Resurgence of congenital syphilis: new strategies against an old foe

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Summary

Congenital syphilis (CS) is a major global cause of foetal loss, stillbirth, neonatal death, and congenital infection. In 2020, the global CS rate was 425 cases/100,000 live births, substantially higher than the World Health Organization (WHO) elimination target of 50/100,000 live births. Case rates are rising in many high-income countries, but CS remains rare in comparison to low-middle income (LMIC) settings. This review aims to summarise the current epidemiology and knowledge on transmission and treatment of syphilis in pregnancy and proposes measures to reduce the rising incidence seen worldwide. Secondly, this review describes emerging diagnostic and treatment tools to prevent vertical transmission and improve management of CS. Finally, a programme of public health priorities, which include research, clinical and preventive strategies is outlined.

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from January, 1970, to February, 2023, by combining syphilis or congenital syphilis with 'epidemiology', ‘diagnosis’, ‘point of care’, ‘treatment’ , ‘pregnan*’, ‘management’ or ‘prevent*.’Additionally, WHO publications since 2007 and datasets which evaluated epidemiological data from regional/national public health bodies that have published detailed data (UK, USA, Canada, European Union, and Australia) were also interrogated. Finally, a clinical trial database search (clinicaltrials.gov, trialsearch.who.int) for any current or recent interventional trials relating to syphilis and CS between 1970 and 2023 was conducted. Articles published in English and Spanish resulting from these searches and relevant references cited in those articles were reviewed. Studies and data cited from South America are in Spanish.

Introduction

Vertical transmission of syphilis can lead to foetal loss, stillbirth, neonatal death and congenital infection resulting in multi-system disease, including meningo-encephalitis, pneumonitis, hepatitis, thrombocytopaenia, osteitis, hepatosplenomegaly, blindness, and hearing loss. Congenital syphilis (CS) is a leading infectious cause of long-term infant disability globally[1]. In 2020, the global CS rate was 425 cases/100,000 live births, substantially higher than the World Health Organization (WHO) 2007 elimination target of 50/100,000 live births[1], despite the availability of acceptable tests and effective treatment. The global community has committed to eliminating vertical transmission of syphilis. Whilst no WHO region has validated elimination of CS, 14 countries or territories had validated elimination as of November 2021. To reach the WHO elimination goal, the programmatic targets are: antenatal care coverage ≥95%, syphilis testing of pregnant women ≥95% among those attending at least one antenatal care visit, and adequate syphilis treatment of syphilis-seropositive pregnant women ≥95%[2].

An estimated 1 million pregnant women worldwide are diagnosed with syphilis annually, with the highest burden in sub-Saharan Africa. Limited antenatal screening, surveillance and healthcare services contribute to challenges in controlling syphilis in pregnancy, with poor political advocacy and ongoing stigma cited as societal barriers preventing testing and treatment[3]. In several high-income countries (HIC), despite widespread availability of routine antenatal screening programmes and accessible benzylpenicillin treatment regimens, the incidence of CS over the last decade in pregnant women has increased[4–9]. The worldwide persistence of CS has occurred despite the WHO commitment of aiming to eliminate CS almost two decades ago.

We summarise current global epidemiology of CS, propose a series of interventions to better manage syphilis in pregnant women and neonates, and outline future public health and research priorities to help eliminate CS.

Increase in rates of CS in low-, middle- and high-income countries over last decade

There remains marked regional variation in CS incidence, with the highest rates in low and middle-income countries (LMIC) (**Fig 1)**. In high-income countries, there has been a resurgence of cases over the last decade, despite overall case rates remaining below the WHO elimination threshold (**Fig 1**)[1]. There were 1120 cases per 100,000 live births in the African region between 2012 and 2016, compared with 19 per 100,000 in the European region. The Americas and Eastern Mediterranean have high incidence rates of 339 and 640 per 100,000 live births respectively[1].

Untreated syphilis in pregnancy, especially earlier stages of infection, has an estimated 60% risk of adverse birth outcomes[10], and cause 350,000 adverse birth outcomes annually worldwide[1]. Historical studies in sub-Saharan Africa suggest 25-50% of stillbirths may be associated with syphilis. However, in a recent prospective observational study only 3% of stillbirths had seropositive mothers[11,12]. Overall, data on adverse birth outcomes secondary to untreated syphilis in pregnancy are of limited quality due to inconsistent testing strategies, small cohorts, high loss to follow-up and retrospective study designs. Moreover, variation in case definitions poses challenges for meaningful comparison of surveillance data across jurisdictions (**Table 1**).

The global CS incidence in 2020 was estimated at 425 per 100,000 births, effectively unchanged from 473 per 100,000 births (95% confidence interval 385-561) in 2016 [1,13]. Despite the establishment of the WHO elimination goal in 2007[3], CS incidence only fell marginally in the African region during this period, and there was no reduction in CS incidence rates in any other WHO region.

