Resurgence of congenital syphilis: new strategies against an old foe

Philip Moseley, Alasdair Bamford, Sarah Eisen, Hermione Lyall, Margaret Kingston, Claire Thorne, Cecilia Piñera, Helena Rabie, Andrew J Prendergast, Seilesh Kadambari

Congenital syphilis is a major global cause of fetal loss, stillbirth, neonatal death, and congenital infection. In 2020, the global rate of congenital syphilis was 425 cases per 100 000 livebirths—substantially higher than WHO's elimination target of 50 cases per 100 000 livebirths. Case rates are rising in many high-income countries, but remain low compared with those in low-income and middle-income 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. We also describe emerging diagnostic and treatment tools to prevent vertical transmission and improve management of congenital syphilis. Finally, we outline a programme of public health priorities, which include research, clinical, and preventive strategies.

Lancet Infect Dis 2023

Published Online August 18, 2023 https://doi.org/10.1016/S1473-3099(23)00314-6

University of Queensland Frazer Institute, University of Queensland, Brisbane, QLD, Australia (P Moseley BMBCh); **Department of Paediatric Infectious Diseases, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK** (A Bamford PhD, S Kadambari PhD); **University College London Great Ormond Street Institute of Child Health, London, UK** (A Bamford, S Kadambari, Prof C Thorne PhD); **University College London Hospitals NHS Foundation Trust, London, UK** (S Eisen MD); **Imperial College Healthcare NHS Trust, London, UK** (Prof H Lyall MD); **Manchester University NHS Foundation Trust, Manchester, UK** (M Kingston MRCP); **Medicine**

Introduction

Vertical transmission of syphilis can lead to fetal loss, stillbirth, neonatal death, and congenital infection resulting in multisystem disease, including meningoencephalitis, pneumonitis, hepatitis, thrombocytopaenia, osteitis, hepatosplenomegaly, blindness, and hearing loss. Congenital syphilis is a leading infectious cause of long-term infant disability globally.[1] In 2020, the global rate of congenital syphilis was 425 cases per 100 000 livebirths, substantially higher than WHO's 2007 elimination target of 50 cases per 100 000 livebirths,[1,8] despite the availability of tests which are acceptable to patients and effective treatment. Eliminating vertical transmission of syphilis is a global commitment. Although no WHO region has validated elimination of congenital syphilis, 14 countries or territories had validated elimination as of November, 2021. To reach WHO's elimination goal, the programmatic targets are: antenatal care coverage of at least 95%, a syphilis testing rate for pregnant women of at least 95% among those attending at least one antenatal care visit, and adequate syphilis treatment for at least 95% of pregnant women with syphilis seropositivity.[3]

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 health-care services contribute to challenges in controlling syphilis in pregnancy, with poor political advocacy and ongoing stigma cited as societal barriers preventing testing and treatment.[4] In several high-income countries, despite widespread availability of routine antenatal screening programmes and accessible benzylpenicillin treatment regimens, the incidence of congenital syphilis in pregnant women over the past decade has increased.[5–10] The worldwide persistence of congenital syphilis has occurred despite WHO's commitment of aiming to eliminate the infection almost two decades ago.

In this Review, we summarise the current global epidemiology of congenital syphilis, 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 the infection.

Increased rates of congenital syphilis in low-income, middle-income, and high-income countries over the past decade

The incidence of congenital syphilis varies regionally, with the highest rates in low-income and middle-income countries (LMICs; figure). In high-income countries, cases have resurged over the past decade, despite overall case rates remaining below WHO's elimination threshold (figure).[1] There were 1120 cases per 100 000 livebirths in the African region between 2012 and 2016, compared with 19 cases per 100 000 livebirths in the European region. The Americas and Eastern Mediterranean have

Key messages

- In 2020, the global rate for congenital syphilis was 425 cases per 100 000 livebirths, which is substantially higher than WHO's elimination target of 50 cases per 100 000 livebirths. Case rates are rising in many high-income countries but remain low compared with the high burden in low-income and middle-income settings.
- Repeat testing in high-risk pregnancies, partner screening, point-of-care testing, and a concerted effort in tackling health inequalities affecting marginalised populations should form a programme of measures that could improve the management of syphilis in pregnant women.
- Both treponemal and non-treponemal serological tests, microscopy, or PCR for direct detection of *Treponema 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 in congenital syphilis.
- Multiple doses of intravenous benzylpenicillin for 10 days is the only proven treatment for congenital syphilis and is based on decades of clinical experience and two small randomised controlled trials. There is an urgent need to trial alternative antibiotics, using shorter durations and oral options, to minimise the health-care burden in low-income and middle-income settings.
- The adoption of a unified case definition, improved regional and national surveillance information systems, screening programmes integrated into existing HIV testing networks, and disease registries could all provide unique epidemiological data to inform the evidence base management of congenital syphilis and develop future interventions.

Faculty, Universidad de Chile, Santiago, Chile (C Piñera MD); **Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa** (Prof H Rabie PhD); **Tygerberg Academic Hospital, Cape Town, South Africa** (Prof H Rabie); **Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe** (Prof A J Prendergast DPhil); **Blizard Institute, Queen Mary University of London, London, UK** (Prof A J Prendergast)

Correspondence to: Dr Seilesh Kadambari, Department of Paediatric Infectious Diseases, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK
seilesh.kadambari@gosh.nhs.uk

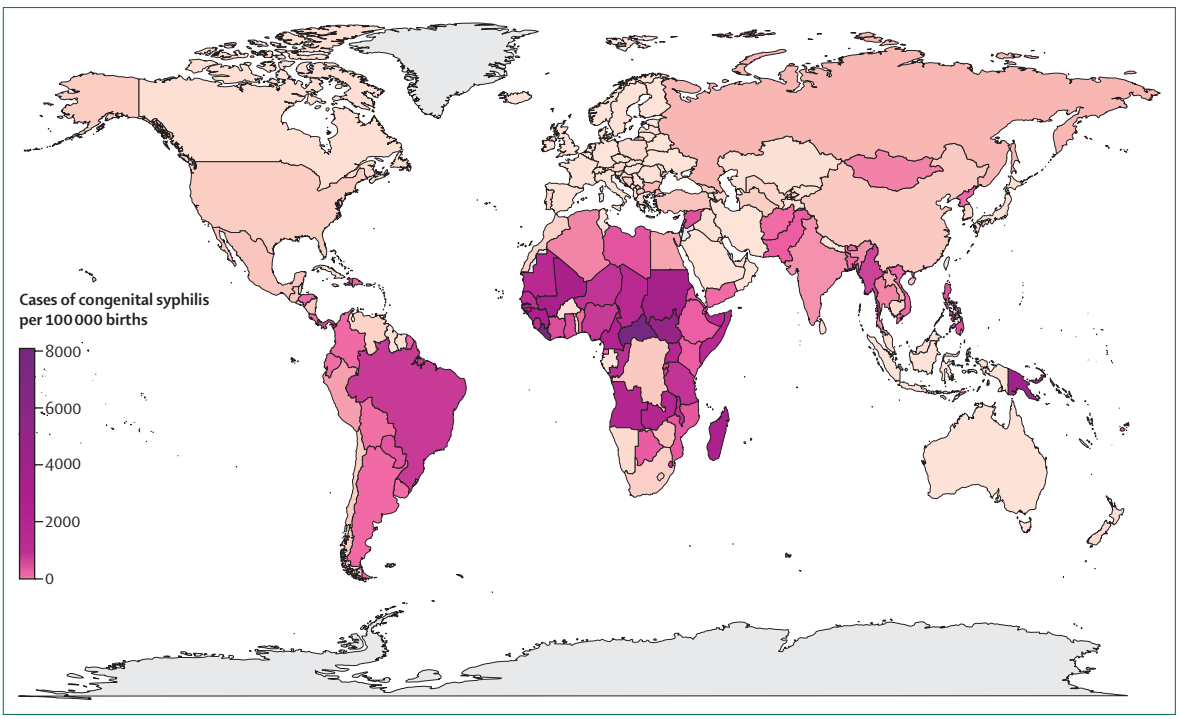

Figure: **World map of congenital syphilis cases per 100 000 births**
Data are sourced from WHO and Korenromp and colleagues' most recent estimates between 2016 and 2021.[1]

high incidence rates of 339 and 640 cases per 100 000 livebirths, respectively.[1]

