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## 2009 H1N1 Influenza and Pregnancy — 5 Years Later

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In April 2009, a novel influenza A virus, now referred to as influenza A(H1N1)pdm09 virus (2009 H1N1), was identified in two children in California, and shortly thereafter, the second U.S. death associated with 2009 H1N1 occurred in a previously healthy pregnant woman. The virus spread rapidly throughout the United States and the world, and on June 11, 2009, the World Health Organization raised the global pandemic alert to 6, its highest level. Five years have now passed since that pandemic, and in that time, much has been learned about influenza's effects on pregnant women and infants. Nevertheless, cases of severe influenza illness, hospitalizations, and deaths among young and middle-aged adults, including pregnant women, were reported during the 2013–2014 influenza season, when 2009 H1N1 was again the predominant circulat-

ing influenza virus in the United States.<sup>1</sup> These severe outcomes among pregnant women prompted us to review lessons learned from the pandemic and ways of reducing influenza's effects during pregnancy in future influenza seasons.

Although data were available before the 2009 pandemic suggesting that pregnant women were at increased risk for influenza-associated complications, the pandemic provided solid data on this vulnerability.<sup>2</sup> Pregnant women with 2009 H1N1 influenza were at substantially higher risk for hospitalization than the general population, and they accounted for approximately 5% of deaths from 2009 H1N1 influenza that were reported to the Centers for Disease Control and Prevention (CDC), even though pregnant women make up only about 1% of the population. Moreover, the 2009 pandemic virus was

also bad for babies: infants born to women who had been severely ill with influenza complications had increased risk for adverse outcomes such as preterm birth or small size for gestational age.<sup>2</sup>

The 2009 H1N1 pandemic brought a change in our approach to treating influenza in pregnancy. Previously, pregnant women with influenza had been treated primarily if they had other high-risk medical conditions or severe disease. During the 2009 pandemic, however, the CDC recommended that empirical antiviral therapy be initiated as soon as possible during the clinical course if the patient was pregnant or had recently delivered. This represented a significant shift in antiviral treatment guidance: it was recommended that pregnant women with suspected 2009 H1N1 influenza receive prompt antiviral therapy, regardless of risk factors, severity of illness,

history, or the results of diagnostic testing.<sup>2</sup>

Before the pandemic, we had little information on the benefits of treating pregnant women with an antiviral medication, since pregnant women had been excluded from clinical trials of these medications. During the pandemic, we learned that treating pregnant women with such a medication makes a difference. A recent systematic review and meta-analysis examining the effects of antiviral medications on mortality due to 2009 H1N1 influenza among hospitalized pregnant women revealed that women who received a neuraminidase inhibitor within the first 2 days after the onset of symptoms were about one fifth as likely to die as women who were treated later or not at all.<sup>3</sup> In addition, although treatment of influenza has been shown to be most effective if initiated in the first 48 hours after symptom onset, observational studies have shown that starting treatment even after 48 hours has clinical benefit.<sup>2</sup> With increased use of antiviral medications, it became possible to collect data regarding their safety during pregnancy, and the findings have been reassuring.<sup>4</sup>

Since the 2009 pandemic, much more information has also become available about the safety and benefits of influenza vaccination during pregnancy. Receiving an influenza vaccine reduces the risk of influenza not only for the pregnant woman but also for her infant during the first 6 months of life. In addition, some studies have showed reduced frequencies of adverse outcomes such as small size for gestational age and preterm birth among infants whose mothers received influenza vaccine during pregnancy.<sup>2</sup>

We have also gained knowl-

edge about the barriers to and motivators for influenza vaccination during pregnancy. We know that recommendations from health care providers are a critical motivator for pregnant women to be vaccinated. We also know that pregnant women are concerned about the safety of influenza vaccine and are more likely to be vaccinated if they understand the benefits, especially to their infants. The CDC used knowledge about these barriers and motivators and worked closely with key partners such as the American Congress of Obstetricians and Gynecologists in order to increase vaccine coverage.

Yet reports of pregnant women becoming severely ill from or dying of 2009 H1N1 influenza during the 2013–2014 influenza season were sadly reminiscent of the pandemic 5 years ago, when we received many calls from clinicians caring for critically ill or dying pregnant women. Why are pregnant women still getting so sick and dying from influenza? In part, the problem may arise from misconceptions about influenza or its prevention or treatment that lead to missed opportunities for preventing influenza illness or its complications during pregnancy.

Despite our knowledge about the benefits and safety of influenza vaccine and recommendations from the Advisory Committee on Immunization Practices and the American Congress of Obstetricians and Gynecologists, not all pregnant women get vaccinated. Substantial increases in vaccination coverage occurred during and after the pandemic, but since the 2010–2011 season, coverage has remained relatively stagnant at less than 50%. Fewer pregnant women follow the recommendation to receive influen-

za vaccine than follow other health care recommendations; for example, in keeping with CDC guidelines, more than 85% of pregnant women are screened for group B streptococcus infection.<sup>5</sup> Some pregnant women, and even a few clinicians, remain concerned about vaccine safety, especially regarding vaccination during the first trimester, even though the evidence indicates that influenza vaccination is safe during pregnancy.<sup>2</sup>

Similarly, not all pregnant women with suspected influenza receive treatment with oseltamivir, despite the current guidelines. We have four main recommendations regarding treatment during pregnancy. First, since some women with signs and symptoms of influenza may not seek treatment promptly, health care providers need to educate pregnant women about these signs and symptoms and the need for early treatment.

Second, treatment should be based on clinical evaluation rather than on diagnostic testing, given the limited sensitivity of rapid influenza antigen tests and the time required for more definitive testing. The sensitivity of the rapid tests is generally 40 to 70% of that of viral culture or reverse-transcriptase–polymerase chain reaction, and a sensitivity range as wide as 10 to 80% has been reported — which means that false negative results are common. Treatment should not be delayed until the results of more definitive testing become available.

Third, pregnant women should be treated regardless of whether they have been vaccinated, because influenza vaccine is only about 60% effective.

Finally, although it is ideal to begin treatment with antiviral medications less than 48 hours

after symptoms begin, there is still clinical benefit when treatment is begun later.

Five years ago, reports of severe illness and deaths of pregnant women from H1N1 influenza called attention to questions about influenza during pregnancy and led to a large number of publications and vastly improved knowledge about influenza and its treatment and prevention in this population. Unfortunately, pregnant women continue to become seriously ill with influenza, and some of them die. Research is needed to further elucidate the reasons why some pregnant women are not vaccinated so that the

problems can be addressed. In addition, by implementing the current antiviral treatment recommendations, clinicians can prevent complications in women with influenza. We need to ensure that the information about influenza and pregnancy that has been gained in the 5 years since the 2009 H1N1 pandemic is translated into reductions in the number of illnesses, hospitalizations, and deaths that occur in future influenza seasons.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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