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The impact of maternal pertussis vaccination recommendation on infant pertussis incidence and mortality in the USA: an interrupted time series analysis

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Abstract

Background: Pertussis is a contagious respiratory disease. Maternal tetanus–diphtheria–acellular pertussis vaccination during pregnancy has been recommended by the United States Centres for Disease Control (US CDC) Advisory Committee on Immunization Practices (ACIP) for unvaccinated pregnant women since October 2011 to prevent infection among infants; in 2012, ACIP extended this recommendation to every pregnancy, regardless of previous vaccination status. The population-level effect of these recommendations on infant pertussis is unknown. This study aimed to examine the impact of the 2011/2012 ACIP pertussis recommendation on pertussis incidence and mortality among US infants.

Methods: We used monthly data on pertussis deaths among infants aged <1 year between January 2005 and December 2017 in the CDC Death Data and yearly infant pertussis incidence data from the CDC National Notifiable Disease Surveillance System to perform an interrupted time series analysis, accounting for the passage of the Affordable Care Act.

Results: This study included 156 months of data. A potential decline in trend in infant pertussis incidence was noted during the post-recommendations period. No appreciable differences in trend were found in population-level infant pertussis mortality after the guideline changes in both adjusted and unadjusted models. Results were similar for all mortality sensitivity analyses.

Conclusions: The 2011/2012 ACIP maternal pertussis vaccination recommendations were not associated with a population-level change in the trend in mortality, but were potentially associated with a decrease in incidence in the USA between 2005 and 2017.

Keywords: Pertussis, Tdap epidemiology, maternal immunization, USA, interrupted time series.

Key Messages

- The population-level effect of current US maternal pertussis vaccination recommendations on infant pertussis in the USA is currently unknown.
- This study was nationally representative and used all pertussis deaths in infants <1 year old in the USA between 2005 and 2017.
- The 2011/12 maternal pertussis vaccination recommendations were not associated with a population-level change in the trend in infant pertussis mortality but were potentially associated with a population-level change in the trend in infant pertussis incidence.

Introduction

Pertussis, a respiratory infection caused by *Bordetella pertussis*, causes significant morbidity and mortality among young infants in the USA.[1] Though most pertussis transmission occurs among adults, pertussis mortality is concentrated among infants <2 months old.[2] This is because infants <2 months old have little immunity against pertussis and are too young to receive acquired protection through primary immunization with the diphtheria, tetanus and pertussis vaccine.[3] Infants who are >2 months old are also at risk of pertussis infection and death from pertussis when their vaccine schedules are delayed or incomplete.[4]

Maternal pertussis vaccination with the Tdap (tetanus–diphtheria–acellular pertussis) vaccine has been shown to protect newborns through transplacentally transferred maternal antibodies.[5] Currently, maternal Tdap vaccination is

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considered the primary pertussis prevention strategy to protect infants <2 months old.[4] In the USA, in 2011, the Advisory Committee on Immunization Practice (ACIP) recommended the Tdap vaccine between Weeks 27 and 36 of pregnancy for all women who were not recently immunized.[6] In 2012, ACIP updated this recommendation to include a Tdap dose during every pregnancy to ensure adequate maternal antibody transfer.[7]

At around the same time as the ACIP recommendation, the Affordable Care Act (ACA) required all insurers to extend coverage to dependents of insured individuals up to the date on which the dependent turns 26 years old.[8] Studies examining the impact of the coverage expansion have found three to six percentage point increases in coverage within this age group post-ACA.[8] Studies have also shown that the ACA improved prenatal care and perinatal outcomes.[9] Dependent coverage expansion improved access to prenatal care for women aged 24–25 years and is associated with a lower incidence of pre-term birth compared with women aged 27–28 years, who would have been ineligible for the coverage expansion.[10] Some studies have also shown that Medicaid expansion due to the ACA improved access to standard prenatal care for low-income women.[11,12] This potentially complicates our understanding of the effect of the ACIP recommendations on pertussis incidence and mortality among US infants.

This study aimed to examine the effect of the introduction of the 2011/12 ACIP Tdap recommendation on pertussis incidence and mortality among infants in the USA, considering the possible competing impact of improved access to care through the ACA.

Methods

Setting, population and data

This study examined changes in pertussis incidence and mortality in infants ≤2 months old and infants <1 year old in the USA between January 2005 and December 2017. This study included all pertussis cases diagnosed and reported to the Centres for Disease Control (CDC) through the National Notifiable Disease Surveillance System (NNDSS) and cases of pertussis in which infants died in the USA as captured by the CDC National Vital Statistics (NVS) programme.