In the Region of the Americas, maternal syphilis prevalence increased between 2012 and 2016, from 0·64%, to 0·86%[14]. Within Latin America, there were 29,149 cases of CS reported by countries of the Americas in 2020 (excluding Brazil), with an incidence rate of 200 per 100,000 live births[14]. Brazil accounts for most of the reported CS in the Americas; in 2020, 115,371 cases of acquired syphilis

(54·5 cases per 100,000 population) were reported, 61,441 cases of syphilis in pregnant women (2160 per 100,000 live births), and 22,065 cases of CS (an incidence rate of 770 per 100,000 live births)[14].

Current prevalence data are likely to under-estimate the true burden of disease due to poor surveillance, inadequate information systems and high rates of unrecognised or asymptomatic infection. Regional modelling studies broadly rely on incidence estimates and use maternal syphilis prevalence, screening and treatment data to derive the incidence of CS. Historical estimates of adverse birth outcome rates[10] are used to derive the current burden of syphilis-attributable adverse birth outcomes; recent data suggest these outcomes may be less common than previously thought[11,12].

Surveillance systems in many LMICs are poor[16,17] with many systems relying on syndromic case reporting for syphilis rather than aetiological case reporting from laboratory testing[16],. Additionally, for CS diagnosis, many countries employ a surveillance definition based on maternal serology and treatment status rather than confirmatory diagnostic tests in the infant (**Table 1**). Comparisons between countries are hindered by variable case definitions used when reporting to the WHO or Global AIDS monitoring (GAM) system[18], with further variability in reporting of stillbirths within these definitions. More robust surveillance and information systems are needed to measure the current incidence of adverse birth outcomes due to syphilis.

In some HICs there have been year-on-year increases in the rates of syphilis in men, and women of childbearing age (**Table 2**)[4–8,19]. In the US, the absolute number of CS cases reported to the CDC has increased from 941 in 2017 to 2677 in 2021[20], resulting in public health campaigns to promote awareness, testing and treatment. These campaigns have targeted high-risk groups: young adults (i.e. 15 – 24 years old), specific ethnic groups (i.e. indigenous populations in Australia, USA and Canada) and those with low socioeconomic status and limited access to healthcare. Additional risk factors include current/previous sexually transmitted infections, multiple sexual partners, bi-sexual male partners, coinfection with HIV or hepatitis B virus (HBV), and unprotected sex with a male partner at risk of having syphilis [21].

The WHO triple elimination initiative adopts a common approach to address the overlapping epidemics of HIV, HBV, and syphilis. In women living with HIV, co-infection rates with syphilis were 3.1% , 4.1% and 6.0 % in African, US and Chinese cohorts respectively [22–24]. In a retrospective cohort from Botswana, HIV and syphilis co-infection led to increased rates of stillbirth compared to syphilis alone (absolute risk increase 3.9%, OR=1.58; 95%, CI 0.77–3.25), suggesting that individuals with coinfection are at greater risk of adverse outcomes[25].

Approaches to improve screening in pregnancy

Prevention of CS is achievable through robust antenatal healthcare systems with rigorous surveillance, screening, testing and treatment. Estimates from 2016 highlighted that 88% of all women have access to antenatal care. However, only 66% are tested for syphilis and only 78% of women testing positive receive adequate treatment, far short of the 95% WHO programme targets[1]. The last decade has seen progress in access to antenatal care, and specifically to syphilis screening: 103 of 111 countries (93%) had policies for antenatal screening and treatment of syphilis in 2019–2020[26]. However, populations with the highest syphilis prevalence have the lowest antenatal care coverage.

Antenatal treatment is highly effective at reducing the risk of CS. A meta-analysis evaluating long-acting penicillin regimens in pregnancy found that in 3450 live births, treatment reduces the relative risk of CS by 97% (95% confidence interval 93%-98%); additionally, stillbirths were reduced by 82%, pre-term delivery by 64%, and neonatal death by 80% [27–29].

Development of evidence-based guidance specifically for primary care during the pregnancy and postnatal period is critical as these services are the gateway to further specialist care. Key recommendations should include frequency of syphilis testing, partner testing and identification of region-specific high risk pregnancies . Most published guidelines, including the UK[30], US[31], Australia[32] and Brazil[33], recommend ‘reverse’ algorithms for screening – a treponemal test followed

by a confirmatory non-treponemal test. WHO syphilis guidelines focus on settings where high-quality laboratory testing is not generally available and testing recommendations accommodate for this, recommending the use of treponemal point of care (PoC) syphilis testing and on-site treatment if the test is positive[34].

Repeat Testing in Pregnancy

In the context of rising syphilis rates in women of childbearing age, repeat testing in pregnancy could increase new case detection and should be strongly considered in screening programmes. The Integrated Screening Outcomes Surveillance Service (ISOSS) report in the UK highlights that several cases of CS occurred where syphilis was acquired later in pregnancy despite having an initial negative syphilis test[19]. Prospective antenatal studies in Tanzania and South Africa report rates of infection during pregnancy of 1·6% and 2·5% respectively[35,36].

