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A brief recent history of the epidemiology of congenital syphilis in the United Kingdom

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Abstract

Within a century, congenital syphilis has been reduced from a major cause of morbidity and mortality to a condition rarely seen in the UK. Here, newly-derived literature and information searches were used to create a contemporary overview of the epidemic, including its epidemiology. Although constrained by high-quality healthcare services and with an incidence below the World Health Organization elimination threshold, congenital syphilis still has the potential to cause major consequences for the health and life chances of affected infants. If the complex challenges presented by this preventable disease are to be resolved, intervention strategies need to be optimised, rigorously assessed and extended across Europe.

Keywords

Congenital syphilis, epidemiology, screening, public health

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Introduction

The first decade of the 20th century was an age of innovation that offered the tools with which to control congenital syphilis. The discovery of *Treponema pallidum* (1905), the development of the Wasserman serological diagnostic test (1906) and chemotherapeutic treatment (1910) were crucial to understanding the natural history and epidemiology of congenital infection, but subsequent attempts at control were problematic and controversial.[1–3] Here, we explore the epidemiology of congenital syphilis in the UK since the start of the 20th century to understand the reasons for the continued importance of testing for this preventable condition.

Methods

Literature searches were carried out using Medline (PubMed) using keywords 'congenital syphilis' and the names of authors known to have published in this area. Initial investigations showed that the literature was widely dispersed. At the outset of the search, electronic resources were useful, but much of the historical literature was not electronically indexed and consequently references had to be sourced through inter-library loans and searching medical libraries

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using local databases and, in some cases, by hand. For example, a search of the Royal Society of Medicine Library resources was initially undertaken electronically using the above keywords and the names of key authors identified in the initial stages. This was followed by a manual search of the basement. Further documents were identified, reviewed and the process repeated. Experts in the field were also contacted for advice on locating published and unpublished documents, and accessing data sources. The intent of this manuscript was to elucidate the epidemiology of congenital syphilis in the 20th century in the UK. However, few epidemiological studies have been undertaken. Where possible, we have fitted them into this brief presentation and discuss the limitations of the information sources used.

Numerator data

Diagnoses were taken from the Venereal Disease Regulations, SBH60, KC60 & GUMCAD STI Surveillance System.[4] There are a number of sources of bias associated with these datasets. The early datasets did not capture diagnoses managed by private practitioners or outside the Venereal Disease Treatment Scheme (the clinical network created by the Venereal Disease Act, 1917).[5] In addition, many deaths were not attributed to congenital syphilis because of the associated stigma. Although stillbirths were included in national statistics from 1938 (England and Wales), 1939 (Scotland) and 1968 (Northern Ireland), cause of death was not investigated consistently and foetal wastage associated with syphilis was never collected routinely. In addition, knowledge of the clinical presentation of disease has developed over time. For example, the definition of early congenital syphilis was changed from <1 year of age to <2 in 1971 because of increased awareness to the length of time over which complications could develop (VD clinic returns VD(R) and SBH60).

Denominator data. Data for live births were taken from datasets published by the Chief Medical Officer (England and Wales), Registrar General for Scotland; Registrar General for Northern Ireland and the Office of National Statistics. Still births were reported in national statistics from 1938 (England and Wales), 1939 (Scotland) and 1968 (Northern Ireland) and were included in the denominator for the years where available.

Diagnosis

Of the sources of bias within the available evidence base, the main limitation is diagnostic accuracy. The Wasserman test lacked both specificity and sensitivity: it could cross-react with tuberculosis, the other disease that dominated early 20th century life in the UK and could not accurately detect early infectious or congenital syphilis.[6] The Harrison-Wyler method, a modified Wasserman test, was used widely in the UK from 1930, but the two-day incubation period and continued low sensitivity and specificity compromised its use. Quality control was not undertaken between laboratories, and consequently, the geographic variation in positivity seen prior to the 1950s may reflect local variations in diagnostic accuracy. Diagnostic techniques were enhanced with the introduction of Venereal Disease Research Laboratory and rapid plasma reagin tests in 1946 and 1961, respectively, specific treponemal tests (fluorescent treponemal-absorption, *T. pallidum* haem/particle agglutination, enzyme immunoassay and line immunoassay), dark field microscopy and, more recently, polymerase chain reaction-based tests.[7–13] Given these limitations and those of the numerator dataset, it is likely that the true incidence of congenital syphilis has been underestimated.

