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Congenital Infections: Priorities and Possibilities for Resource-limited Settings

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Key Words: congenital, syphilis, cytomegalovirus, herpes simplex virus

Congenital infections are an under-recognized cause of morbidity and mortality in resource-limited settings (RLS). The “SCORTCH” acronym highlights the range of congenital infections: **S**yphilis, **C**ytomegalovirus (CMV), “**O**ther” (eg, Zika, malaria, Chagas disease, parvovirus, enterovirus), **R**ubella, **T**oxoplasmosis, **C**hickenpox, and all the **H**’s, Herpes simplex virus (HSV), HIV, Hepatitis B and C, Human T-lymphotropic virus-1.[1] Clinical severity depends on a range of factors, including timing of infection, pathogenicity of strain, and the relative maturity of the fetal/maternal immune system. Most infections are asymptomatic in the mother and neonate. In high-income countries (HICs), screening programs, routine obstetric and neonatal care, specific treatments and vaccination have reduced the incidence of congenital infections. However, these interventions are often not available in RLS. Moreover, in the absence of population-based surveillance and limited laboratory testing capacity, it is likely that the burden of undiagnosed congenital infections is higher in RLS. Public health strategies and interventional programs could have a huge impact on reducing congenital infections in these settings. This review focuses on the priorities and possibilities for managing congenital syphilis, CMV and HSV.

Accepted for publication August 19, 2022
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The authors have no funding or conflicts of interest to disclose.
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ISSN: 0891-3668/22/0000-0000
DOI: 10.1097/INF.0000000000003710

CONGENITAL SYPHILIS

Mother-to-child transmission of syphilis can lead to a wide spectrum of complications including stillbirth, neonatal death and symptomatic infant infection (Table 1). In 2016, the global congenital syphilis rate was 473 cases/100,000 livebirths, substantially higher than the WHO target of 50 of 100,000.[2] An estimated 1 million women worldwide live with syphilis, with the highest burden in sub-Saharan Africa. A 2007 WHO framework highlighted the need to improve political advocacy, antenatal healthcare services, screening and surveillance to eliminate congenital syphilis (https://www.who.int/publications/i/item/the-global-elimination-of-congenital-syphilis-rationale-and-strategy-for-action). However, in 2017, the WHO and the Gates Foundation reported that little progress had been made, mainly due to stigma, difficulty capturing cases related to stillbirth, limited access to benzathine benzylpenicillin, and a lack of coordinated responses across agencies. A WHO global progress report in 2020 showed that 95% coverage of antenatal screening for HIV and syphilis was achieved in only 70% of countries (https://www.who.int/publications/i/item/9789240027077). Improving accessibility to a range of public health measures could enable an immediate reduction in the burden of congenital syphilis in RLS.

PUBLIC HEALTH MEASURES

WHO has outlined a pathway to the elimination of mother-to-child transmission of syphilis (https://www.who.int/publications/i/item/9789240039360). To achieve the targets of <50 cases/100,000, at least 1 dual HIV/syphilis test should be conducted in the first trimester to facilitate early antenatal treatment. Dual testing assays are cheap, highly sensitive and produce rapid results, and WHO ultimately aims to include hepatitis B surface antigen as a triple test. Intramuscular benzathine penicillin at least 30 days before delivery remains the gold standard for treatment of syphilis in pregnancy, but a WHO target of >95% coverage of one dose for syphilis-seropositive pregnant

TABLE 1. Clinical Presentations of Neonates with Symptomatic Congenital Infections

