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## COVID-19 vaccines and neglected pregnancy

On June 18, 2020, WHO presented a strategic framework to ensure the equitable allocation of scarce COVID-19 resources, including vaccines.<sup>1</sup> Health-care workers, people older than 65 years, and people with cardiovascular disease, chronic respiratory disease, cancer, diabetes, or obesity will be prioritised for initial vaccination. Pregnant women do not appear to constitute a high-priority group, despite representing a cohort who are at increased risk for severe complications of COVID-19. A growing body of evidence exists to suggest that pregnant women are at a higher risk of morbidity and mortality from COVID-19, including increased risk of respiratory failure with the need for admission to intensive care and mechanical ventilation, compared with age-matched women who are not pregnant.<sup>2,3</sup> COVID-19 has also been associated with an increased rate of stillbirth.<sup>4</sup>

Two trials of adenovirus-vectored vaccines (phase 1/2 and phase 2)<sup>5,6</sup> for COVID-19 have shown sustained T-cell and neutralising antibody responses against the trimeric spike glycoprotein of severe acute respiratory syndrome coronavirus 2 in healthy adult participants who were not pregnant. Replication-defective adenoviruses, when chemically attenuated, are ideal vectors because of their ability to accommodate large transgenes and encode proteins without viral integration into the host cell genome.

ChAdOx1, the chimpanzee adenovirus-vectored vaccine platform that was used in the Oxford trials,<sup>5</sup> has previously been shown to safely induce potent humoral and cell-mediated immune responses that confer robust protection from Rift Valley fever disease in pregnant sheep that were vaccinated in the first trimester, without risks of maternal viraemia or miscarriage.<sup>7</sup> Murine studies of gorilla adenovirus-vectored vaccines for Zika

virus have similarly been shown to prevent in-utero transmission of Zika virus.<sup>8</sup> The immunity paradox during pregnancy that favours tolerance to the fetus (ie, stops the maternal immune system from rejecting the fetus), but leaves the mother susceptible to viral infections, can be opportunistically leveraged by simian adenoviral vectors. The ChAdOx1 vaccine platform is non-replicating and could be used to deliver proteins to the mother for the induction of an immune response without adversely affecting the fetus. Transplacental transfer of maternal induced antibodies can ensue, but without transfer of the virus vector to the fetus. Unfortunately, pregnant women have historically been excluded from pharmaceutical research, owing to well intentioned, but sometimes misguided, concerns about fetal safety.

The development of an effective COVID-19 vaccine is a global health priority. Pregnant women, who are at increased risk of adverse outcomes from COVID-19, would be additionally harmed if they were unable to access evidence-based chemoprophylaxis from vaccine trials. WHO's global commitment to fair access to COVID-19 vaccines should, therefore, include pregnant women. Accordingly, we advocate that pregnant women should be included in the phase 3 trial protocols of adenovirus-vectored vaccines and also protein-based vaccines (eg, NVX-CoV2373, a recombinant nanoparticle vaccine [NCT04368988]) for COVID-19, for which there are even less safety concerns, and implore international obstetric societies to endorse their recruitment. The protocols should include provisions for monitoring of maternal and fetal safety and for documentation of iatrogenic complications, including follow-up of offspring after delivery.

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