It has been suggested that serial testing could be prioritised for those with risk factors such as housing instability, specific ethnic minority group ethnicity, new incident STIs, drug use and sex work [19,31,37]. In the EU, 22/24 countries screen for syphilis in the first trimester, however only three recommend re-testing in high-risk groups[38]. In Latin America, most countries have national strategic protocols with repeat testing[15]. Chile, for example, has 3 screening points for syphilis during pregnancy with non-treponemal tests at first antenatal visit, 24 and 32-34 weeks and at delivery for all women[39]. However, prioritising high-risk groups may further stigmatise and marginalise these populations, which contrasts sharply with the aim of providing holistic and inclusive antenatal care. Additionally, the main limit to the effectiveness of risk-based screening, is reliable identification of high-risk groups and missing significant number of cases among ‘low-risk’ groups.

Universal re-screening may be a better alternative to a risk-based approach. Several Canadian states changed guidance in 2019 to recommend universal re-screening of mothers at delivery to reflect increasing prevalence and changing epidemiology of syphilis[37]. In a UK cost-effectiveness modelling

analysis, universal re-screening would prevent 5·5 cases of CS per year (from 8·8 cases to 3·3), consistent with findings that new infections during pregnancy are a significant cause of CS[40]. However, due to the relatively low prevalence of syphilis among women of childbearing age in the UK, universal re-screening is not cost-effective[40]. Screening would become cost-effective if the maternal risk of acquiring syphilis between screening reached an incidence of 0.005% pregnancies, where the current infection rate during pregnancy is predicted as 0.0017%. No HIC has integrated universal PoC testing into standard care; however, newer treponemal and non-treponemal antibody-based PoC tests discriminating between active and past infection could be integrated in specific contexts such as late antenatal presentation or presentation in labour, particularly if combined with HIV testing.

Partner screening

Rates of syphilis in partners of pregnant women with syphilis is markedly higher than the general population and is a major risk factor for both initial infection and re-infection post-treatment. Of concern is that 68·8% of partners of seropositive pregnant women have unknown syphilis status[41–43]. A Ugandan trial found 81·7% partners of pregnant syphilis-infected women did not attend syphilis screening after their pregnant partner received a syphilis diagnosis despite multiple reminders[43]. Similarly, cohort studies in South Africa and Botswana showed that despite notification of STIs, partners had low sexual health clinic attendance and treatment rates of 63%[44,45]. Notably, 7-16% of pregnant women did not notify their partners in these cohort studies. Successful diagnosis and treatment of partners is crucial to reducing re-infection rates, yet these studies suggest there are multiple challenges including inadequate partner notification and limited engagement.

Greater understanding of the barriers to partner screening are needed to address this issue. In a Brazilian study of 400 pregnant women inviting their partners to attend STI screening, only 64% attended[46]. Notably, the partners who attended all consented to full screening, and subsequently had high treatment rates when indicated, suggesting that increasing initial partner attendance could

significantly improve testing and treatment rates[46]. Studies of antenatal partner HIV screening in Brazil and sub-Saharan Africa have highlighted several important factors which affect partner engagement including HIV related stigma; fear of testing positive; and poor awareness of the risk and benefits of screening[47,48]. Unfortunately, there is limited specific data on attitudes and barriers to partner screening for syphilis.

Barriers to antenatal screening

Health inequalities are associated with highly divergent rates of syphilis between and within countries. CS disproportionately affects marginalised and disenfranchised populations. In both HIC and LMIC, stigma, discrimination, and institutional racism present significant barriers to appropriate screening and antenatal care. Stigma is maintained through institutional barriers (e.g. criminalisation of sex work), structural barriers (poor access to sexual and reproductive health education) and societal factors (e.g. language used in the medical community to describe 'high-risk sexual behaviours' and 'unsafe sex')[49,50].

Among women attending antenatal care globally, syphilis screening rates are 66%, suggesting missed opportunities for screening among those within antenatal care[1] – however it is unclear whether this is due to declining or failure to offer testing. Women may decline screening in pregnancy for multiple reasons including fear of stigma, poor awareness of consequences of syphilis in pregnancy and perception of low risk. Concomitantly, poor quality antenatal care may be integral in causing this discrepancy through capacity issues, poor education among healthcare providers and failing to offer testing.

Universal access to sexual and reproductive healthcare, reducing health inequalities and lowering neonatal deaths below 12 per 1,000 live births are major aims of the UN Sustainable Development Goals 3 and 10. These goals have heavily informed the UNAIDS strategy for tackling the HIV pandemic, and the WHO triple elimination initiative. Key relevant priorities include targeting

resources to populations facing the greatest inequalities, focusing on 'social enabling' policies to reduce gender-based inequalities and stigma, and developing resilient health, social and education systems. Such policies can have impact beyond a single disease, mitigating against other sexually transmitted and congenital infections.