Outcomes

Monthly data from January 2005 through to December 2017 were used in this analysis (Figure 1) for a total of 156 independent time points. Data on the at-risk population were extracted from the CDC NVS Natality files. A death was considered pertussis-related if whooping cough [International Classification of Disease (ICD) 10 code: A37] was listed as a multiple or underlying cause of mortality on the infant's death certificate as reported to the National Vital Statistics System.

Pertussis is a notifiable condition and reporting is managed by the CDC through the NNDSS. NNDSS is a passive surveillance system that relies on case reporting to local and state health departments by patient care providers and laboratories.[13] We extracted incidence data from January 2005 through to December 2017 for children <6 months of age and <1 year old from annual NNDSS reports.[14–26] Incidence was reported and analysed as the number of reported new cases in <6 months of age or <1 year old per 100 000 persons. Further information on the collection of incidence data is included in the Supplemental material (available as Supplementary data at *IJE* online).

Statistical analyses

Using an interrupted time series design, we analysed the impact of the 2011/12 ACIP maternal Tdap recommendations, accounting for underlying trends in pertussis incidence and mortality in the USA over the study period. We allowed for slope changes over three segments—the pre-recommendations period (January 2005–September 2011), the transition period (October 2011–February 2013) and the post-recommendations period (March 2013–December 2017). Timing of these periods was assigned based on the publication dates of the ACIP recommendation. A transition period was assigned given the changes in the ACIP recommendation between 2011 and 2012 (published in February 2013). We thus allowed for a transition window ending in February 2013. The recommendations' publication dates were used instead of ACIP recommendation approval dates to reflect a more likely implementation period.

Model parameters

Pertussis incidence

The incidence model was a linear mean model estimating mean incidence differences [Equation (1)]. The incidence model contained parameters for time, number of years since the beginning of the transition period and number of years after the beginning of the post-recommendations period. This model is a combination of models from previous studies.[27–29]

Equation (1) (linear mean model):

$$I_t = \beta_0 + \beta_1 * time_t + \beta_2 * time\ since\ transition_t + \beta_3 * time\ since\ post_t + e_t \quad (1)$$

where I_t represents the yearly pertussis incidence rate among infants ≤6 months or ≤1 year at year t; $time_t$ represents the continuous variable representing how many years have elapsed since time = 0 ($year_i$–2005); $time\ since\ transition_t$ represents the time elapsed since the beginning of the transition period ($year_i$–2012); $time\ since\ post_t$ represents the time elapsed since the beginning of post-recommendations period ($year_i$–2013); β_0 represents the baseline level of pertussis incidence in 2005; β_1 represents the estimated yearly change in pertussis incidence prior to the transition period (2005–12) controlling for trend changes after the transition and post-periods; β_2 represents the estimated yearly change in the pertussis incidence trend after the transition period (2012–17) controlling for baseline trend and trend change after the post-period; and β_3 represents the estimated yearly change in the pertussis incidence trend after the post-recommendations period (2013–17) controlling for baseline trend and trend change after the transition period. The yearly incidence rate differences presented in the results for the transition and post-periods were calculated as $ID_{transition} = \beta_2$ and $ID_{post} = \beta_3$, respectively.

Pertussis mortality

The unadjusted mortality model was a log-linear rate model estimating mortality rate ratios [Equation (2)]. The mortality model contained parameters for time, number of years since the beginning of the transition period, number of years after the beginning of the post-recommendations period and an

