methods differed (the

previous survey excluded women seen only by their obstetricians), the increase is in line with the rise in infectious syphilis in women observed since 1999. Although diagnostic and treatment information was obtained for most pregnancies, it was clear that links between maternity and GUM services were not always satisfactory. Contrary to national standards,[9] key information on diagnosis and treatment was not always known to maternity teams, even after delivery, and despite repeated requests for information, 5% of confirmed screen-positive pregnancies remained unclassified. Although women with newly diagnosed infections were almost all referred to a specialist, about 20% of previously-diagnosed women were not, even though all screen-positive women should be evaluated by a GU physician;[6, 9] in addition, basic information on whether referral had occurred was missing for 11%.

Current UK management guidelines also recommend that infants born to women treated for syphilis during or before pregnancy should be monitored.[6] This study showed that even infants with newly-diagnosed mothers were not always followed up. Where further appointments were planned, these were not always attended, suggesting issues around retention in care. Despite improvements in follow up of mothers and infants since earlier audits,[11] our findings highlighted some inadequacies and inconsistencies in the management and follow up of pregnancies in syphilis-positive women, which could potentially lead to avoidable cases of congenital infection. Nevertheless, with routine screening in place and high uptake of testing (>97%) and treatment (96%), few cases of congenital syphilis were reported. The timely diagnosis and treatment of several hundred maternal infections will also have prevented other adverse pregnancy outcomes (reported to occur in approximately two-thirds of untreated pregnancies[1]) and transmission to sexual partners, neither of which were measured here.

It was reassuring that over 95% of women reported to require treatment were treated, in line with WHO targets,[4] but the fact that almost one in five women were treated in the third trimester was concerning, given the increased risk of adverse outcomes.[20] Furthermore, three of the cases of

congenital syphilis were associated with delayed maternal treatment and two with lack of treatment. Treatment in the third trimester was associated with being born abroad and more recent arrival in the UK. However, over half of women treated in the third trimester experienced a delay of almost 10 weeks between first antenatal appointment and treatment initiation, and about a quarter had been in contact with antenatal services in the first trimester. These observations suggest that issues around both access to and engagement with care contributed to treatment delays. The finding that one in 11 syphilis-positive women screened positive for another blood-borne infection and one in 20 (a minimum estimate) had social issues or problems taking up care or treatment highlights the complex healthcare needs of this population. Furthermore, the prevalence of HIV in this population was high, at 4%, compared with 0.22% among all pregnant women in the UK in 2011.[21] The majority of syphilis-positive women in this study were from Eastern Europe, Africa or Asia, areas where historically the prevalence of syphilis has been much higher than in Western Europe, and coverage of antenatal testing and treatment much lower.[1, 22]

Most women in this study should also have been tested for other sexually transmitted infections at their GUM appointment, but full details were not collected here. Although this study was carried out through antenatal clinics and therefore included few miscarriages and terminations, efforts should be made to follow up all pregnant women screening positive for syphilis regardless of pregnancy outcome, particularly as many women will have subsequent pregnancies. It was reassuring that the preterm delivery rate among women treated in pregnancy (8%) was not substantially higher than the general population, although infant birth weight was significantly lower,[13] probably due to socio-demographic and other factors. For syphilis treatment before the third trimester, UK guidelines recommend a single dose of benzathine penicillin for women with early syphilis;[6] however over three quarters of women with early syphilis in this study received two or more doses, possibly reflecting a precautionary approach to treatment.

Conclusions

Despite high uptake of antenatal syphilis screening and treatment in the UK, this study has highlighted areas where management of syphilis could be improved, including earlier diagnosis and treatment of pregnant women, better communication between maternity and GUM services, and more consistent follow-up of exposed infants. Optimal care and management of syphilis-positive women in pregnancy requires a coordinated multidisciplinary approach involving antenatal, GUM and paediatric teams, to ensure that guidelines are followed, and testing, referral and treatment are not delayed.

Acknowledgements

We gratefully acknowledge the contribution of the midwives, obstetricians, genitourinary physicians, antenatal and newborn screening coordinators, paediatricians, paediatric secretaries, and all other colleagues who reported to this study, and the Regional Antenatal and Newborn Screening Teams for supporting this work. We also thank Barry Evans, Beng Goh, Cathy Ison, and Hermione Lyall, for helping with the development of this study; Ian Simms, for helping with the development of the study and providing data from the BPSU study of congenital syphilis; Sharon Webb, Programme Manager, Public Health England (PHE) National Health Service (NHS) Infectious Diseases in Pregnancy Screening Programme, for facilitating the study; Icina Shakes and Cathy Long for administrative support; and Laura Byrne, Nigel Field and Helen Fifer for their helpful comments on drafts of this paper. We would also like to acknowledge the invaluable contribution of our colleague Janet Masters, who died in December 2012.