Point of care screening

In LMIC settings, where challenges include limited follow-up and delayed treatment, PoC testing could significantly improve delivery of care since tests have 75-90% sensitivity and 95-99% specificity compared to standard serological assays[51]. In 2019, dual HIV/syphilis PoC tests were recommended by the WHO as first-line tests for HIV/syphilis screening, which hopefully will increase testing capacity and equity of access. HIV screening exceeds syphilis screening across many countries, and introduction of dual PoC testing would thus immediately increase screening coverage of syphilis[52]. Syphilis PoC testing compared to serological tests at first antenatal visit increased screening rates (from 0-58% to 70-100% across several studies and sites), treatment rates (allowing same-day testing and treatment) and improved outcomes (93% reduction in CS)[28,53–56]. PoC tests are emerging which detect both treponemal and non-treponemal antibodies, enabling distinction between active and past infection. Distribution of PoC testing is facilitated by reduction of unit cost to under $1 USD following partnership between the Clinton Health Access Initiative, MedAccess and SD Biosensor. Emerging challenges include frequent shortages of devices, fragile supply chains, and maintaining quality assurance[57–59].

Syphilis PoC tests followed by immediate treatment may have a role in hard-to-reach populations such as rural Australian and Canadian populations, and significantly reduce delays between sampling, results, and treatment[37]. Populations where follow-up is not assured, may benefit from PoC testing followed by treatment without confirmatory testing, in particular when there is no known history of syphilis infection or treatment. Furthermore, PoC testing may be more acceptable to groups such as indigenous populations as it can be implemented by a wider range of health-care providers,

295 encourages participation in the diagnostic process, and does not require skilled phlebotomy [60,61].
296 Testing and treatment of sexual partners could also reduce the risk of re-infection.
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298 **Adopting novel diagnostic and treatment approaches in the neonate**
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300 Diagnosing CS remains challenging due to the lack of widely available molecular assays to detect
301 *Treponema pallidum*, and reliance on serology, which is challenging to interpret in the context of
302 transplacental transfer of antibodies[62,63]. Furthermore, most neonates infected with syphilis have
303 unrecognised or asymptomatic infection and the signs in symptomatic neonates are typically non-
304 specific. Several current definitions use a combination of clinical features with supportive serology
305 (**Table 1**)[64]. Most consider visualisation or isolation of *T. pallidum or* treponemal DNA as the gold-
306 standard; however, these tests have limited sensitivity and availability. Investing resources into
307 developing syphilis PCR availability could divert critical funding away from strengthening healthcare
308 infrastructures to deliver robust screening using cheap, accurate and rapid serology-based assays,
309 enabling prompt treatment during pregnancy.
310
311 *Serology interpretation*
312
313 Serological tests for syphilis can be divided into treponemal (qualitative assays which detect
314 antibodies against *T. pallidum* antigens) or non-treponemal assays (quantitative assays which detect
315 antibodies against cardiolipin and lecithin released during host cell damage and are therefore not
316 specific to syphilis infection).
317
318 IgG treponemal antibodies detected in an infant may indicate congenital infection or transplacental
319 transfer of maternal antibodies, and must be interpretated with expertise. Treponemal tests are useful
320 when they remain positive in the infant beyond 6 months of age, which is suggestive of endogenous
321 production and therefore CS. An infant with positive non-treponemal antibody (e.g. RPR/VDRL)
322 titres at least 4-fold greater than the maternal titre, or treponemal IgM seropositivity, both suggest

endogenous antibody production in the infant consistent with congenital infection. However, several studies indicate that using a threshold of 4-fold is too high, with sensitivity estimates of 4-13%[62]. Non-treponemal antibodies levels are used to track response to treatment.

Both treponemal and non-treponemal serological tests, microscopy or PCR for direct detection of *T.pallidum*, together with knowledge of maternal serology and treatment for syphilis are all used to evaluate clinical presentation and diagnose active, latent or past syphilis infection.

Direct detection of *T.pallidum*

PCR and experienced observation of an appropriate sample by dark-field microscopy can detect *T. pallidum* bacteria in an infected individual. PCR has been shown to demonstrate increased sensitivity compared with dark-field microscopy[65,66]. Most studies in adults show nested-PCR (nPCR) has the highest sensitivity[67]. Sensitivity ranges between 75·8-93·8% in samples from primary chancre in adults depending on the reference standard[65,67,68].

Specificity and positive predictive value of PCR tests taken from appropriate sites and samples approaches 100% in most published series[67]. Evaluating the performance of PCR in CS is challenging due to limited study cohorts, variation in standard reference comparator, lack of standardised assays and variability in patient sample used. A prospective study of 22 cases of CS had positive PCR results from a variety of sources including placental tissue, CSF, nasal secretions, amniotic fluid and skin biopsies[70]. In neonates, the optimal sample will depend on clinical presentation, though a greater number of appropriate samples is associated with higher sensitivity.