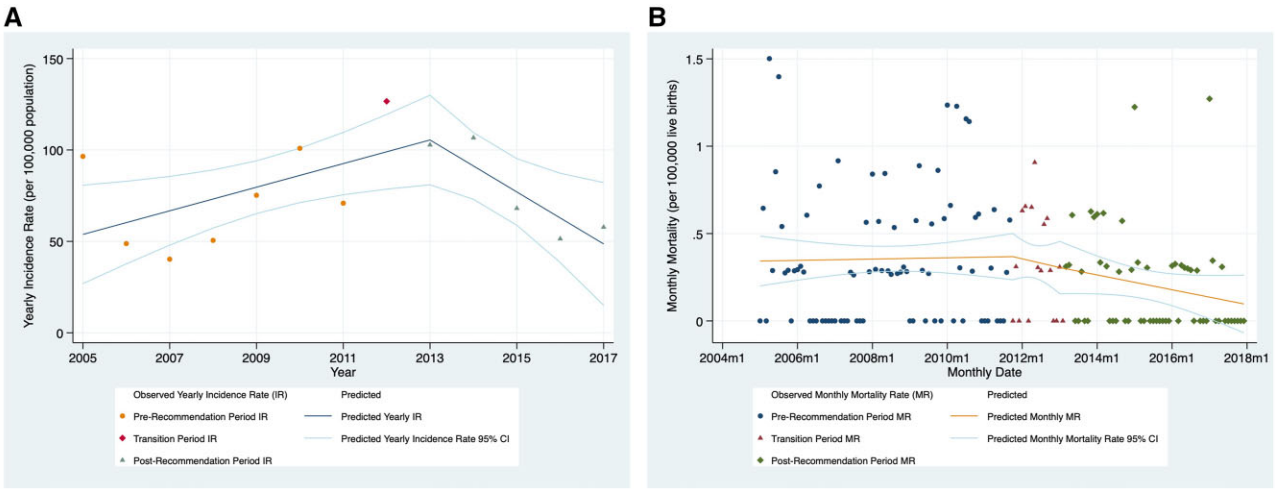

Figure 1. Observed and predicted incidence rates and pertussis-related mortality among <1-year-olds per 100 000 in infants in the USA, 2005–17, in relation to United States Centres for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy. (A) Crude incidence rate ratio (IRR) comparing average incidence rates in transition period to pre-recommendations period: 1.84 (95% CI: 1.36–2.50). Crude IRR comparing average incidence rates in post-period with pre-recommendations period: 1.12 (95% CI: 0.80–1.57). (B) Crude mortality rate ratio comparing average mortality rates in transition period to pre-recommendations period: 0.91 (95% CI: 0.55–1.52). Crude mortality rate ratio comparing average mortality rates in post-recommendations period to pre-recommendations period: 0.57 (95% CI: 0.31–1.02)

offset for the log number of live births in month t. If there was evidence of potential heteroskedasticity, Huber–White robust standard errors were used. This model is also a combination of models from other studies.[27–29]

Equation (2) (log-linear rate model):

$$\begin{aligned}\log(Y_t) = \; & \log(population) + \beta_0 + \; \beta_1 * time_t \\ & + \beta_2 * time\ since\ transition_t \\ & + \beta_3 * time\ since\ post_t + e_t\end{aligned} \tag{2}$$

where Y_t represents the number of pertussis deaths in month t; $time_t$ is the continuous variable representing how many months elapsed since time = 0 (January 2005); *time since transition*$_t$ represents the time elapsed since the beginning of the transition period ($month_t$–October 2011); *time since post*$_t$ represents the time elapsed since the beginning of post-recommendations period ($month_t$–February 2013); $\beta_0$represents the baseline level of pertussis mortality in January 2005; $\beta_1$represents the estimated monthly change in pertussis mortality, controlling for transition and post-period trends in pertussis mortality; $\beta_2$represents the estimated monthly change in the pertussis mortality trend during and after the transition period, controlling for baseline and post-period trends in pertussis mortality; and β_3 represents the estimated monthly change in the pertussis mortality trend during the post-recommendations period, controlling for baseline and transition-period trends in pertussis mortality. The monthly mortality rate ratio presented in the results for the transition and post-periods were calculated as $MR_{transition} = e^{\beta_2}$ and $MR_{post} = e^{\beta_3}$, respectively.

Confounder control

To account for potential confounding by the 2010 passage of the ACA (a proxy for the probability of receiving the Tdap vaccine during pregnancy), we stratified our primary mortality model by maternal age (a proxy for being affected by the expansion of dependent coverage under the ACA). Deaths occurring in infants of mothers aged 12–18 and ≥26 years were considered unaffected by the ACA-dependent coverage expansion. Those aged 19–25 years were considered affected by the ACA-dependent coverage. The base model was then run on each group separately.

This methodology was not used for the incidence analyses because information on infant and maternal characteristics, such as maternal age, was not available for pertussis cases through the available CDC NNDSS.

Sensitivity analyses

Multiple sensitivity analyses were completed including varying the presence and timing of the transition period, using the recommendation passage dates instead of publication dates, examining trends in both ≤2-month-olds and ≤1-month-olds, addressing potential homoscedasticity violations and using different proxies for the ACA such as number of prenatal care visits and the adequacy of prenatal care. The methodology and results for these further sensitivity analyses are provided in the Supplementary data (available as Supplementary data at *IJE* online). All analyses were completed in Stata/IC 16.1.[30]

Results

Between January 2005 and December 2017, nearly 40 000 pertussis cases and 155 pertussis-related deaths occurred among infants <1 year old (Table 1). Ninety-nine deaths occurred during the pre-recommendations period (January 2005–September 2011), 18 deaths occurred during the transition period (October 2011–February 2013) and 38 deaths occurred during the post-recommendations period (March 2013–December 2017).

Crude incidence and mortality rate ratios among <1-year-olds, unadjusted for underlying time trends, comparing the transition and post-recommendations periods with the pre-recommendations period are presented in Table 2.

