CONTENTS

Congenital Syphilis: Controversies and Questions

A Global Perspective

Bridget Freyne, MBBchBAO, PhD,† Clare Nourse, FRACP, MD,‡§ and Tony Walls, FRACP, MD¶‖*

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BACKGROUND

Syphilis, the infection caused by the spirochete *Treponema pallidum subsp. Pallidum*, has been a disease of public health concern for over 100 years. Gestational syphilis is the second leading infectious cause of stillbirth worldwide after malaria. Untreated primary syphilis in pregnancy results in adverse birth outcome 50%–80% of affected pregnancies.[1] Modeling of sentinel surveillance data in 2016 indicated that the global prevalence of gestational syphilis was 0.69% (95% confidence intervals: 0.57%–0.81%), which translated into an estimated rate of congenital syphilis of 473 (385–561)/100,000 live births. In the African region, these rates are 3 times the global average at 1.62% and 1377/100,000 live births, respectively.[2] Since these estimates were reported, there have been significant increases in syphilis notifications in high-income countries (HICs) which have included proportional increases in women of childbearing age. In Australia, there was a 90% increase in reported syphilis cases between 2015 and 2020, with a 40% increase among women of child bearing age. In the United States, a 21% increase total notifications between 2019 and 2020 included a 21% increases in primary and secondary syphilis among women aged 20–24 and a 32% increase among women aged 25–30.[3] Despite the widespread availability of affordable diagnostics and effective treatment, syphilis in pregnancy threatens the attainment of the sustainable development goal for reduction of child mortality through impact on global preterm and stillbirth rates.

In 2007, the World Health Organization (WHO) launched a strategy for the elimination of mother to child transmission (EMTCT) of syphilis by 2030, which was expanded in 2014 to include HIV. Cuba and Thailand became the first low and middle-income countries (LMICs) to achieve WHO validation goals for EMTCT of both HIV and syphilis. In recognition of the high prevalence rates and implementation challenges for LMICs, the roadmap was adapted in 2017 to include tiered entrance onto the elimination pathway. Successful elimination strategies were underpinned by political engagement, consistent health infrastructure, and engagement with high risk populations.[4] These lessons will be important for HICs dealing with a resurgence of syphilis. The aim of this review is to present a global perspective on several key controversies in the prevention of mother to child transmission of syphilis and to highlight opportunities for global collaboration.

CONTROVERSY 1: OPTIMIZING DIAGNOSTIC ALGORITHMS FOR MOTHERS AND INFANTS

Due to the limitations of serology-based diagnostics for syphilis, algorithms combining treponemal tests, nontreponemal tests, and clinical information are required to ascertain the stage of maternal syphilis and guide treatment of both mother and infant. The diagnosis of congenital syphilis depends on: (i) comparison of paired maternal and neonatal nontreponemal titers (with a 4-fold relative increase in neonatal titers compared with maternal titers being considered congenital infection) ± the presence of neonatal IgM where available, (ii) evaluation of the adequacy of maternal treatment [defined by stage appropriate dosing of penicillin (1–3 doses) at least 4 weeks before delivery and a concomitant drop in nontreponemal titers where retesting is available] and (iii) no evidence reinfection.[3] In low-income settings, the introduction of rapid screening tests

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From the *Department of Paediatric Infectious Diseases, Children's Health Ireland, Dublin, Ireland; †Division of Women & Children's Health, School of Medicine, University College Dublin, Ireland; ‡Queensland Children's Hospital, Brisbane, Australia; §Faculty of Medicine, University of Queensland, Brisbane, Australia; ¶Department of Paediatrics, University of Otago, Christchurch, New Zealand; and ‖Research for Children Aotearoa, New Zealand https://www.healthprecinct.org.nz/research-for-children-aotearoa/.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Tony Walls, FRACP, MD, Department of Paediatrics, University of Otago, Christchurch, New Zealand. E-mail: tony.walls@otago.ac.nz.

