The study by Mupanomunda et al presents a thoughtful analysis of the association between severe maternal morbidities (SMM) and SARS-CoV-2 infection in a retrospective cohort spanning 4 time periods that represent dominant circulating SARS-COV-2 variants in the US. Specifically, 3129 patients with SARS-CoV-2 infection diagnosed during the delivery hospitalization were compared with a propensity-matched cohort of 12,504 patients without infection at the delivery hospitalization. Mupanomunda et al found that in all variant periods except for Omicron, there was a significantly higher rate of any SMM, with highest odds associated with Delta variant predominance (odds ratio [OR], 7.69 [95% CI, 5.19-11.54]). Compared with patients without evidence of SARS-CoV-2 at delivery, respiratory morbidity was increased across all variant periods among patients with SARS-CoV-2 at the delivery hospitalization. Secondary outcomes evaluated included an analysis of only nontransfusion-related SMM, which increased in association with the wild-type SARS-CoV-2 strain (OR, 2.16 [95% CI, 1.40-3.27]) and Alpha variant (OR, 1.96 [95% CI, 1.20-3.12]) and was significantly higher in association with the Delta variant period (OR, 4.65 [95% CI, 2.97-7.29]) but not with Omicron.

Over the last 2 years through the pandemic, obstetricians, infectious disease experts, and epidemiologists have attempted to understand the impact of SARS-COV-2 infection on pregnancy outcomes. As variants evolved, and as vaccinations became widely available and population immunity increased, this issue became a more difficult one to address.

Mupanomunda and colleagues lend clarity to this question through a particular lens: that of acute SARS-CoV-2 infection at the delivery hospitalization. Their findings are consistent with other recent observational studies demonstrating an association between acute SARS-CoV-2 infection and adverse pregnancy outcomes. However, as noted by Mupanomunda et al, it cannot be assumed that SARS-CoV-2 infection at any time during pregnancy is associated with adverse pregnancy outcomes, although some evidence suggests this to be the case when severe clinical disease occurs. Variability in study designs, source populations, eligibility criteria, and case ascertainment make direct comparison of different studies challenging; thus, individualized evaluation is necessary.

The use of a propensity score offers advantages in the absence of randomization by balancing measured covariates and confounders and closely matching participants in each comparator group. Thus, a reasonable conclusion can be made that among patients with a balanced distribution of risk factors, the presence of SARS-CoV-2 infection at delivery is associated with increased odds of SMM compared with absence of SARS-CoV-2 infection. Propensity scores are useful when randomization is not possible, when all confounders are measurable, and when there is little residual confounding that could alter the association between the exposure and outcome. One might conclude from the analysis by Mupanomunda et al that the Omicron variant is associated with less morbidity, and this would be consistent with findings from other studies. However, the underlying reasons for this lack of association are not clear. Whether herd immunity from prior infection or vaccination factored into the lack of a significant association between Omicron variant predominance and SMM is not known and cannot be determined at present.

Understanding the role of prior immunity from either natural infection or vaccination will be increasingly important as we measure respiratory and maternal morbidity in future SARS-CoV-2 variants in pregnancy, immune response to COVID-19 vaccine boosters, and health disparities that may impact these
outcomes. Clinical efficacy and safety data on vaccines and therapeutics in pregnancy is a long-standing, significant knowledge gap that was highlighted during the pandemic. Given the unique immunologic state of pregnancy, the scientific community now face additional challenges in understanding how prior immunity impacts morbidity and immune response to infection or vaccination in pregnancy, and whether this immune response alters neonatal antibodies and risk for neonatal infectious morbidity. Indeed, SARS-CoV-2 infection is not the only vaccine-preventable viral illness to pose such challenges. Efforts continue to elucidate the impact of repeated seasonal influenza vaccination or natural infection on the immune response to subsequent vaccination or infection and disease. What is clear is that inclusion of pregnant patients in early clinical trials of vaccine safety and efficacy, as well as in postmarketing observational studies, is critical to fully understand how to target preventive and therapeutic treatments in people of childbearing age and what infections to prioritize for maternal or neonatal benefit. Despite Congressional interest and a Department of Health and Human Services Task Force with these specific recommendations published in 2018—ie, before the pandemic—these populations were again left behind in the development of the SARS-CoV-2 vaccination. Until we move to an environment of inclusion of pregnant individuals in both the design and conduct of studies, optimizing maternal and infant health will continue to lag. The findings from Mupanomunda emphasize the negative impact on maternal health and only serve to highlight the importance of an ounce of prevention.

ARTICLE INFORMATION
Published: August 12, 2022. doi:10.1001/jamanetworkopen.2022.26444
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Corresponding Author: Catherine Y. Spong, MD, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Ste H6-106, Dallas, TX 75390 (catherine.spong@utsouthwestern.edu).
Author Affiliations: Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas (Adhikari, Spong); Parkland Health and Hospital System, Dallas, Texas (Adhikari, Spong).
Conflict of Interest Disclosures: None reported.
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