Table 1. Characteristics of pertussis deaths in the USA, 2005–17, in relation to United States Centers for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy

Characteristic	US CDC ACIP recommendation for Tdap vaccination during pregnancy			
	Pre-recommendations period[a]	Transition period[b]	Post-recommendations period[c]	Total period (2005–17)
Deaths (*n*)	99	18	38	155
Pertussis mortality rate per 100 000 live births	0.35 (0.38)	0.32 (0.30)	0.20 (0.29)	0.29 (0.34)
Infant age				
14–20 days	2 (2%)	0	2 (5%)	4 (3%)
21–27 days	11 (11%)	1 (6%)	7 (18%)	19 (12%)
1 month	48 (48%)	9 (50%)	17 (45%)	74 (48%)
2 months	24 (24%)	6 (33%)	9 (24%)	39 (25%)
3 months	9 (9%)	2 (11%)	3 (8%)	14 (9%)
4 months	4 (4%)	0	0	4 (3%)
6 months	1 (1%)	0	0	1 (1%)
Maternal age at birth (years), mean (SD)	26 (6)	29 (5)	26 (6)	26 (6)
Birthweight (g)				
227–1499	6 (6%)	0	0	6 (4%)
1500–2499	22 (22%)	3 (17%)	8 (21%)	33 (21%)
2500–8165	71 (72%)	15 (83%)	30 (79%)	116 (75%)
Maternal race				
White	84 (85%)	16 (89%)	29 (76%)	129 (83%)
Black	9 (9%)	1 (6%)	5 (13%)	15 (10%)
American Indian or Alaska Native	3 (3%)	1 (6%)	2 (5%)	6 (4%)
Asian or Pacific Islander	3 (3%)	0	2 (5%)	5 (3%)
Mother's education (highest degree obtained)				
Less than high school	28 (28%)	8 (44%)	2 (5%)	38 (25%)
High school or GED	34 (34%)	5 (28%)	5 (13%)	44 (28%)
College (Associate or Bachelor)	2 (2%)	2 (11%)	1 (3%)	5 (3%)
Post-college	3 (3%)	1 (6%)	0	4 (3%)
Missing	32 (32%)	2 (11%)	30 (79%)	64 (41%)
Number of prenatal care visits, mean (SD)	8 (5)	9 (6)	10 (4)	9 (5)
Adequacy of Prenatal Care Utilization Index (APNCU)				
Inadequate care (APNCU=1)	33%	36%	17%	29%
Intermediate care (APNCU=2)	18%	17%	20%	19%
Adequate care (APNCU=3)	23%	17%	23%	22%
Adequate+ care (APNCU=4)	26%	30%	40%	30%

GED, general educational development tests.
[a] January 2005–September 2011, before US CDC ACIP recommendation for maternal Tdap vaccination during pregnancy.
[b] October 2011–February 2013, when maternal Tdap vaccination during pregnancy was recommended by US CDC ACIP and when these recommendations were extended to all pregnant women regardless of previous vaccination status.
[c] March 2013–December 2017, after US CDC ACIP recommendations for maternal Tdap vaccination during pregnancy.

Table 2. Crude pertussis incidence and mortality rate ratios among <1-year-olds, 2005–17, in relation to United States Centers for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy

	Rate per 100 000	Rate ratio[d]
Incidence		
Pre-recommendations period[a]	69	Reference
Transition period[b]	127	1.84 (1.36–2.50)
Post-recommendations period[c]	77	1.12 (0.80–1.57)
Mortality		
Pre-recommendations period[a]	0.35	Reference
Transition period[b]	0.32	0.91 (0.55–1.52)
Post-recommendations period[c]	0.20	0.57 (0.31–1.02)

[a] January 2005–September 2011, before US CDC ACIP recommendations for maternal Tdap vaccination during pregnancy.
[b] October 2011–February 2013, when maternal Tdap vaccination during pregnancy was recommended by US CDC ACIP and when these recommendations were extended to all pregnant women regardless of previous vaccination status.
[c] March 2013–December 2017, after US CDC ACIP recommendations for maternal Tdap vaccination during pregnancy.
[d] Rate ratio presented as point estimate (95% CI).

Effect of ACIP recommendation on pertussis incidence

The results of the pertussis incidence interrupted time series analyses are presented in Table 3. In the uncontrolled interrupted time series analysis using a linear mean model, there were 54 fewer incident cases per 100 000 per year (95% CI: –148, 39) among <6-month-olds in the post-recommendations period compared with the pre-recommendations period. Results were similar among infants <1 year old [mean difference per year: –23 (95% CI: –89, 44)].

Effect of ACIP recommendation on pertussis-related mortality

Results of the unadjusted mortality analyses are shown in Table 4. In the uncontrolled interrupted time series analysis using a quasi-Poisson regression, the mortality rate ratio (MRR) comparing the change in trend in the mortality rate in the post-recommendation period with the pre-recommendations period was 0.99 (95% CI: 0.93–1.05) among infants ≤2 months old.

