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Heterogeneity in seasonal influenza vaccination opportunity and disease risk during pregnancy and in infants <6 months

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Abstract

Pregnant women and infants <6 months are at increased risk of severe influenza but can receive protection through influenza vaccination administered during pregnancy. Since influenza vaccination and virus transmission are seasonal in the United States, the calendar timing of pregnancy could impact the opportunity for influenza vaccination and risk of influenza for pregnant women and their infants. Using data on laboratory-confirmed influenza-associated hospitalizations from 2005/06 to 2022/23 (excluding the 2009/10 and 2020/21 seasons), we assessed the risk of hospitalization by influenza season timing and by pregnancy start and infant birth months. We then used 2022/23 influenza vaccination coverage data, and the weekly number of influenza positive specimens identified from 2005/06 to 2022/23 (excluding 2009/10 and 2020/21), to quantify how the opportunity for seasonal influenza vaccination and risk of influenza exposure varied with pregnancy and birth timing. We found that pregnancy start and infant birth months with the greatest hospitalization risk varied between seasons. In seasons peaking before the second week in January, the greatest percentage of hospitalizations occurred among pregnancies beginning March–June with births in October–December. In seasons peaking later, the greatest percentage occurred among pregnancies beginning May–August with births in November–January. Opportunities for protection through maternal vaccination also varied between pregnant women and infants who were most at risk for influenza. Most pregnant women at risk of influenza had an opportunity for current season vaccination during or before pregnancy (93–98% depending on season timing). However, only 17–54% of infants at risk had an opportunity for current season protection as many were born before most influenza vaccines were administered. Our results highlight heterogeneity in influenza vaccination opportunity and risk of influenza and severe disease among pregnant women and young infants and could inform strategies to increase vaccine-mediated protection in those at greatest risk.

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Keywords

pregnancy; infants; influenza; maternal vaccination

Introduction

Influenza causes between three to five million cases of severe illness and 290,000 to 650,000 deaths globally each year[1,2], and pregnant women and infants <6 months old are at increased risk of severe influenza-associated complications[3-8]. Maternal influenza vaccination is safe and effective in reducing the risk of influenza and influenza-associated hospitalizations among pregnant women, and among infants <6 months who are not yet eligible for vaccination and receive protection through placental transfer of maternal antibodies before birth[9-19]. As such, the World Health Organization includes pregnant women among the groups at highest priority for seasonal influenza vaccination in countries considering the initiation or expansion of influenza immunization programs[20].

In temperate climates, influenza vaccination and disease activity are seasonal and occur predominately during the fall and winter months. In the United States, peak influenza activity typically occurs between December and March and lasts two to three months[21], during which time over 80% of a season's influenza-positive specimens may be identified[22]. The Advisory Committee on Immunization Practices (ACIP) recommends that anyone who is pregnant, or who might become pregnant or postpartum during the influenza season, receive an influenza vaccine[23]. Although influenza vaccines can be administered at any time during pregnancy, before and during the influenza season, ACIP recommends that they are offered in September or October so that protection lasts throughout the season. Earlier vaccination in July or August can also be considered for those in their third trimester to confer protection to infants during the first months after birth when they are too young to be vaccinated.

Given influenza seasonality, pregnant women and their infants will have different risks of influenza disease, and different opportunities for vaccination while pregnant or in utero, depending on the timing of pregnancy[18]. First, risks of disease will depend on the timing of pregnancy in relation to the timing of the influenza season and when the greatest likelihood of influenza exposure occurs. Exposure later in pregnancy is also associated with a greater risk of maternal influenza-associated hospitalization[24-26], and so hospitalization may be more likely among those whose latter trimesters overlap with a large portion of the influenza season. Second, the timing of pregnancy will impact the opportunity for vaccination and the protection conferred to a pregnant woman during pregnancy, and to her infant during the first six months of life[18]. For example, a vaccine administered to a pregnant woman who delivers in September will primarily provide protection against influenza illness to her infant (who would be <6 months of age during the season), while a vaccine administered to a pregnant woman who delivers the following March will primarily provide protection to the pregnant woman (who would be in the second or third trimester during the season). There is also evidence that vaccines administered later in pregnancy, during the third trimester, may confer greater protection to infants than those administered earlier[27]. Understanding

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the health and economic impact of maternal influenza vaccination among pregnant women and their infants requires accounting for these complexities in the timing of pregnancy, vaccination, and risk of influenza exposure.

We explore differences in the risk of influenza-associated hospitalization among pregnant women and infants <6 months with different pregnancy timings using data on laboratory-confirmed influenza-associated hospitalizations from 2005/06 to 2022/23 (excluding the 2009/10 and 2020/21 pandemic seasons). We then explain these differences by developing a method that quantifies the opportunity for vaccination and risk of influenza disease among cohorts with different pregnancy timings. We apply the method to publicly available data on influenza vaccination coverage in 2022/23 and the number of influenza-positive specimens identified from 2005/06 to 2022/23 in the United States (excluding 2009/10 and 2020/21). Our framework can help quantify how pregnancy timing impacts the opportunity for influenza vaccination and the risk of exposure to influenza viruses for pregnant women and their infants.