Clinical presentation of congenital syphilis

Observations from the syphilis outbreaks in Barcelona (1493), Naples (1494) and Rome (1497) suggested that vertical transmission was possible, although infants were assumed to have acquired the infection from wet nurses.[14] Charles-Paul Diday (1812–1894) eloquently described a typical case as 'a little, wrinkled, pot-bellied old man with a cold in his head', the simplicity of which belies the complex clinical presentation that ranges from asymptomatic to multi-system damage.[14,15] Clinical presentation is divided into two stages: early (under 2 years of age) and late (age 2 or over). The early and late clinical stigmata (signs) together with differential diagnoses of early infection are shown in Table 1.

Familial clustering of diagnoses known as Kassowitz's 'law', also noted by Sir Jonathan Hutchinson (1828–1913), was seen in the pre-antibiotic era.[16,17] Briefly, pregnancies which coincided with congenitally-transmissible untreated maternal infection (primary, secondary and early latent infectious syphilis) frequently ended in miscarriage or stillbirth and infants that were born experienced severe illness and high mortality rates. Pregnancies that coincided with later stages of syphilis were associated with congenital syphilis manifesting in childhood with various deformities including deafness. Healthy pregnancies and children might result some considerable time after the acquisition of syphilis infection by the mother. However, re-infection, and partial treatment and

Table 1. Clinical manifestations of congenital syphilis: symptoms, signs and differential diagnoses of early infection.

Early onset (<2 years of age) (most aged <3 months at diagnosis)	Late onset (≥2 years of age)
Premature delivery	Bones
Growth retardation	Frontal bossing, saddle nose, saber shins,
Hydrops fetalis	Clutton's joints – chronic painless knee swelling
Rhinitis and nasal discharge – 'snuffles'	
Blood abnormalities: anaemia, thrombocytopaenia, neutrophilia and leucoerythroblastic presentation	Teeth
	Hutchinson's peg-shaped notched central incisors[a], mulberry multicusped first molars
Rash	
Desquamation, especially palms and soles	Skin
Condylomata lata	Rhagades (linear scars fanning out from the angles of the mouth)
Bony abnormalities: metaphysitis; periostitis; osteitis – often symmetrical, usually long bones (legs) – may be painful and cause 'pseudoparalysis'	
Generalised lymphadenopathy	
Hepato-splenomegaly	Eyes
Hepatitis/jaundice	Interstitial keratitis[a]
Neurosyphilis (asymptomatic with abnormal CSF; acute leptomeningitis – usually three to six months of age; chronic meningovascular – usually 9–12 months of age)	Neurology
	Mental motor and sensory deficits
	Sensorineural hearing impairment
Eyes (loss of eyebrows, chorioretinitis, uveitis, cataract, glaucoma)	
Myocarditis (rare)	
Pneumonitis (rare)	
Nephrotic syndrome (rare)	
Differential diagnoses of congenital syphilis	
Congenital infection with another organism, such as toxoplasma, cytomegalovirus and rubella	
Sepsis	
Malignancy	
Metabolic disease	

[a]'Hutchinson's Triad' of defects unique to congenital syphilis (see text).

immunity meant that many exceptions to Kassowitz's 'law' were seen.[18]