Untreated syphilis in pregnancy, especially earlier stages of infection, has an estimated 60% risk of adverse birth outcomes[11] and causes 350 000 adverse birth outcomes annually worldwide.[1] Historical studies in sub-Saharan Africa suggest 25–50% of stillbirths might be associated with syphilis. However, in a longitudinal prospective observational study, only 3% of stillbirths had seropositive mothers.[12,13] Overall, data on adverse birth outcomes secondary to untreated syphilis in pregnancy are of poor 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 countries (which have local and national surveillance mechanisms) and regions (as defined by WHO; table 1).

The global incidence of congenital syphilis in 2020 was estimated at 425 cases per 100 000 livebirths, which is effectively unchanged from 473 cases per 100 000 livebirths (95% CI 385–561) in 2016.[1,3] Despite the establishment of WHO's elimination goal in 2007,[3] the incidence of congenital syphilis has fallen only marginally in the African region between 2007 and 2020, and incidence rates have not reduced in any other WHO region.

In the Americas, maternal syphilis prevalence increased from 0·64% in 2012 to 0·86% in 2016.[19] Within Latin America, 29 149 cases of congenital syphilis were reported in 2020 (excluding Brazil), with an incidence rate of 200 per 100 000 livebirths.[19] Brazil accounts for most of the reported cases of congenital syphilis in the Americas. In 2020, 115 371 cases of acquired syphilis (54·5 cases per 100 000 population), 61 441 cases of syphilis in pregnant women (2160 per 100 000 livebirths), and 22 065 cases of congenital syphilis (an incidence rate of 770 per 100 000 livebirths) were reported.[19]

Current prevalence data are likely to underestimate 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 congenital syphilis. Historical estimates of adverse birth outcome rates[11] are used to derive the current burden of syphilis-attributable adverse birth outcomes; data suggest these outcomes might be less common than previously thought.[12,13]

Surveillance systems in many LMICs are poor,[20,21] with many systems relying on syndromic case reporting for syphilis rather than aetiological case reporting from laboratory testing.[20] Additionally, when diagnosing congenital syphilis, many countries use 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

	Confirmed congenital syphilis	Presumptive congenital syphilis
WHO[3]	NA	A live birth or fetal death at more than 20 weeks' gestation or a livebirth or stillborn infant weighing more than 500 g born to a woman with positive syphilis serology and without adequate syphilis treatment; a livebirth or stillborn infant born to a woman with positive syphilis serology or with unknown serological status but with laboratory, radiological, or clinical evidence of syphilis infection
US Centers for Disease Control and Prevention[14]	An abnormal physical examination that is consistent with congenital syphilis; and a serum quantitative non-treponemal serologic titre that is four-fold (or greater) higher than the mother's titre at delivery (eg, a maternal titre of 1:2 and a neonatal titre of ≥1:8, or a maternal titre of 1:8 and a neonatal titre of ≥1:32); or a positive dark-field test or PCR of placenta, cord, lesions, or body fluids, or a positive silver stain of the placenta or cord	Possible diagnosis: normal physical examination and a serum quantitative non-treponemal serologic titre equal to or less than four-fold of the maternal titre at delivery, when the mother was untreated or inadequately treated less than 30 days before delivery
UK[15]	*Treponema pallidum* identified on dark ground microscopy, PCR, or histology; rising RPR/VDRL over 3 months or RPR/VDRL not becoming negative within 4 months; 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 3 months of birth; positive treponemal tests in a child older than 18 months or major clinical features and positive RPR/VDRL/IgM	NA
Australia Centre for Disease Control[16]	In a livebirth: mother and child both seropositive by a treponemal-specific test, and definitive laboratory evidence through direct demonstration of *T pallidum*, detection of *T pallidum*-specific IgM in the child, or if the child's serum non-treponemal serology titre at birth is at least four-fold greater than the mother's titre; in a stillborn infant: mother is seropositive by a treponemal-specific test,[3] the pregnancy outcome is a stillbirth, and there is definitive laboratory evidence of infection in utero	Suggestive laboratory evidence and probable clinical evidence required: a reactive cerebrospinal fluid non-treponemal test (ie, VDRL), or positive maternal serology and child is seropositive on non-treponemal testing, or child remains seropositive by a treponemal-specific test at age 15 months
Chile[17]	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 congenital syphilis; reactive non-treponemal test at two-fold or greater compared to that of the mother in infants without symptoms	NA
Brazil[18]	Every newborn, stillborn infant, or miscarriage to women with untreated or inadequately treated syphilis; clinical evidence, cerebrospinal fluid evidence, or radiological evidence of congenital syphilis and a positive non-treponemal test; infant non-treponemal titres at two-fold or greater difference to that of the mother; increasing non-treponemal titres infant of at least two dilutions; non-treponemal titres still reactive after 6 months; microbiological evidence of *T pallidum* infection in sample of nasal discharge, skin lesions, or from biopsy samples from miscarriage or stillbirth	NA

NA=not available. RPR=rapid plasmid regain. TPPA=*Treponema pallidum* particle agglutination assay. VDRL=venereal disease research laboratory.

Table 1: **Summary of different case definitions used for congenital syphilis in different regions**

reporting to WHO or the global AIDS monitoring system,[22] 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 high-income countries, syphilis rates in men and women of childbearing age have increased each year (table 2).[5–9,25] In the USA, the absolute number of congenital syphilis cases reported to the Centers for Disease Control and Prevention increased from 941 in 2017 to 2677 in 2021,[26] resulting in public health campaigns to promote awareness, testing, and treatment. These campaigns have targeted high-risk groups, such as young adults (ie, 15–24-year-olds), specific ethnic groups (ie, indigenous populations in Australia, the USA, and Canada) and people with low socioeconomic status and poor access to health care. Additional risk factors include having current or previous sexually transmitted infections (STIs), multiple sexual partners, bisexual male partners, co-infection with HIV or hepatitis B virus, and unprotected sex with a male partner at risk of having syphilis.[27] WHO's triple elimination initiative adopts a common approach to address the overlapping epidemics of HIV, hepatitis B virus, and syphilis. In women living with HIV, co-infection rates with syphilis were 3·1% in African cohorts, 4·1% in US cohorts, and 6·0 % in Chinese cohorts.[28–30] In a retrospective cohort from Botswana, HIV and syphilis co-infection led to increased rates of stillbirth compared with syphilis alone (absolute

	Cases per 100 000 people in 2016		Cases per 100 000 people in 2019		Cases per 100 000 people in 2021	
	Women of childbearing age	Men	Women of childbearing age	Men	Women of childbearing age	Men
Australia (age 15–44 years)[23]	7·7	25·2	16·5	39·7	16·1	37
Canada (age 15–39 years)[24]	4·3	19·8	19·3*	35·5	NA	41
England (age 15–44 years)[25]	1·7	20·3	3·28	25·8	NA	23·4
EU or EEA (age 25–34 years)[9]	~3	10·5	~4	12·8	NA	NA
USA (age 15–44 years)[26]	8·2	15·5†	8·7	20†	15·6	24·4†
Brazil[18]	13·4‡	54·0	21·5‡	95·4	27·1‡	100·7
Chile[17]	21·0‡	30	28·0‡	49	NA	45·5

EEA=European economic area. NA=not available. *Data from 2018. †Primary and secondary syphilis only. ‡Antenatal screening rate.