Methods

Identifying differences in hospitalization risk

To identify pregnancy timings associated with the greatest risk of influenza-associated hospitalization, we used data on laboratory-confirmed influenza-associated hospitalizations among pregnant women and infants <6 months from the Influenza Hospitalization Surveillance Network (FluSurv-NET)[28]. FluSurv-NET conducts population-based surveillance on persons of all ages across multiple sites and has been described previously[29,30]. We collated data from 2005/06 to 2022/23, excluding the 2009 H1N1 influenza pandemic and the 2020/21 season that coincided with the first year of the COVID-19 pandemic. For most seasons, data were collected between October to April, with the exception of 2021/22 when collection continued through June 2022 due to unusually late influenza activity[31].

Pregnant women with a laboratory-confirmed influenza-associated hospitalization were identified among women of childbearing age, defined as 15–44 years prior to the 2022/23 season and 15–49 years in 2022/23. The age range was expanded in 2022/23 to reflect the trend towards women becoming pregnant at older ages, but resulted in a small number of additional hospitalizations (2 out of a total of 319 that season) and so was unlikely to impact our results. We obtained information from medical chart abstraction that included admission date and weeks of gestation (for pregnant women) or birth month (for infants)[32]. For pregnant women, we used weeks of gestation to infer the month the pregnancy started. This information was not collected in 2007/08 or 2008/09, and so those seasons were excluded from our analysis of hospitalizations among pregnant women. We also excluded data from premature infants born prior to 37 weeks gestation due to inherently higher risks of hospitalization than those born ≥37 weeks (Table S1). Finally, in 2019/20 and 2022/23, medical chart review (including identification of gestation week) in some sites was conducted for a subset of all laboratory-confirmed hospitalizations. This sampling was conducted randomly across site, age, and discharge outcome (alive or deceased) in order to reduce the burden of data collection[30]. We excluded data from patients not sampled for

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chart review but do not expect this to impact our results as previous analyses have found no systematic differences in key demographic factors between sampled and non-sampled cases[33].

To explore the impact of influenza season timing, we stratified seasons by the timing of the peak[34], with seasons peaking on or before the first week in January (2012/13, 2013/14, and 2014/15) defined as 'early' seasons and seasons peaking after the first week in January defined as 'late' seasons (2005/06–2011/12 and 2015/16–2019/20). Seasons following the first year of the COVID-19 pandemic had atypical timing (2021/22 was unusually late and 2022/23 was unusually early) and were analyzed separately. For each season category, we calculated the average proportion of hospitalizations occurring in each pregnancy start month (for pregnant women) or birth month (for infants). We assessed differences in the distribution of pregnancy start or birth months between season categories using X^2-tests.

Defining cohorts with different pregnancy timings

To more fully explore how pregnancy timing might impact the risk of influenza and the opportunity to gain protection through vaccination, we first constructed cohorts of pregnant women and their infants that were stratified by the week the pregnancy started (i.e., the week which included the first day of the last menstrual period). We assumed the pregnancy period started this week and ended 40 weeks later[35], whereas the infancy period started at the end of the pregnancy period and ended 26 weeks (6 months) later. Deliveries before 40 weeks gestation, fetal losses, and infant deaths were not explicitly considered. We also defined a pre-pregnancy period spanning 30 weeks prior to the pregnancy start week to account for vaccinations administered before pregnancy[36]. We used the most recent complete influenza season (2022/23 at the time of writing) as an anchor point and included cohorts in the analysis if any week of the pregnancy or infancy period overlapped with the period when the majority of influenza activity typically occurs (October 2022—June 2023). These criteria ensured that we captured a wide range of cohorts, from those with pregnancies starting in early July 2021 (and giving birth in April 2022) to those with pregnancies starting in late June 2023 (and giving birth in April 2024). We note that the cohorts were designed to represent all the different possible weeks in which a pregnancy may start within our study time frame, and although they account for the timing of pregnancy, they do not account for the number of pregnancies occurring in those cohorts.

Opportunity for vaccination

We refer to the period when seasonal influenza vaccines are administered in the US as the 'vaccination campaign'. To approximate how influenza vaccination opportunity among pregnant women changes over time, we first extracted monthly cumulative coverage estimates for the 2022/23 vaccination campaign from FluVaxView for adults aged 18-49 years at higher risk for influenza complications (Figure S1A)[37]. This population includes adults with asthma, diabetes, heart disease, and pregnant women[23], and we assumed the timing of vaccination among these groups was representative of the timing of vaccination among pregnant women. For each month, we calculated incident coverage by subtracting coverage in the previous month from that of the current month. We then divided by the total coverage achieved at the end of the season to estimate the proportion of total vaccines

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administered that month among pregnant women. Finally, we imputed the proportion administered each week by dividing the monthly proportion by the total number of weeks in each month (Figure S1B).