Table 3. Mean differences in infant pertussis incidence (incident cases per 100 000 live births) comparing time before, during and after the United States Centers for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) made recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy

	Model 1 (≤6 months)	Model 2 (≤1 year)
Time since beginning of pre-recommendations period[a] (yearly change in number of incident pertussis cases per 100 000 live births; $year_i$)	5.76 [–5.94, 17.46] (0.29)	6.29 [–2.08, 14.66] (0.12)
Time since transition period (yearly change in number of incident pertussis cases per 100 000 live births after 2012; $year_i$–2012)	22.40 [–60.88, 105.69] (0.56)	1.87 [–57.72, 61.47] (0.95)
Time since post-recommendations period (yearly change in number of incident pertussis cases per 100 000 live births after 2013; $year_i$–2013)	–54.35 [–147.71, 39.00] (0.22)	–22.69 [–89.49, 44.11] (0.46)
Total years	13	13

95% CIs in brackets; *P*-values in parentheses.
Mean $difference_{time} = incidence_{year\_i} - incidence_{year\_i-1}$.
Mean $difference_{timetransition} = incidence_{year\_i} - incidence_{year\_i-1}$ for years after 2012.
Mean $difference_{timepost} = incidence_{year\_i} - incidence_{year\_i-1}$ for years after 2013.
[a] January 2005–September 2011, before US CDC ACIP recommendations for maternal Tdap vaccination during pregnancy.

Results were similar among infants <1 year old (MRR: 0.99, 95% CI: 0.93–1.06).

When stratified by maternal ACA-dependent coverage expansion eligibility at birth, no appreciable differences in trend were found in infant pertussis mortality after the guideline changes (Table 5). There may be slight evidence that baseline time trends differed between maternal ACA-eligible and ACA non-eligible groups. The baseline trend in pertussis mortality among infants <1 year old over time appears to be slightly increasing for the non-ACA group and decreasing over time for the ACA-eligible group [non-ACA MRR: 1.01 (95% CI: 1.00–1.02); ACA MRR: 0.99 (95% CI: 0.98–1.01)].

Sensitivity analyses

When varying the presence and timing of the transition period, using the recommendation publication dates instead of passage dates, examining trends in both ≤2-month-olds and ≤1-month-olds, addressing potential homoscedasticity violation and using different proxies for the ACA such as number of prenatal care visits and the adequacy of prenatal care, results were little changed (see Supplemental material, available as Supplementary data at *IJE* online).

Discussion

In this study, including nearly 40 000 pertussis cases and 155 pertussis-related deaths among US infants between 2005 and 2017, no appreciable population-level differences in infant pertussis mortality were observed following the 2011/12 ACIP maternal pertussis recommendation changes in comparison to the pre-period (January 2005–September 2011). This result was robust to limiting infant age at death to <2 months and other sensitivity analyses, including attempts to account for the potential competing effects of the introduction of the ACA. Possible decreases in infant pertussis incidence were noted. However, due to the small sample size (13 data points) and lack of ACA-related confounding control in the incidence analyses, these results should be interpreted with caution.

There are multiple plausible explanations for these findings in the mortality analyses. These results would suggest that although maternal pertussis vaccination rates were increasing prior to 2022 in the USA, there has not been an accompanying population-level change in infant pertussis mortality.[31] Pertussis incidence among infants in the USA is low and maternal vaccination rates may not yet have reached a level to translate into decreased pertussis-related mortality. Another possibility could be that we did not have the power to detect an appreciable change in infant pertussis mortality. When examining pertussis mortality over time, there does appear to be a decline in mortality rates in the post-period in comparison with the pre-period. However, these data exhibited large fluctuations from month to month, which may have led to wide and overlapping CIs. Though our results in the two-term analysis using the maternal age-stratified model were inconsistent with the null hypothesis prior to cubic spline inclusion, viewing the results of all analyses holistically, our data do not strongly support a substantial change in the pertussis mortality trend post-ACIP recommendations.

These analyses show potential evidence for a decrease in infant pertussis incidence among both <6-month-old infants and <1-year-old infants. This would be consistent with previous studies that have shown a decrease in pertussis incidence and hospitalizations among infants born to mothers receiving the Tdap vaccine during pregnancy.[5,32,33]

Our study offers important evidence on the US population-level effects of maternal pertussis vaccination recommendations in an ecological time trend analysis. The results in the ecological time trend may differ from those results found at the individual level. Maternal pertussis vaccination has been shown to be effective for reducing infant pertussis incidence when analysing individual-level data,[2,34] which is consistent with our results on pertussis incidence among infants. Heterogeneity of guideline implementation, low overall maternal Tdap vaccination coverage or failure to reach mothers with infants at the highest risk of pertussis mortality may explain the lack of change in mortality found in this ecological study.