Point of care testing

PoC tests have not been evaluated in neonatal populations. Most PoC tests currently approved are IgG-based treponemal assays, which may result in false positives in neonates due to trans-placental

IgG as this may represent prior treated maternal infection. High sensitivity and specificity dual non-treponemal/treponemal PoC assays are becoming available in adults, although none are currently WHO recommended[71]. Non-treponemal PoC tests are currently unable to report a quantitative titre, which is needed to evaluate adequate maternal treatment, compare maternal and infant titres and for follow-up serial infant non-treponemal titres.

Treatment in pregnant women and neonates

Standard treatment of CS is 10 days of intravenous (IV) benzylpenicillin (every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days)[64]. This regimen originates from decades of clinical experience and two randomised clinical trials in 1989 (n=152 cases) and 1997 (n=8 cases)[72].

Effective non-penicillin-based regimes are required in pregnant women with true penicillin allergy, would provide alternative treatments during shortages of penicillin, and may be more conducive to administration and outpatient management. Procaine and benzathine benzylpenicillin shortages have occurred in many countries over the last decade and have a major negative impact for delivery of recommended regimes[73–75]. For example, in 2015 during a penicillin shortage in Brazil, 55.2% of CS cases had inadequate maternal treatment[76]. Challenges within the supply chain will be compounded by increasing global demand for penicillin. More widespread PoC testing is estimated to increase the number of doses required from 414,459 doses in 2019 to 1,078,428 in 2030[77].

Despite the use of alternative treatments during penicillin shortages, there are limited data on infant outcomes. There are no randomised trials evaluating alternative regimes in neonates or in pregnancy. 10-days of IV ceftriaxone has been shown to have equivalence compared to standard regimes in non-pregnant adult populations in both early syphilis and more recently in neurosyphilis[78–80] . However, the use of ceftriaxone in pregnancy has been limited to case studies and non-randomised studies and currently no strong recommendation on its use in preventing CS is possible[81]. Understanding the

potential role of ceftriaxone as a therapeutic agent is merited as it is only given once daily and would therefore require fewer doses than a penicillin-based regimen, allowing ambulatory treatment. However, ceftriaxone is given as a 10-day IV or intramuscular (IM) course which presents a significant burden to healthcare systems and may not be suited to LMICs.

Oral regimes could be very useful, particularly in LMIC countries where use of IV antibiotics is demanding on health care systems and patients. In neonates or pregnancy there is no evidence to support use of any oral agents. A phase II trial of cefixime – an oral third-generation cephalosporin – is currently enrolling non-pregnant women to test treatment efficacy and would form the basis of a future trial in pregnant women if successful[82]. Cefixime has been used in pregnant women for urinary tract infectious (UTIs) previously and has demonstrated 87% efficacy (95% CI, 69%–100%; 13/15 patient) in a small pilot trial in non-pregnant early syphilis[83]. The largest molecular epidemiological study of *T. pallidum* has revealed an increasing trend in azithromycin resistant isolates across European and North American lineages. Azithromycin has been trialled in adult populations previously, however azithromycin resistance can be as high as 56%, resulting in treatment failure in adult, and pregnant and non-pregnant populations[84–86]. UK-based ISOSS data and published reports from China have demonstrated treatment failure in pregnant women receiving azithromycin resulting in CS, including neonatal deaths[85]. 14-day courses of oral amoxicillin with and without probenecid have shown overall treatment efficacies of 94-95% including in early and late syphilis and those with HIV[87,88]. However, in a case series of pregnant women treated with oral amoxicillin alone, benefit was limited to those with early syphilis (0/26 cases of CS) as 33% (15/45 cases) of infants born to women with late syphilis were diagnosed with CS[89].

Research Priorities

Epidemiology

Strengthening national surveillance and information systems is essential to accurately monitor syphilis and congenital syphilis. The COVID-19 pandemic highlighted the inadequacy of surveillance and information systems in many countries and the need for modern replacements.

Use of a unified case definition would facilitate better comparisons between countries but is challenging due to varying access to diagnostic testing between countries. The WHO surveillance definition (**Table 1**) would be effective in resource-poor and rural areas with limited laboratory access as it requires less neonatal testing compared to CDC and UK definitions, does not require testing of stillbirths, and captures neonates at risk of CS. However, this definition risks overestimating the true burden of disease. Additionally, the WHO definition may not be optimal in middle- and high-income countries where there is high testing capacity. An important future consideration is the feasibility to include PoC test into surveillance definitions.

Investing in effective information systems can facilitate real-time responses to emerging epidemics and case clusters. The UK currently has strong surveillance systems through ISOSS which centralises data collection and screening outcomes in pregnancy. Currently the US CDC is undergoing a multi-billion-dollar Data Modernisation Initiative to strengthen the public health landscape in response to gaps identified during the COVID-19 pandemic[90]. To gain effective real-time data, new semi-automated platforms were designed which integrate data from multiple sources and have a single platform of access[90]. Key barriers include poor data sharing between different health and government agencies, limited investment in information systems and a stretched public health workforce.

