Optimal timing of influenza vaccination in young children: population based cohort study

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ABSTRACT

OBJECTIVE

To assess optimal timing of influenza vaccination in young children.

DESIGN

Population based cohort study.

SETTING

United States.

PARTICIPANTS

Commercially insured children aged 2-5 years who were vaccinated against influenza during 2011-18.

MAIN OUTCOME MEASURE

Rates of diagnosis of influenza among children who were vaccinated against influenza, by birth month.

RESULTS

Overall, 819 223 children aged 2-5 received influenza vaccination. Children vaccinated in November and December were least likely to have a diagnosis of influenza, a finding that may be confounded by unmeasured factors that influence the timing of vaccination and risk of influenza. Vaccination commonly occurred on days of preventive care visits and during birth months. Children born in October were disproportionately vaccinated in October and were, on average, vaccinated later than children born in August and earlier than those born in December. Children born in October had the lowest rate of influenza diagnosis (for example, 2.7% (6016/224 540) versus 3.0% (6462/212 622) for those born in August; adjusted odds ratio 0.88, 95% confidence interval 0.85 to 0.92).

CONCLUSIONS

In a quasi-experimental analysis of young children vaccinated against influenza, birth month was associated with the timing of vaccination through its influence on the timing of preventive care visits. Children born in October were most likely to be vaccinated in October and least likely to have a diagnosis of influenza, consistent with recommendations promoting October vaccination.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Annual influenza vaccination is an important strategy to reduce morbidity and mortality from seasonal influenza, but large scale studies of the optimal timing of vaccination are unavailable

Annual influenza vaccinations are recommended during September or October, with the goal of ensuring immunity during the peak of influenza season

Among young children, preventive care visits frequently occur during birth months and are a convenient time to receive influenza vaccination

WHAT THIS STUDY ADDS

In commercially insured children aged 2-5 years, birth month was associated with the timing of vaccination through its influence on the timing of preventive care visits

Children born in October were most likely to be vaccinated in October and least likely to have a diagnosis of influenza

The study's findings are consistent with current recommendations promoting October vaccination

Introduction

The US Centers for Disease Control and Prevention (CDC) recommends that annual influenza vaccinations be administered in September or October to maximize vaccine induced immunity over the coming influenza season.[1 2] Although the upcoming season's vaccine may be available in the summer months, receiving the vaccine too early may result in waning effectiveness, particularly among children and older adults, before the end of the flu season.[3-9] Meanwhile, delaying vaccination may result in exposure to circulating influenza without the protection of vaccine induced immunity.[10] As such, the CDC recommends that vaccination programs "balance maximizing the likelihood of persistence of vaccine-induced protection through the season with avoiding missed opportunities to vaccinate or vaccinating after onset of influenza circulation occurs."[1]

Annual influenza vaccination is particularly important for young children, who are at elevated risk of influenza and severe infection necessitating admission to hospital[11 12]; however, little clinical evidence exists to precisely guide the timing of vaccination in this population. One way to study the optimal timing of vaccination would be to measure antibody titers or in vitro antiviral activity of immunized patients at different times following vaccination[11 13-17]; however, this method focuses on an intermediate outcome that is imperfectly correlated with real world effectiveness and may be limited by study size and representativeness.[18] Another way would be to examine vaccine effectiveness as a function of time since vaccination in observational data. Such studies in other age groups suggest that effectiveness peaks within several weeks of vaccination and wanes with each month[5 19-22]; children, however, may have a longer duration of vaccine effectiveness.[23] Such observational studies are often limited by generalizability and selection bias (for example, patients at higher risk of clinically significant infection may choose to get vaccinated earlier).

A child's birthday may influence the timing of influenza vaccination. Preventive care visits for young children are a convenient time to administer vaccines; these visits are often purposefully timed around birthdays and coordinate with the recommended childhood vaccine schedule, which includes annual influenza vaccination.[24 25] As such, children who happen to be born in the fall and early winter, when the seasonal influenza vaccine becomes available, are

both more likely to be vaccinated against influenza and less likely to have a diagnosis of influenza infection.[26] Moreover, among children who are vaccinated, those born in August or September may also be vaccinated earlier owing to earlier preventive care visits. If so, earlier vaccination may be associated with waning vaccine induced immunity toward the end of the flu season, whereas children vaccinated later may have insufficient vaccine induced immunity before being exposed to the influenza virus.