To quantify the vaccination opportunity for each pregnant cohort in the current season, we calculated the sum of the proportion of vaccines administered across all weeks in their pre-pregnancy and pregnancy periods (except the two weeks prior to delivery, assuming there would be insufficient time for antibody protection to develop while they remained pregnant[38]). Infants <6 months are ineligible for influenza vaccination but may receive protection from maternal vaccination while in utero through the transfer of maternal antibodies[9]. We therefore quantified the vaccination opportunity for each infant cohort as the sum of the proportion of vaccines administered across all weeks of their period in utero (assuming a term gestation and excluding the two weeks prior to delivery[39]). For infant cohorts, we also stratified estimates of vaccination opportunity by pregnancy trimester given that maternal vaccination during the third trimester may confer greater protection than vaccination during earlier trimesters[27].

Risk of influenza

We estimated the risk of influenza for each week of the pregnancy or infancy period using weekly numbers of influenza-positive specimens reported to the U.S. World Health Organization (WHO) Collaborating Laboratories System or the National Respiratory and Enteric Virus Surveillance System (NREVSS)[22]. These data have been shown to be highly correlated with other metrics for influenza circulation at the national level, such as surveillance for influenza-like illness, and electronic health record data[40]. As influenza season timing is more variable than the timing of vaccination, we collated data from a range of seasons spanning 2005/06 to 2022/23 (excluding 2009/10 and 2020/21). Reports were available for all seasons from week 40 (October) to week 24 (June) the following year. In 2008/09, we excluded weeks 17–24 (from the end of April to June) which coincided with the beginning of the 2009/10 pandemic. For each season, we calculated the proportion of influenza-positive specimens identified each week by dividing the number of positive specimens identified that week by the total number of positive specimens identified over the entire season. We stratified seasons as early, late, 2021/22, or 2022/23 as described above (Figure S2), then calculated average weekly proportions of influenza-positive specimens identified across all seasons within these categories. For each season category, we quantified the influenza risk for each cohort as the sum of the proportion of influenza-positive specimens identified across all weeks in their pregnancy or infancy periods. For pregnant women, the risk of illness and hospitalization due to influenza may increase in the latter stages of pregnancy[24-26,41,42], and so we repeated this calculation for the subset of weeks coinciding with the third trimester.

Overlap between vaccination opportunity and influenza risk

We estimated the combined overlap between vaccination opportunity and influenza disease risk for pregnant women and infants as

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$$\frac{\sum_{j=1}^{n}(V_j \times I_j)}{\sum_{j=1}^{n} V_j},$$

(1)

where j represents each cohort (defined by a different pregnancy start week); n is the total number of cohorts; V_j is the vaccination opportunity for cohort j (i.e., the total proportion of vaccines administered over the pre-pregnancy and pregnancy periods for pregnant women, or the total proportion of vaccines administered while in utero for infants); and I_j is the influenza risk for cohort j for a particular season category (i.e., the total proportion of influenza-positive specimens identified during the pregnancy or infancy period for that season category). Intuitively, this formula quantifies how much of the overlap between different cohorts and the vaccination campaign also overlaps with the influenza season, and can be used to approximate the fraction of vaccines that could be administered to cohorts who will be at risk of influenza disease. Conversely, we approximated the fraction of those at risk of influenza disease who had an opportunity for vaccination using the same approach, but instead dividing by the sum of influenza risk values across all cohorts, i.e.,

$$\frac{\sum_{j=1}^{n}(V_j \times I_j)}{\sum_{j=1}^{n} I_j}.$$

(2)

Alternative vaccination timing

Our main analyses assumed that the timing of vaccination among pregnant women was equivalent to that of all adults aged 18-49 years at higher risk for influenza complications. However, coverage may increase earlier in the season among pregnant women, in part due to recommendations from ACIP that those in their third trimesters can consider early vaccination in July or August[23]. We explored the potential impact of an earlier increase in vaccine administration by shifting the weekly vaccination time series earlier by four or eight weeks and then repeating the overlap analyses described above. These shifts will cause the greatest change in coverage among those in their third trimester, whose pregnancies would have otherwise ended before the main expansion of the original campaign.

All analyses were performed in R version 4.2.0 and our main workflow is outlined schematically in Figure S3. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.

Results

Risk of influenza-associated hospitalization by pregnancy timing and season timing

We identified 3,622 laboratory-confirmed influenza-associated hospitalizations among pregnant women and 2,788 among full-term infants during the study period. Pregnancy start month could be estimated for 3,393 pregnant women and birth month could be estimated for all infants. Hospitalization risk varied according to the timing of pregnancy or birth,

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and the timing of the influenza season (Figure 1). Pregnancies starting between March–June experienced the greatest percent of influenza-associated hospitalizations in early seasons, whereas those starting between May–August experienced the greatest percent in late seasons (Figure 1A, represented by the months with the tallest bars). These patterns shifted in seasons following the COVID-19 pandemic, with the greatest risk concentrated among earlier start months in 2022/23 (February–April) and more diffusely spread among later start months in 2021/22 (April–August). We verified that the distribution of pregnancy start months was significantly different between early and late seasons ($p < 0.0001$) and between all season categories including 2021/22 and 2022/23 ($p < 0.0001$).

Similar to pregnancy start months, the distribution of infant birth months was significantly different between early and late seasons ($p < 0.0001$) and between all seasons ($p < 0.0001$). Birth months associated with the greatest percent of infant influenza-associated hospitalizations occurred between October–December in early seasons and November–January in late seasons (Figure 1B). This latter period was also associated with the greatest percent of hospitalizations in 2021/22, whereas hospitalizations in 2022/23 were elevated among earlier births (July–November). These findings demonstrate that the risk of influenza-associated hospitalization among pregnant women and infants <6 months varies by season timing and by the timing of pregnancy or birth.