Disclosure of interests. Dr. Tookey reports grants from the PHE NHS Infectious Diseases in Pregnancy Screening Programme, during the conduct of the study; grants from Public Health England, grants from AbbVie Inc, grants from the PHE NHS Infectious Diseases in Pregnancy Screening Programme, grants from PENTA Foundation, grants from IATEC/Kendle/IncResearch (CROs) - for Antiretroviral Pregnancy Registry, outside the submitted work; and Member of National Screening Programme's Antenatal Screening Advisory Groups (advisory, unpaid). Dr. Townsend reports grants from the PHE NHS Infectious Diseases in Pregnancy Screening Programme, during the conduct of the study; grants from The Wellchild Trust, grants from The Wellcome Trust, outside the submitted work. Dr. Peckham and Ms. Francis have nothing to disclose.

Author contributions. CP and PAT developed the concept of and designed the study. CLT coordinated the study, carried out the statistical analyses and drafted the paper. CLT and KF

collected the data. PAT and CLT contributed to developing the concept of the paper. All authors contributed to interpreting the results and critically revising the paper, and saw and approved the final version. PAT is the guarantor.

Ethics approval. The study was reviewed and approved by the London Multi-Centre Research Ethics Committee on 7th October 2009 (MREC/09/H0718/45).

Funding. This work was supported by the PHE NHS Infectious Diseases in Pregnancy Screening Programme. The work was undertaken in the Population, Policy & Practice Programme at the Institute of Child Health, University College London (UCL), which previously benefited from funding support from the Medical Research Council (MRC) in its capacity as the MRC Centre of Epidemiology for Child Health (grant number G0400546). The UCL Institute of Child Health receives a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The views expressed in this paper are those of the authors and not necessarily those of the funders.

Presentation. These findings were presented at the Public Health England Conference, September 2013, University of Warwick, UK (Poster 152); the 'Population Health – Methods and Challenges' Conference, April 2012, Birmingham, UK; and the British Association of Sexual Health and HIV Spring Meeting, May 2011, Newcastle, UK (Abstract P51).

Reference List

1. Newman L, Kamb M, Hawkes S, Gomez G, Say L, Seuc A*, et al.* Global estimates of syphilis in pregnancy and associated adverse outcomes: analysis of multinational antenatal surveillance data. *PLoS Med.* 2013;10(2):e1001396.

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;91(3):217-226.

3. De Santis M, De Luca C, Mappa I, Spagnuolo T, Licameli A, Straface G*, et al.* Syphilis Infection during pregnancy: fetal risks and clinical management. *Infect Dis Obstet Gynecol.* 2012;2012:430585.

4. World Health Organization. *Elimination of mother-to-child transmission (EMTCT) of HIV and syphilis. Global guidance on criteria and processes for validation*. Geneva, Switzerland: World Health Organization, 2014. Available at: http://www.who.int/reproductivehealth/publications/rtis/9789241505888/en/ (Accessed 7 May 2015).

5. Galvao TF, Silva MT, Serruya SJ, Newman LM, Klausner JD, Pereira MG*, et al.* Safety of benzathine penicillin for preventing congenital syphilis: a systematic review. *PLoS One.* 2013;8(2):e56463.

6. Kingston M, French P, Goh B, Goold P, Higgins S, Sukthankar A*, et al.* UK National Guidelines on the Management of Syphilis 2008. *Int J STD AIDS.* 2008;19(11):729-740.

7. Public Health England. *Syphilis and Lymphogranuloma Venereum: Resurgent Sexually Transmitted Infections in the UK: 2009 report*. 2009. Available at: https://www.gov.uk/government/publications/syphilis-and-lymphogranuloma-venereum-lgv-resurgent-sexually-transmitted-infections-in-the-uk (Accessed 7 May 2015).

8. Public Health England. *Infectious syphilis and congenital syphilis: recent epidemiology*. Health Protection Reports, 2013; 7(44). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/336760/hpr4413_sphls.pdf (Accessed 7 May 2015).

9. UK National Screening Committee. *Infectious Diseases in Pregnancy Screening Programme: Programme Standards*. 2010. Available at: infectiousdiseases.screening.nhs.uk/standards (Accessed 20 January 2014).

10. Public Health England. Antenatal screening for infectious diseases in England: summary report for 2014. *Health Protection Report - Infection Reports.* 2015;9(43).