Though there had been an increase in maternal pertussis vaccination prior to 2022, this may not have targeted those infants at the highest risk of pertussis mortality. According to a survey commissioned by the CDC, women aged 25–34 years, non-Hispanic White women, women with post-college education, women with private or military insurance and those living at or above poverty were the most likely to have received the Tdap vaccine during pregnancy.[35] Other analyses based on surveys have found disparities in Tdap receipt by race/ethnicity, geographic region and income status.[36,37] Low birthweight, Hispanic ethnicity and low maternal education have all been associated with increased risk of infant pertussis mortality in the USA.[38] We could not examine these subgroups individually due to a lack of data and adequate power; however, this could be an important area for further research.

Another potential reason for a lack of effect on infant pertussis mortality is that maternal Tdap vaccination coverage in

Table 4. Unadjusted monthly mortality rate ratios comparing transition and post-recommendations periods with the pre-recommendations period[a] trend in relation to the United States Centers for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy

	Pertussis MRR ($e^{ß}$) [95% CI] (*P*)			
	≤2 months		≤1 year	
	Quasi-Poisson	NBR[b]	Quasi-Poisson	NBR[b]
Time since transition period (monthly change in number of pertussis deaths per 100 000 live births after October 2011; $month_i$–October 2011)	0.99 [0.94, 1.05] (0.73)	0.99 [0.94, 1.05] (0.73)	0.99 [0.94, 1.05] (0.73)	0.99 [0.94, 1.04] (0.71)
Time since post-recommendations period (monthly change in number of pertussis deaths per 100 000 live births after March 2013; $month_i$–March 2013)	0.99 [0.93, 1.05] (0.76)	0.99 [0.93, 1.05] (0.76)	0.99 [0.93, 1.06] (0.78)	0.99 [0.94, 1.05] (0.73)

$e^{ß}$, exponentiated beta coefficient from model; MRR, mortality rate ratio; NBR, negative binomial regression.
[a] January 2005–September 2011.
[b] NBR with Huber–White robust standard error estimates to account for possible heteroscedasticity.

Table 5. Pertussis mortality rate ratio estimates in relation to the United States Centers for Disease Control Advisory Committee on Immunization Practices (US CDC ACIP) recommendations for tetanus–diphtheria–acellular pertussis (Tdap) vaccination during pregnancy, stratified by maternal Affordable Care Act (ACA)-dependent coverage expansion eligibility at birth to account for potential confounding

	Exponentiated mortality rate ratio [95% CI] (*P*)			
	Non-ACA[b] (2 months)	Non-ACA[b] (1 year)	ACA[c] (2 months)	ACA[c] (1 year)
Time since beginning of pre-recommendations period[a] (monthly change in number of pertussis deaths per 100 000 live births; $month_i$–January 2005)	1.01 [1.00, 1.03] (0.06)	1.01 [1.00, 1.02] (0.15)	0.99 [0.98, 1.01] (0.41)	0.99 [0.98, 1.01] (0.20)
Time since transition period (monthly change in number of pertussis deaths per 100 000 live births after October 2011; $month_i$–October 2011)	0.96 [0.90, 1.03] (0.22)	0.96 [0.90, 1.03] (0.29)	1.00 [0.92, 1.10] (0.96)	1.03 [0.95, 1.12] (0.49)
Time since post-recommendations period (monthly change in number of pertussis deaths per 100 000 live births after March 2013; $month_i$–March 2013)	1.01 [0.93, 1.09] (0.85)	1.01 [0.93, 1.09] (0.86)	1.00 [0.90, 1.11] (0.97)	0.97 [0.88, 1.06] (0.48)
Months	156	156	156	156

[a] January 2005–September 2011.
[b] Mortality rate ratio among infants born to mothers who were ineligible for the ACA-dependent coverage expansion at the time of infant birth (maternal age <19 years or ≥26 years).
[c] Mortality rate ratio among infants born to mothers who were eligible for the ACA-dependent coverage expansion at the time of infant birth (maternal age 19–25 years).

the USA is quite poor.[37] For example, between 2016 and 2018, Australia had maternal Tdap coverage rates of between 70% and 90%.[39] It is possible that Tdap maternal immunization coverage rates of <50% are not sufficient to translate into decreased infant mortality.

Strengths and limitations

Unlike studies limited to commercial databases or smaller databases, the study population was representative of the US population. All pertussis deaths captured by the National Vital Statistics centre were included in the analyses. We were also able to include monthly data from multiple years pre and post the ACIP recommendation due to the detail of the mortality available data from the National Centre of Health Statistics (NCHS).