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

	2016	2018	2020
Eritrea	0·8%	1·3%	1·0%
Gabon	0·4%	3·6%	1·3%
Kenya	1·2%	0·9%	1·3%
Madagascar	3·8%	2·7%	2·8%
Malawi	1·4%	1·2%	2·3%
Nigeria	1·2%	0·5%	0·4%
Senegal	4·9%	0·9%	0·5%
Togo	2·3%	1·5%	2·1%
Uganda	2·9%	2·1%	2·3%
Tanzania	2·2%	1·7%	1·2%
Zambia	3·5%	5·0%	4·5%
Zimbabwe	2·4%	2·5%	2·0%

Countries included with completed data set reported over years specified. Data are from WHO's global health observatory.[33]

Table 3: **Proportion of antenatal care attendees with positive syphilis serology in low-income settings**

risk increase 3·9%, odds ratio 1·58, 95% CI 0·77–3·25), suggesting that individuals with co-infection are at greater risk of adverse outcomes.[31]

Approaches to improve screening in pregnancy

Prevention of congenital syphilis is achievable through robust antenatal health-care 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, which is far short of WHO's target of at least 95%.[1] The past 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 2019–20.[32] However, populations with the highest syphilis prevalence have the lowest antenatal care coverage (table 3).

Antenatal treatment is highly effective at reducing the risk of congenital syphilis. A meta-analysis evaluating long-acting penicillin regimens in pregnancy found that in 3450 livebirths, treatment reduces the relative risk of congenital syphilis by 97% (95% CI 93–98); additionally, stillbirths were reduced by 82%, preterm delivery by 64%, and neonatal death by 80%.[24,34,35]

Development of evidence-based guidance specifically for primary care during the pregnancy and postnatal period is essential, 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 for the UK,[36] the USA,[14] Australia,[37] and Brazil[38] recommend reverse algorithms for screening, comprised of a treponemal test followed by a confirmatory non-treponemal test. WHO syphilis guidelines focus on settings in which high-quality laboratory testing is not generally available, and recommend the use of treponemal point-of-care syphilis testing and on-site treatment if the test is positive.[39]

Repeat testing in pregnancy

In the context of rising syphilis rates in women of childbearing age, repeat testing in pregnancy could increase the detection of new cases and should be strongly considered in screening programmes. The Integrated Screening Outcomes Surveillance Service (ISOSS) report in the UK highlights several cases in which syphilis was acquired later in pregnancy despite the mothers initially having a negative syphilis test.[23] Prospective antenatal studies in Tanzania and South Africa report rates of infection during pregnancy of 1·6% and 2·5%, respectively.[40,41]

Serial testing could be prioritised for people with risk factors, such as specific minority ethnic populations, people with housing instability or STIs, people who use drugs, and sex workers.[14,25,42] In the EU, 22 out of 24 countries screen for syphilis in the first trimester; however, only three recommend re-testing in high-risk groups.[43] In Latin America, most countries have national strategic protocols with repeat testing.[17] Chile, for example, has three screening points for syphilis for all women during pregnancy, with non-treponemal tests at the first antenatal visit, at weeks 24 and 32–34, and one test at delivery.[44] However, prioritising high-risk groups might 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 a substantial number of cases among low-risk groups.

Universal re-screening could 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 a changing epidemiology of syphilis.[42] In a UK cost-effectiveness modelling analysis, universal re-screening would prevent 5·5 cases of congenital syphilis per year (from 8·8 cases to 3·3), which is consistent with findings that new infections during pregnancy are a notable cause of the infection.[45] However, due to the relatively low prevalence of syphilis among women of childbearing age in the UK, universal re-screening is not cost-effective.[45] Screening would become cost-effective if the maternal risk of acquiring syphilis between screening reached an incidence of 0·005% pregnancies, but the current infection rate during pregnancy is predicted as 0·0017%. No high-income country has integrated universal point-of-care testing into standard care; however, newer treponemal and non-treponemal antibody-based point-of-care tests that discriminate 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 are markedly higher than in the general population and are 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 an unknown syphilis status.[46–48] A Ugandan trial found that 81·7% of partners of pregnant women with syphilis did not attend syphilis screening after their pregnant partner received a syphilis diagnosis, despite multiple reminders.[48] 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%.[49,50] 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, but these studies suggest multiple challenges are present, including inadequate partner notification and poor engagement with health care.

A greater understanding of the barriers to partner screening are needed to address the issue of poor uptake. In a Brazilian study of 400 pregnant women inviting their partners to attend STI screening, only 64% attended.[51] 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 substantially improve testing and treatment rates.[51] Studies of antenatal partner HIV screening in Brazil and sub-Saharan Africa have highlighted several important factors that affect partner engagement, including HIV-related stigma, fear of testing positive, and poor awareness of the risks and benefits of screening.[52,53] Unfortunately, specific data on attitudes and barriers to partner screening for syphilis are scarce.

Barriers to antenatal screening

Health inequalities are associated with highly divergent rates of syphilis between and within countries. Congenital syphilis disproportionately affects marginalised and disenfranchised populations. In high-income countries and LMICs, stigma, discrimination, and institutional racism present notable barriers to appropriate screening and antenatal care. Stigma is maintained through institutional barriers (eg, the criminalisation of sex work), structural barriers (eg, poor access to sexual and reproductive health education), and societal factors (eg, language used in the medical community to describe so-called high-risk sexual behaviours and unsafe sex).[54,55]

Among women attending antenatal care globally, syphilis screening rates are 66%, which suggests missed opportunities for screening among those within antenatal care.[1] Whether these missed opportunities are due to declining rates of testing or a complete absence of screening is unclear. Women might decline screening in pregnancy for multiple reasons, including fear of stigma, poor awareness of consequences of syphilis in pregnancy, and a perception of low risk. Concomitantly, poor-quality antenatal care might be integral in causing this discrepancy through capacity issues, poor education among health-care providers, and failing to offer testing.