Quantifying disease burden

Prior to the 20th century the absence of an identified aetiological agent or serological tests meant that the clinical presentation, pathology and epidemiology of congenital syphilis were difficult to establish. Several children's hospitals were founded in the late 19th century including Great Ormond Street Hospital (1852), the Victoria Hospital for Sick Children (1866), Evelina Hospital for Sick Children (1869), Belfast Hospital for Sick Children and the Ulster Hospital for Children (1873) and Royal Hospital for Sick Children, Glasgow (1882). The first dedicated children's hospital in Wales opened in 2005. Opportunistic cohorts based on attendances at Great Ormond Street and other specialist institutions provide glimpses into the epidemic but the first attempt at quantifying the burden of disease associated with late congenital disease was the case definition proposed by Hutchinson in 1861.[17,19,20] 'Hutchinson's triad' consisted of three clinical features: eighth cranial nerve deafness; notched, widely spaced peg-shaped upper central incisors and interstitial keratitis.[17] During his career, Hutchinson is reputed to have seen around one million such cases in London.[21] The first epidemiological study of congenital syphilis was conducted by Fildes (1882–1971) between March and July 1914 amongst the population living within a one-mile radius of The London Hospital (now The Royal London Hospital), Whitechapel, East London.[22]

Charles Booth's study of the London sought to understand the lives of Londoners through their places of work and working conditions, their homes and urban environments.[23] The Poverty Maps highlight the diverse socio-economic circumstances of the population within Fildes' study area which ranged from 'well to do middle class' to 'vicious, semi criminal class'. However, only married couples from the 'respectable labouring classes' with a postal address were invited to take part.[22] The 10% of the population that lived in slums were overlooked and, like Charles Booth (1840–1916), Fildes ignored the destitute who

relied on sex work to survive on the streets. The overall incidence of congenital syphilis was 0.59% (4/677). The case definition used was solely based on clinical presentation and the denominator consisted of 660 infants examined at birth; seven infants stillborn and examined at birth only; ten infants dead and examined at birth only. A positive Wasserman reaction was seen in 3.99% (27/677) of women. But given the participation bias and the test characteristics, the findings are unlikely to reflect the true incidence of disease. The considerable impact of mother-to-child transmission was illustrated by a study amongst 'the poorest section of the London community' conducted at the West London Hospital in 1917.[24] Harman (1869–1945) contrasted pregnancy outcomes and infant deaths during the first year of life in 150 women with syphilis (cases) with 150 mothers who were considered to be healthy (controls). Cases had more pregnancies (1001) than controls (826) but gave birth to 390 (39%) healthy children compared to 654 (79%) of controls. Amongst cases, 611 (61.1%) pregnancies ended in miscarriage, still birth, infant death and syphilitic disease compared with 172 (21%) in the control group.

Intervention in the early 20th century

Since syphilis was first recognised, attempts to control the disease through a mixture of blame, shame, social stigma, intolerance, quarantine, incarceration, forced treatment, legislation and ineffective therapy had failed.[25] At the beginning of the 20th century, one-fifth of the European urban population were infected and congenital syphilis was common. The Report of the Royal Commission (1916) concluded that the threat to public health posed by venereal disease (VD) could only be addressed effectively through state intervention offering confidential services that utilised the most recent advances in diagnostics and therapy together with partner notification free at the point of care.[26] The Venereal Diseases Act which created the specialist clinic network was passed in June 1917. Awareness of the new services was raised through advertisements, public engagement and education. Other interventions were also considered including the removal of infected women from maternity wards to specialist antenatal and post-natal therapy. The first was established by the Local Government Board in 1917 at Thavies Inn (the offices of a legal association), Holborn and accommodated 20 women together with an out-patient department. But, as syphilis diagnoses rose from 26,912 (1918) to peak at 42,805 (1920), demand swamped services (Figure 1).