Because a child's birthday is as good as random with respect to influenza outcomes, the timing of a child's birthday, through its influence on the timing of preventive care visits and influenza vaccination, provides a unique opportunity to assess the optimal timing of influenza vaccination by using observational data. We examined patterns of influenza vaccination and infection, by birth month, among vaccinated children born in months when the annual influenza vaccine is typically available.

Methods

Data sources

Data came from the MarketScan Research Database, which contains insurance claims for approximately 30-40 million Americans covered by employer sponsored health insurance plans each year. Data are generated when a healthcare provider or organization submits a claim to insurance to pay for services or when insurance is used to pay for prescription drugs. Care for which a claim is not submitted to insurance will not appear in the database. These data have been used to study patterns of childhood vaccination, including influenza.[26-32]

Study population

The study cohort comprised children aged 2-5 years during 2011-18 who were continuously enrolled in insurance over the course of at least one influenza season, defined as September to May of the subsequent year. We focused on these ages because previous research suggested that children of this age are most likely to have preventive care visits near their birthday and that influenza vaccination commonly occurs during these visits.[26] We restricted our analysis to children with birthdays between August 1 and January 31, as the timing of influenza vaccination in these children could plausibly be influenced by the timing of preventive visits; vaccinated children born in other months so far outside the typical vaccination window would be unlikely to have their birthday influence the timing of their vaccination in an as good as random fashion.

Because our objective was to examine the optimal timing of influenza vaccination among children who are vaccinated, the cohort included only children who were vaccinated against influenza, defined by an insurance claim with any of the Current Procedural Terminology (CPT) codes for influenza vaccination (supplementary table A) or ICD-9 (international classification of diseases, 9th revision) code V04.81, between August and January of the subsequent year.

Study measures and covariates

As the flu season spans two calendar years, we defined a child's age as the maximum age achieved between August 1 and December 31 of a given influenza season (for example, for the 2012-13 season, we considered a child's age to be their maximum age in 2012). We based a child's birth month on monthly enrollment files and determined it as the month in which age changed in those files.

We defined influenza infection by the presence of at least one insurance claim for an ambulatory, emergency department, or inpatient visit containing any of several ICD-9 or ICD-10 influenza diagnosis codes (supplementary table A) or a prescription claim for oseltamivir, the preferred anti-influenza drug for young children. Studies estimate that approximately one third to one half of children with influenza-like illness present for care,[33 34] although this proportion may be higher for young children.

We obtained characteristics of children, siblings, and parents covered by the same insurance policy from the MarketScan database. Model covariates included the child's age, sex, healthcare use (mean number of office visits, emergency department visits, and hospital admissions per year over the study period), medical comorbidities, and family size (number of beneficiaries on the same policy) and the medical comorbidities and healthcare use of siblings and parents. Comorbidities included an indicator for previous pulmonary disease and the overall number of comorbidities, both defined using Elixhauser Comorbidity Software,[35] for the duration of a person's inclusion in the database before flu season.

Overview of study design

Using observational data to assess the optimal timing of influenza vaccination is complicated by the possibility that timing of vaccination is not random and may be affected by observed or unobserved characteristics of children or their families. For example, children at higher risk of influenza related complications (or with family members at higher risk) may get vaccinated earlier, which could spuriously suggest that earlier vaccination causes worse influenza related outcomes. Alternatively, children who get vaccinated earlier may belong to families that are highly motivated to receive the vaccine, are wealthier, or are more educated, which may be correlated with better outcomes.

To counter this, we exploited the natural experiment created when children, by chance, are vaccinated at different points during influenza season simply because of the month in which they happened to be born, as preventive care visits timed near birthdays are occasions to administer influenza vaccinations when they are available. Previous work suggested that among children aged 2-5 a child's birth month affects the probability that a child is vaccinated at all, as many children (for example, those with birth months during January-July) have annual visits during months when the upcoming vaccine is unavailable.[26] Moreover, children with birthdays in October, a month when

vaccination is encouraged and vaccines are widely available, are both the most likely to be vaccinated and the least likely to have a diagnosis of influenza compared with children born in other months.[26]

If birth month affects the likelihood of vaccination at all, it may also influence the timing of vaccination among vaccinated children in a way that is as good as random with respect to a patient's clinical characteristics. For this analysis, birth month functions as an instrumental variable (supplementary figure A).

Statistical analyses

We studied the optimal timing of influenza vaccination by examining how rates of influenza diagnosis vary according to a vaccinated child's birth month, as birth month may influence the timing of vaccination but be otherwise unrelated to risk of influenza. To motivate the need for this quasi-experimental design, we first explored how risk of influenza varied according to the actual month of vaccination, estimating a logistic model of influenza diagnosis as a function of vaccination month (indicator variables) and covariates described above at the child-influenza season level.

