



HHS Public Access

Author manuscript

J Womens Health (Larchmt). Author manuscript; available in PMC 2025 January 13.

Published in final edited form as:

J Womens Health (Larchmt). 2024 December ; 33(12): 1591–1598. doi:10.1089/jwh.2024.0893.

Preventing Influenza Virus Infection and Severe Influenza Among Pregnant People and Infants

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Abstract

The landscape of research on the benefits of influenza vaccines and antivirals to protect pregnant persons and infants has increased in recent years, while influenza vaccination rates and antiviral usage have declined. Pregnant people and infants <6 months of age are at increased risk of hospitalization with influenza, making protection of this population essential. Maternal influenza vaccination at any time during pregnancy is the best way to reduce the risk of influenza and severe influenza in both pregnant people and their infants <6 months of age. Influenza antiviral medications for pregnant people and infants are also recommended as early as possible if influenza is confirmed or suspected. This report will update on the current research on the benefits of influenza vaccination during pregnancy and influenza antiviral medication for the pregnant person and infant, current Advisory Committee on Immunization Practices recommendations for influenza vaccination in pregnancy and vaccination coverage rates, current influenza antiviral medication guidance and usage rates in pregnancy and among infants, and future directions for influenza pregnancy research. With over half a century of maternal influenza vaccination in the United States, we have improved protection for pregnant persons and infants against influenza, but we still have room for improvement and optimization with new challenges to overcome following the COVID-19 pandemic. By continuing to fill research gaps and increase vaccination coverage and antiviral usage, there is potential for significant reductions in the domestic and global burden of influenza in pregnant persons and infants.

Keywords

antivirals; influenza; vaccination; infants; pregnancy

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Author Disclosure Statement

Ms Olson reports travel support from the Gates Foundation. No other potential conflicts of interest were disclosed.

Introduction

Pregnant people and infants <6 months of age are at increased risk of hospitalization with influenza. Therefore, preventing influenza in these populations is important, as well as timely treatment of influenza. Maternal influenza vaccination during pregnancy is the best way to reduce the risk of influenza and severe influenza in both pregnant people and their infants <6 months of age, who are too young to receive influenza vaccination. The U.S. Advisory Committee on Immunization Practices (ACIP), the U.S. Centers for Disease Control and Prevention (CDC), and the American College of Obstetricians and Gynecologists (ACOG) recommend influenza vaccination for pregnant people during any trimester of pregnancy. Those at higher risk for influenza complications, especially children younger than two years of age (including infants) and pregnant and postpartum people up to two weeks after pregnancy, are also recommended to receive influenza antiviral treatment as early as possible if influenza is confirmed or suspected.

This report will provide an update on the

- Benefits of influenza vaccination during pregnancy and influenza antiviral medication for both pregnant people and their infants,
- ACIP 2024–2025 seasonal recommendations for influenza vaccination during pregnancy and influenza vaccination coverage rates for recent seasons,
- Current influenza antiviral medication guidance and usage rates among pregnant persons and infants, and
- Future directions for influenza pregnancy research.

Strategies to protect both the pregnant person and infant from influenza could lead to significant reductions in the domestic and global burden of influenza in these populations.

Risk of influenza for pregnant people and infants

Pregnant and postpartum.—Pregnant people are at increased risk of hospitalization with influenza. A systematic review showed the risk of influenza-associated hospitalization is three times higher in pregnant persons compared to nonpregnant women of reproductive age.¹ Previous reports have estimated approximately 3.9% of U.S. women of reproductive age (aged 15–49 years) are pregnant at any point in time,² and among the pregnant population, a little less than half of pregnancies are between 23 and 42 weeks gestation, or in the period of highest risk for severe influenza in pregnancy.³ In previous seasons, pregnant women accounted for more than a quarter of all influenza-associated hospitalizations.⁴ More recently, in the 2022–2023 influenza season, early season surveillance estimates showed that nearly half of women of reproductive age who were hospitalized with influenza were pregnant.⁵ However, these surveillance differences in hospitalizations among pregnant and nonpregnant women are likely influenced by differences in clinical testing practices, and a further comparison of these populations is needed.