Trends in diagnoses of congenital and infectious syphilis, early 20th century. The high burden of diagnoses of infectious syphilis observed at the establishment of the VD service fell gradually during the 1920s and 1930s (Figure 1). In contrast, infant mortality fell quickly, a trend brought

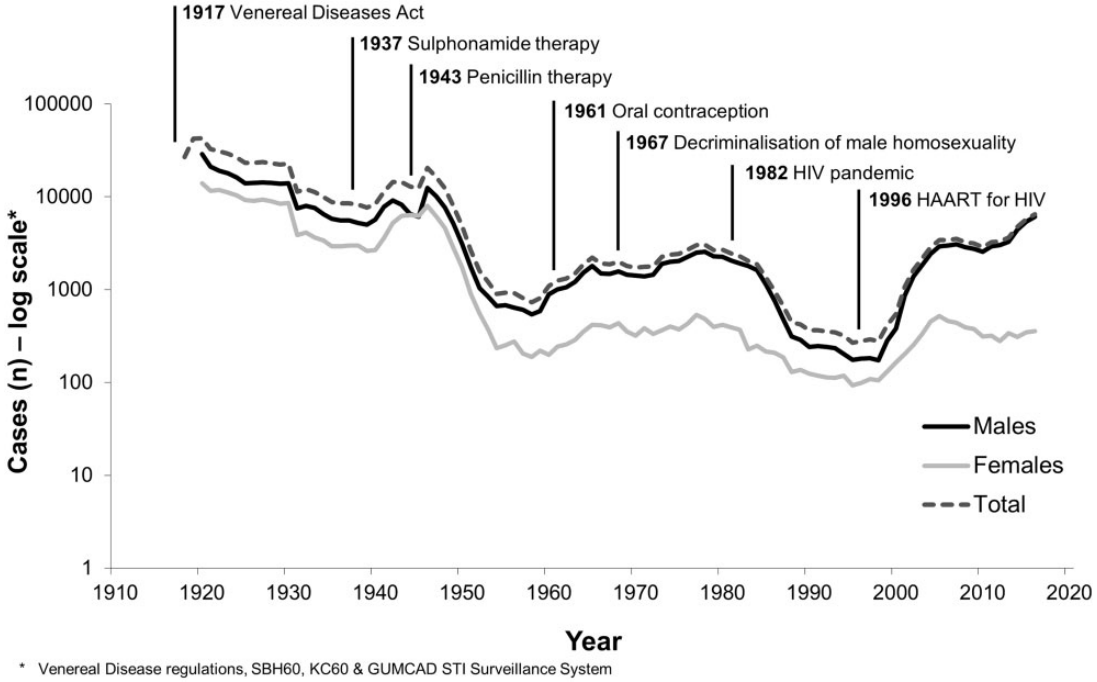

Figure 1. Diagnoses of infectious syphilis, England, Wales and Scotland: 1918 to 2015.
HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus.

about by falling fertility rates, increased educational attainment, improved nutrition and better living conditions.[27] Deaths attributed to congenital syphilis followed this trend, but congenital syphilis remained a major cause of morbidity (Figures 2 and 3). The high incidence of congenital syphilis seen in Scotland compared to England and Wales (Figure 3) has been attributed to the high level of case ascertainment achieved by the Glasgow Corporation Antenatal Clinics.[28] Nationally at least 16,000 pregnant women needed to be treated each year, a gap in syphilis control that was gradually closed as local demands from the public, midwives and general practitioners were addressed.[29] The Glasgow scheme, which started in 1924, was amongst the first local screening initiatives. As well as providing insight into the true incidence of disease, the schemes were successful in preventing foetal infection: diagnoses in Glasgow fell from 335 (1922) to 113 (1928) and 32 in 1942.[28] In 1928, the Medical Society for the Study of Venereal Disease, now British Association for Sexual Health and HIV, suggested that antenatal testing and treatment should be routinely available.[28] Screening was delivered by maternity, child welfare and VD services linked by short clinical pathways. Patients diagnosed with infectious syphilis and their partners were treated with Salvarsan (arsphenamine) and supported by health visitor-led health education.[28,30] Neosalvarsan alone or in combination with bismuth administered before and during pregnancy was effective, resulting in the birth of non-syphilitic children in 98% of pregnancies.[30] However, Salvarsan was difficult to dilute and the injections were painful. Side effects included nausea, vomiting, abdominal pain, diarrhoea, chills, fever and headache. Maternal deaths also occurred.[30] Although antenatal screening for syphilis was emerging as a crucial method of control, its public health impact was restricted by a shortage of serologists.[31] This, together with the increase in infectious syphilis through the Second World War and the pressure on the healthcare budget from the war economy, resulted in an increase in diagnoses of congenital syphilis and infectious syphilis (Figures 1 and 2).