Universal access to sexual and reproductive health care, reducing health inequalities, and lowering neonatal deaths below 12 per 1000 livebirths 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 WHO's 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, challenges in eliminating congenital syphilis include poor follow-up rates and delayed treatment. Point-of-care testing could substantially improve delivery of care, as these tests have 75–90% sensitivity and 95–99% specificity compared with standard serological assays.[56] In 2019, dual HIV and syphilis point-of-care tests were recommended by WHO as first-line tests for screening, which will hopefully increase testing capacity and equity of access. HIV screening exceeds syphilis screening across many countries, and the introduction of dual point-of-care testing would therefore immediately increase screening coverage of syphilis.[57] Syphilis point-of-care testing at first antenatal appointments increased screening rates compared with serological tests (from 0–58% to 70–100% across several studies and sites) and treatment rates (when allowing for same-day testing and treatment), and improved outcomes (93% reduction in congenital syphilis).[35,58–61] Point-of-care tests are emerging that detect both treponemal and non-treponemal antibodies, enabling distinction between active and past infection. The distribution of point-of-care testing is facilitated by a reduction in the unit cost to less than US$1 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.[62–64]

Syphilis point-of-care tests followed by immediate treatment might have a role in hard-to-reach populations, such as those in rural Australia and Canada, and could reduce delays between sampling, results, and treatment.[42] Populations in which follow-up care is not guaranteed could benefit from point-of-care testing followed by treatment without confirmatory testing, particularly for individuals with no known history of syphilis infection or previous treatment. Furthermore, point-of-care testing might be more

acceptable to groups such as indigenous populations, as it can be implemented by a wider range of health-care providers, encourages participation in the diagnostic process, and does not require skilled phlebotomy.[65,66] Testing and treatment of sexual partners could also reduce the risk of re-infection.

Adopting novel diagnostic and treatment approaches in the neonate

Diagnosing congenital syphilis remains challenging due to the short supply of widely available molecular assays to detect *Treponema pallidum*, and the health system's reliance on serology, which is challenging to interpret in the context of transplacental transfer of antibodies.[67,68] Furthermore, most neonates infected with syphilis have unrecognised or asymptomatic infection and the signs in symptomatic neonates are typically non-specific. Several current definitions use a combination of clinical features with supportive serology (table 1).[69] Most consider visualisation or isolation of *T pallidum* or treponemal DNA as the gold standard; however, these tests have low sensitivity and availability. Investing resources into developing syphilis PCR testing availability could divert essential funding away from strengthening health-care infrastructures to deliver robust screening using cheap, accurate, and rapid serology-based assays that enable prompt treatment during pregnancy.

Serology interpretation

Serological tests for syphilis can be divided into treponemal (qualitative assays that detect antibodies against *T pallidum* antigens) or non-treponemal assays (quantitative assays that detect antibodies against cardiolipin and lecithin, which are released during host cell damage and are therefore not specific to syphilis infection).

IgG treponemal antibodies detected in an infant might indicate congenital infection or transplacental transfer of maternal antibodies, and should be interpreted with expertise. Treponemal tests are useful when they remain positive in the infant beyond 6 months of age, which is suggestive of endogenous production and therefore of congenital syphilis. An infant with positive non-treponemal antibody (eg, rapid plasma reagin and venereal disease research laboratory) titres at least four-fold greater than the maternal titre, or treponemal IgM seropositivity, both suggest endogenous antibody production in the infant, which is consistent with congenital infection. However, several studies indicate that using a threshold of four-fold is too high, with sensitivity estimates of 4–13%.[67] Non-treponemal antibody concentrations are used to track the infant's 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 an infant's 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 shows increased sensitivity compared with dark-field microscopy,[70,71] and most studies in adults show that nested PCR has the highest sensitivity.[72] Sensitivity ranges between 75·8 and 93·8% in samples from primary chancres in adults, depending on the reference standard.[70,72,73]

Specificity and positive predictive values of PCR tests taken from appropriate sites and samples approach 100% in most published series.[72] Evaluating the performance of PCR in congenital syphilis is challenging due to a short supply of study cohorts, variation in standard reference comparator, an absence of standardised assays, and variability in patient samples used. A prospective study of 22 people with congenital syphilis showed positive PCR results from a variety of sources, including placental tissue, cerebrospinal fluid, nasal secretions, amniotic fluid, and skin biopsies.[74] In neonates, the optimal sample will depend on clinical presentation, although a greater number of appropriate samples is associated with higher sensitivity.

Point-of-care testing

Point-of-care tests have not been evaluated in neonatal populations. Most point-of-care tests currently approved are IgG-based treponemal assays, which might result in false positives in neonates due to transplacental IgG representing previously treated maternal infection. Dual non-treponemal and treponemal point-of-care assays with high sensitivity and specificity are becoming available for adults, although none are currently recommended by WHO.[75] Non-treponemal point-of-care tests are currently unable to report a quantitative titre, which is needed to evaluate adequate maternal treatment, compare maternal and infant titres, and follow up on serial non-treponemal titres from infants.

Treatment in pregnant women and neonates

Standard treatment for congenital syphilis is 10 days of intravenous benzylpenicillin (every 12 h during the first 7 days of life, and every 8 h thereafter for a total of 10 days).[69] This regimen originates from decades of clinical experience and two randomised clinical trials in 1989 (n=152 cases) and 1997 (n=8 cases).[76]

Effective non-penicillin-based regimens are required in pregnant women with true penicillin allergy, would provide alternative treatments during shortages of penicillin, and might be more conducive to administration and outpatient management. Procaine and benzathine benzylpenicillin shortages have

occurred in many countries over the past decade and have a major negative effect on the implementation of recommended regimens.[77–79] For example, during a penicillin shortage in Brazil in 2015, 55·2% of pregnant women with congenital syphilis had inadequate treatment.[80] Challenges within the supply chain will be compounded by increasing global demand for penicillin. More widespread point-of-care testing is estimated to increase the number of doses required for pregnant women, from 414 459 in 2019 to 1 078 428 in 2030.[81]

Despite the use of alternative treatments during penicillin shortages, data on infant outcomes are scarce. No randomised trials evaluate alternative regimens in neonates or in pregnancy. 10 days of intravenous treatment with ceftriaxone has been shown to have equivalence compared with standard regimens in non-pregnant adult populations in both early syphilis and, more recently, in neurosyphilis.[82–84] However, the use of ceftriaxone in pregnancy has been limited to case studies and non-randomised studies, and no strong recommendation on its use in preventing congenital syphilis is currently possible.[85] 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, which would allow for ambulatory treatment. However, ceftriaxone is given as a 10-day intravenous or intramuscular course, which presents a substantial burden to health-care systems, and might not be suited to LMICs.

Oral regimens could be useful, particularly in LMICs in which the use of intravenous antibiotics is demanding on health-care systems and patients. However, no evidence exists to support the use of oral agents in pregnancy or neonates. A phase 2 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.[86] Cefixime has been previously used in pregnant women for urinary tract infections and has shown 87% efficacy (95% CI 69–100; 13/15 patients) in a small pilot trial in men and non-pregnant women with early syphilis.[87] 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, pregnant, and non-pregnant populations.[88–90] UK-based ISOSS data and published reports from China have shown treatment failure in pregnant women receiving azithromycin resulting in congenital syphilis and neonatal deaths.[89] 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 in people with HIV.[91,92] However, in a case series of pregnant women treated with oral amoxicillin alone, benefit was limited to those with early syphilis. There were no cases (0/26) of congenital syphilis in infants born to women with early syphilis, but 33% (15/45 cases) of infants born to women with late syphilis were diagnosed with congenital syphilis.[93]

Research priorities

Epidemiology

Strengthening national surveillance and information systems is essential to accurately monitor cases of 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. WHO's surveillance definition (table 1) would be effective in resource-poor and rural areas with restricted laboratory access as it requires less neonatal testing compared with definitions used in the USA and the UK, does not require testing of stillborn babies, and captures neonates at risk of congenital syphilis. However, this definition risks overestimating the true burden of disease. Additionally, WHO's definition might not be optimal in middle-income and high-income countries with high testing capacities. An important future consideration is the feasibility to include point-of-care testing in 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. The US Centers for Disease Control and Prevention is currently undergoing a multibillion-dollar data modernisation initiative to strengthen the public health landscape in response to health information gaps identified during the COVID-19 pandemic.[94] To gain effective real-time data, new semi-automated platforms were designed that integrate data from multiple sources and have a single platform of access.[94] Key barriers include poor data sharing between different health and government agencies, low investment in information systems, and an overstretched public health workforce.