We next examined whether young children tend to have annual visits near their birthday, calculating the proportion of children whose visits occurred within two weeks of their birth month. Among vaccinated children, we compared rates of influenza vaccination on the day of such preventive visits compared with surrounding days, to establish whether the actual visit presents an important opportunity for influenza vaccination. We then analyzed how the timing of vaccination varied according to birth month, to assess whether children with earlier birth months (for example, August) received vaccines earlier, on average, than children with later birth months (for example, December). For each vaccinated child, we calculated the time elapsed from August 1 to the day of vaccination in each influenza season. We compared mean differences in weeks elapsed between birth month cohorts by using analysis of variance and did a time to event Kaplan-Meier analysis to visualize differences in vaccine timing between birth month groups, comparing differences by using the log-rank test. We also compared distributions of vaccination timing across birth months.

Next, we assessed whether vaccinated children born in different months are similar to each other, as the validity of using birth month as a quasi-experimental device to influence timing of vaccination requires that a child's birth month not be otherwise correlated with risk of influenza infection. We compared demographic, clinical, and healthcare use characteristics of vaccinated children, their siblings, and their parents between children's birth months by using standardized mean differences, with differences <0.1 not considered clinically important.[36-39] We also estimated the predicted risk of influenza infection for a given child in each influenza season by using a logistic regression of influenza infection as a function of the covariates described above. We calculated predicted rates of influenza by birth month, hypothesizing that predicted risk would not vary by birth month, consistent with a natural experiment.

Next, we analyzed how observed rates of influenza diagnosis varied according to a child's birth month, our primary objective. Firstly, we measured the unadjusted rate of influenza diagnosis by birth month, at the level of the child-season (for example, a child present over four influenza seasons contributed four child-seasons to the analysis). Secondly, we estimated a logistic regression of influenza diagnosis as a function of birth month and the covariates above, at the child-season level in the primary analysis that combined all influenza seasons as well as models for each individual influenza season conducted at the child level. In this model, we assumed birth month to influence the timing of vaccination and to be associated with the risk of influenza only through its influence on vaccine timing.

Additional analyses

We did several analyses to evaluate whether the relation between birth month and influenza risk was due to confounding or chance. In falsification analyses, we examined the relation between birth month and rate of superficial injury visits, an outcome that is unrelated to influenza but might be related to a propensity of a child's family to seek medical care. We also did similar analyses examining the relation between birth month and diagnosis of two common non-influenza infectious diseases in this age group, conjunctivitis and viral gastroenteritis, to evaluate for a broader pattern for infectious diseases beyond influenza. ICD code based definitions for these falsification conditions are listed in supplementary table A. Next, we repeated our primary analysis after assigning children random birth months, to evaluate whether findings were due to chance alone.

To evaluate whether the magnitude of benefit associated with optimal vaccination timing may vary depending on the child's health, we did subgroup analyses according to presence of previous pulmonary disease and number of Elixhauser comorbidities (categorized into thirds). As the magnitude of benefit associated with optimal vaccine timing may also be greater in periods or regions (for example, metropolitan statistical areas, or MSAs) with greater severity of influenza, we did subgroup analyses based on the third of influenza severity in an MSA-season (calculated from influenza diagnoses among all patients in the MarketScan database during an MSA-season).

Research suggests that experiences in one flu season can affect vaccination rates in subsequent flu seasons.[40] To evaluate whether a child's experience with the influenza vaccine and/or influenza disease in one season might lead to different behaviors in subsequent seasons in a way that could differ by birth month, we repeated the primary analysis while including only one influenza season per child, which we chose at random for children who were vaccinated in more than one season.

We used R and Stata version 15 for all analyses. The 95% confidence interval around adjusted estimates represents a two tailed α level of 0.05.

Patient and public involvement

This study was a retrospective observational study. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Results

The study included 819 223 children aged 2-5 who received influenza vaccination between August 1 and January 31 of a given flu season, for a total of 1 261 164 child-seasons (48.9% (616 162/1 261 164) female; mean age 3.5 years) (table 1). As expected, the overall timing of influenza vaccination followed a similar pattern each year, whereas timing of the peak of influenza diagnoses varied (supplementary figure B).