Cohort studies may be better suited to evaluate adverse outcome rates and prevalence in populations with limited uptake of antenatal care. Studies could include large-scale population-based screening programmes integrated into existing HIV testing networks, utilising routine healthcare data, and integration of regional microbiology testing with national databases **(Table 4)**. Targeted investigation or minimally invasive tissue samples of stillborn infants would help determine prevalence estimates

of syphilis-related stillbirths[91]. Additionally, establishment of disease registries could capture disease trends, long-term neurodevelopmental outcomes, and provide a platform for future interventions.

Holistic and non-discriminatory antenatal care

There are few studies evaluating interventions to improve adherence to antenatal or postnatal care in individuals with syphilis infection[92]. Future research could evaluate models of testing (mobile units, PoC testing, pharmacy testing such as a current Canadian trial (NCT05534633)) and methods of result reporting to evaluate population-specific acceptability, particularly with regard to confidentiality. There is also scope to evaluate the impact of community champions and tailored community approaches to reduce stigma and promote access to and awareness of syphilis testing. Highly successful approaches in HIV prevention such as the 'Greater Involvement of People living with AIDS' initiative by UNAIDS can be translated into programmes to prevent syphilis and need evaluating in this context. Health communications campaigns should be targeted at both public and health professionals. Whilst campaigns relating to HIV have been highly effective, syphilis presents its own public awareness challenges including lower awareness of risk to neonates and should be considered in the design of these campaigns.

Crucially, a programme of qualitative (e.g. community based public engagement, targeted focus groups, individual interviews) and quantitative (e.g. capturing epidemiological trends, disease incidence, treatment outcomes) work should be conducted to improve the screening, treatment and engagement of sexual partners with active infection.

Diagnosis and management

As highlighted, diagnosis of CS remains challenging due to limitations of available tests and high rates of undiagnosed and asymptomatic infections. In LMICs, development and validation of PoC

tests for diagnosis of CS could contribute to increasing treatment rates, reducing treatment delays and collection of epidemiological data in LMIC.

There is a marked absence of randomised controlled trials evaluating treatment regimes in pregnant women and neonates. Randomised trials in neonates should be focused within LMICs as they face the greatest burden of disease, disproportionate risk of penicillin shortages and greatest resource limitations. Initial trials could focus on effectiveness of non-penicillin regimes (i.e. third generation cephalosporin compared to standard care) and oral regimes (i.e. amoxicillin plus probenecid compared to standard care) **(Table 4).** Key additional questions include what the minimal effective duration of 3rd generation cephalosporin, effectiveness of single dose penicillin in some high-risk neonates and the treatment duration of asymptomatic compared to symptomatic infection.

Vaccine development

There are no vaccines currently in human clinical trials and the optimal vaccine platform or target antigen has not been established. There is limited knowledge about immune correlates of protection from syphilis infection[93,94]. The immune response to syphilis is markedly different to that of conventional bacteria due to an outer membrane which does not contain lipopolysaccharide and few transmembrane proteins. In humans, there are no studies which have identified a protective response or evaluated immune correlates against re-infection[94]. In animal models, complete protection has been challenging to establish - in rabbits, injection of antibodies only appears to delay lesion development[95]. Antibodies appear to facilitate opsonisation and complement-mediated destruction[96]. Vaccine design could be informed by presence of broadly neutralising antibodies in human populations and corresponding antigens, however it is unclear if these would be protective. Cellular immunity appears important based on immunofluorescent studies demonstrating prominent infiltration of macrophages, CD4+ and CD8+ T-cells, however functional studies evaluating the requirement for these cells in clearance are lacking. However adoptive transfer of T-cells in guinea pigs suggest that these alone are not protective against infection[97].

Current evidence suggests limited genetic diversity in most syphilis genes, though there is variation within outer membrane proteins (OMPs) which appears to be a major immunogenic surface molecule. More studies are needed to evaluate genetic diversity in high prevalence areas so that antigenic variations can be considered in vaccine design. In the most comprehensive global assessment of antigenic diversity only 19 of 300 samples were from the African region with over 200 from the UK[98].

A recent important advance has been *in vitro* culture and genetic manipulation of T.*pallidum* without the requirement for propagation in rabbits[99,100]. Future studies should focus on using these new methods to establish surface proteins important for pathogenesis and establishing potential targets for vaccine development [100].