11. Cross A, Luck S, Patey R, Sharland M, Rice P, Chakraborty R. Syphilis in London circa 2004: new challenges from an old disease. *Arch Dis Child.* 2005;90(10):1045-1046.

12. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Trends in management and outcome of pregnancies in HIV-infected women in the UK and Ireland, 1990-2006. *BJOG.* 2008;115(9):1078-1086.

13. Moser K, Stanfield KM, Leon DA. Birthweight and gestational age by ethnic group, England and Wales 2005: introducing new data on births. *Health Stat Q.* 2008(39):22-55.

14. NHS Infectious Diseases in Pregnancy Screening Programme. *2011-12 Summary Report*. 2013. Available at: http://infectiousdiseases.screening.nhs.uk/publications (Accessed 15 July 2015).

15. Public Health England. Antenatal screening for infectious diseases in England: summary report for 2013. *Health Protection Report - Infection Reports.* 2015;8(43).

16. Public Health England. *False positive treponemal (syphilis) IgM enzyme immunoassay results: Adverse incident report*. 2013. Available at: https://www.gov.uk/government/publications/false-positive-treponemal-syphilis-igm-enzyme-immunoassay-results-adverse-incident-report (Accessed 7 May 2015).

17. Walker DG, Walker GJ. Forgotten but not gone: the continuing scourge of congenital syphilis. *Lancet Infect Dis.* 2002;2(7):432-436.

18. UK National Screening Committee. *Screening for syphilis in pregnancy: External Review against programme criteria for the UK National Screening Committee (UK NSC)*. 2013. Available at: http://legacy.screening.nhs.uk/syphilis (Accessed 23 February 2016).

19. Hurtig AK, Nicoll A, Carne C, Lissauer T, Connor N, Webster JP*, et al.* Syphilis in pregnant women and their children in the United Kingdom: results from national clinician reporting surveys 1994-7. *BMJ.* 1998;317(7173):1617-1619.

20. Hawkes SJ, Gomez GB, Broutet N. Early antenatal care: does it make a difference to outcomes of pregnancy associated with syphilis? A systematic review and meta-analysis. *PLoS One.* 2013;8(2):e56713.

21. Health Protection Agency. *Data Tables of the Unlinked Anonymous Dried Blood Spot Survey of Newborn Infants - Prevalence of HIV in Women Giving Birth*. 2012. Available at: http://webarchive.nationalarchives.gov.uk/20140722091854/http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287144874352 (Accessed 17 June 2015).

22. World Health Organization. *The global elimination of congenital syphilis: rationale and strategy for action*. 2007. Available at: http://www.who.int/reproductivehealth/publications/rtis/9789241595858/en/ (Accessed 12 December 2015).