This study was also able to account for many different facets of the ACA in the mortality analyses, which would be a potential threat to internal validity if otherwise not accounted for. The detail of the Infant Birth Death Linked data from the CDC allowed four separate models to be utilized in exploring potential confounding due to the ACA. The maternal age-stratified analysis examined the effects of the dependent coverage expansion policy under the ACA. The prenatal care was stratified and controlled analyses were able to investigate both the dependent care coverage and Medicaid expansion policies, as both would be expected to affect pertussis mortality through their effects on prenatal care.

Starting in 2005, geographic mortality data were withheld from the CDC public-use files due to a privacy policy change within the NCHS, thereby precluding a comparison of states with expanded Medicaid policies and those without to account for potential time-varying confounding from the ACA. The prenatal care-controlled and stratified analyses should have ascertained this to some level.

In addition, there is little information on power analysis in interrupted time series studies. Power in interrupted time series study designs depends on a range of factors and there is no widely agreed-upon minimum number of time points.[40] However, it is accepted that the higher the number of time points included, the greater the power. There were relatively few pertussis deaths in the USA. It is possible that there was a change in the pertussis mortality trend post-recommendations, but this model was underpowered to detect it. This model, however, includes all reported pertussis deaths in the USA. Lack of statistical power need not prevent exploration of this research question.[41]

Conclusion

There is a potential decrease in infant pertussis incidence after the 2011/12 ACIP maternal pertussis vaccine recommendations, whereas no appreciable differences were found in infant mortality in the post-recommendations period compared with the pre-recommendations period.

Ethics approval

UCLA Institutional Review Board approval was waived as this study did not meet the requirements to be considered human patients research.

Data availability

The mortality data underlying this article are available in the CDC NCHS Vital Statistics Online Data Portal, at https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm. The incidence data sets were derived from sources in the public domain: CDC Morbidity and Mortality Weekly Reports and CDC Pertussis Surveillance Reports.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

C.P., A.K.R. and M.J.S. designed the study. C.P. and M.J.S. designed the analytical strategy with help from R.N. and O.A.A. C.P. implemented the analytical strategy. C.P. conducted the literature review and wrote the manuscript. C.P., A.K.R., R.N., O.A.A. and M.J.S. reviewed the manuscript and helped to interpret the findings.

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Conflict of interest

None declared.

References

1. Bocka JJ, McNeil BK, Aronoff SC. *Pertussis: Practice Essentials, Background, Etiology and Pathophysiology*. https://emedicine.medscape.com/article/967268-overview#a5 (1 February 2021, date last accessed).
2. Gkentzi D, Katsakiori P, Marangos M *et al.* Maternal vaccination against pertussis: a systematic review of the recent literature. *Arch Dis Child Fetal Neonatal Ed* 2017;**102**:F456–63.
3. Winter K, Harriman K, Zipprich J *et al.* California Pertussis epidemic, 2010. *J Pediatr* 2012;**161**:1091–96.
4. Forsyth K, Plotkin S, Tan T, Von König CHW. Strategies to decrease pertussis transmission to infants. *Pediatrics* 2015; **135**:e1475–82.
5. Centers for Disease Control and Prevention. *Pregnancy and Whooping Cough. CDC Evaluation Found Maternal, Admission and Shorter Hospital Stays*. 2017. https://www.cdc.gov/pertussis/pregnant/hcp/vaccine-effectiveness.html#:~:text=A (31 January 2021, date last accessed).
6. Centers for Disease Control and Prevention (CDC). *Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months—Advisory Committee on Immunization Practices (ACIP)*. 2011. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm (5 January 2021, date last accessed)
7. Centers for Disease Control and Prevention (CDC). *Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women–Advisory Committee on Immunization Practices (ACIP)*. 2012. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm (5 January 2021, date last accessed)
8. Dahlen HM. 'Aging out' of dependent coverage and the effects on us labor market and health insurance choices. *Am J Public Health* 2015;**105**(Suppl 5):S640–50.
9. Lee LK, Chien A, Stewart A *et al.* Women's coverage, utilization, affordability, and health after the ACA: a review of the literature. *Health Aff (Millwood)* 2020;**39**:387–94.
10. Daw JR, Sommers BD. Association of the affordable care act dependent coverage provision with prenatal care use and birth outcomes. *JAMA* 2018;**319**:579–87.
11. Harvey SM, Oakley LP, Gibbs SE, Mahakalanda S, Luck J, Yoon J. Impact of Medicaid expansion in Oregon on access to prenatal care. *Prev Med* 2021;**143**:106360.
12. Bhatt CB, Beck-Sagué CM. Medicaid expansion and infant mortality in the United States. *Am J Public Health* 2018;**108**:565–67.
13. Centers for Disease Control and Prevention (CDC). *How NNDSS Conducts Case Surveillance | CDC*. https://www.cdc.gov/nndss/about/conduct.html (22 May 2021, date last accessed).
14. Centers for Disease Control and Prevention (CDC). *Summary of Notifiable Diseases—United States*. 2006. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5553a1.htm (6 June 2021, date last accessed).
15. Centers for Disease Control and Prevention (CDC). *Summary of Notifiable Diseases—United States*. 2007. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5653a1.htm (6 June 2021, date last accessed).
16. Centers for Disease Control. *2018 Final Pertussis Surveillance Report*. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2018-508.pdf (6 June 2021, date last accessed).
17. Centers for Disease Control. *2019 Final Pertussis Surveillance Report*. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2019-508.pdf (6 June 2021, date last accessed).
18. Centers for Disease Control. *Reported Pertussis Incidence by Age Group and Year | CDC*. https://www.cdc.gov/pertussis/surv-reporting/cases-by-age-group-and-year.html (6 June 2021, date last accessed).
19. Centers for Disease Control. *Summary of Notifiable Diseases—United States*. 2008. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5754a1.htm (6 June 2021, date last accessed).
20. Centers for Disease Control. *Summary of Notifiable Diseases—United States*. 2009. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5853a1.htm (6 June 2021, date last accessed).
21. Centers for Disease Control. *Summary of Notifiable Diseases–United States*. 2010. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5953a1.htm (5 January 2021, date last accessed).
22. Centers for Disease Control. *2013 Final Pertussis Surveillance Report Notice to Readers: Final 2013 Reports of Notifiable Diseases*. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2013.pdf (6 June 2021, date last accessed).
23. Centers for Disease Control. *2014 Final Provisonal Pertussis Surveillance Report—Factsheet*. https://www.cdc.gov/pertussis/