Pregnant and postpartum persons have also been observed to be at higher risk for severe illness and complications from influenza, particularly during the second and third

trimesters.⁶ However, studies to assess this are older and have limitations. One study showed an increased risk of hospitalization for respiratory illness, during every trimester, with the highest rates in the third trimester and especially among those with preexisting conditions,⁷ and another showed an increasing risk of acute cardiorespiratory hospitalizations during the influenza season with increasing lengths of pregnancy.⁸ When examining other characteristics of these pregnant persons hospitalized with influenza, one multiseason US surveillance study found the majority were in their third trimester, a little less than half had an underlying condition (with asthma as the most common), median length of hospital stay was 2 days, and most were still pregnant at discharge.⁹

These data help elucidate the severity of influenza in pregnancy; however, there is still work needed to understand if some admissions are because a person is pregnant versus the severity of the influenza illness. There are few studies that have assessed more severe seasonal influenza illness in pregnancy; one US study assessed pregnancy-related influenza deaths prior to the H1N1 2009 pandemic and found that on average five influenza-related deaths among pregnant women were reported per year compared to 28 reported during the first 4 months of the 2009 pandemic.¹⁰ Thus, it is unclear if illness severity, especially death, is primarily associated with a novel pandemic influenza virus that may evade immunity from prior influenza vaccinations and infections versus seasonal influenza.

Pregnancy outcomes.—Influenza during pregnancy may also increase the risk of some adverse pregnancy outcomes; however, reviews on this are mixed. Influenza may be associated with preterm birth, small for gestational age, and fetal loss,¹¹ but a systematic review found that the impact of seasonal influenza on adverse perinatal outcomes were of low quality.¹² A subsequent multinational cohort study of pregnant women in middle-income countries found that influenza illness was associated with a reduction in birthweight and an increased risk of stillbirth but was not associated with preterm birth.¹³ One US surveillance study assessing deliveries among women hospitalized with influenza found that almost a quarter of deliveries were born preterm, which was higher than national percentages of preterm births,¹⁴ and this study also found a higher proportion of fetal losses. Another study assessed the risk for birth defects and demonstrated the impact of seasonal influenza in the first trimester was associated with two times the risk of any birth defect, including increased risk for neural tube defects, hydrocephaly, congenital heart defects, cleft lip, and limb reduction defects.¹⁵ However, recent data assessing pregnancy outcomes in more recent seasons are lacking.

Infants.—Infants aged <6 months have the highest risk for influenza-associated hospitalization and death of all children but are too young to receive influenza vaccines. A US surveillance study showed that adjusted seasonal influenza-associated hospitalization rates were highest among infants <6 months old and similarly, in-hospital mortality rates were highest compared to all other pediatric groups.¹⁶ Further, infants <6 months of age were five times more likely to be hospitalized and had twice the incidence of death compared to those 6–23 months of age.¹⁶ However, in this same analysis, hospitalizations in infants aged <6 months were less likely to be associated with pneumonia, ICU admission, mechanical ventilation, and all-cause in-hospital mortality compared to children 13–17

years of age even after adjusting for underlying conditions.¹⁶ Similar to pregnant persons, there may be a lower threshold for hospitalization for infants, which may result in higher hospitalization rates; thus, we need to better understand the severity of these illnesses for pregnant persons and infants.^{16,17}

Benefits of influenza vaccination during pregnancy

Pregnant persons.—Maternal influenza vaccination prevents hospitalizations and influenza illness in pregnant persons. Clinical trials conducted in low- and middle-income countries found an influenza vaccine efficacy in pregnant women of 50–70% against laboratory-confirmed influenza.^{18–21} Additional observational studies have shown similar results, including 44–64% reduction in laboratory-confirmed influenza and a 40% reduction in hospitalization.^{22–24} Overall, these studies demonstrate protection for the vaccinated pregnant person that is similar to vaccine effectiveness (VE) estimates in adult populations.²⁵

Infancy.—Maternal influenza vaccination in pregnancy also prevents influenza-associated hospitalization and illness in infants <6 months of age and is the primary protection for infants too young to be vaccinated. Clinical trials also assessed efficacy for infants born to mothers that were vaccinated during pregnancy and are the primary body of evidence of infant protection through maternal vaccination, demonstrating an efficacy of 30–63% against laboratory-confirmed influenza.^{18,19,21} Several other observational studies, some conducted in the United States and some internationally, have provided similar results.^{24,26–29} More recently, an observational study conducted in the United States demonstrated a higher point estimate against hospitalization, among infants <3 months of age, and among those born to mothers vaccinated later in pregnancy, specifically in the third trimester.³⁰ However, another study in Canada demonstrated similar maternal VE against laboratory-confirmed influenza regardless of the trimester of vaccination, infant age at testing, and gestational age at birth.³¹ Overall, all published studies indicate that maternal influenza vaccination is effective in preventing both influenza and influenza-associated hospitalizations in infants aged <6 months, including during recent influenza seasons and across care settings.