Cohort studies might be better suited to evaluating adverse outcome rates and prevalence of congenital syphilis in populations with low uptake of antenatal care. Studies could include large-scale, population-based screening programmes integrated into existing HIV testing networks using routine health-care data, and integration of regional microbiology testing with national databases (table 4). Targeted investigation or minimally invasive tissue samples of stillborn infants would help to establish prevalence estimates of syphilis-related

	Issues	Study suggestions
Epidemiology	Poor knowledge of the true incidence of congenital syphilis and syphilis in pregnancy in LMIC settings; rates of stillbirths and adverse birth outcomes in pregnant women with syphilis are unclear; long-term outcomes of asymptomatic and symptomatic neonates are unknown; no single definition of congenital syphilis; weak information systems with little data integration and data sharing	Strengthen surveillance networks and information systems, particularly in LMICs, drawing on more widely available point-of-care 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	Public health value of repeat testing in pregnancy should be reviewed; the role of point-of-care testing as a screening tool in pregnancy should be made clear; incidence of syphilis in partners of pregnant women is unknown; few strategies to improve testing and treatment of partners	Population-based studies that evaluate cost-effectiveness and outcomes of repeat testing in pregnancy in high-risk groups; targeted screening studies using point-of-care testing in specific populations to assess acceptability and efficacy of testing; qualitative studies to understand how partner testing and screening can be improved
Diagnosis	Utility of point-of-care testing in neonates is unknown; sensitivity of PCR testing in congenital syphilis is unknown	Measure the utility (ie, added rates of detection, number of cases treated, and cost burden) using point-of-care testing; validation of different commercially available PCR assays to assess sensitivity and specificity of different biological samples
Treatment	Is ceftriaxone an effective treatment for congenital syphilis? Can the duration of antibiotic treatment for congenital syphilis be shortened without negatively impacting cure? Is there a role for single-dose penicillin in the treatment or prevention of congenital syphilis in high-risk infants? Can oral antibiotics be a treatment option for congenital syphilis?	Randomised controlled trial comparing different durations of ceftriaxone and penicillin treatment for the treatment of congenital syphilis
Vaccine development	What are the corrolates of protective immunity from syphilis? What are the essential proteins required for syphilis 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

Table 4: **Research priorities to improve diagnosis and management of congenital syphilis**

stillbirths.[95] Additionally, establishment of disease registries could capture disease trends and long-term neurodevelopmental outcomes, and provide a platform for future interventions.

Holistic and non-discriminatory antenatal care

Few studies evaluate interventions to improve adherence to antenatal or postnatal care in individuals with syphilis infection.[96] Future research could evaluate models of testing (eg, mobile units, point-of-care testing, and pharmacy testing, such as a current Canadian trial [NCT05534633]) and methods of result reporting to evaluate population-specific acceptability, particularly with regard to confidentiality. Scope also exists to evaluate the effect 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 HIV/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. Although campaigns relating to HIV have been highly effective, syphilis presents its own public awareness challenges—such as low awareness of its risk to neonates—and should be considered in the design of these campaigns.

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

Diagnosis and management

As highlighted, diagnosing congenital syphilis remains challenging due to limitations of available tests and high rates of undiagnosed and asymptomatic infections. In LMICs, development and validation of point-of-care tests for diagnosing congenital syphilis could contribute to increasing treatment rates, reducing treatment delays, and collecting epidemiological data.

Randomised controlled trials evaluating treatment regimens in pregnant women and neonates are notably absent. 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 the effectiveness of non-penicillin regimens (ie, third-generation cephalosporin compared with standard care) and oral regimens (ie, amoxicillin plus probenecid compared with standard care; table 4). Key additional questions pertain to the minimal effective duration of third-generation cephalosporin, the effectiveness of single-dose penicillin in some high-risk neonates, and the treatment duration of asymptomatic versus symptomatic infection.

Vaccine development

No vaccines are currently in human clinical trials, and the optimal vaccine platform or target antigen has not been established. Knowledge about immune correlates of protection from syphilis infection is poor.[97,98] Due to an outer membrane that does not contain lipopolysaccharides, and few transmembrane proteins, the immune response to syphilis is markedly different to that of conventional bacteria. In humans, no studies have identified a protective response or evaluated immune correlates against re-infection.[98] In animal models,

complete protection has been challenging to establish—in rabbits, the injection of antibodies only appears to delay lesion development.[99] Antibodies appear to facilitate opsonisation and complement-mediated destruction.[100] Vaccine design could be informed by the presence of broadly neutralising antibodies in human populations and corresponding antigens; however, it is unclear if these antibodies would be protective. Cellular immunity appears important based on immunofluorescent studies showing prominent infiltration of macrophages, $CD4^+$, and $CD8^+$ T cells, but functional studies evaluating the requirement for these cells in clearance are scarce. However, the adoptive transfer of T cells in guinea pigs suggest that these alone are not protective against infection.[101]

Current evidence suggests low genetic diversity in most syphilis genes, although there is variation within outer membrane proteins, 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 more than 200 from the UK.[102]

An important advance has been in-vitro culture and genetic manipulation of *T pallidum* without the requirement for propagation in rabbits.[103,104] Future studies should focus on using these new methods to identify the surface proteins important for pathogenesis and establish potential targets for vaccine development.[104]

Conclusions

This Review highlights the persistent and under-recognised global burden of congenital syphilis, and the poor progress made in eliminating the infection. In high-income countries with low incidence of congenital syphilis, rates of syphilis in women of childbearing age have increased more than 200% over the past 5 years and, in high-burden LMICs, little progress was made in reducing rates of congenital syphilis between 2012 and 2016. There has been only patchy progress in the implementation of point-of-care diagnostics, and antenatal screening coverage remains low. Important priorities to address this low level of implementation include a better understanding of current epidemiology of the disease, including its true burden and the proportion of syphilis-related adverse birth outcomes. Strengthening antenatal care systems is essential 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 2022–30 WHO triple-initiative strategy, encapsulate the broad and interconnected approaches that are required to overcome the challenges of the infection. Congenital syphilis 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 STIs.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed for articles published from Jan 1, 1970, to Feb 28, 2023, by combining "syphilis" or "congenital syphilis" with "epidemiology", "diagnosis", "point of care", "treatment", "pregnan*", "management", or "prevent*". WHO publications since 2007 and datasets that evaluated epidemiological data from regional or national public health bodies that have published detailed data (for the UK, the USA, Canada, the EU, and Australia) were also interrogated. Finally, a clinical trial database search of https://www.clinicaltrials.gov and https://www.trialsearch.who.int for any current or recent interventional trials relating to syphilis and congenital syphilis between Jan 1, 1970 and Feb 28, 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.

