

## Pregnancy and Pandemic Disease

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What could antiseptics,<sup>1,2</sup> immunosuppressive therapy,<sup>3</sup> prevention of transfusion reaction,<sup>4</sup> elimination of pediatric syphilis and AIDS,<sup>5</sup> prevention of diabetes sequelae,<sup>6</sup> and prevention of birth defects<sup>7</sup> all possibly have in common? We need not dig too deeply into the history of each to find the role that maternal health care and investigation played in heralding each of these triumphs of modern medicine.

In contrast to such achievements, we have only been able to chip away at tuberculosis (TB), despite the availability of effective treatment for almost 80 years. One hardly needs to be reminded of the scope of the TB pandemic: Two billion, or one-quarter of the world's population infected; 10 million new infections per year, every year; and the distinction of being the leading cause of mortality from a single infectious disease, with 1.5 million deaths in 2018 alone. Once infected, those living with latent TB have a 5-15% lifetime risk of developing active disease, which, if untreated, will end in death for about half.<sup>8</sup>

Pillar 1 of the WHO End TB Strategy calls for diagnosis, contact and high risk screening, treatment and prevention – each of which presents a formidable challenge.<sup>9</sup> In most countries with high disease burden, incidence and population prevalence have never been measured directly. At best, incidence estimates rely on historic tuberculin surveys in children combined with estimates of disease duration.<sup>8</sup> Even less reliably, approximations of incidence are derived from case notification data (i.e. infection diagnosed by sputum smear microscopy of symptomatic individuals presenting for care) combined with expert opinion on case-detection gaps from regional workshops or country missions.<sup>8</sup> Many assumptions underlying such estimates may not hold true.<sup>9</sup> Case notification data can be confounded by

access to care as well as care-seeking patterns. For example, the accepted notion of higher TB prevalence among men than women could be because men are more likely to seek out care than women.<sup>10</sup> Some with active TB may be smear negative, but culture positive.

So, what of pregnancy and TB? Globally, estimates suggest it is a disease of men (57%), however women (32%) and children < age 15 (11%) together make up close to half of those living with TB. Although overall global prevalence has remained constant in recent years, best estimates suggest that new infections and deaths are falling by about 2.5% yearly.<sup>8</sup> In endemic regions, TB is a major cause of death in women of reproductive age, and has been reported to be the major non-obstetric cause of maternal death, especially in the setting of HIV coinfection.<sup>11</sup> Extrapulmonary manifestations of the infection may be more common with pregnancy, and latent TB reactivation risk is increased in the postpartum period.<sup>12</sup> Two-thirds or more of pregnant women are asymptomatic at presentation, and signs and symptoms of active infection such as fatigue may be attributed to normal pregnancy. With active disease, increased risk of adverse outcomes such as preterm delivery, low birth weight and perinatal death has recently been confirmed in a comprehensive meta-analysis.<sup>13</sup> Peripartum lymphatic and hematogenous vertical transmission have been described, but the greatest risk of newborn infection is not congenital, but post-partum, via newborn inhalation of infected droplets.<sup>12</sup>

In this issue of Clinical Infectious Diseases, Walles and colleagues from Adama Regional Laboratory in Ethiopia and Lund University, Sweden confirm the truism that pregnancy may be one of the few opportunities to assess a woman's health, particularly in resource-limited regions.<sup>10</sup> They report an unexpectedly high proportion of women (37%) living with TB, determined either by state of the art interferon gamma release assays or by clinical history of active TB. Multivariate analysis revealed that age and HIV infection were independently associated with TB. Among HIV-uninfected women, 20% of 18 year-olds had TB; after age

26, 45% tested positive. In the communities represented, the authors calculated an absolute yearly risk of TB acquisition of 2.1%.

The strong implication of these pregnancy data, that exposure and transmission in the population studied is both continuous and ongoing, is striking. The authors also found that none of the 85 women with past or currently active TB had known exposure to active infection, and that most women (61%) with past or current TB were HIV-uninfected. Taken together, ample evidence is provided that successful TB control will likely require vigorous case finding beyond traditional target populations such as individuals living with HIV and those exposed to known active TB.

We might go even further and suggest that Walle et al. have provided proof of concept data that routine testing during pregnancy could be an ideal method of assessing the extent of community spread of both recognized endemic infection as well as emerging infectious diseases.

Other proof-of-concept data for such a proposal exist. First, pregnancy not only provided us with our earliest evidence that antiretroviral prophylaxis (or even better, treatment<sup>14</sup>) prevents transmission.<sup>15</sup> The universally accepted and lauded goal of prevention of pediatric AIDS also created the political/social will and mandate to introduce HIV testing, prevention and treatment to much of the world. Today, we continue to rely on universal HIV testing of pregnant women to estimate community HIV prevalence and to prevent vertical transmission, both in resource-rich and resource-limited regions.

Second, our earliest evidence-based insights into community prevalence in the months-old COVID-19 pandemic in the United States came from the study of pregnant women. Nine days after the first diagnosis of a pregnant woman with COVID-19 their hospital system, despite severe testing shortages, obstetricians at Columbia University were able to begin universal testing of all women admitted for delivery. Their report<sup>16</sup> of results for the first 14 days of testing was revealing: 33 of 214 (15%) were SARS-CoV-2 PCR positive and 29 (88%) of those 33 were asymptomatic. Put differently, 14%, or almost one in seven women with no symptoms of infection were in fact positive. Beyond the critical importance of these data to local hospital infection control, their rapid dissemination on television and in scholarly journals was the first evidence that forced us to recognize the high prevalence of infection in New York, that most of those infected are asymptomatic, and the likelihood of substantial community spread of infection among healthy appearing individuals.

The hypothesis proposed by Walle et al, that direct measurement of TB prevalence in a well-characterized convenience cohort of pregnant women, could serve to better understand TB transmission in the community, is both globally relevant and timely. It offers a tool that could be critically useful to the WHO End TB Strategy. Beyond TB, universal testing and treatment of pregnant women continues to be a lynchpin of our goal to eliminate HIV. Earlier testing of pregnant United States women at select sites could have helped both epidemiologists and politicians alike characterize, understand and prevent the national catastrophe of CoVID-19 at a time when infections were not counted in the millions, and number of deaths in this country was not approaching 100,000.

Pregnant women actively seek care and testing in both sickness and health. The vast majority request screening for a wide variety of disorders. The opportunity to extend such screening to emerging infectious diseases must not be lost again.

**Notes:**

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