The antibiotic era

Trends in diagnoses of congenital and infectious syphilis, mid- to late-20th century. The introduction of penicillin in 1943 led to a sharp fall in the incidence of infectious syphilis in adults and in infant deaths attributed to congenital syphilis (Figures 1 and 2).[32] Reduction in the burden of syphilis led to suggestions that the venereology specialty would quickly disappear, as had been speculated after the introduction of sulphonamides in 1937[33] (Figure 1). However, the continued incidence of infectious syphilis indicated gaps within the coverage of prenatal care delivery systems and intervention strategies aimed at adults. Over the subsequent decades, diagnoses of infectious syphilis fluctuated, influenced by a variety of factors including the introduction

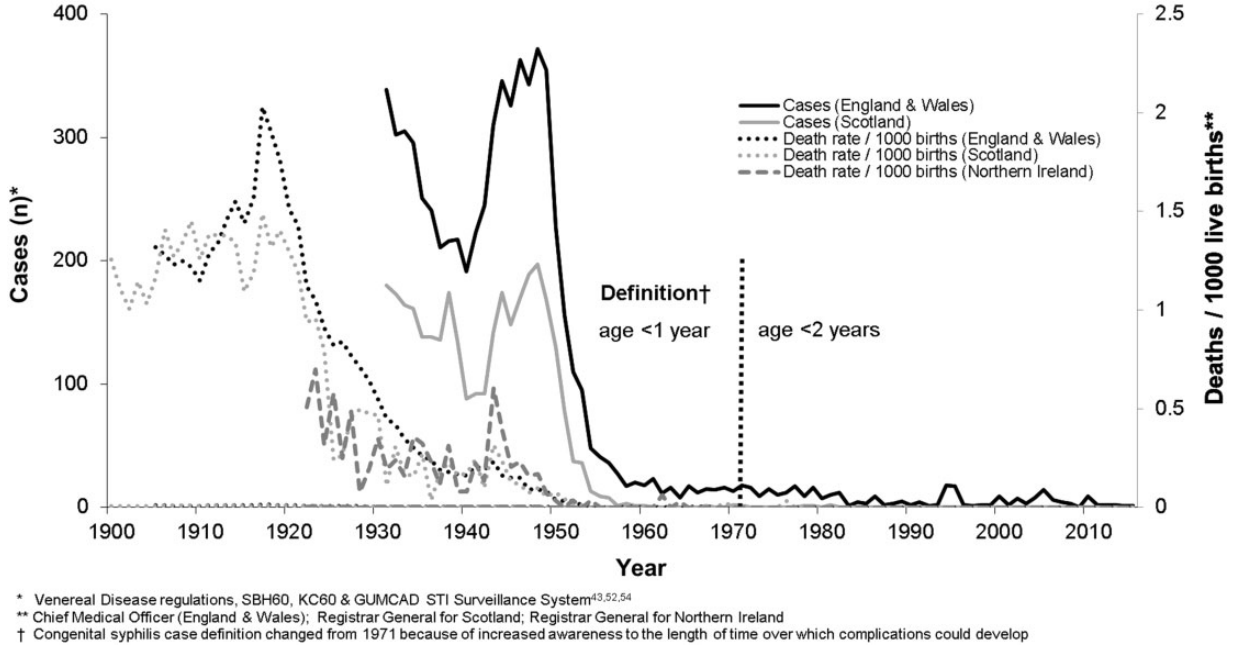

Figure 2. Congenital syphilis: diagnoses and deaths, England, Scotland, Wales and Northern Ireland: 1906 to 2016.