Contributors

SK and PM conceptualised the paper, conducted the literature review, and devised all tables and the figure. PM wrote the first draft of the paper. All authors contributed to the literature review and provided scientific content for each section of the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

References

1 Korenromp EL, Rowley J, Alonso M, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes—estimates for 2016 and progress since 2012. *PLoS One* 2019; **14:** e0211720.

2 WHO. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030. Geneva: World Health Organization, 2022.

3 WHO. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus. Geneva: World Health Organization, 2021.

4 WHO. The global elimination of congenital syphilis: rationale and strategy for action. Geneva: World Health Organization, 2007.

5 Hui BB, Ward JS, Guy R, Law MG, Gray RT, Regan DG. Impact of testing strategies to combat a major syphilis outbreak among Australian Aboriginal and Torres Strait Islander peoples: a mathematical modeling study. *Open Forum Infect Dis* 2022; **9:** ofac119.

6 Nelson R. Congenital syphilis increases in the USA. *Lancet Microbe* 2022; **3:** e171.

7 Benoit P, Tennenhouse L, Lapple A, et al. Congenital syphilis re-emergence in Winnipeg, Manitoba. *Can Commun Dis Rep* 2022; **48:** 89–94.

8 Kanai M, Arima Y, Shimada T, et al. Increase in congenital syphilis cases and challenges in prevention in Japan, 2016–2017. *Sex Health* 2021; **18:** 197–99.

9 European Centre for Disease Prevention and Control. Syphilis—annual epidemiological report for 2019. Stockholm: European Centre for Disease Prevention and Control, 2022.

10 National Institute of Infectious Diseases. Syphilis, Japan. April 9, 2020. https://www.niid.go.jp/niid/en/iasr-e.html (accessed July 25, 2023).

11 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:** 217–26.

12 Madhi SA, Briner C, Maswime S, et al. Causes of stillbirths among women from South Africa: a prospective, observational study. *Lancet Glob Health* 2019; **7:** e503–12.

13 Folgosa E, Osman NB, Gonzalez C, Hägerstrand I, Bergström S, Ljungh A. Syphilis seroprevalence among pregnant women and its role as a risk factor for stillbirth in Maputo, Mozambique. *Genitourin Med* 1996; **72:** 339–42.

14 US Centers for Disease Control and Prevention. Syphilis during pregnancy: sexually transmitted infections treatment guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/syphilis-pregnancy.htm (accessed Aug 25, 2022).

15 Kingston M, French P, Higgins S, et al. UK national guidelines on the management of syphilis 2015. *Int J STD AIDS* 2016; **27:** 421–46.

16 Communicable Diseases Network Australia. Syphilis (congenital): Australian national notifiable diseases case definition. Jan 1, 2021. https://www.health.gov.au/sites/default/files/documents/2022/06/syphilis-congenital-surveillance-case-definition.pdf (accessed July 25, 2023).

17 Departamento de Epidemiología. Informe Epidemiológico anual sífilis 2021. http://epi.minsal.cl/wp-content/uploads/2022/12/Informe-Anual-Sifilis-Chile-2021.pdf (accessed July 25, 2023).

18 Ministério da Saúde. Boletim epidemiológico de sífilis—número especial. Oct 17, 2022. https://www.gov.br/aids/pt-br/centrais-de-conteudo/boletins-epidemiologicos/2022/sifilis/boletim_sifilis-2022_internet-2.pdf/view (accessed July 25, 2023).

19 Pan American Health Organization, WHO. Epidemiological review of syphilis in the Americas, December 2021. June 14, 2022. https://iris.paho.org/handle/10665.2/56085 (accessed July 25, 2023).

20 WHO. Report on global sexually transmitted infection surveillance. Geneva: World Health Organization, 2018.

21 Worsley-Tonks KEL, Bender JB, Deem SL, et al. Strengthening global health security by improving disease surveillance in remote rural areas of low-income and middle-income countries. *Lancet Glob Health* 2022; **10:** e579–84.

22 UNAIDS. Indicators and questions for monitoring progress on the 2021 Political Declaration on HIV and AIDS—global AIDS monitoring 2023. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS), 2022.

23 UNSW Sydney, Kirby Institute. Australian sexually transmitted infection rates. https://data.kirby.unsw.edu.au/STIs (accessed July 25, 2023).

24 Watson-Jones D, Gumodoka B, Weiss H, et al. Syphilis in pregnancy in Tanzania. II. The effectiveness of antenatal syphilis screening and single-dose benzathine penicillin treatment for the prevention of adverse pregnancy outcomes. *J Infect Dis* 2002; **186:** 948–57.

25 Public Health England. Infectious diseases in pregnancy screening: ISOSS congenital syphilis report 2015 to 2020. July 27, 2021. https://www.gov.uk/government/publications/infectious-diseases-in-pregnancy-screening-isoss-congenital-syphilis-report-2015-to-2020 (accessed July 25, 2023).

26 US Centers for Disease Control and Prevention. CDC sexually transmitted disease surveillance 2020. 2021. https://www.cdc.gov/std/statistics/2021/default.htm#:~:text=In%202021%20alone%2C%20there%20were,and%20over%202%2C800%20cases%20reported (accessed July 25, 2023).

27 Fang J, Silva RM, Tancredi DJ, Pinkerton KE, Sankaran D. Examining associations in congenital syphilis infection and socioeconomic factors between California's small-to-medium and large metro counties. *J Perinatol* 2022; **42:** 1434–39.

28 Gilbert L, Dear N, Esber A, et al. Prevalence and risk factors associated with HIV and syphilis co-infection in the African Cohort Study: a cross-sectional study. *BMC Infect Dis* 2021; **21:** 1123.

29 Wu Y, Zhu W, Sun C, et al. Prevalence of syphilis among people living with HIV and its implication for enhanced coinfection monitoring and management in China: a meta-analysis. *Front Public Health* 2022; **10:** 1002342.

30 Kidd S, Torrone E, Su J, Weinstock H. Reported primary and secondary syphilis cases in the United States: implications for HIV infection. *Sex Transm Dis* 2018; **45** (suppl 1)**:** S42–47.

31 Shava E, Moyo S, Zash R, et al. Brief report: high rates of adverse birth outcomes in HIV and syphilis coinfected women in Botswana. *J Acquir Immune Defic Syndr* 2019; **81:** e135–40.

32 WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. https://www.who.int/publications/i/item/9789240027077 (accessed Aug 25, 2022).

33 World Health Organization. Global Health Observatory data repository. Syphilis in pregnancy. Data by country. 2022. https://apps.who.int/gho/data/view.main.23610 (accessed July 31, 2023).

34 Terris-Prestholt F, Watson-Jones D, Mugeye K, et al. Is antenatal syphilis screening still cost effective in sub-Saharan Africa. *Sex Transm Infect* 2003; **79:** 375–81.

35 Blencowe H, Cousens S, Kamb M, Berman S, Lawn JE. Lives Saved Tool supplement detection and treatment of syphilis in pregnancy to reduce syphilis related stillbirths and neonatal mortality. *BMC Public Health* 2011; **11** (suppl 3)**:** S9.

36 Public Health England. Infectious diseases in pregnancy screening programme handbook 2016 to 2017. London: Public Health England, 2016.

37 Australian Government Department of Health and Aged Care. Pregnancy care guidelines: syphilis. https://www.health.gov.au/resources/pregnancy-care-guidelines/part-f-routine-maternal-health-tests/syphilis (accessed July 25, 2023).