October was the most common month for children to be vaccinated (37.3% (469 809/1 261 164) of child-seasons) (supplementary figure C). Children vaccinated in November and December had the lowest probability of having a diagnosis of influenza compared with children vaccinated in other months (supplementary figure D). However, because the timing of vaccination may be influenced by both measured and unmeasured factors, a causal relation between vaccine timing and influenza infection cannot be inferred from this analysis alone. We therefore investigated the relations between birth month, timing of preventive care visits and influenza vaccination, and influenza risk.

Birth month and timing of influenza vaccination

Overall, 90.2% (1 137 983/1 261 164) of children who were vaccinated between August 1 and January 31 in a given flu season had a preventive care visit during that period; 716 751 (56.8%) had a visit in the two weeks surrounding their birth month (73.6% (241 484/328 239) of 2 year olds, 59.6% (189 730/318 102) of 3 year olds, 51.4% (161 246/313 686) of 4 year olds, and 41.3% (124 291/301 137) of 5 year olds). Among children with preventive visits, the most common day to be vaccinated was the day of that visit, consistent with these visits being a convenient time for vaccination (fig 1). The likelihood of being vaccinated on the day of a preventive visit was lower for children born in December or January, as many of these children may receive vaccination earlier in the fall.

Table 1 | Characteristics of study population*

Characteristics	Overall (n=1 261 164)	August (n=212 622)	October (n=224 520)	December (n=208 012)	Standardized mean difference (95% CI) Aug *v* Oct	Aug *v* Dec	Oct *v* Dec
Children							
Mean age, years	3.5	3.5	3.5	3.5	0.03 (0.02 to 0.04)	0.02 (0.01 to 0.03)	0.01 (0.00 to 0.02)
% (No) female	48.9 (616 162)	48.8 (103 776)	48.8 (109 608)	48.8 (101 561)	<0.01 (-0.01 to 0.01)	<0.01 (-0.01 to 0.01)	<0.01 (-0.01 to 0.01)
% (No) with previous pulmonary disease	23.4 (295 649)	23.7 (50 460)	23.1 (51 836)	23.1 (48 129)	0.01 (0.01 to 0.02)	0.02 (0.01 to 0.02)	<0.01 (-0.01 to 0.01)
Mean No of Elixhauser conditions	0.5	0.6	0.6	0.6	<0.01 (0.00 to 0.01)	0.02 (0.02 to 0.03)	0.02 (0.01 to 0.02)
Mean (median) No of annual office visits	5.8 (4)	5.8 (4)	5.5 (4)	6.0 (4)	0.03 (0.02 to 0.04)	0.04 (0.03 to 0.04)	0.06 (0.06 to 0.07)
Mean (median) No of annual ED visits	0.2 (0)	0.2 (0)	0.2 (0)	0.2 (0)	0.03 (0.02 to 0.03)	<0.01 (0.00 to 0.01)	0.03 (0.02 to 0.03)
Mean predicted risk of flu diagnosis, %	2.9	2.9	2.9	2.9	0.02 (0.01 to 0.02)	0.02 (0.01 to 0.02)	0.03 (0.03 to 0.04)
Families							
Mean family size	4.0	4.0	3.9	3.9	0.07 (0.06 to 0.07)	0.04 (0.03 to 0.04)	0.02 (0.02 to 0.03)
Mean No of children in household	2.0	2.1	2.0	2.0	0.07 (0.06 to 0.08)	0.04 (0.04 to 0.05)	0.03 (0.02 to 0.04)
Mean No of Elixhauser conditions, sibling	0.4	0.4	0.4	0.4	0.03 (0.02 to 0.04)	0.03 (0.03 to 0.04)	<0.01 (0.00 to 0.01)
Mean No of Elixhauser conditions, parent	1.4	1.4	1.4	1.4	<0.01 (-0.01 to 0.01)	0.02 (0.01to 0.02)	0.02 (0.01 to 0.02)
% (No) with previous pulmonary disease, sibling	21.2 (266 845)	21.6 (45 838)	20.6 (46 153)	20.5 (42 568)	0.03 (0.02 to 0.03)	0.03 (0.02 to 0.03)	<0.01 (0.00 to 0.01)
% (No) with previous pulmonary disease, parent	28.0 (352 951)	28.2 (59 943)	27.5 (61 771)	28.0 (58 341)	<0.01 (0.00 to 0.01)	0.02 (0.01 to 0.02)	0.01 (0.01 to 0.02)
Mean (median) No of office visits, sibling	4.8 (3.7)	4.8 (4.0)	4.6 (3.5)	4.8 (3.8)	0.02 (0.01 to 0.02)	0.05 (0.04 to 0.06)	0.03 (0.03 to 0.04)
Mean (median) No of office visits, parent	6.9 (4.5)	6.9 (4.5)	6.8 (4.5)	6.9 (4.5)	<0.01 (0.00 to 0.01)	<0.01 (0.00 to 0.01)	0.01 (0.01 to 0.02)
Mean (median) No of ED visits, sibling	0.1 (0)	0.1 (0)	0.1 (0)	0.1 (0)	<0.01 (-0.01 to 0.01)	0.01 (0.01 to 0.02)	0.01 (0.01 to 0.02)
Mean (median) No of ED visits, parent	0.2 (0)	0.2 (0)	0.2 (0)	0.2 (0)	<0.01 (0.00 to 0.01)	<0.01 (0.00 to 0.01)	0.01 (0.00 to 0.02)