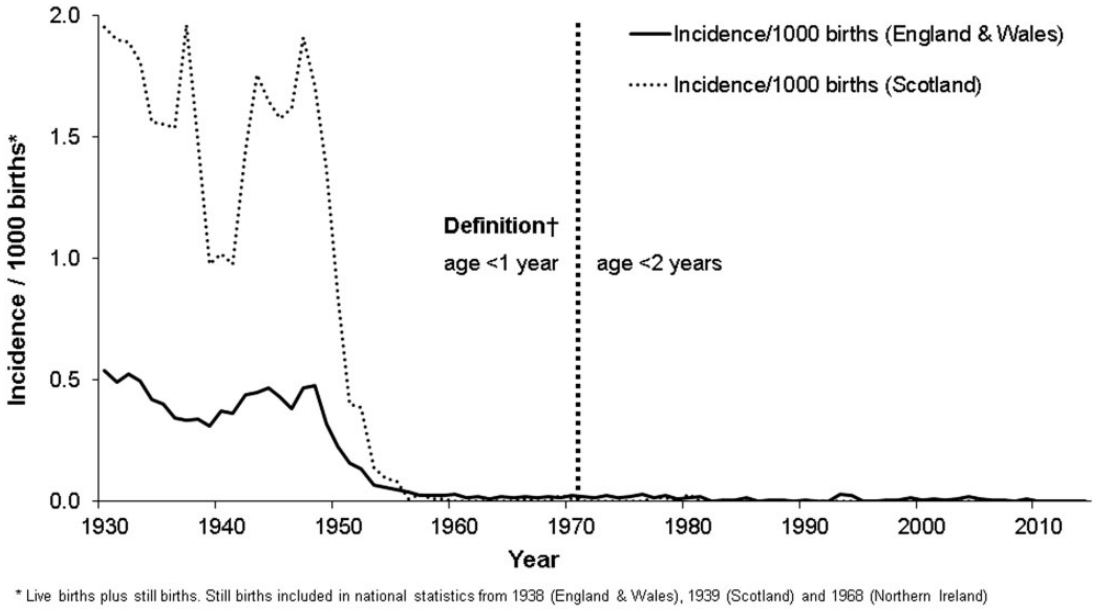

Figure 3. Incidence of congenital syphilis, England, Wales and Scotland: 1931 to 2016.

of oral contraception (1961), decriminalisation of male homosexuality (1967), the emergence of the HIV pandemic (1982) and the introduction of effective highly active antiretroviral therapy for HIV (1996) (Figure 1).

Antenatal screening for syphilis. Serological screening for antibodies to *T. pallidum* was included in routine antenatal care in the 1950s. But, as was shown in the investigation of a cluster of syphilis cases in Northern Ireland (1978–1980), diagnosis of congenital syphilis is dependent on attendance at clinical services and effective partner notification.[34] Unfortunately, a national assessment of the need for and effectiveness of antenatal screening for syphilis was not undertaken.[35] The only national recommendation to screen pregnant women for syphilis was made by the Public Health Laboratory Service (now Public Health England [PHE]) in 1990.[36] No policy, programme standards or quality assurance mechanisms were published, and antenatal screening for syphilis was only integrated with other antenatal screening programmes to the extent that they were undertaken on the same blood specimen.[36,37] Nevertheless by 1997, almost all health authorities had a policy of universal syphilis screening.[38,39] In 2010, a formal programme was established for Infectious Diseases in Pregnancy Screening (IDPS) as part of the wider antenatal and newborn screening programmes with national standards, guidance, governance and quality assurance processes for England.[40]

The re-emergence of syphilis

By the 1990s, syphilis had become a rarity, annual diagnoses of infectious syphilis seen in GUM services in the UK having stabilised at around a hundred per annum (Figure 1).[41] Between 1988 and 1996, 37 cases of early congenital syphilis were diagnosed in England and Wales, around four each year.[36] Syphilis was considered a low public health priority and several health authorities questioned the need for antenatal syphilis screening.[36] The ensuing debate highlighted the lack of knowledge of congenital syphilis epidemiology and the cost-effectiveness of antenatal screening.[35,38] At the time, globally the World Bank considered that antenatal screening was cost-effective at a prevalence of 0.07% (similar to that seen in industrialised countries), the benefit:cost ratio being 2.8.[42] The subsequent three-year study (1994–1997) found 17 cases, an incidence of 0.006/1000.[43] Eight diagnoses were from the Thames region and nine from ethnic minority groups. Seven mothers had not received antenatal care or did so too late to receive treatment. Three children had minor clinical abnormalities.