38 Domingues CSB, Duarte G, Passos MRL, Sztajnbok DCDN, Menezes MLB. Brazilian protocol for sexually transmitted infections, 2020: congenital syphilis and child exposed to syphilis. *Rev Soc Bras Med Trop* 2021; **54** (suppl 1)**:** e2020597.

39 WHO. WHO guideline on syphilis screening and treatment for pregnant women. Geneva: World Health Organization, 2017.

40 Lawi JDT, Mirambo MM, Magoma M, et al. Sero-conversion rate of syphilis and HIV among pregnant women attending antenatal clinic in Tanzania: a need for re-screening at delivery. *BMC Pregnancy Childbirth* 2015; **15:** 3.

41 Hoque M, Hoque ME, van Hal G, Buckus S. Prevalence, incidence and seroconversion of HIV and syphilis infections among pregnant women of South Africa. *S Afr J Infect Dis* 2021; **36:** 296.

42 Public Health Agency of Canada. Syphilis in Canada, technical report on epidemiological trends, determinants and interventions. https://www.canada.ca/en/services/health/publications/diseases-conditions/syphilis-epidemiological-report.html (accessed July 25, 2023).

43 ECDC. Antenatal screening for HIV, hepatitis B, syphilis and rubella susceptibility in the EU/EEA. Stockholm: European Centre for Disease Prevention and Control, 2016.

44 Ministerio de Salud, Gobierno de Chile. Norma conjunta de prevención de la transmisión vertical del VIH y la sífilis. https://diprece.minsal.cl/wrdprss_minsal/wp-content/uploads/2015/01/NORMA-DE-PTV-VIH-SIFILIS.pdf (accessed July 25, 2023).

45 Huntington S, Weston G, Seedat F, et al. Repeat screening for syphilis in pregnancy as an alternative screening strategy in the UK: a cost-effectiveness analysis. *BMJ Open* 2020; **10:** e038505.

46 Liao K-J, Zhang S-K, Liu M, et al. Seroepidemiology of syphilis infection among 2 million reproductive-age women in rural China: a population-based, cross-sectional study. *Chin Med J (Engl)* 2017; **130:** 2198–204.

47 Dou L, Wang X, Wang F, et al. Epidemic profile of maternal syphilis in China in 2013. *BioMed Res Int* 2016; **2016:** 9194805.

48 Parkes-Ratanshi R, Mbazira Kimeze J, Nakku-Joloba E, et al. Low male partner attendance after syphilis screening in pregnant women leads to worse birth outcomes: the Syphilis Treatment of Partners (STOP) randomised control trial. *Sex Health* 2020; **17:** 214–22.

49 Green H, Taleghani S, Nyemba D, Myer L, Davey DJ. Partner notification and treatment for sexually transmitted infections among pregnant women in Cape Town, South Africa. *Int J STD AIDS* 2020; **31:** 1282–90.

50 Offorjebe OA, Wynn A, Moshashane N, et al. Partner notification and treatment for sexually transmitted infections among pregnant women in Gaborone, Botswana. *Int J STD AIDS* 2017; **28:** 1184–89.

51 Yeganeh N, Kreitchmann R, Leng M, Nielsen-Saines K, Gorbach PM, Klausner JD. Diagnosis and treatment of sexually transmitted infections in male partners of pregnant women in Brazil. *Int J STD AIDS* 2021; **32:** 1242–49.

52 Yeganeh N, Simon M, Mindry D, et al. Barriers and facilitators for men to attend prenatal care and obtain HIV voluntary counseling and testing in Brazil. *PLoS One* 2017; **12:** e0175505.

53 Morfaw F, Mbuagbaw L, Thabane L, et al. Male involvement in prevention programs of mother to child transmission of HIV: a systematic review to identify barriers and facilitators. *Syst Rev* 2013; **2:** 5.

54 Martin K, Olaru ID, Buwu N, et al. Uptake of and factors associated with testing for sexually transmitted infections in community-based settings among youth in Zimbabwe: a mixed-methods study. *Lancet Child Adolesc Health* 2021; **5:** 122–32.

55 Matsick JL, Wardecker BM, Oswald F. Treat sexual stigma to heal health disparities: improving sexual minorities' health outcomes. *Policy Insights Behav Brain Sci* 2020; **7:** 205–13.

56 Jafari Y, Peeling RW, Shivkumar S, Claessens C, Joseph L, Pai NP. Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLoS One* 2013; **8:** e54695.

57 Storey A, Seghers F, Pyne-Mercier L, Peeling RW, Owiredu MN, Taylor MM. Syphilis diagnosis and treatment during antenatal care: the potential catalytic impact of the dual HIV and syphilis rapid diagnostic test. *Lancet Glob Health* 2019; **7:** e1006–08.

58 Swartzendruber A, Steiner RJ, Adler MR, Kamb ML, Newman LM. Introduction of rapid syphilis testing in antenatal care: a systematic review of the impact on HIV and syphilis testing uptake and coverage. *Int J Gynaecol Obstet* 2015; **130** (suppl 1)**:** S15–21.

59 Brandenburger D, Ambrosino E. The impact of antenatal syphilis point of care testing on pregnancy outcomes: a systematic review. *PLoS One* 2021; **16:** e0247649.

60 Saweri OPM, Batura N, Al Adawiyah R, et al. Economic evaluation of point-of-care testing and treatment for sexually transmitted and genital infections in pregnancy in low- and middle-income countries: a systematic review. *PLoS One* 2021; **16:** e0253135.

61 Munkhuu B, Liabsuetrakul T, Chongsuvivatwong V, McNeil E, Janchiv R. One-stop service for antenatal syphilis screening and prevention of congenital syphilis in Ulaanbaatar, Mongolia: a cluster randomized trial. *Sex Transm Dis* 2009; **36:** 714–20.

62 Plate DK. Evaluation and implementation of rapid HIV tests: the experience in 11 African countries. *AIDS Res Hum Retroviruses* 2007; **23:** 1491–98.

63 Benzaken AS, Bazzo ML, Galban E, et al. External quality assurance with dried tube specimens (DTS) for point-of-care syphilis and HIV tests: experience in an indigenous populations screening programme in the Brazilian Amazon. *Sex Transm Infect* 2014; **90:** 14–18.

64 Montoya PJ, Lukehart SA, Brentlinger PE, et al. Comparison of the diagnostic accuracy of a rapid immunochromatographic test and the rapid plasma reagin test for antenatal syphilis screening in Mozambique. *Bull World Health Organ* 2006; **84**: 97–104.

65 Bergman J, Gratrix J, Plitt S, et al. Feasibility and field performance of a simultaneous syphilis and HIV point-of-care test based screening strategy in at risk populations in Edmonton, Canada. *Aids Res Treat* 2013; **2013:** 819593.

66 Gliddon HD, Peeling RW, Kamb ML, Toskin I, Wi TE, Taylor MM. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. *Sex Transm Infect* 2017; **93:** S3–15.

67 Herremans T, Kortbeek L, Notermans DW. A review of diagnostic tests for congenital syphilis in newborns. *Eur J Clin Microbiol Infect Dis* 2010; **29:** 495–501.

68 Satyaputra F, Hendry S, Braddick M, Sivabalan P, Norton R. The laboratory diagnosis of syphilis. *J Clin Microbiol* 2021; **59:** e0010021.