Conclusions

This review highlights the persistent and underrecognized global burden of CS, and the lack of progress to elimination. In low incidence HICs, rates of syphilis in women of childbearing age have increased more than 200% over the last 5 years, and in high burden LMICs, there was limited progress in reducing rates of CS between 2012-2016. There has been only patchy progress in implementation of PoC diagnostics and antenatal screening coverage remains low. Important priorities to address this include a better understanding of current epidemiology, including true burden of disease and the proportion of syphilis-related adverse birth outcomes. Strengthening antenatal care systems is vital but must be built around the communities they serve. Tools such as improved diagnostics and treatment strategies will enhance flexibility and capacity of care systems. Multisector strategies such as the 2022-2030 WHO triple initiative strategy encapsulates the broad and interconnected approaches that are required to overcome the challenges of CS. CS will only be eradicated once we simplify and optimise detection, surveillance, reporting and treatment, alongside social strategies to support women and men with syphilis and other sexually transmitted infections.

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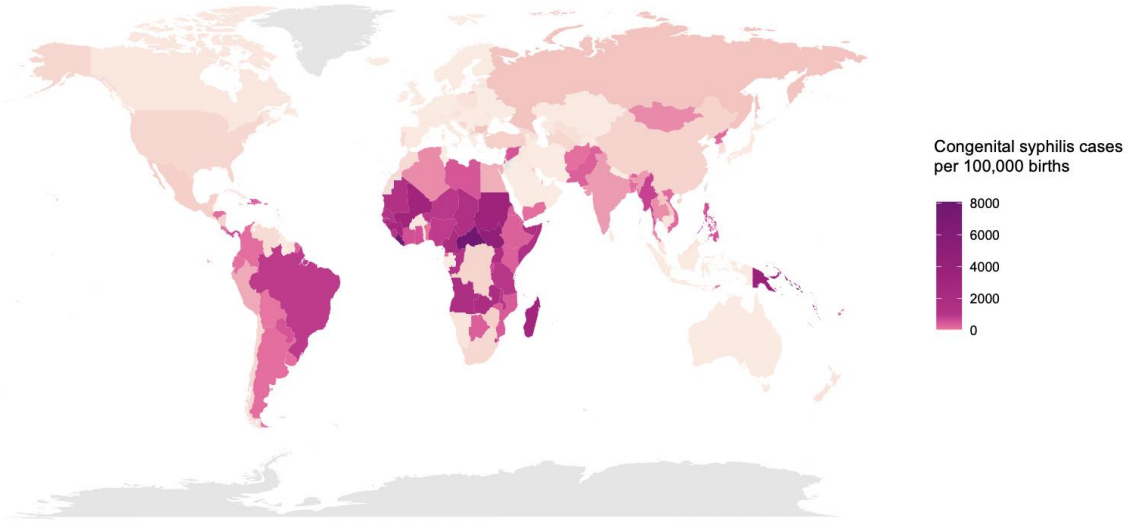

Figure 1. World map of congenital syphilis case per 100,000 births. Data sourced from WHO and Korenromp et al most recent estimate between 2016-2021[1]

Table 1: Summary of different case definitions used for congenital syphilis in different regions. RPR – rapid plasmid regain; TPPA – treponema pallidum particle agglutination assay; VDRL – venereal disease research laboratory;

Congenital syphilis	Confirmed	Presumptive
WHO[2]	NA	- A live birth or fetal death at >20 weeks of gestation or >500 g (including stillbirth) born to a woman with positive syphilis serology and without adequate syphilis treatment OR - A live birth, stillbirth or child born to a woman with positive syphilis serology or with unknown serological status but with laboratory and/or radiological and/or clinical evidence of syphilis infection.
US CDC[31]	- An abnormal physical examination that is consistent with congenital syphilis; AND - a serum quantitative nontreponemal serologic titre that is fourfold (or greater) higher than the mother's titre at delivery (e.g., maternal titre = 1:2, neonatal titre ≥1:8 or maternal titre = 1:8, neonatal titer ≥1:32); - OR A positive darkfield test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.	"Possible"- Normal physical examination and a serum quantitative nontreponemal serologic titre equal to or less than fourfold of the maternal titre at delivery AND - Mother was untreated or inadequately treated - Mother was treated <30 days before delivery
UK[101]	- *T. pallidum* identified on dark ground microscopy, PCR or histology - OR Rising RPR/VDRL over three months or positive OR RPR/VDRL not becoming negative within four months - OR A four-fold or greater difference of RPR/ VDRL titre or TPPA titre above that of the mother, . A four-fold or greater increase in RPR/VDRL or TPPA titre within three months of birth, . In a child more than 18 months age, positive treponemal tests - OR major clinical features AND positive RPR/VDRL/IgM	NA
Australia CDC [102]	Live birth - Mother and child both seropositive by a treponemal specific test, AND *definitive* laboratory evidence:	*Suggestive* laboratory evidence AND probable clinical evidence required:

	- Direct demonstration of *T. pallidum* - OR detection of *T. pallidum* specific IgM in the child. - OR the child's serum non-treponemal serology titre at birth is at least fourfold greater than the mother's titre. Stillbirth - Mother is seropositive by a treponemal specific test3, AND the pregnancy outcome is a stillbirth, AND there is definitive labratyory evidence of infection in-utero	Suggestive lab requires positive maternal serology AND - Child seropositive on non-treponemal testing - OR A reactive cerebrospinal fluid non-treponemal test (i.e. VDRL). - OR A child who remains seropositive by a treponemal specific test at 15 months of age.
Chile [15]	- Reactive non-treponemal serology in first 2 years of life with history of mother with syphilis not treated or inadequately treated - Non-treponemal test at any dilution with clinical features compatible with CS - Reactive non-treponemal test at two-fold or greater compared to that of the mother in infants without symptoms	NA
Brazil [103]	- Every newborn, stillborn or miscarriage to women with untreated or inadequately treated syphilis. - OR clinical evidence, CSF evidence or radiological evidence of CS AND positive non-treponemal test. - OR Infant non-treponemal titres at two-fold or greater difference to that of the mother - OR Increasing non-treponemal titres infant of at least two dilutions - OR Non-treponemal titres still reactive after 6 months - OR Microbiological evidence of *T. pallidum* infection in sample of nasal discharge, skin lesions or from biopsy samples from miscarriage of stillbirth.	NA

810

811 **Table 2: Rates of syphilis in men and women of childbearing age across high income and middle-income settings.**

Rate of syphilis	**2016** rate / 100,000		**2019** rate / 100,000		**2021** rate / 100,000	
	Women of childbearing age	**Men**	**Women of childbearing age**	**Men**	**Women of childbearing age**	**Men**
Australia (age 15-44) [104]	7·7	25.2	16·5	39.7	16·1	37
Canada (age 15-39)[37]	4·3	19.8	19·3*	35.5	N/A	41
England (age 15-44)[19]	1·7	20.3	3·28	25.8	N/A	23.4
EU/EEA (age 25-34) [8]	~3	10.5	~4	12.8	N/A	N/A
USA (age 15-44) [20]	8·2	15.5**	8·7	20**	15·6	24.4**

Brazil [103]	13.4***	54,0	21.5***	95,4	27.1***	100,7
Chile [15]	21.0***	30	28.0***	49	NA	45.5

812 *Data from 2018, **Primary and secondary syphilis only ***Antenatal screening rate

813

Table 3. Proportion of antenatal care attendees with positive syphilis serology (%) in low-income settings. Countries included with completed data set reported over years specified. Data from WHO The Global Health Observatory

Seropositivity proportion (%)	2016	2018	2020
Eritrea	0.78	1.33	1.02
Gambon	0.37	3.64	1.28
Kenya	1.24	0.93	1.25
Madagascar	3.77	2.7	2.76
Malawi	1.38	1.16	2.28
Nigeria	1.22	0.5	0.4
Senegal	4.82	0.87	0.47
Togo	2.29	1.49	2.12
Uganda	2.92	2.12	2.29
Tanzania	2.21	1.7	1.22
Zambia	3.52	4.98	4.54
Zimbabwe	2.37	2.51	2

819

820 **Table 4. Research priorities to improve diagnosis and management of CS**

	Issues	Study suggestions
Epidemiology	• What is the true incidence of CS and syphilis in pregnancy in LMIC settings? • What are the rates of stillbirths and adverse birth outcomes in pregnant women with syphilis? • Understand the long term outcomes of asymptomatic and symptomatic neonates • No single definition of CS • Weak information systems with limited data integration and data sharing	• Strengthen surveillance networks and information systems particularly in LMICs, drawing on more widely available PoC testing. • Integration of regional microbiology testing with national databases • Disease registry that allows prospective longitudinal follow up and opportunity to trial novel interventions
Screening and antenatal care	• Review the public health value of repeat testing in pregnancy? • Characterise the role of PoC as a screening tool in pregnancy. • What is the incidence of syphilis in partners of pregnant women? • Devise strategies to improve testing and treatment of partners	• Population based studies which evaluate cost effectiveness and outcomes of repeat testing in pregnancy in high risk groups. • Targeted screening studies using PoC testing in specific populations to assess acceptability and efficacy of testing • Qualitative studies understanding how to improve partner testing/screening
Diagnosis	• Determine the utility of PoC testing in neonates • Determine the sensitivity of PCR testing in CS	Measure the utility (i.e. added rates of detection, number of cases treated, cost burden) using PoC testing Validation of different commercially available PCR assays to assess

		sensitivity/specificity different biological samples
Treatment	• Is ceftriaxone an effective treatment of CS? • Can the duration of antibiotic treatment for CS be shortened without negatively impacting cure? • Is there a role for single dose penicillin in the treatment/prevention of CS in high-risk infants? • Investigate use of oral antibiotics in the treatment of CS.	RCT comparing different duration of ceftriaxone and penicillin treatment in treatment of CS

Vaccine development	• What are there corrolates of protective immunity from spyhilis? • What are the essential proteins required for syphillis survival and pathogenesis?	Prospective studies evaluating humoral immune responses against syphilis and risk of re-infection Identify individuals who appear to have protective immune responses. In vitro and animal model studies using knock out syphilis organisms

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