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(RSTs) has increased the coverage of syphilis testing at first antenatal visit and has proven cost-effective. The most widely used RSTs are treponemal tests alone, which have high specificity but are unable to differentiate the stage of disease or success of prior treatment. These have been chosen over traditional nontreponemal tests (rapid plasma regain or Venereal Disease Research Laboratory test) as they do not require phlebotomy, laboratory reagents or a microscope and results are available in real-time facilitating same day test and treat strategies.[5]

Figure 1 compares 3 WHO-recommended algorithms for diagnosis and management of syphilis in pregnancy, which can be chosen by Ministries of Health depending on local availability of tests. Each algorithm assumes over-treatment, with women who are RST positive without documentation of treatment automatically qualifying for retreatment with up to 3 doses of IM Benzathine Penicillin (BPG).[6] Over-treatment may be justified in high prevalence settings given the affordability of BPG and the fact that 50%–80% of untreated pregnancies will end in an adverse birth outcome. By contrast, the algorithm from the Australian & New Zealand Paediatric Infectious Diseases Group recommends an intensive diagnostic and follow-up testing regimen with a higher threshold for treatment. However, this is associated with a heavy burden of clinical and laboratory capacity only feasible in well-resourced systems. While this approach will prevent unnecessary treatment of mothers and infants and ensure adequate follow-up, the converse challenge is high rates of biologic false positives requiring re-evaluation. In practice, in the absence of adequate treatment information, most clinicians in both HIC and LMIC settings will opt to treat potentially exposed infants.

Investment in accurate, affordable RSTs could substantially reduce over-treatment in LMICS and may have a role in reaching vulnerable populations in HICs. Current areas of active research include RSTs which combine both treponemal and nontreponemal components and rapid nucleic acid amplification tests on perinatal swabs and tissues. Prior collaborative Global Health initiatives for malaria and tuberculosis diagnostics can act as templates to advocate for development of these tools.

CONTROVERSY 2: UNIVERSAL RETESTING OF PREGNANT WOMEN AFTER THE 3RD TRIMESTER

Of the 62 national guidelines identified in the review by Trinh et al,[7] 46 (81%) recommended universal rescreening in the 3rd trimester or at delivery. An alternative approach is to retest only high-risk populations, defined as patients living in areas with rates of primary and secondary syphilis greater than 2/100,000, women who are uninsured or low income, women who are diagnosed with another sexually transmitted infection during pregnancy or who sell sex for money or drugs. The limitations of this approach include the dependence on adequate identification of high-risk women who frequently do not disclose or may not be aware of the risks associated with certain practices.[8]

Globally, universal rescreening at delivery serves 3 functions, the importance of which vary depending on local epidemiology and health systems challenges. First, it ensures that women and infants affected by gestational syphilis and not yet tested are diagnosed and receive treatment, which can prevent late sequelae of congenital syphilis not apparent at birth. Second, it will capture women who tested positive during antenatal care but were unable to access treatment for themselves and their partners. Finally, it will identify women who have become infected during pregnancy. In Malawi, modeling data suggests that only 23% of pregnant women may currently have access to service coverage in line with EMTCT process outcomes and