69 US Centers for Disease Control and Prevention. Congential syphilis: sexually transmitted infections treatment guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/congenital-syphilis.htm (accessed Aug 25, 2022).

70 Vrbová E, Mikalová L, Grillová L, et al. A retrospective study on nested PCR detection of syphilis treponemes in clinical samples: PCR detection contributes to the diagnosis of syphilis in patients with seronegative and serodiscrepant results. *PLoS One* 2020; **15:** e0237949.

71 Gayet-Ageron A, Sednaoui P, Lautenschlager S, et al. Use of *Treponema pallidum* PCR in testing of ulcers for diagnosis of primary syphilis. *Emerg Infect Dis* 2015; **21:** 127–29.

72 Gayet-Ageron A, Lautenschlager S, Ninet B, Perneger TV, Combescure C. Sensitivity, specificity and likelihood ratios of PCR in the diagnosis of syphilis: a systematic review and meta-analysis. *Sex Transm Infect* 2013; **89:** 251–56.

73 Noda AA, Rodríguez I, Grillová L, Bosshard PP, Lienhard R. Accuracy of PCR and serological testing for the diagnosis of primary syphilis: both tests are necessary. *Int J STD AIDS* 2019; **30:** 1087–94.

74 Garel B, Grange P, Benhaddou N, et al. Congenital syphilis: a prospective study of 22 cases diagnosed by PCR. *Ann Dermatol Venereol* 2019; **146:** 696–703.

75 Marks M, Yin Y-P, Chen X-S, et al. Meta-analysis of the performance of a combined treponemal and nontreponemal rapid diagnostic test for syphilis and yaws. *Clin Infect Dis* 2016; **63:** 627–33.

76 Walker GJ, Walker D, Molano Franco D, Grillo-Ardila CF. Antibiotic treatment for newborns with congenital syphilis. *Cochrane Database Syst Rev* 2019; **2:** CD012071.

77 US Centers for Disease Control and Prevention. Procaine penicillin G shortage. https://www.cdc.gov/std/treatment/drugnotices/procaine-peng.htm (accessed Aug 25, 2022).

78 WHO. Global shortages of penicillin. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/stis/treatment/shortages-of-penicillin (accessed Aug 25, 2022).

79 Nurse-Findlay S, Taylor MM, Savage M, et al. Shortages of benzathine penicillin for prevention of mother-to-child transmission of syphilis: an evaluation from multi-country surveys and stakeholder interviews. *PLoS Med* 2017; **14:** e1002473.

80 Rocha AFB, Araújo MAL, Taylor MM, Kara EO, Broutet NJN. Treatment administered to newborns with congenital syphilis during a penicillin shortage in 2015, Fortaleza, Brazil. *BMC Pediatr* 2021; **21:** 166.

81 Shah S, Garg S, Heath K, et al. Estimation of benzathine penicillin G demand for congenital syphilis elimination with adoption of dual HIV/syphilis rapid diagnostic tests in eleven high burden countries. *PLoS One* 2021; **16:** e0256400.

82 Liang Z, Chen Y-P, Yang C-S, et al. Meta-analysis of ceftriaxone compared with penicillin for the treatment of syphilis. *Int J Antimicrob Agents* 2016; **47:** 6–11.

83 Liu HY, Han Y, Chen XS, et al. Comparison of efficacy of treatments for early syphilis: a systematic review and network meta-analysis of randomized controlled trials and observational studies. *PLoS One* 2017; **12:** e0180001.

84 Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. *Lancet Infect Dis* 2021; **21:** 1441–47.

85 Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis* 2005; **32:** 495–98.

86 Taylor MM, Kara EO, Araujo MAL, et al. Phase II trial evaluating the clinical efficacy of cefixime for treatment of active syphilis in non-pregnant women in Brazil (CeBra). *BMC Infect Dis* 2020; **20:** 405.

87 Stafylis C, Keith K, Mehta S, et al. Clinical efficacy of cefixime for the treatment of early syphilis. *Clin Infect Dis* 2021; **73:** 907–10.

88 Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. *Clin Infect Dis* 2006; **42:** 337–45.

89 Zhou P, Qian Y, Xu J, Gu Z, Liao K. Occurrence of congenital syphilis after maternal treatment with azithromycin during pregnancy. *Sex Transm Dis* 2007; **34:** 472–74.

90 Zhou P, Li K, Lu H, et al. Azithromycin treatment failure among primary and secondary syphilis patients in Shanghai. *Sex Transm Dis* 2010; **37:** 726–29.

91 Tanizaki R, Nishijima T, Aoki T, et al. High-dose oral amoxicillin plus probenecid is highly effective for syphilis in patients with HIV infection. *Clin Infect Dis* 2015; **61:** 177–83.

92 Ikeuchi K, Fukushima K, Tanaka M, Yajima K, Imamura A. Clinical efficacy and tolerability of 1·5 g/day oral amoxicillin therapy without probenecid for the treatment of syphilis. *Sex Transm Infect* 2022; **98**: 173–77.

93 Nishijima T, Kawana K, Fukasawa I, et al. Effectiveness and tolerability of oral amoxicillin in pregnant women with active syphilis, Japan, 2010–2018. *Emerg Infect Dis* 2020; **26:** 1192–200.

94 US Centers for Disease Control and Prevention. Data modernization initiative: strategic implementation plan. https://www.cdc.gov/surveillance/pdfs/final-dmi-implementation-strategic-plan-12-22-21.pdf (accessed July 25, 2023).

95 Madhi SA, Pathirana J, Baillie V, et al. An observational pilot study evaluating the utility of minimally invasive tissue sampling to determine the cause of stillbirths in South African women. *Clin Infect Dis* 2019; **69** (suppl 4)**:** S342–50.

96 Esopo K, Derby L, Haushofer J. Interventions to improve adherence to antenatal and postnatal care regimens among pregnant women in sub-Saharan Africa: a systematic review. *BMC Pregnancy Childbirth* 2020; **20:** 316.

97 Kojima N, Konda KA, Klausner JD. Notes on syphilis vaccine development. *Front Immunol* 2022; **13:** 952284.

98 Cameron CE, Lukehart SA. Current status of syphilis vaccine development: need, challenges, prospects. *Vaccine* 2014; **32:** 1602–09.

99 Bishop NH, Miller JN. Humoral immunity in experimental syphilis. I. The demonstration of resistance conferred by passive immunization. *J Immunol* 1976; **117:** 191–96.

100 Lafond RE, Lukehart SA. Biological basis for syphilis. *Clin Microbiol Rev* 2006; **19:** 29–49.

101 Schell RF, Chan JK, Le Frock JL. Endemic syphilis: passive transfer of resistance with serum and cells in hamsters. *J Infect Dis* 1979; **140:** 378–83.

102 Beale MA, Marks M, Cole MJ, et al. Global phylogeny of *Treponema pallidum* lineages reveals recent expansion and spread of contemporary syphilis. *Nat Microbiol* 2021; **6:** 1549–60.

103 Edmondson DG, Hu B, Norris SJ. Long-term in vitro culture of the syphilis spirochete *Treponema pallidum* subsp. *pallidum*. *mBio* 2018; **9:** e01153-18.

104 Romeis E, Tantalo L, Lieberman N, Phung Q, Greninger A, Giacani L. Genetic engineering of *Treponema pallidum* subsp. *pallidum*, the syphilis spirochete. *PLoS Pathog* 2021; **17:** e1009612.