Influenza vaccination opportunity

We identified 105 cohorts with pregnancy or infancy periods falling within our analysis timeframe (Figure S4). These cohorts had different opportunities for influenza vaccination in 2022/23 depending on the timing of their pregnancy (Figure 2). Cohorts with pregnancies starting between February–October 2022 were pregnant when more than 50% of vaccines were administered (Figure 2A, shown by dark shaded bars exceeding 50%), and thus had the greatest opportunity for vaccination. These cohorts had anticipated births between November 2022 – July 2023, and the subset with births between November 2022 – January 2023 had the greatest opportunity for vaccination during the third trimester when protection for infants may be greatest (Figure 2B). Conversely, more than 50% of vaccines were administered during the pre-pregnancy period for pregnancies that started between November 2022 – May 2023 (Figure 2A, shown by light shaded bars exceeding 50%). These cohorts had anticipated births during the next influenza season (August 2023 – February 2024). Finally, cohorts with pregnancies starting before February 2022 overlapped with less than 50% of the 2022/23 vaccination campaign but had anticipated births up to the start of the influenza season (October 2022).

Risk of influenza disease

The cohorts with greatest risk of influenza disease varied by season timing and by the timing of pregnancy (Figure 2, Table 1). In early seasons, pregnancies starting between April 2022 – January 2023 overlapped with more than 50% of the influenza season (Figure 2A, shown by the short, dashed line exceeding 50%), and those starting between April–June 2022 overlapped with more than 50% of the season during their third trimester (Table 1). These periods were typically shifted one month later in late seasons, a further month later in 2021/22, and one month earlier in 2022/23. There was substantial overlap between

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the pregnancy start months with greatest estimated risk during the third trimester and the pregnancy start months experiencing the greatest percent of hospitalizations in FluSurv-NET (Figure 1A, Table 1).

Among infants <6 months, those born between July 2022 – January 2023 overlapped with more than 50% of early influenza seasons during their first six months of life (Figure 2B, Table 1). These time periods typically shifted one month later in late seasons, a further month later in 2021/22, and a month earlier in 2022/23. These estimated months of greatest risk also overlapped with the months of greatest hospitalizations among infants <6 months in FluSurv-NET (Figure 1B, Table 1).

Combined overlap between vaccination opportunity and risk of influenza

Intuitively, the potential impact of vaccination will be greatest for pregnant or infant cohorts with a large combined overlap between both the vaccination campaign and the influenza season because they will have the greatest opportunity for vaccination and the greatest risk of disease. Conversely, cohorts with little combined overlap could have a substantial opportunity for vaccination with low subsequent disease risk, or little opportunity for vaccination but substantial disease risk. We found that the combined overlap varied with season timing and the timing of pregnancy or birth (Figure 2, Table 2). In earlier seasons, pregnant cohorts experiencing at least 50% overlap with both the vaccination campaign and the influenza season were primarily those vaccinated during pregnancy, whereas in later seasons there was a shift towards those vaccinated before pregnancy. Infants also experienced greater combined overlap in later seasons.

To summarize combined overlap at the population-level, we used Equations 1 and 2. We estimated that 57–59% of influenza vaccinations were administered to women who were at risk of influenza during their pregnancy, depending on the season (Table 3), and that the percent of those vaccines that were administered before pregnancy increased with later season timing, from 21% in 2022/23 to 51% in 2021/22. In addition, almost all pregnant women at risk of influenza were pregnant or within 30 weeks of pregnancy when influenza vaccines were administered, from 93% in 2022/23 to 98% in late seasons. Strikingly, we estimated that just 12–39% of vaccines administered were to pregnant women whose infants were at risk of influenza during the first six months of life, and just 17–54% of infants at risk of influenza were in utero when vaccines were administered (Table 3). Both metrics increased with later season timing.

Impact of earlier vaccination coverage

Finally, we explored how earlier vaccination coverage among pregnant women might impact our combined overlap summary metrics (Figure 3A). In general, earlier vaccination resulted in a slight improvement in the combined overlap between vaccination opportunity and influenza season risk among pregnant women, and a larger improvement in the corresponding overlap among infants (Figures 3B-C, Table S2). The greatest improvement for infants occurred in the earliest seasons. For example, in 2022/23, the percentage of infants at risk of influenza who had an opportunity for vaccination while in utero increased

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from 17% with the original timing of vaccination to 27% and 38% when vaccination was shifted four and eight weeks earlier, respectively.

Discussion

Pregnant women and infants <6 months old are at increased risk of severe influenza complications, and influenza vaccination during pregnancy can reduce the likelihood of such complications occurring. Using several independent datasets, we have shown that the timing of pregnancy consistently and significantly impacts the potential opportunity for influenza vaccination and the risk of influenza disease. This may complicate efforts to estimate the health and economic impact of influenza and influenza vaccination in pregnant women and infants <6 months, particularly compared to other populations with more temporally stable conditions associated with increased risk of influenza complications, such as asthma or heart disease.