Cost-effectiveness.—In addition to the clinical benefits of vaccination, there are also studies highlighting the cost-effectiveness of a maternal vaccination strategy.³ A systematic review of pregnant and postpartum cost-effectiveness studies found that vaccinating all pregnant and postpartum persons versus only women at increased risk of severe influenza, such as those with certain underlying conditions, was cost-effective, with incremental cost-effectiveness ratios ranging from \$9,773 per quality-adjusted life years (QALY) from a societal perspective to \$58,000 per QALY from a healthcare system perspective.^{3,32} Further, vaccinating postpartum persons was cost-saving in one study that examined influenza vaccination prior to postpartum hospital discharge compared to no vaccination and found an incremental net societal benefit of \$12.57 per postpartum pregnant person vaccinated.^{32,33}

Many of these cost-effectiveness studies do not account for the additional benefit of protection for the infant born to a vaccinated mother, which would likely increase the economic value. One study that accounted for the timing of vaccination and the benefit

for the pregnant person and infant found that the greatest benefit was if pregnant persons were vaccinated as soon as possible after vaccines were available.³ Earlier vaccination had a larger impact on infant morbidity because infants were at increased risk during the peak of influenza season while the pregnant person was not.³ Studies that can further quantify the degree of economic impact for both populations might drive policy changes and convince healthcare systems of the dual benefit of this intervention.

Influenza vaccination guidance & coverage in pregnancy

Vaccination guidance.—In the United States, receipt of influenza vaccination in pregnancy has occurred every year for over half a century. Any licensed, recommended, and age-appropriate inactivated (IIV) or recombinant influenza vaccine (RIV) can be used.⁶ Live attenuated influenza vaccine is contraindicated in pregnancy, but it can be used postpartum.⁶

In 1960, the Surgeon General’s statement on influenza immunization identified three groups that should be routinely immunized, one of which was pregnant women (Fig. 1).³⁴ However, after 1960, there was a time period when there was not a firm recommendation to vaccinate pregnant persons against influenza and pregnancy alone was not considered a risk factor for influenza. In 1995, the recommendation was clear from ACIP, and over the years, ACIP’s recommendations for influenza vaccination in pregnant persons changed to include specific groups of pregnant persons.^{35–38} Following the 2009 H1N1 pandemic, universal influenza vaccination was recommended for all persons ≥ 6 months. A few years later, the most recently licensed influenza vaccines available to pregnant persons were introduced, including the first cell-cultured (ccIIV) derived influenza vaccine and RIV that became available in 2012 and 2013, respectively.^{39,40}

More recently, recommendations around the timing of vaccination during pregnancy have evolved.^{6,41,42}

As of the 2024–2025 influenza season, the guidance is,⁶

“Early vaccination (i.e., during July and August) can be considered for persons who are in the third trimester during these months if vaccine is available because this can **provide protection for the infant during the first months of life when they are too young to be vaccinated.**”

For the 2024–2025 season, ACIP did not have specific changes to the recommendations or considerations for pregnant and postpartum persons. However, due to the lack of B/Yamagata circulation after March 2020, CDC, the U.S. Food and Drug Administration, and the World Health Organization have recommended influenza vaccinations should transition from quadrivalent to trivalent vaccines, removing the B/Yamagata strain.⁴³ Prior to the transition to quadrivalent, there were data supporting the safety, efficacy, and effectiveness of trivalent vaccines in pregnancy, with potentially more data to support these vaccines in pregnancy than the accumulation of data for quadrivalent vaccines. Thus, it is not anticipated that this change in formulation will impact the safety or effectiveness of influenza vaccines for pregnant persons or their infants, but new studies, following the change in formulation, that continue to assess safety and effectiveness will be valuable to continue to encourage influenza vaccination uptake in pregnancy.