CI=confidence interval; ED=emergency department.
*Sample size is at the level of the patient-flu season.

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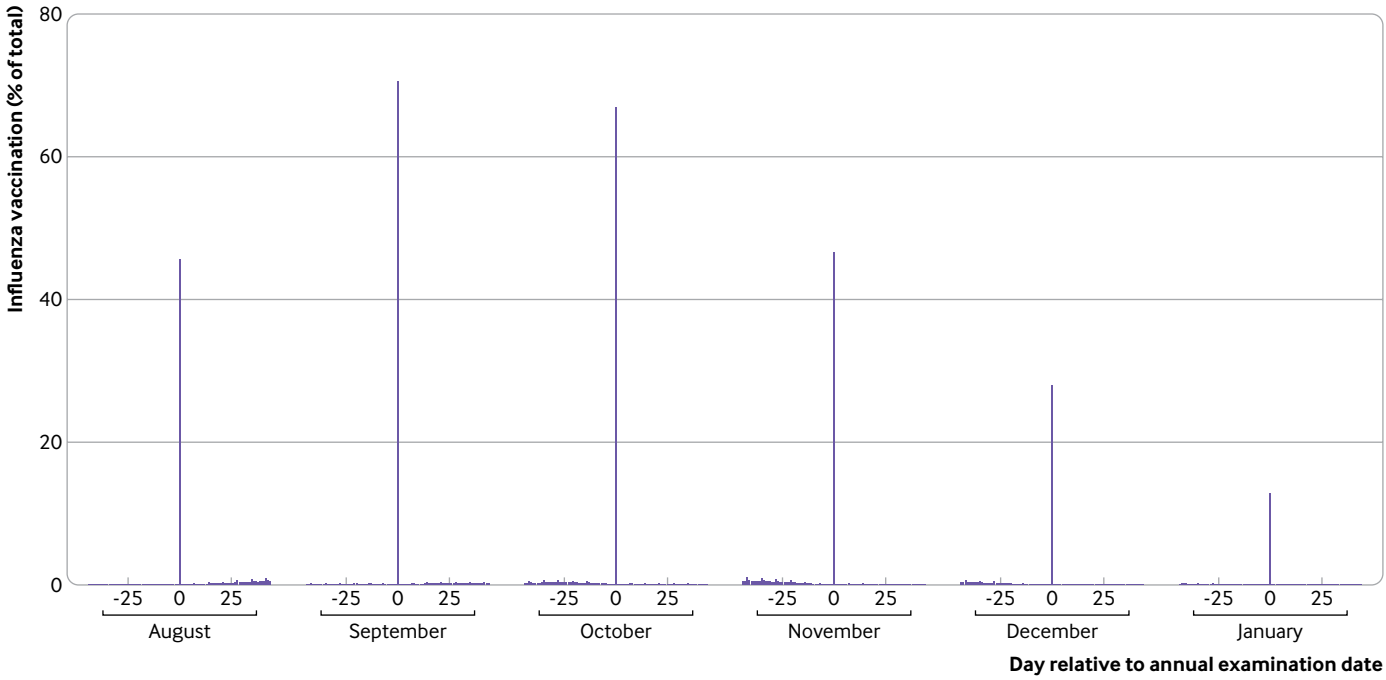
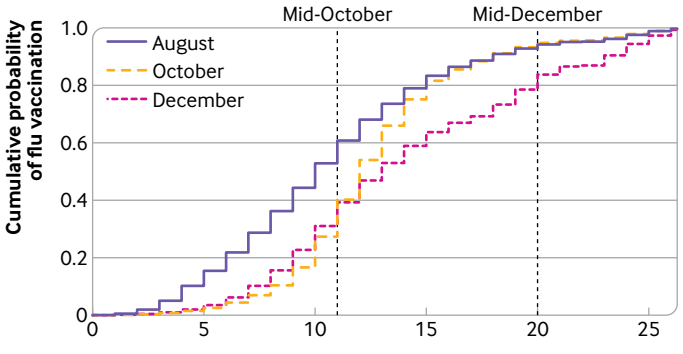