Past health and economic studies conducted for pregnant women or infants <6 months have often ignored challenges of timing by assuming a constant opportunity for vaccination and/or risk of influenza[43-46]. However, such an assumption may overestimate the benefits of influenza vaccination, especially for infants <6 months, many of whom we found were at risk of influenza but were not in utero during the vaccination campaign. One study that did account for the timing of vaccination and illness estimated that 40% of pregnant women vaccinated in October would give birth before the peak of the influenza season and thus before the period when vaccination could have the greatest impact, thereby reducing vaccine cost-effectiveness[47]. This aligns with our estimates that, in seasons before the COVID-19 pandemic, 59% of influenza vaccines were administered to those who were at risk of influenza during their pregnancy (or, equivalently, 41% of vaccines were administered to those who were not at risk during pregnancy). Methods to estimate the health and economic impacts of influenza and influenza vaccination in the pregnant and infant population should account for this heterogeneity in influenza risk and vaccination opportunity during pregnancy and early infancy. We have demonstrated one such approach that should be relevant for any region with strong seasonality in influenza activity and/or vaccination distribution, and uses data readily available in many different countries. Our method may also be applicable to other pathogens with time-varying activity and vaccine administration.

Our work also highlights asymmetry in the potential protection provided by influenza vaccination to pregnant women compared to infants, with vaccination more likely to protect a pregnant woman during the current influenza season than her infant. For example, in seasons before the COVID-19 pandemic just 34–47% of infants <6 months who were at risk for influenza had an opportunity to be protected by vaccination, compared to almost all pregnant women. This gap in vaccination opportunity was worse for seasons with earlier peaks, particularly the 2022/23 season when just 17% of at-risk infants had an opportunity for protection. Any season with atypical timing could substantially alter the cohorts most at risk. Therefore, it is important to consider additional ways to optimize protection of infants <6 months, particularly those born early in a season, such as through influenza vaccination of household contacts and caregivers[23]. Given that the first doses of influenza

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vaccine become available in the United States as early as July, future work could investigate the impacts of efforts to increase early vaccine uptake among pregnant women in their third trimester and thereby improve protection among their infants who may be born before the main vaccination campaign begins. Our findings may also provide insights for the timing of other seasonal respiratory vaccines that are administered during pregnancy and provide protection to infants, such as vaccines against RSV.

Finally, we found that administering influenza vaccines to women who were not yet pregnant could account for 21–51% of protection among pregnant women at risk for influenza, depending on the season. In the United States, it is recommended that those who might be pregnant during an influenza season receive an influenza vaccine[23]. Countries with similar influenza seasonality that do not make these same recommendations may miss a sizable fraction of people who could become pregnant after the vaccination campaign and still be at risk of influenza. In addition, our results highlight the challenges in estimating vaccination coverage among pregnant women. Data are difficult to collect and interpret due to changes in pregnancy status throughout the season that affect both the numerator and denominator of calculated coverage estimates. Appropriately accounting for those who are vaccinated before pregnancy but will become pregnant during the influenza season is one such example. Investigating ways to address these issues is critical to enhancing surveillance of vaccination coverage among pregnant women and improving health and economic assessments of maternal vaccination.

There are several limitations to this study. First, our estimates of the timing of influenza-associated hospitalization risk and influenza exposure risk were based on nationally-aggregated data and may not capture differences in timing at finer spatial resolutions. We also did not account for other influenza-associated outcomes such as emergency department visits. Second, we did not account for seasonality in the incidence of pregnancy, which typically peaks between spring and fall in the United States, depending on the state[48]. This could impact the absolute benefits of vaccination timing among all pregnant women and infants <6 months, although should not impact our comparisons of the relative impacts of vaccination between cohorts with different pregnancy timings as these are independent of the size of each cohort. Third, we assumed in our main analysis that the pattern of influenza vaccine administration among pregnant women was similar to all adults aged 18-49 years at higher risk for influenza complications. Sensitivity analyses around vaccine timing suggested that infants at risk of influenza may have greater opportunity for protection from maternal vaccination if vaccines were instead administered earlier among pregnant cohorts, echoing previous work[47]. However, ACIP only recommends consideration of earlier vaccination for pregnant women in their third trimester, and we did not explicitly account for this distinction. Furthermore, we did not account for the complexities of waning vaccine protection, which could occur among those vaccinated at the beginning of the season who are in the early stages of pregnancy, or among those who are vaccinated before they become pregnant[18,23]. Finally, we did not track any further benefits of vaccination to pregnant women once they had given birth, or to infants in future influenza seasons (for example, infants born in July who could have been exposed to vaccination in the previous season). We also did not consider protection gained from maternal influenza antibodies transferred through breastmilk postpartum. Maternal vaccination while breastfeeding could provide

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additional opportunities for protection among infants who were born before the current season's vaccination campaign[49]. However, since less than 60% of infants are breastfed up to 6 months in the United States (and only 25% are breastfed exclusively during that time), this is unlikely to fully bridge the gap in vaccination opportunity that we have identified here[50].