Phase I of the current infectious syphilis epidemic emerged in the late 1990s influenced in part by the rapidly expanding epidemic within the Russian Federation.[41,44] Insight into the drivers in the congenital syphilis epidemic can be gained from contemporary outbreak investigations. In 1997, three maternally-transmissible infections were detected by antenatal screening as part of the response to an outbreak of heterosexually-acquired syphilis in Bristol.[45] Details

Table 2. Summary of characteristics of reported congenital syphilis cases: 1997 to 2003.

Year	Location	Description of case	Ref
1997	Not known	• Stillbirth caused by congenital syphilis • Mother was a Russian visitor to the UK who had not attended antenatal care in Russia or the UK	PHLS Communicable Disease Surveillance Centre and the PHLS Syphilis Working Group[36]
2000	Peterborough	• Diagnosed during an outbreak investigation based on a 'swingers' heterosexual sex club • Index case identified through routine Blood Transfusion Service screening • Source of infection was sex worker in Warsaw, Poland	CDSC[46]
2002/2003	Walsall	• Seen as part of a cluster of heterosexually-acquired syphilis cases • Mother (sex worker and 'crack' cocaine user) was infected in third trimester and had not attended antenatal care • Infant had signs of hepatosplenomegaly, thrombocytopenia and failure to thrive	Pugh et al.[47]

of the three cases seen between 1997 and 2003 are summarised in Table 2.[36,46,47]

Developing control measures in the 21st century

The UK National Screening Committee recommends systematic population screening in pregnancy for HIV, hepatitis B and syphilis.[48] Screening should be offered and recommended to all pregnant women early in pregnancy to enable timely detection and treatment that can significantly reduce the risk of vertical transmission from mother to child. Women who decline screening for any of the infections should be formally re-offered screening and counselled about the benefits by a member of the multidisciplinary screening team. Women can be tested any time in pregnancy including those considered to be at risk of infection after the booking visit. Despite the high screening coverage (>97% in 2015), concerns were raised about the effectiveness of control strategies.[49] Around nine diagnoses of congenital syphilis were made annually up to 2009 and in some circumstances failures within clinical pathways had prevented effective management.[50,51]

Insight into the changing epidemiology of congenital syphilis was provided by a study undertaken between 2010 and 2015.[52] Clinical presentation varied and was life threatening in some cases. Several mothers were born in Eastern Europe reflecting increased population movement across the European Union. Social marginalisation of migrants through age, social circumstances and drug use had been suggested as contributory to the resurgence of congenital syphilis in Italy.[53] These characteristics were also common to the majority of UK diagnoses. Many mothers had experienced difficulties accessing healthcare and presented to antenatal services close to the time of delivery. Several of the affected children were taken into the care of social services. More recently, six diagnoses were seen in the UK in 2016/2017, including a second trimester intrauterine death in a woman who had not attended first trimester screening. Of the five women screened in early pregnancy, four were syphilis negative indicating that they had acquired infection later in pregnancy.[54] Although this scenario was seen previously, the number recorded in this short time was unusual. Some women had acquired infection later in pregnancy from heterosexual male partners, and the investigation identified social vulnerabilities that were highlighted in previous studies. An ecological analysis indicated that a greater-than-expected proportion of men diagnosed with syphilis in the wider incident areas were behaviourally bisexual, which may have facilitated bridging between sexual networks.