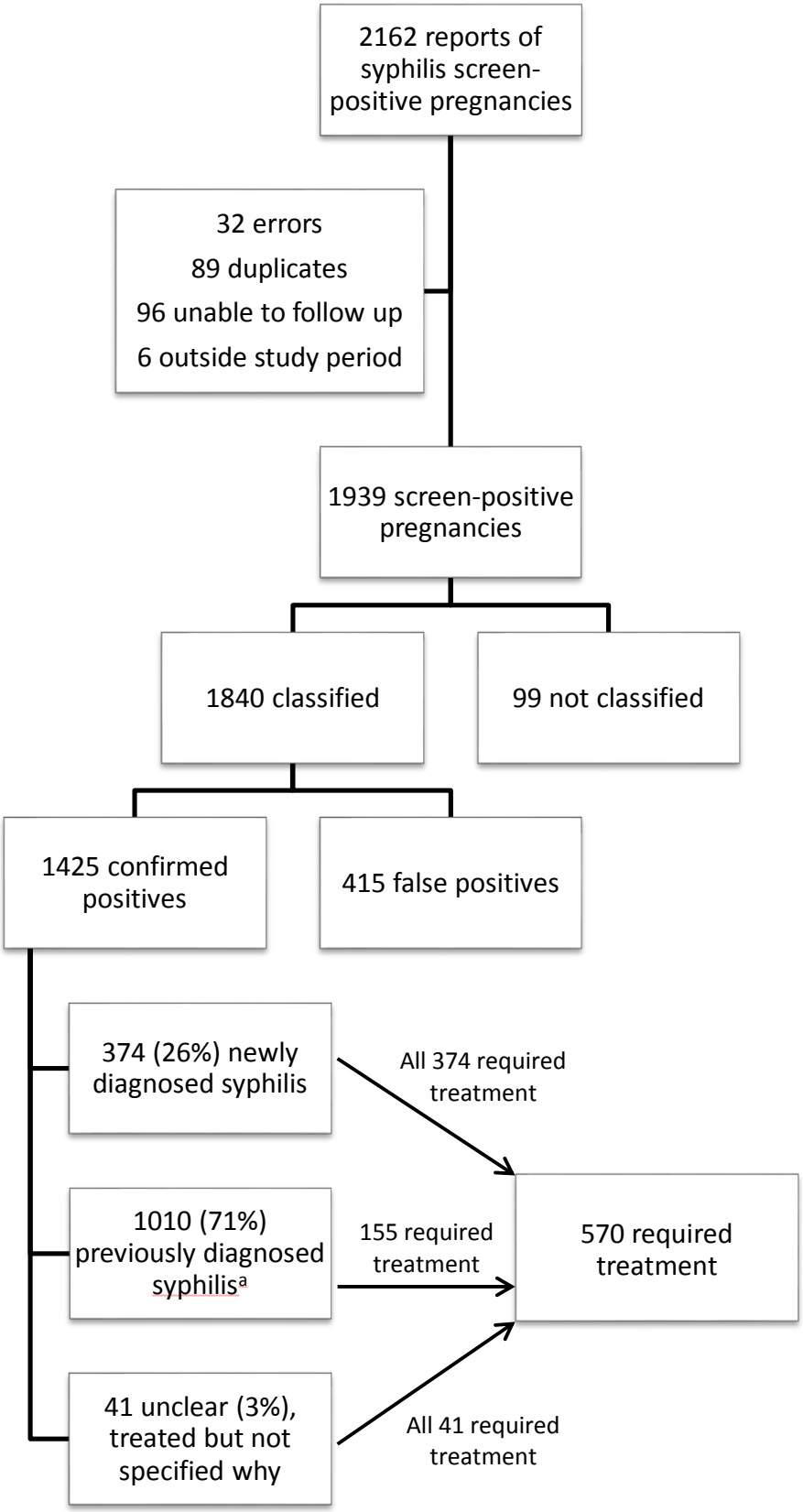
2162 reports of syphilis screen-positive pregnancies
32 errors
89 duplicates
96 unable to follow up
6 outside study period
1939 screen-positive pregnancies
1840 classified
99 not classified
1425 confirmed positives
415 false positives
374 (26%) newly diagnosed syphilis
All 374 required treatment
1010 (71%) previously diagnosed syphilis[a]
155 required treatment
570 required treatment
41 unclear (3%), treated but not specified why
All 41 required treatment

Figure 1. Reports of syphilis screen-positive pregnancies in the UK, 2010-2011.[a] Includes those adequately treated requiring no further treatment, and those requiring treatment due to inadequate documentation of previous treatment (e.g. no previous treatment, incomplete or uncertain treatment) or suspected re-infection.