The burden of influenza among pregnant women and their infants, and the body of evidence demonstrating the safety and effectiveness of maternal influenza vaccination, supports ACIP and other global recommendations that all pregnant women receive an influenza vaccine to decrease the likelihood of influenza illness and influenza-related complications for themselves and their infant. However, complexities in the timing of pregnancy and infancy periods, relative to the timing of vaccine administration and influenza activity, hinder efforts to accurately estimate the health and economic impact of maternal influenza vaccination. We provide a quantitative method to account for this complexity that uses readily available data and can help inform strategies and communications to increase coverage in those at greatest risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

All data were the result of secondary analyses. Data on vaccine coverage and influenza positive specimens are publicly available, and the relevant links are cited in the text. Data from FluSurv-NET are not publicly available due to privacy restrictions but are available upon reasonable request to the authors.

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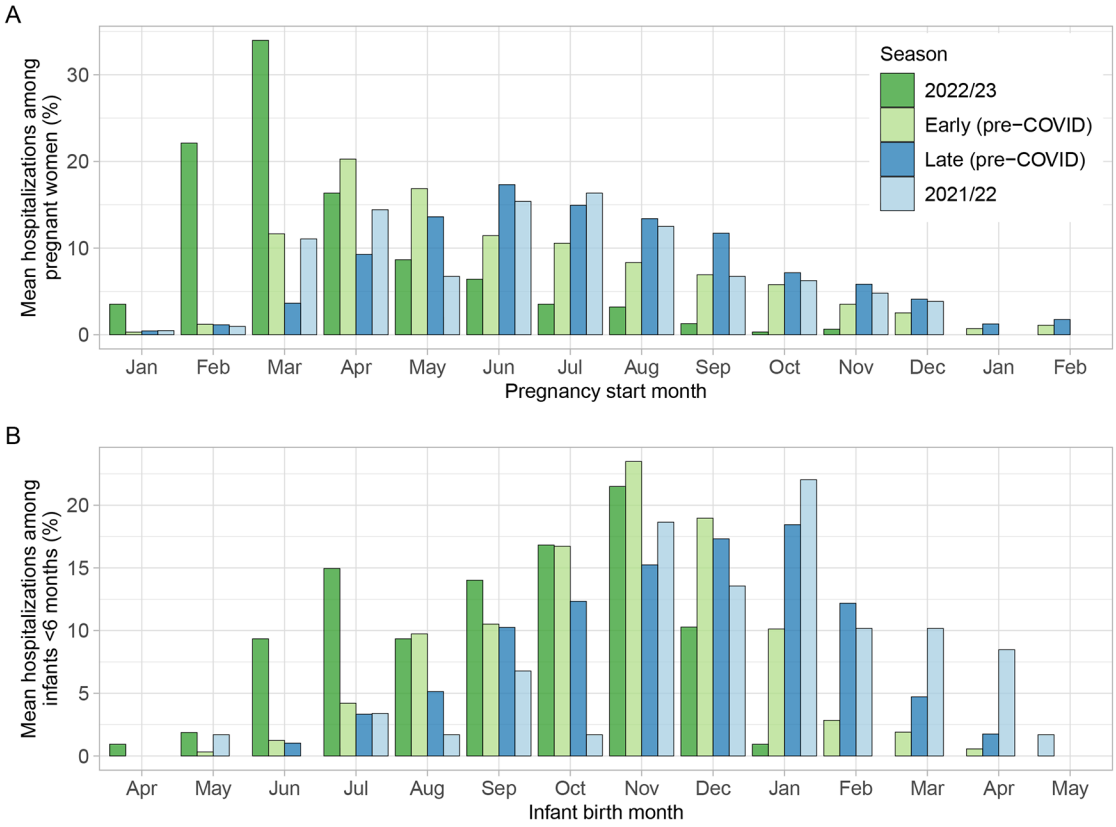


Figure 1. Impact of season timing and pregnancy or birth timing on the risk of influenza-associated hospitalization.

Distribution of FluSurv-NET laboratory-confirmed hospitalizations by pregnancy start month (A) or birth month (B) among pregnant women and infants <6 months, respectively. The legend is ordered by peak season timing, from earliest to latest.