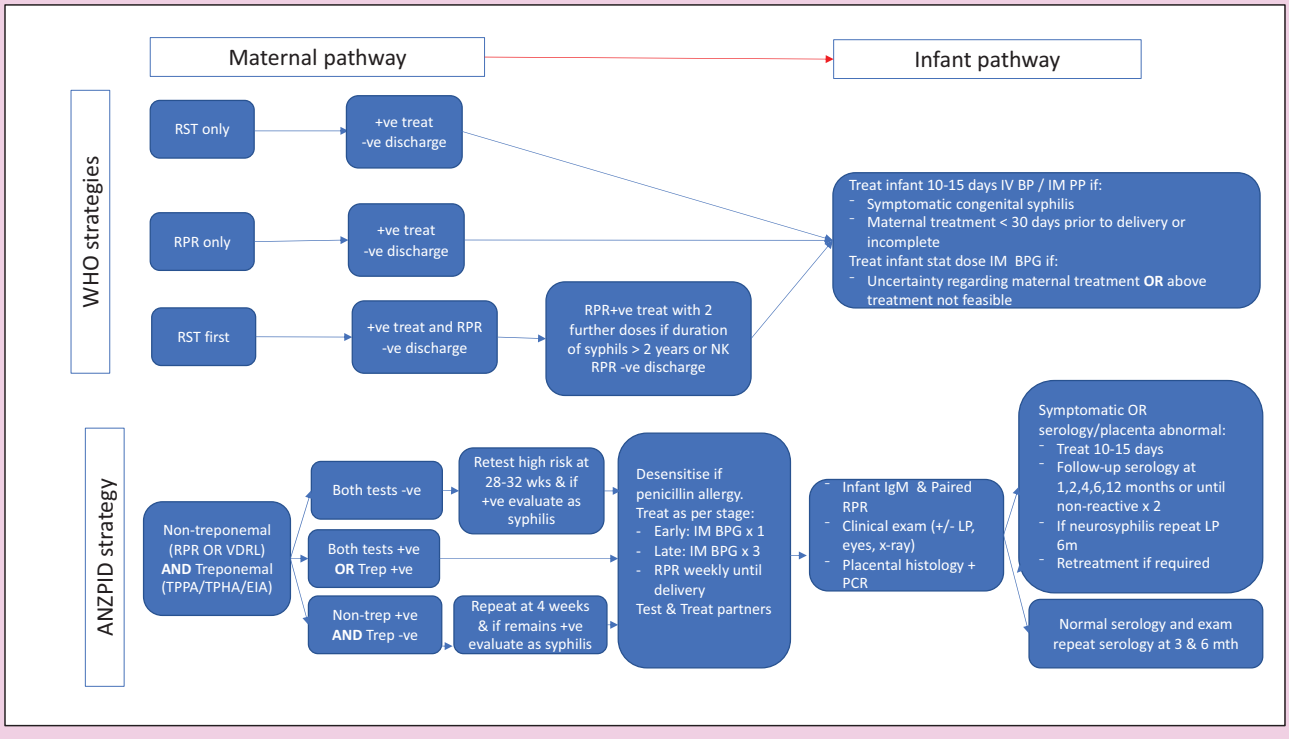

FIGURE 1. Comparison of potential recommended strategies for the diagnosis, management and follow-up of pregnancies affected by syphilis in LMIC (WHO) and HIC (Australian & New Zealand Paediatric Infectious Diseases Group ANZPID). BP indicates aqueous benzylpenicillin; IM BPG, intra-muscular benzathine penicillin; EIA, enzyme immunoassay antibody test; LP, lumbar puncture; NK, not known; PCR, polymerase chain reaction; PP, procaine penicillin; RPR, rapid plasma regain; TPHA, Treponema Pallidum Hemagglutinin Test; TPPA, Treponema Pallidum Particle Agglutination Test; VDRL, Venereal Disease Research Laboratory test.

the introduction of universal rescreening at delivery would overcome some of these barriers. While universal retesting in LMICs with available treponemal RSTs will again lead to over-treatment the risk benefit ratio remains favorable. Conversely, in HICs retesting at delivery using the dual treponemal/nontreponemal testing strategy in the mother and infant may generate too many false positives in low-risk patients to be acceptable.

The decision to adopt universal syphilis rescreening in the 3rd trimester is ultimately dependent on local cost-effectiveness. A decision tree analysis of universal 3rd trimester retesting in the United Kingdom concluded that the intervention would result in a reduction of congenital syphilis cases of 5.5 (3.3–8.8)/yr with a cost of 1.8 million GBP per life saved and was thus not cost-effective in that country.[9] Similarly, a study done in the United States in 2014 did not favor 3rd trimester testing. However, a repeat of this analysis in 2019 when the prevalence of primary and secondary syphilis had increased by 71.4% indicated that the incidence of congenital syphilis had crossed the cost-effectiveness threshold of 10/100,000 live births.[8] This highlights that cost-effectiveness is dynamic and requires frequent review and potentially even regional application. Retesting in the 3rd trimester may be a feasible intervention to reduce the burden of community infection and the late sequelae of congenital infection in asymptomatic infants. National and regional data on the optimal strategies for implementation of this strategy and the associated cost-effectiveness are lacking globally, particularly in LMICS.