Fig 1 | Proportion of vaccinated children who receive vaccination on day of preventive care visit versus surrounding days, by birth month. Among children who received influenza vaccination, figure shows proportion who were vaccinated on day of annual preventive care visit (day zero) compared with surrounding days, according to child's birth month (August through January)

We observed no meaningful differences across birth months in children's demographic and clinical characteristics, including the predicted risk of influenza infection (table 1; supplementary figure E). For example, children born in August, October, and December had similar age, sex, comorbidities, healthcare use, predicted influenza risk, family size, and comorbidities and healthcare use among family members.

However, timing of influenza vaccination differed across birth months. Vaccination occurred, on average, earlier for children with earlier birth months (fig 2; supplementary figure F; log-rank P<0.001 in unadjusted time-to-event analysis). For instance, the mean time between August 1 and date of vaccination was 10.8 weeks for children born in August, 12.7 weeks for those born in October, and 14.1 weeks for those born in December (P<0.001 for difference). October vaccinations were also disproportionately greater in children with October birth months compared with other birth months (for example, 48.9% (109 721/224 520) of children born in October were vaccinated in October compared with 34.0% (72 230/212 622) of children born in August, 40.2% (88 534/220 235) of those born in September, 27.3% (57 044/209 014) of those born in November, and 33.7% (70 130/208 012) of those born in December) (supplementary figure G).



No at risk

August	212 622	190 865	118 309	44 696	15 299	5191
October	224 520	221 099	187 101	55 838	15 150	4803
December	208 012	203 822	160 689	85 415	44 642	11 634

Fig 2 | Timing of influenza vaccination among vaccinated children, by birth month. Figure shows unadjusted time to event Kaplan-Meier analysis showing cumulative probability of vaccination (vertical axis) by number of weeks since August 1 before influenza season (horizontal axis), stratified by birth month

Influenza diagnosis by birth month

Unadjusted rates of diagnosis of influenza varied by birth month and were lowest for children born in October (fig 3). For example, among children born in August, the average rate of influenza diagnosis across flu seasons studied was 3.0% (6462/212 622), compared with 2.7% (6016/224 540) for children born in October and 2.9% (6041/208 012) for those born in December. We observed a similar relation between birth month and influenza risk in adjusted analysis (fig 3). Children born in October were least likely to have a diagnosis of influenza compared with other birth months (adjusted odds ratio compared with children born in August 0.88, 95% confidence interval 0.85 to 0.92) (supplementary table B). This was the most

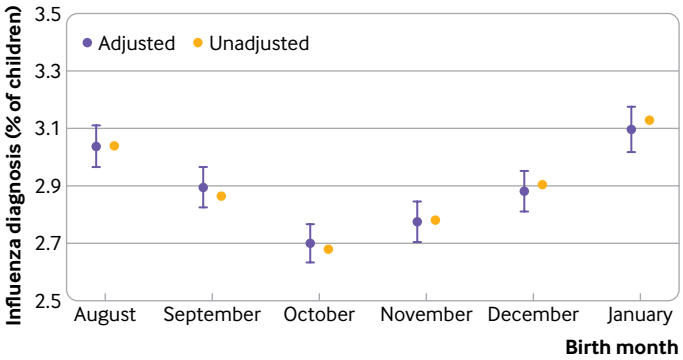


Fig 3 | Influenza diagnosis by birth month. Bars around adjusted values represent 95% confidence intervals from logistic regression of influenza diagnosis on birth month, adjusted for children's age, sex, healthcare use, medical comorbidities, and family size and parents' and siblings' comorbidities and healthcare use

common pattern in analyses of individual influenza seasons (supplementary table C).

Additional analyses

In falsification analyses, we observed no meaningful patterns between birth months when substituting randomly generated birth months or when substituting superficial injury, conjunctivitis, or viral gastroenteritis as the outcome (supplementary figures H and I). We observed a larger absolute reduction in influenza infection among children born in October compared with other birth months in subgroup analyses that focused on children with previous pulmonary disease (fig 4; supplementary table B) or in higher thirds of Elixhauser comorbidities (fig 4) and in MSA regions with greater influenza severity (fig 4), consistent with optimal timing of influenza vaccination having larger absolute benefit in these subgroups. We observed no meaningful differences in the results of an analysis that included only one influenza season per child (supplementary table B).