Vaccine safety.—Influenza vaccination during pregnancy has a well-described safety profile for the pregnant person and the developing fetus. Substantial evidence supports the use of IIV during pregnancy. Data specifically reflecting the administration of influenza vaccines during the first trimester are limited, but most studies indicate no association between influenza vaccination and adverse pregnancy outcomes, including spontaneous abortion.⁶ There are fewer studies of more recently licensed influenza vaccines (e.g., RIV or ccIIV) during pregnancy compared with IIV.⁶ However, of the available ccIIV and RIV studies and safety reporting, all have supported the safety of these vaccines in pregnancy.^{6,44–47}

Vaccination coverage.—Influenza vaccination coverage rates in the United States have changed over time.^{48,49} For Healthy People 2020, the goal was 80% coverage among pregnant persons.⁵⁰ Prior to the 2009 H1N1 pandemic, US influenza vaccination coverage among pregnant persons was consistently low at around 15%.^{4,36,51} However, by the 2019–2020 influenza season, about half of pregnant people in the United States were vaccinated,⁴⁹ but racial and ethnic disparities in maternal vaccination were present.⁴ Following the COVID-19 pandemic, vaccination rates have declined among pregnant persons across all races and ethnicities, and disparities have persisted (Fig. 2). Overall influenza vaccination rates in pregnancy have declined from 56% in March 2020 to 38% in March 2024.⁴⁹ One solution to these declining coverage rates is a healthcare provider recommendation including offering vaccination during the healthcare visit, which has been consistently associated with willingness to receive influenza vaccine among pregnant people in the United States and globally even following the COVID-19 pandemic.⁵² Additionally, vaccine acceptance in pregnancy may extend to vaccine acceptance for infant influenza vaccination during their first eligible season.⁵³

Communication and media campaigns have been sponsored by CDC and other organizations to increase vaccination in pregnancy. Recent 2023–2024 influenza campaigns, such as the “Wild to Mild” campaign and “From Me, To You,” included pregnant persons as one of the priority audiences.^{54,55} In preparation for the 2024–2025 influenza season, focus groups among pregnant persons have been conducted to ensure influenza vaccination campaign messages will resonate with pregnant persons. Additionally, the CDC has also recently conducted in-depth interviews among providers to better understand provider beliefs, trusted sources of information, and the acceptability of maternal vaccination, including coadministration and multiple vaccines in pregnancy.

Antiviral guidance and usage

Although maternal influenza vaccination is the mainstay of influenza prevention in pregnant people and their infants aged <6 months, influenza treatment with antiviral medications is an important adjunct to reduce morbidity and mortality from influenza when influenza is suspected or confirmed among pregnant people and infants. Antiviral treatment is recommended for any patient with suspected or confirmed influenza who is at higher risk for influenza complications, including infants, pregnant people, and postpartum people up to 2 weeks following their pregnancy.⁵⁶ Antiviral treatment should be started as soon as possible after illness onset and should not be delayed while awaiting test results when influenza

is suspected based on clinical presentation and local circulation patterns. Additionally, treatment initiated even after 48 hours has shown benefit in severe, complicated, or progressive illness and in hospitalized patients. One US study showed that early initiation of influenza antiviral treatment among pregnant persons reduced length of stay, from a week to 2 days in those with severe influenza and from 3 to 2 days in those with lower severity. Another US study during the 2009 H1N1 pandemic demonstrated a fourfold reduction in the relative risk of ICU admission among pregnant persons who were treated earlier.⁵⁷

Oral oseltamivir is the preferred option for influenza treatment during pregnancy, and CDC, IDSA, and ACOG recommend oseltamivir treatment for pregnant people with suspected or confirmed influenza.^{56,58,59} Oral oseltamivir is safe during pregnancy and when breastfeeding, with the same dosage given to pregnant and nonpregnant persons.⁵⁶ Although controlled clinical studies of oseltamivir have not been conducted to assess the safety for pregnant people, there have been multiple observational studies of treatment with oral oseltamivir during pregnancy that have shown antiviral treatment with these medications is safe during pregnancy and does not increase the risk of adverse events or adverse pregnancy outcomes. Further, the frequency of antiviral usage among pregnant persons is high, with one US study, prior to the COVID-19 pandemic, showing the vast majority (88%) of hospitalized pregnant people with influenza received antiviral treatment.⁹ However, studies have not assessed the frequency of use of influenza antivirals among pregnant or postpartum persons following the COVID-19 pandemic.