CONTROVERSY 3: THE OPTIMAL APPROACH TO THE MANAGEMENT OF SEXUAL PARTNERS

Management of the risk of reinfection following successful antenatal treatment is an essential component of EMTCT strategies for congenital syphilis. Pregnant women in concordant couples have higher rates of adverse birth outcomes than women in discordant couples, underscoring the clinical importance of successful partner notification and treatment.[10] Fifty-nine (95%) of reviewed national guidelines on syphilis in pregnancy included recommendations on the management of sexual partners.[7] There were differences between guidelines as to whether partners should receive BPG or whether expedited partner treatment with oral doxycycline or azithromycin would be sufficient. The optimal strategies for achieving adequate partner management, which includes notification, education, and adequate treatment will be context dependent.[7]

Worldwide, notification strategies include passive notification, which relies on the pregnant woman informing her sexual partner(s), and provider notification using phone or e-mail. The latter approach is favored in high-income settings as it allows ease of contact to multiple sexual partners, provides confidentiality for the index case and protects pregnant women from any threat of intimate partner violence when disclosing their diagnosis. The feasibility of this approach in LMICs is variable and efficacy studies from China and Uganda showed that investment in provider notification did not translate into attendance for treatment.[10] Conversely, strategies aimed at inclusion of men more broadly in antenatal clinic and MTCT services, which adapted antenatal clinic service delivery to promote privacy and male attendance and which included nurse or video-led partner specific education were more effective in promoting partner attendance for treatment following notification across a range of settings from Malawi to Thailand. In high-burden settings, optimizing strategies to treat sexual partners is an essential component of both the individual clinical and public health response to syphilis.

CONTROVERSY 4: TREATMENT OPTIONS TO PREVENT CONGENITAL SYPHILIS

BPG IM is the backbone of global EMTCT syphilis strategies. Determination of the clinical stage of syphilis in the mother dictates the number of doses required to adequately treat the infant. Consistent delivery of this schedule is challenging and failure to deliver or adequately document the treatment schedule can result in the need for additional investigations and treatment in the infant. Global shortages of BPG, which have disproportionately affected sub-Saharan Africa, Brazil, South East Asia and Australasia, have hampered the progress of EMTCT programs in these areas. In addition, the inability of testing strategies in LMIC settings to differentiate between the stages of syphilis infection leads to universal 3-dose treatment strategies in many countries which may exacerbate the problem and is relatively unacceptable to pregnant women who may not be able to travel to health centers on multiple occasions.[8] There is an urgent need to assess the efficacy of alternative drug strategies in pregnant women and infants.

Alternatives to BPG in nonpregnant patients include azithromycin, doxycycline, tetracyclines and ceftriaxone. Erythromycin is recommended in some guidelines as treatment for pregnant women allergic to Penicillin where the option for safe desensitization is not present. In these cases, however clinicians must assume that macrolides do not cross the placenta effectively and that these infants have congenital syphilis. Phase I and II trials of high dose amoxicillin and ceftriaxone in pregnant women have shown promising results although the participant numbers are small. Randomized controlled studies of alternative agents such linezolid and oral cephalosporins including cefixime are actively recruiting nonpregnant patients and may provide efficacy data in potentially useful drugs for pregnant women and infants.[8] The use of innovative adaptive and ecological trial designs as well as inclusion of pregnant women in clinical trials with rigorous safety profiles should be employed to assess the safety and efficacy of alternative drugs with activity against *T. pallidum* in this population.

CONCLUSIONS AND RECOMMENDATIONS

Gestational syphilis is responsible for a major preventable burden of adverse perinatal outcomes globally and threatens attainment of the sustainable development goals on child mortality. Syphilis disproportionately affects vulnerable and marginalized populations worldwide and is exacerbated by cultural factors which affect female autonomy in care-seeking. Given the recent dramatic rises in the incidence of gestational syphilis in HICs, persistently elevated and under-reported rates in LMICs and high rates of international migration, a global approach to resolving the diagnostic, therapeutic and implementation controversies in EMTCT of syphilis is warranted. Global efforts to innovate against these challenges for other endemic diseases of public health concern such as HIV, tuberculosis and malaria can provide a template for success.

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