	Syphilis	CMV	HSV
Prematurity	Yes	Yes	Yes
Low birth weight	Yes	Yes	Yes
Lymphadenopathy	Yes	No	No
Hepatosplenomegaly	Yes	Yes	Yes (disseminated HSV)
Jaundice (may be conjugated)	Yes	Yes	Yes (disseminated HSV)
Hepatitis	Yes	Yes	Yes (disseminated HSV)
Anemia	Yes	Yes	Yes (disseminated HSV)
Thrombocytopenia	Yes	Yes	Yes (disseminated HSV)
White blood count	High or low	Normal or low	Normal or low
Hearing	Sensorineural deafness	Sensorineural deafness	N/A
Skeletal	Osteochondritis, periostitis	N/A	N/A
Renal	Glomerulonephritis, nephrotic syndrome	N/A	N/A
Pneumonitis	Yes	Yes	Yes (disseminated HSV)
Central nervous system	Meningitis, microcephaly, hydrocephaly, intracranial calcification	microcephaly, ventriculomegally, cysts, polymicrogyria, abnormal white matter, intracranial calcification	Encephalitis, meningitis
Eyes	Cataracts, corneal scarring, glaucoma, chorioretinitis, microphthalmia.	Retinal scarring, chorioretinitis	Keratitis/corneal scarring in all forms of HSV disease
Rash	Usually maculopapular, but any possible, including blueberry muffin rash Palms and soles may be red, mottled and swollen Severe desquamation of hands/feet is pathognomonic Vesiculobullous lesions, condylomata lata in moist areas/perioral fissures	Rare, may have blueberry muffin rash	Vesicular/ulcerative lesions

N/A, not applicable.

women has yet to be achieved in part due to shortages in the production and distribution of benzathine penicillin. Oral options such as amoxicillin and cefixime may be more readily available alternatives, but their efficacy in randomized trials merit further investigation.[3]

CONGENITAL CMV

Congenital CMV (cCMV) is the most common nongenetic cause of sensorineural hearing loss. Congenital infection also causes neurodevelopmental impairment in 20% of infants. A meta-analysis, including 23 and 54 studies from RLS and HIC settings respectively, found a 3-fold higher birth prevalence of cCMV in RLS (1.4%) compared with HIC (0.5%).[4] Population risk factors for cCMV include maternal CMV and HIV seroprevalence and younger maternal age. Compared with HIC, CMV in RLS is usually acquired earlier in life; CMV seroprevalence in adulthood is close to 100% in sub-Saharan Africa, in contrast to 58% seroprevalence among women of childbearing age in the United States.[5] Almost all pregnant women in sub-Saharan Africa are therefore CMV seropositive, but it is active, replicating CMV (defined as detectable CMV DNA in plasma, urine or saliva) that is associated with mother-to-child transmission, which may occur at initial infection, through viral reactivation, or after reinfection with a different strain. Transmission is more likely in the small proportion of women who acquire primary infection during pregnancy, but the infant can be as severely affected whether the mother is already CMV seropositive or seroconverts during pregnancy. CMV transmission in the first/early second trimester is associated with the most severe end-organ damage. In symptomatic neonates, 6 months of oral valganciclovir, started within the first month of life, has a modest impact on preventing hearing deterioration and improving neurodevelopmental outcomes. However, valganciclovir is not available in most RLS. Reducing the burden of cCMV therefore relies upon measures to reduce transplacental transmission through a range of hygiene measures during the antenatal period.

ANTENATAL HYGIENE MEASURES

A systematic review evaluating hygiene measures during pregnancy in HIC found that a range of behavioral and education measures could reduce CMV seroconversion during pregnancy.[6] Improving antenatal water, sanitation and hygiene (WASH) may therefore prevent cCMV secondary to maternal reinfection, but would likely have no impact on congenital infection through maternal CMV reactivation.