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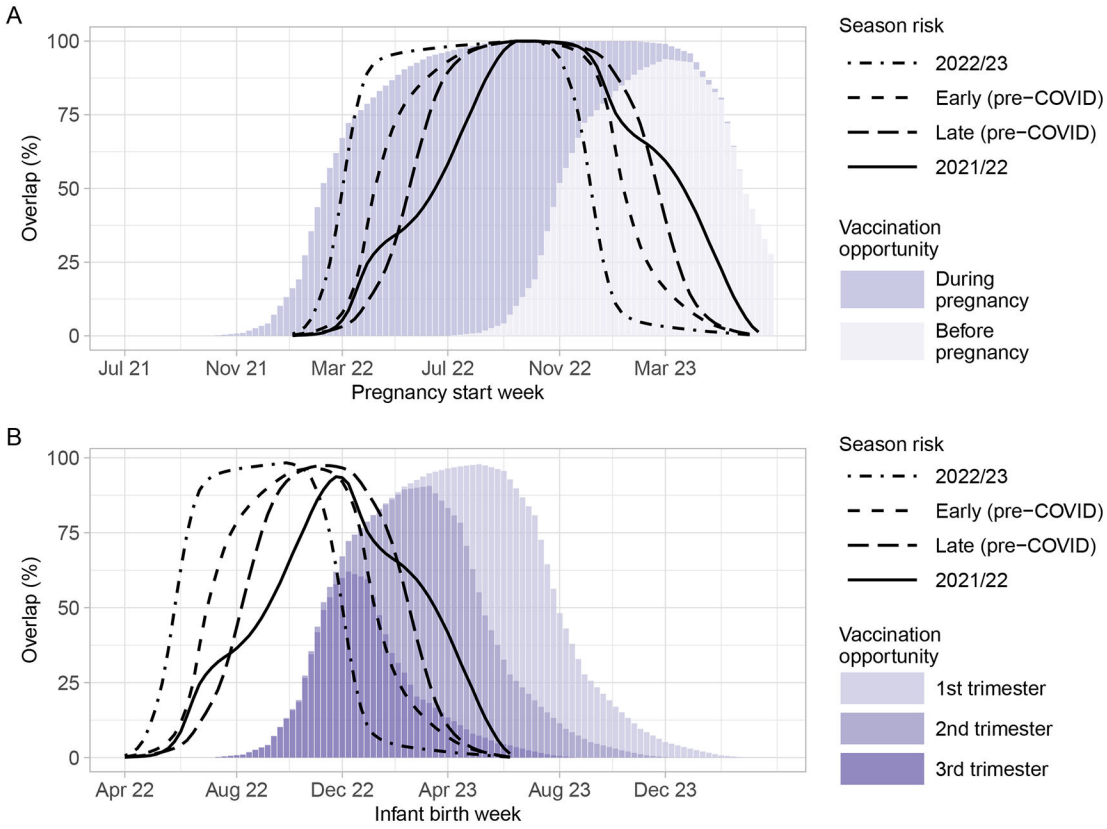


Figure 2. Overlap between different pregnancy and infancy periods and influenza vaccination opportunity and season risk.

(A) Vaccination opportunity and season risk among pregnant cohorts. Vaccination opportunity represents the total proportion of vaccines administered during pregnancy or pre-pregnancy and season risk represents the total proportion of influenza positive specimens identified during pregnancy for a particular season category. Pregnant cohorts are organized along the x-axis by pregnancy start week. (B) Vaccination opportunity and season risk among infant cohorts. Vaccination opportunity represents the total proportion of vaccines administered during the period in utero (for each trimester) and season risk represents the total proportion of influenza positive specimens identified during the first six months of life. Infant cohorts are organized along the x-axis by infant birth week. The legends for season risk are ordered by peak season timing, from earliest to latest.

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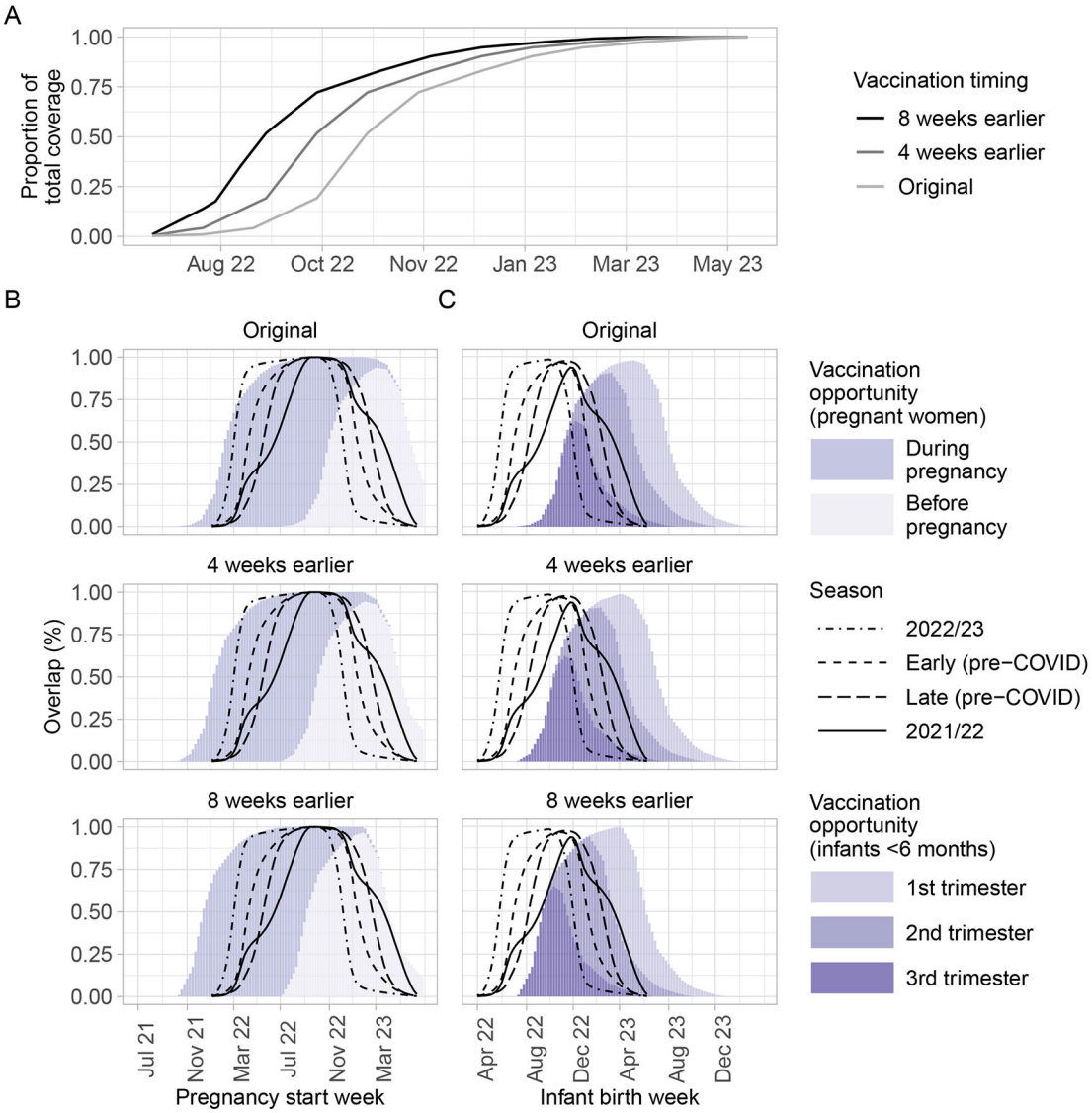