Discussion

In an analysis of children aged 2-5 years who were vaccinated against influenza, birth month was associated with both timing of influenza vaccination and the likelihood of diagnosis of influenza. Children born in October, who were disproportionately likely to be vaccinated in October compared with children with other birth months, were least likely to have a diagnosis of influenza, particularly compared with children born in August, who tended to be vaccinated sooner, and those born in December, who tended to be vaccinated later. These quasi-experimental results, which rely on the observation that preventive care visits tend to occur during birth months and are a convenient time to receive the influenza vaccine, support current recommendations for October being the optimal month for influenza vaccination in young children in typical influenza seasons. Notably, the optimal timing of influenza vaccination that can be inferred from using birth month as a natural experiment differs from what would be inferred from analyses of influenza risk by actual month of vaccination.

Studies of vaccine effectiveness suggest that immunity against influenza wanes over the course of the flu season; meanwhile, vaccinated patients who are exposed to the virus before acquiring vaccine induced immunity are at higher risk of infection.[3-12 16-19 21-23] This suggests that an optimal time may exist for children to be vaccinated before the flu season and that this question could be evaluated using observational data and quasi-experimental empirical methods. Under the assumption that children born in October are otherwise similar to children born in other months, our findings suggest that the specific timing of influenza vaccination among children born in October may lead to lower rates of influenza infection.

Comparison with other studies

Previous work has suggested that the convenience of being able to be vaccinated at preventive care visits—frequently timed near birthdays—likely leads to increased vaccination rates.[26] This same convenience may also affect the timing of vaccination among children who are vaccinated. Taking these studies together, children born in October seem to have two advantages when it comes to influenza vaccination that likely lead to lower infection rates: they are more likely to be vaccinated at all because it is more convenient, and, conditional on vaccination, they are more likely to have optimal vaccine induced immunity because of the specific timing of their vaccination. This study's approach complements those of previous studies examining optimal timing of vaccination by measuring antibody concentrations, which may not correspond to real world vaccine effectiveness, and other observational studies of influenza outcomes using methods that cannot account for unmeasured confounding factors.[5 16-23] Our findings suggest that US public health interventions focused on vaccination of young children in October may yield the best protection in typical flu seasons.

This study adds to the growing evidence base establishing and characterizing links between birth month—an arbitrary characteristic—and specific healthcare behaviors and outcomes across the lifespan.[26 41 42] In young children, for example, arbitrary age cut-offs for starting school create a relative age effect wherein children born in certain months who are relatively younger than their peers are more likely to receive a diagnosis of and treatment for attention deficit/hyperactivity disorder.[43-45] Although a variety of birth month associated outcomes later in life may have origins in early childhood, because this study focuses on an outcome that is so proximal to the exposure (diagnosis following vaccination within the same influenza season), other birth month related differences are highly unlikely to introduce bias that would affect our interpretation of the results.

Strengths and limitations of study

Our study has several limitations. Firstly, despite its quasi-experimental approach and the similarity of children across birth months, including predicted influenza risk, residual confounding is possible.