downloads/pertuss-surv-report-2014.pdf (6 June 2021, date last accessed).
24. Centers for Disease Control. *Notice to Readers: Final 2015 Reports of Nationally Notifiable Infectious Diseases and Conditions*. https://www.cdc.gov/mmwr/volumes/65/wr/mm6546a9.htm (6 June 2021, date last accessed).
25. Centers for Disease Control. *Final 2016 Pertussis Surveillance Report-Updated February*. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2016.pdf (6 June 2021, date last accessed).
26. Centers for Disease Control. *2017 Final Pertussis Surveillance Report -Revised 2018*. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2017.pdf (6 June 2021, date last accessed).
27. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;**27**:299–309.
28. Carrasquilla G, Porras A, Martinez S *et al.* Incidence and mortality of pertussis disease in infants <12 months of age following introduction of pertussis maternal universal mass vaccination in Bogotá, Colombia. *Vaccine* 2020;**38**:7384–92.
29. Kinlaw AC, Stürmer T, Lund JL *et al.* Trends in antibiotic use by birth season and birth year. *Pediatrics* 2017;**140**:e20170441.
30. StataCorp. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC; 2019.
31. Ghaswalla P, Poirrier JEM, Packnett ER, Irwin DE, Gray SR, Buck PO. Maternal Immunization in the U.S.: a Nationwide Retrospective Cohort Study. *Am J Prev Med* 2019;**57**:e87–93.
32. Skoff TH, Deng L, Bozio CH, Hariri S. US infant pertussis incidence trends before and after implementation of the maternal tetanus, diphtheria, and pertussis vaccine. *JAMA Pediatr* 2023;**177**:395–400.
33. Boulet SL, Chamberlain AT, Biswas HH, Jamieson DJ. Trends in infant pertussis hospitalizations in the United States, 2009-2017. *JAMA* 2019;**322**:2134–36.
34. Skoff TH, Blain AE, Watt J *et al.* Impact of the US maternal tetanus, diphtheria, and acellular pertussis vaccination program on preventing pertussis in infants <2 months of age: a case-control evaluation. *Clin Infect Dis* 2017;**65**:1977–83.
35. Centers for Disease Control and Prevention (CDC). *Pregnant Women and Tdap Vaccination, Internet Panel Survey | CDC*. https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/tdap-report.html#data-source-methods (3 May 2021, date last accessed)
36. Kriss JL, Albert AP, Carter VM *et al.* Disparities in Tdap vaccination and vaccine information needs among pregnant women in the United States. *Matern Child Health J* 2019;**23**:201–11.
37. Razzaghi H, Kahn KE, Black CL *et al.* Influenza and Tdap vaccination coverage among pregnant women–United States, April 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1391–97.
38. Haberling DL, Holman RC, Paddock CD, Murphy TV. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. *Pediatr Infect Dis J* 2009;**28**:194–98.
39. McRae JE, McHugh L, King C *et al.* Influenza and pertussis vaccine coverage in pregnancy in Australia, 2016–2021. *Med J Aust* 2023;**218**:528–41.
40. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;**46**:348–55.
41. Hernán MA. Causal analyses of existing databases: no power calculations required. *J Clin Epidemiol* 2022;**144**:203–205.