Figure 3. Impacts of earlier influenza vaccination coverage among pregnant women.

(A) Scenarios for the timing of influenza vaccine administration. The original timing scenario represents the timing of the 2022/23 vaccination campaign among high-risk adults aged 18-49 years. (B) Influenza vaccination opportunity and season risk among pregnant women. Pregnant cohorts are organized along the x-axis by pregnancy start week. (C) Influenza vaccination opportunity and season risk among infants <6 months. Infant cohorts are organized along the x-axis by birth week. The legends for season risk are ordered by peak season timing, from earliest to latest.

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Table 1. Pregnant and infant cohorts experiencing the greatest risk of influenza for different season categories.

Cohorts with the greatest risk are those whose entire pregnancy (column 2), third trimester of pregnancy (column 3), or first 6 months of life (column 4) overlap with at least 50% of the influenza-positive specimens identified in each season category. Rows are ordered by peak season timing, from earliest to latest.

Season category	Pregnancy start months with >50% overlap	Pregnancy start months with >50% overlap in 3rd trimester	Infant birth months with >50% overlap
2022/23	March 2022 – December 2022	March 2022 – May 2022	June 2022 – December 2022
Early (pre-COVID)	April 2022 – January 2023	April 2022 – June 2022	July 2022 – January 2023
Late (pre-COVID)	May 2022 – February 2023	May 2022 – August 2022	August 2022 – February 2023
2021/22	June 2022 – March 2023	August 2022 – September 2022	September 2022 – March 2023

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Table 2. Pregnant and infant cohorts experiencing the greatest combined overlap with the 2022/23 influenza vaccination campaign and different influenza season categories.

Cohorts with the greatest reported overlap are those whose (i) pregnancy periods overlapped with at least 50% of the 2022/23 vaccination campaign and at least 50% of the respective influenza season (column 2); (ii) pre-pregnancy periods overlapped with at least 50% of the 2022/23 vaccination campaign and pregnancy periods overlapped with at least 50% of the respective influenza season (column 3); or (iii) periods in utero overlapped with at least 50% of the 2022/23 vaccination campaign and infancy periods overlapped with at least 50% of the respective influenza season (column 4). Rows are ordered by peak season timing, from earliest to latest.

Season category	Pregnancy start months with greatest combined overlap: (i) vaccination during pregnancy	Pregnancy start months with greatest combined overlap: (ii) pre-pregnancy vaccination	Infant birth months with greatest combined overlap: (iii) vaccination while in utero
2022/23	March 2022 – October 2022	November 2022 – December 2022	November 2022 – December 2022
Early (pre-COVID)	April 2022 – October 2022	November 2022 – January 2023	November 2022 – January 2023
Late (pre-COVID)	May 2022 – October 2022	November 2022 – February 2023	November 2022 – February 2023
2021/22	June 2022 – October 2022	November 2022 – March 2023	November 2022 – March 2023

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Table 3. Combined overlap summarized at the population-level.

Combined overlap is summarized as the percentage of influenza vaccines that were administered to cohorts at risk of influenza (Equation 1), and the percentage of cohorts at risk of influenza with an opportunity for vaccination (Equation 2). For pregnant cohorts, we included vaccines administered during pregnancy and pre-pregnancy, whereas for infant cohorts we included vaccines administered while in utero. Rows are ordered by peak season timing, from earliest to latest.

Season category	Vaccines administered to cohorts at risk of influenza		Cohorts at risk of influenza with an opportunity for vaccination	
	Pregnant women	Infants <6 months	Pregnant women	Infants <6 months
2022/23	57%	12%	93%	17%
Early (pre-COVID)	59%	24%	97%	34%
Late (pre-COVID)	59%	33%	98%	47%
2021/22	59%	39%	97%	54%