CMV VACCINES

Studies of vaccine candidates, mainly aimed to protect against infection in solid organ transplant recipients, have been ongoing for 40 years. In congenital infection, the aim of vaccination is not to create sterilizing immunity in the mother but to prevent transplacental transmission. In seropositive women, a CMV vaccine would need to generate sufficient antibody and T-cell responses to prevent fetal infection. There are close relationships between CMV, HIV and tuberculosis, so the indirect protective effects of a CMV vaccine on reducing the burden of these infections in RLS may be an important additional benefit.[7]

A phase III trial in the United States is evaluating safety and efficacy of an mRNA candidate vaccine in women of childbearing age (https://clinicaltrials.gov/ct2/show/NCT05085366). The primary outcome measure is seroconversion in seronegative women. The applicability of such a trial in RLS is unclear given the rarity of CMV seronegativity and the cold-chain storage requirements of mRNA vaccines. An immediate research priority should be the development of an international congenital CMV registry to capture robust epidemiologic data to inform vaccine trials and to evaluate vaccine effectiveness in seropositive women in RLS.

NEONATAL HSV

Neonatal HSV has 3 phenotypes: skin eye mouth, central nervous system and disseminated disease, with up to 30% mortality in the latter syndrome. The majority of cases occur after exposure in the genital tract at delivery, and the highest risk for transmission occurs for neonates born to women with recent primary infection. A WHO global estimate of the burden of neonatal HSV concluded that approximately a third of all neonatal HSV cases occurred in Africa are due to a high incidence of HSV-2, although this may be an underestimate due to poor quality surveillance data. Observational data

from South Africa showed that genital HSV-2 shedding at delivery among HSV-seropositive women living with HIV was almost twice as high as among HSV-seropositive women without HIV (23% vs. 12%), suggesting a higher burden of neonatal HSV in HIV endemic regions.[8]

BEHAVIORAL STRATEGIES

A range of preventive measures, including suppressive acyclovir in late pregnancy, selective cesarean sections, and careful obstetric care at delivery to identify genital lesions all rely on well-funded antenatal and peripartum care. Ideally, a premembrane rupture cesarean section should be undertaken in women with active genital herpes lesions to prevent transmission. However, neonatal HSV infection often occurs in the absence of genital lesions, and surgery often carries inherent risks in RLS, changing the risk-benefit balance in RLS compared with HIC. Preventing maternal HSV acquisition through sex education may reduce the burden of disease. Recent WHO guidance reiterates the importance of not engaging in sexual activity if genital lesions are present, and this is especially important in late pregnancy when the risk of neonatal HSV is highest (https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus). Pregnant women with genital lesions should undergo HSV, HIV and syphilis testing.

HSV MICROBICIDES AND VACCINES

Microbicides applied topically to the vagina and/or rectum offer some protection against primary HSV. In a trial of 422 HSV-2-seronegative South African women, pericoital tenofovir gel halved seroconversion (10.2/100-person-years vs. 21.0/100-person-years) and reached higher concentrations than oral preparations.[9] In vitro studies have demonstrated novel microbicide candidates with dual protection against HIV-1 and HSV-2, but efficacy trials are required.

There are no licensed HSV vaccines, but several candidates are in preclinical and phase I/II trials.[10] A *prophylactic vaccine* would prevent transmission and active infection, indirectly preventing latent infection and reactivation. As with human papilloma virus, prophylactic vaccination should occur before sexual debut. A *therapeutic vaccine* would prevent severe complications of HSV in seropositive recipients. Again, a disease registry is crucial to capture the burden of neonatal HSV infection and impact of vaccination.

CONCLUSION

Syphilis, CMV and HSV can cause catastrophic illness in the newborn, and the long-term burden of these infections in RLS remains unknown. Surveillance studies are required to elucidate the consequences of congenital infections and will help inform preventive strategies. Vaccine trials designed for RLS must consider context-specific factors including: antenatal seroprevalence, maternal and infant immunity, HIV prevalence, capacity for cold chain storage and availability of antivirals. Disease registries which capture epidemiologic trends, assess long-term neurodevelopmental outcomes, and act as an opportunity to conduct interventional studies could be modeled on existing HIV surveillance frameworks (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/strategic-information/hiv-surveillance). Population-based data could better inform the health economic cost of managing infants with congenital infections, and potential benefits of interventions. Overall, the promotion of holistic, nonstigmatizing pregnancy care is essential to support women in RLS and protect infants from congenital infections.

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