Although the UK incidence is below the World Health Organization (WHO) elimination threshold ($\leq$0.5/1000) and measures of health service provision recommended by WHO have been achieved, congenital syphilis continues to present a complex clinical, social and public health problem.[55] Untreated cases have the potential to cause major consequences for the health and life chances of affected infants. Effective management of all cases of mother-to-child transmission of syphilis is a challenge in the face of difficulties of case detection and the rising incidence of infectious syphilis. Controlling infectious syphilis in men who have sex with men is a priority and should include behavioural interventions, increased testing coverage and frequency

in those at greatest risk. Disease awareness should also be raised amongst heterosexuals and clinicians working outside the main urban centres. In areas where cases have been seen, reviews of care management and pathways, including antenatal services, sexual health services, general practices, high-risk pregnancy units and social services have been undertaken. As a result, services have been developed through the introduction of electronic referral systems, developing patient records to include partner notification, sexual health screening and treatment and follow-up.[56,57]

Antenatal screening in early pregnancy is crucial to disease prevention because the teratogenic effects of transplacental infection are highest at this stage. Late booking at antenatal services can lead to the diagnosis of critical health problems. For infection acquired late in pregnancy, the effectiveness of treatment may also be reduced because of transplacental infection for the same reason. Consequently, efforts to prevent the severe consequences of maternal infection need to focus on treating pregnant women with syphilis sufficiently early in pregnancy.[58] This emphasises the need for early screening, rapid diagnosis and referral for assessment and treatment, and for repeat screening in early third trimester as appropriate in structurally-disadvantaged women. In communities that have low rates of general practice registration and antenatal care attendance local, proactive multi-agency interventions aimed at improving service access for women, their children and sexual partners play a vital role in increasing engagement with healthcare services and case ascertainment. Clinicians also need to be able to identify 'vulnerable' women who may be at risk of missing appropriate interventions and expedite interventions for 'late bookers'.

The cases of congenital syphilis seen in 2016/2017 emphasise the need to maintain sexual health throughout pregnancy and the vital role played by midwives and other healthcare professionals (HCPs) in raising patient awareness to sexual health throughout pregnancy. They also indicate that, as the incidence of infectious syphilis rises, acquisition of maternal infection after a negative antenatal screen becomes an area of increasing concern. The PHE IDPS programme advocates that pregnant women who consider themselves at an increased risk or who change sexual partners can request rescreening at any time. The screening programme is developing a bespoke e-learning package and in-consultation information resource to educate and support midwives and other HCPs in raising awareness to sexual health amongst all women and their partners in pregnancy. The cessation of antenatal screening for rubella led to a focused promotion of MMR vaccinations pre-conceptually and during the postnatal period.[59] This resulted in the production of a patient information leaflet 'Protecting you and your baby from infection' to support midwives in delivering information to women.[60] A similar approach is being considered to increase professional knowledge and awareness of mothers to the risks of acquiring infections including syphilis after a negative screen, signs and symptoms of disease, the reasons why infection can have serious consequences for their pregnancy, and the risk of re-infection. New key performance indicators on screening coverage for syphilis and hepatitis B have also been collected in England since April 2017 which are concerned with population and coverage of syphilis screening, test turnaround time and timely assessment for screen-positive and known-positive women.[61] Reviewing the delivery of screening and clinical pathways together with maternal and neonatal outcomes, including diagnoses and monitoring of congenital syphilis, will form part of the new IDPS National Integrated Maternal and Paediatric Outcomes Surveillance (NIMPOS) System being developed by PHE Screening, UCL Institute of Child Health and PHE National Infection Service teams. It is anticipated that this system will be extended to include syphilis in 2018.

Conclusions

Since Fildes' first epidemiological investigation in 1914, the incidence of congenital syphilis in the UK has been constrained by high-quality healthcare services and a century later is below the WHO elimination threshold. Nevertheless, rare and sporadic, untreated cases of congenital syphilis continue to have the potential to cause major consequences for the health and life chances of affected infants in the UK. If the complex challenges presented by this preventable disease are to be resolved, intervention strategies need to be optimised, rigorously assessed and extended across Europe.

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