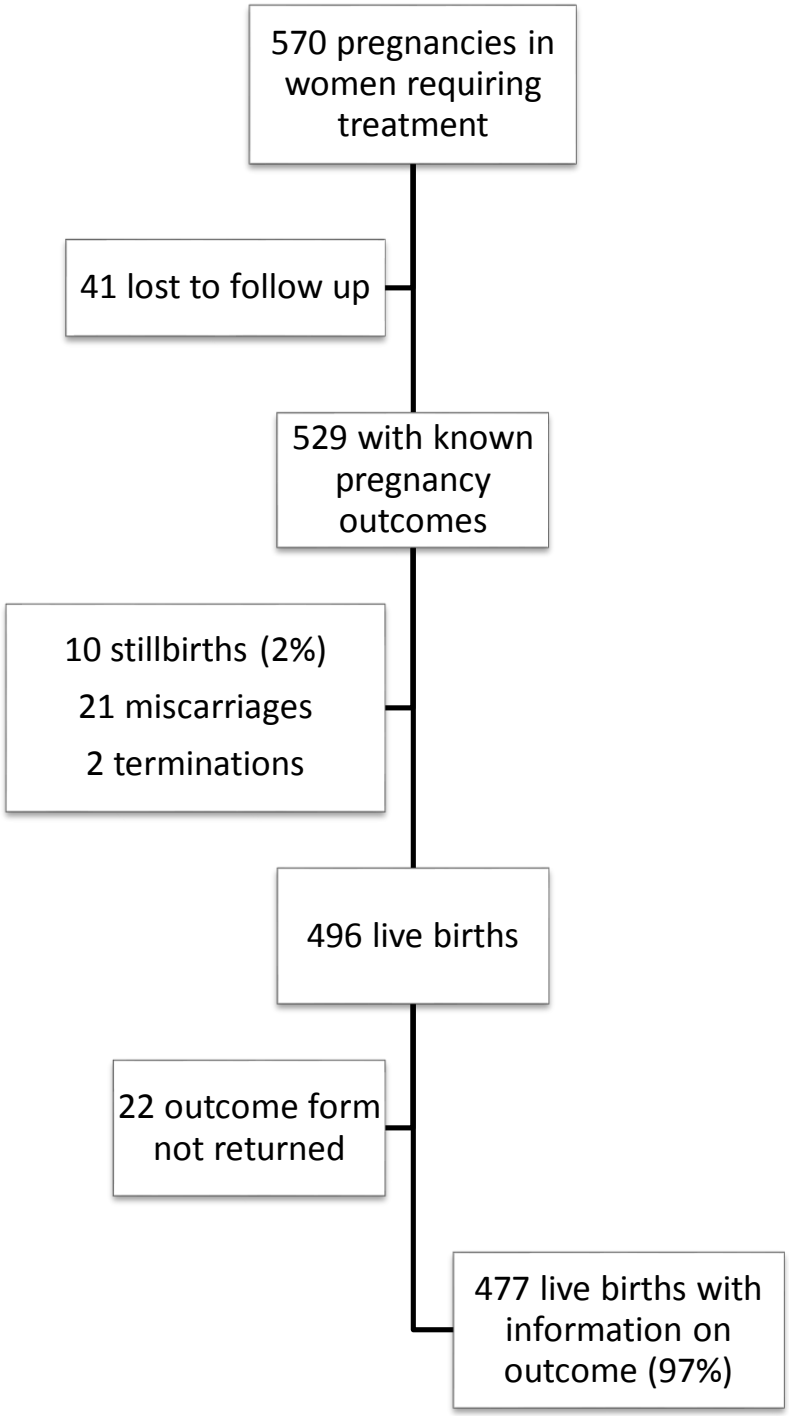

Figure S1. Follow up of women requiring treatment for syphilis in pregnancy, 2010-2011.

Table 1. Baseline characteristics of 1425 pregnancies in 1394 women with newly or previously diagnosed syphilis infection in the UK, 2010-2011

	n	%
Maternal ethnic group (*n*=1348)		
White	667	49
Black	436	32
Asian	188	14
Other	28	2
Mixed	29	2
Maternal region of birth (*n*=1266)		
Europe	687	54
British Isles	*377*	*30*
Eastern Europe	*268*	*21*
Elsewhere in Europe	*42*	*3*
Africa	310	24
Asia	164	13
Other	105	8
Previous pregnancies (*n*=1292)		
None	234	18
One	331	26
Two or more	727	56
Previous syphilis diagnosis (*n*=1384) [a]		
No	374	27
Yes	1010	73
Other positive screening tests in pregnancy (*n*=1248) [b]		
HIV	51	4
Hepatitis B virus	52	4
Hepatitis C virus	24	2
At least one of the above	115	9
	Median (IQR)	
Maternal age (*n*=1419)	31.4 (27.0, 35.5)	
Years since arrival in the UK [c] **(*n*=373)**	5 (1, 9)	
Years since previous syphilis diagnosis [d] **(*n*=722)**	4 (2, 7)	
Gestation at antenatal booking (*n*=1271)	11.7 (9.9, 15.1)	

[a] 41 women required treatment for syphilis in pregnancy, but it was unclear whether they had been previously diagnosed (see Figure 1).

[b] Categories are not mutually exclusive; 12 women were reported to have two of the three specified co-infections.

[c] At first antenatal appointment; year of arrival in the UK was only reported for 42% (373/889) of women born abroad.

[d] At first antenatal appointment; year of diagnosis was only reported for 71% (722/1010) of women with a previous syphilis diagnosis.

Table 2. Treatment details for 570 women requiring treatment for syphilis in pregnancy, 2010-2011

	n	%
Treated in pregnancy (*n*=537)		
Yes	516	96
No [a]	21	4
Drugs (*n*=494)		
Benzathine penicillin	439	89
Procaine penicillin	17	3
Erythromycin	15	3
Doxycycline	10	2
Unspecified/other drugs	13	3
Timing of treatment in pregnancy (*n*=456)		
First or second trimester	373	82
Third trimester	83	18
Doses of benzathine penicillin (*n*=433)		
One	66	15
Two	49	11
Three or more	318	73

[a] 10 women declined treatment, three delivered before their GUM appointment and three were diagnosed at or after delivery; for the remaining four, no further information was given.