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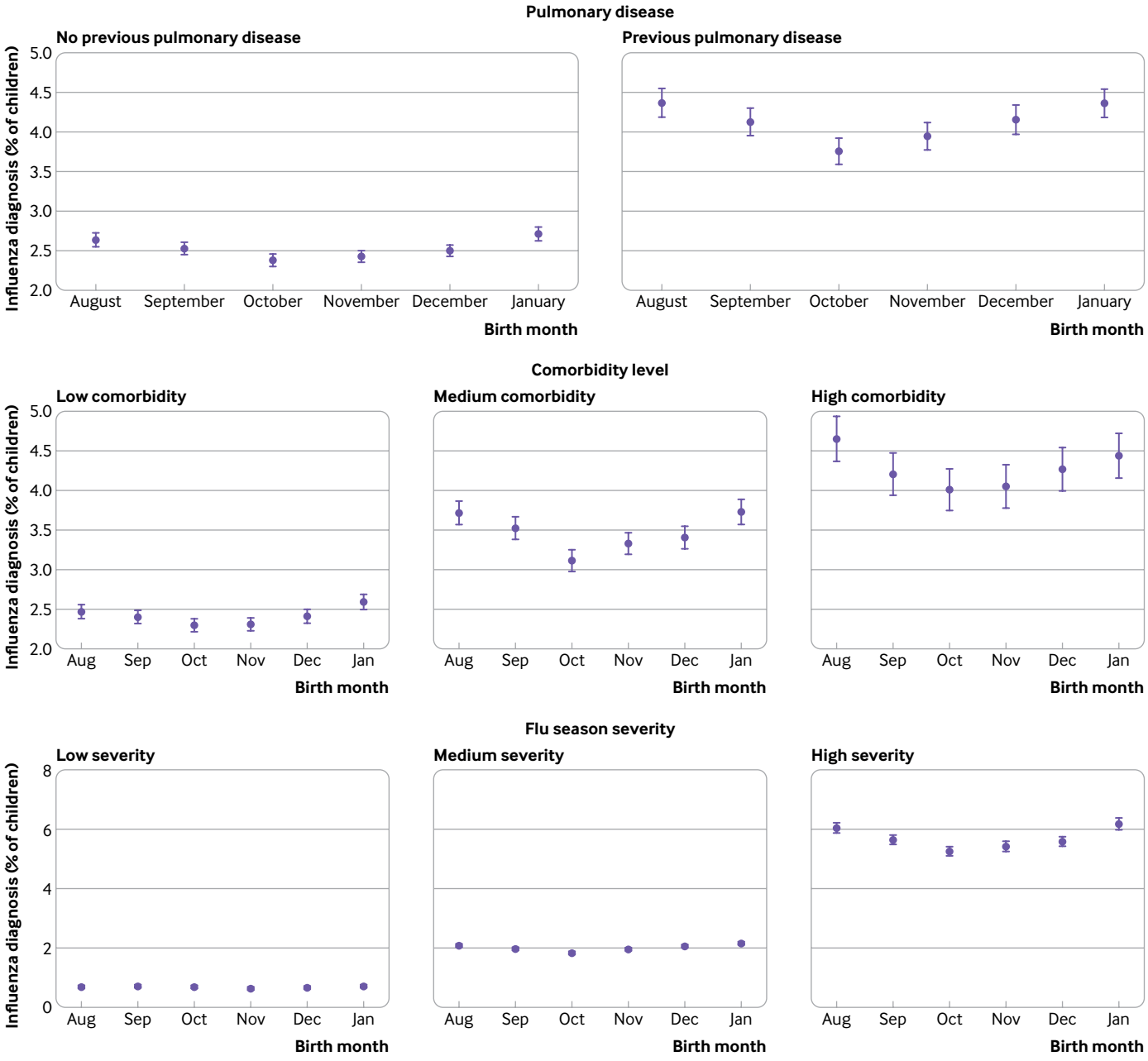

Fig 4 | Influenza diagnosis by birth month, stratified by previous pulmonary disease, comorbidities, and influenza season severity. Figure shows relation between influenza diagnosis and birth month stratified by previous pulmonary disease as defined by Elixhauser comorbidity classification (first panel), thirds of Elixhauser comorbidity count (second panel), and influenza season severity third (third panel). Influenza severity level was determined at level of metropolitan statistical area-season, based on diagnoses of influenza infection among entire population in MarketScan database. Bars around adjusted values represent 95% confidence intervals in logistic regression of influenza diagnosis adjusted for children's birth month, age, sex, healthcare use, medical comorbidities, and family size and parents' and siblings' comorbidities and healthcare use. Separate models were estimated for children with versus without previous pulmonary disease

Secondly, claims data limit our ability to measure care that was not submitted to insurance, including vaccinations and influenza cases in which patients did not seek medical care. To account for this, we restricted this analysis to patients with a confirmed vaccination defined by the presence of a claim; meanwhile, care seeking behavior for influenza diagnosis should not differ across birth month groups in a way that would bias our results. Additionally, influenza infections included in the database for which patients sought medical care are the most clinically significant from a standpoint of public health policy. Thirdly, the availability of influenza vaccines and the timing and peak of seasonal influenza infections vary across years and geography, limiting generalizability to any specific influenza season, region, or country. Fourthly, we analyzed children with employer sponsored insurance, limiting generalizability to other populations.

Conclusions

In a large quasi-experimental study of children aged 2-5 years vaccinated against influenza, children who happened to have been born in October tended to be vaccinated later than children born in August and earlier than those born in December, were more likely than other children to be vaccinated in the month of October, and were least likely to have a diagnosis of influenza in the following flu season. The findings support current recommendations that children be vaccinated in October preceding a typical influenza season.

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The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: There are no plans to disseminate the results of the research to study participants or the relevant patient community. The results of this work will be disseminated to the public through institutional press release, ensuing news articles, and an opinion piece authored by the study's authors that describe the study's findings for the public.

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Web appendix: Supplementary materials