

Respiratory Syncytial Virus During Pregnancy

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(See the Major Article by Madhi et al on pages 1658–65.)

Respiratory syncytial virus (RSV) is the main viral cause of hospitalization in infants and young children worldwide [1]. More than 3 million severe cases and close to 100 000 pediatric deaths every year, half of them at home, demand effective interventions to mitigate disease burden [1]. Addressing this challenge is not easy, however, in part because more than 90% of severe cases and 99% of fatalities due to RSV occur in the developing world [1]. In fact, severe cases in industrialized countries almost exclusively affect high-risk groups that represent only a subset of those burdened by serious illness in developing nations. Congenital heart disease, neuromuscular disorders, chronic lung illness, and/or Down syndrome are almost ubiquitous in fatal cases in industrialized countries [2]. On the other hand, secondary bacterial infections and pneumothoraces, in addition to the aforementioned comorbid conditions, seem to be critical contributors to poor outcomes in developing country hospitals [3]. Poor medical care (or lack thereof) probably

explains numerous “silent deaths” of RSV-infected hypoxic infants in underprivileged communities. Common sense would indicate that the best overarching approach to mitigate these complex interactions between RSV and various risk factors is early disease prevention through vaccination or administration of protective monoclonal antibodies.

An attractive approach to disease prevention in infants is immunization of pregnant women to boost transplacental transfer of protective antibody during the third trimester of pregnancy [4]. The strategy follows on the footsteps of effective influenza and pertussis immunization during pregnancy [5, 6] and is currently under evaluation in a phase III clinical trial. Other vaccine candidates may follow. Both influenza and pertussis maternal vaccines prevent severe disease in infants, but they differ in their impact on maternal illness during pregnancy. Whereas influenza can elicit severe disease in pregnant women and may affect timing of delivery and fetal growth (and therefore the vaccine can offer a direct benefit to immunized mothers), *Bordetella pertussis* elicits relatively mild disease in adults [7, 8]. We are only starting to learn whether RSV vaccines belong to the first or second group of immunogens. Prospective observational studies to define RSV disease burden during pregnancy would require very large populations, intense outpatient follow-up, and considerable resources.

In their article in this issue of *Clinical Infectious Diseases*, Nunes et al [9] leverage a randomized controlled trial of

inactivated influenza vaccine during pregnancy and take us “through the looking glass” to start to comprehend the maternal side of RSV disease burden. This interesting article follows studies of febrile RSV disease during pregnancy in Nepal and Mongolia [10, 11]. Gradually, the impact of RSV in pregnant women is starting to become clear.

First, we now know that RSV can cause symptomatic disease that prompts women to seek medical care. Second, we can probably affirm that RSV illness in this group is not more severe than influenza. Respiratory symptoms are indistinguishable in subjects infected with either virus, and hospitalization rates were not significantly different between both viruses in South Africa [9]. However, we lack sufficient evidence to convincingly argue that disease elicited by RSV is significantly milder than that elicited by influenza. RSV is frequently mild during pregnancy but, like influenza, can be detected in women with acute respiratory failure [12].

In fact, fever is not a frequent sign associated with RSV infection in this population [9–11], and RSV and influenza seasons often do not overlap exactly. Therefore, studies using variations of influenzalike illness to prompt sick visits or collect samples from mothers, and/or designed based on the influenza season, probably underestimate the RSV disease burden [9–11]. Despite these limitations, studies like that by Nunes et al [9] represent important contributions to the RSV field, improving our understanding of the potential benefits offered by different prevention strategies. More granular details on the role of

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coinfections, occasional predisposition to bacterial secondary infections, and/or the existence of specific subgroups of pregnant women with enhanced susceptibility to disease (eg, human immunodeficiency virus [9] or asthmatics) may be unraveled during clinical trials or in postlicensure studies.

Another interesting observation in the study reported by Nunes et al [9] and in Nepal [10] is the frequency of “simultaneous” RSV infections in mothers and their infants [9, 10]. Immediate virus transmission from mother to infant leaves little time for boosting maternal responses and transferring virus-specific immunoglobulin A through breastfeeding to prevent infection. Hence, these observations—coupled with the short half-life of immunoglobulin in the oropharynx and sex differences in human milk protection against respiratory infections—challenge the concept of breast milk-mediated protection through pathogen-specific mucosal antibodies. Human milk may mediate its remarkable protection by other mechanisms.

Our understanding of RSV disease and prevention has changed dramatically in the last decade. None of the questions discussed in this brief commentary were even addressable 10 years ago. Furthermore, maternal immunization was not perceived as an attractive strategy for disease prevention. We are witnessing the systematic resolution of longstanding questions that hampered our ability to

define the best strategies to prevent disease caused by this virus. Novel reports describe critical epitopes for protective responses determined by conformation of the fusion protein [13]. Systematic descriptions of acute and long-term disease burden in different populations of the world bring us closer to estimating the benefit of potential interventions [1–3, 14–16]. Nunes et al [9] address one of the lingering questions in the field, and we now know that RSV can cause disease in pregnant women, often mild but also frequently requiring outpatient medical care.

Note

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