Oral oseltamivir is also the recommended option for influenza treatment in young infants, and published studies have shown that oseltamivir is well tolerated in infants.⁶⁰ Both the CDC and AAP recommend oseltamivir for influenza treatment in infants starting at birth from the first day of symptoms and onward.⁶¹ The dosage for infants is 3 mg/kg/dose twice daily, and pharmacokinetic studies have shown that this dosage provides a similar effect to the recommended dosage in adults.^{56,62} Premature infants might have slower renal clearance of oral oseltamivir because of immature renal function, and doses recommended for full-term infants might lead to very high drug concentrations in this age group. Guidance for oseltamivir dosing in premature infants is available.⁵⁶

Prior to the COVID-19 pandemic, antiviral use in infants hospitalized with influenza was high at ~81%, and infants were one of the more frequently treated pediatric age groups.⁶³ However, data to assess current usage of influenza antiviral medications in infants across settings are limited, and there has been some indication of a decline in pediatric antiviral usage, with one study reporting only ~65% of children hospitalized with influenza receiving antivirals during the 2022–2023 influenza season.⁶⁴

Future directions

Clinical.—Clinical guidance and research on influenza during pregnancy and in infants has been published for decades, but more efforts are needed to address vaccine coverage, education, and availability. First, both influenza vaccination coverage and use of influenza antiviral treatment have declined since the COVID-19 pandemic, underscoring the need to increase vaccination coverage during pregnancy and increase the appropriate use of influenza antiviral treatment among both pregnant persons and infants. Healthcare

professionals who provide care for pregnant persons, pediatricians, and other healthcare professionals are critical resources in modifying this trajectory. Healthcare professional organizations should continue to educate clinical professionals about the burden and impact of influenza among pregnant people and young infants and the effectiveness and benefits of vaccination and influenza antiviral treatment.⁶⁵ Additionally, pregnant persons have been shown to modify their behavior in pregnancy when advised that their behavior change can benefit the developing fetus or the infant.

To increase vaccination coverage, we not only need to continue to educate providers on the importance of vaccination in pregnancy but we also need to ensure the availability of vaccines in healthcare provider offices, including availability early in the influenza season to meet ACIP's consideration of early vaccination in July or August for pregnant persons in the third trimester. Additionally, availability could include offering vaccines at additional locations, such as pediatrician offices, pharmacies, and workplaces, with the advertisement that pregnant persons can be vaccinated at these locations. Studies have shown obstetrician/gynecologist offices are the primary vaccination locations,⁶⁶ but many of these studies were conducted prior to the COVID-19 pandemic before declines in vaccination coverage and increases in pharmacy vaccine administration and authorization.

Research.—For research, efforts to continue to understand vaccine safety and newer vaccines are needed, as well as further observational studies to elucidate opportunities for policy impact. Substantial data support the safety of influenza vaccines in pregnancy; however, research on the risk of longer-term potential adverse health outcomes and on the administration of first trimester vaccination and newer influenza vaccines (e.g., RIV and ccIV) could increase confidence in vaccine safety.⁶⁷ Additionally, pregnant persons cite safety as a top concern of receiving any vaccine in pregnancy⁶⁸; thus, additional education and clinical counseling is needed to continue to share vaccine safety findings with pregnant persons.

Pregnant persons can also be included early in clinical trials to better understand the safety and efficacy of new vaccines.⁶⁹ Early inclusion in trials may benefit the long-term acceptance and uptake of a vaccine for pregnant populations. For influenza vaccines, there are a few new interventions in the pipeline, including combined modified RNA (mRNA) vaccine candidates against COVID-19 and influenza^{70–72} and mRNA vaccines against influenza^{73–75}; some of which are in Phase 3 clinical trials. Further, there are preclinical animal models for an mRNA vaccine against highly pathogenic avian influenza.⁷⁶ For influenza, there is always a need for pandemic preparedness, and thus, in the event of future pandemics, pregnant persons should also be considered.

For influenza vaccines, there are limited data on the efficacy/effectiveness of RIV and ccIV. The United Kingdom not only has adopted a preferential recommendation for RIV or ccIV vaccines in pregnancy but has also recommended these vaccines for other groups at increased risk of severe illness.⁷⁷ Additionally, questions remain about the optimal timing of influenza vaccination in pregnancy for the protection of the pregnant person and infant.⁷⁸ Canada's vaccination guidance specifically states that when a pregnancy extends over two influenza seasons that two doses of influenza vaccine may be received during pregnancy,

one in each influenza season,⁷⁹ which could also occur following the US guidance but is not explicitly stated. Other countries specify the second or third trimester for vaccination⁸⁰ and others specify different timing for healthy pregnant persons versus pregnant persons with chronic conditions. And still, some countries do not include pregnant persons in their immunization programs, including high-income and lower-middle income countries. Given the differences in global policies, the research has not elucidated a clear timing for the benefit of the pregnant person and infant.⁷⁸ Additionally, research assessing the use of two doses in an influenza season for pregnant persons could help address concerns about the level of protection for both the pregnant person and infant. For example, one vaccine could be administered before they become pregnant, and a second could be administered later in the season once they are pregnant (e.g., if their first vaccination was received in October, per ACIP guidelines, and they became pregnant after vaccination then they could receive a second dose in January or February). Another consideration could be early vaccination in July or August for pregnant persons in their third trimester for the benefit of the infant and a second dose postpartum to benefit the postpartum person at increased risk.

Observational data on pregnant persons and young infants with severe influenza have accumulated. However, there are still gaps in knowledge, and by better understanding who is most at risk, we can better tailor future interventions and modify policies around existing interventions. Further, there could be additional benefits from influenza vaccination and antivirals that research has not yet measured or where data are currently less robust that could encourage vaccination uptake in these populations, such as reductions in adverse pregnancy outcomes. Observational studies could also assess VE in postpartum persons, VE among infants who are preterm (who may not have sufficient time for antibody transfer), the impacts of breastfeeding combined with maternal vaccination, and waning VE for pregnant persons and infants.

Lastly, in an age of increased vaccine hesitancy and a steady decline in vaccination coverage, efforts are needed to reverse these trends. Also, in an era of new maternal vaccines, including RSV and COVID-19, and other vaccines potentially being licensed in the near future, we need to understand pregnant people's willingness to receive a larger number of vaccines during pregnancy. To improve uptake of maternal vaccines and optimize their impact on the health of pregnant people and their infants, a multifaceted approach will be needed, including coordinated efforts between public health policymakers and healthcare professionals, clear and easily implementable guidance about vaccine recommendations, and additional efforts to communicate the benefits and safety of maternal vaccines.

Conclusion

In summary, the landscape of research on the benefits of influenza vaccines and antivirals for the pregnant person and infant has increased, as vaccination rates and antiviral usage have declined. Recent ACIP considerations have sought to optimize vaccination timing to decrease the burden of influenza and increase protection for pregnant persons and infants. With over half a century of maternal influenza vaccination in the United States, we have improved protection for pregnant persons and infants against influenza, but we still have

room for improvement and optimization with new challenges to overcome following the COVID-19 pandemic.

Funding Information

No funding was received for this article.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention (CDC).

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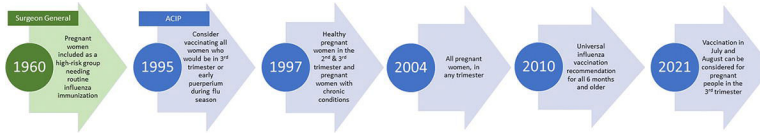


FIG. 1.
Evolution of influenza vaccination recommendations in pregnant persons.

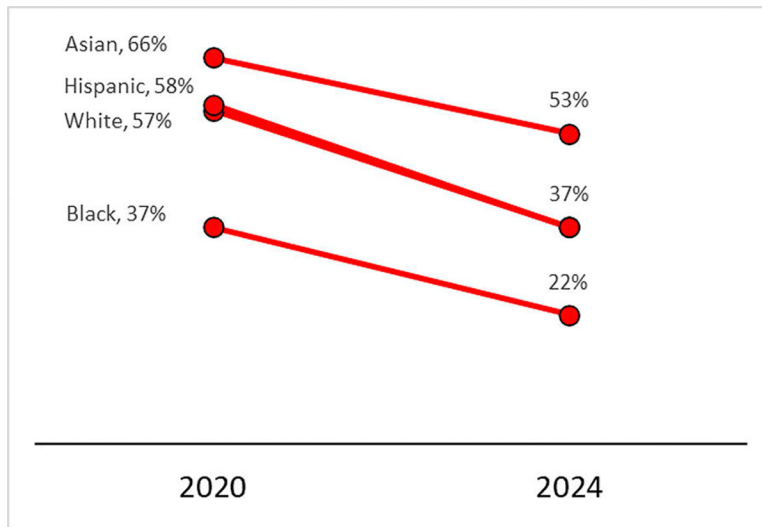


FIG. 2. Influenza Vaccination Coverage among US Pregnant Persons in March 2020 compared to March 2024, Vaccine Safety Datalink.⁵⁰