Title
The Impact of the 2011/2012 CDC ACIP Maternal Pertussis Vaccination Recommendation on Infant Pertussis Incidence and Mortality in the United States

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The Impact of the 2011/2012 CDC ACIP Maternal Pertussis Vaccination Recommendation on Infant Pertussis Incidence and Mortality in the United States

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Epidemiology

by

Catherine Psaras

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ABSTRACT OF THESIS

The Impact of the 2011/2012 CDC ACIP Maternal Pertussis Vaccination Recommendation on Infant Pertussis Incidence and Mortality in the United States

by

Catherine Psaras

Master of Science in Epidemiology

University of California, Los Angeles, 2021

Professor Marissa J. Seamans, Chair

Background. Pertussis is a highly contagious respiratory disease, for which maternal tetanus-diphtheria-acellular pertussis (Tdap) vaccination during pregnancy is the primary prevention strategy in infants. In October 2011, the CDC Advisory Committee on Immunization Practices (ACIP) recommended Tdap vaccination for all unvaccinated pregnant women. In 2012, ACIP extended this recommendation to include all pregnant women, regardless of previous vaccination. The effects of these recommendations in the United States (US) on infant pertussis morbidity and mortality are currently unknown. **Objectives.** To examine the impact of the 2011/2012 ACIP pertussis recommendation on pertussis morbidity and mortality among US infants. **Methods.** We used monthly data of pertussis deaths among infants <1 year from January 2005 to December 2017 in the CDC Linked Birth/Infant Death Data to perform an interrupted

time series (ITS) analysis. We compared trends in pertussis mortality at <1 year before and after the guideline changes. We fit segmented quasi-Poisson regression models for pertussis deaths with monthly live births as an offset to estimate the time trend during three time periods: pre-recommendation, transition, and post-transition. To account for possible bias due to trends in access to healthcare following the 2010 Affordable Care Act (ACA), four comparative and controlled ITS analyses were conducted. These included maternal age stratified analyses, number of prenatal care visit stratification, adequacy of prenatal care utilization (APNCU) stratification, and a behavior-based control. **Results.** 156 months of data were included in the analysis. No appreciable differences in trend were found in infant pertussis morbidity or mortality after the guideline changes in both the adjusted and unadjusted models. These results were similar for in sensitivity analyses that varied the timing of the transition and post periods and varied the existence of the transition period. **Conclusions.** The 2011/2012 ACIP maternal pertussis vaccination recommendations were not associated with a change in trend in infant pertussis morbidity or mortality in the US between 2005 and 2017. Future analyses should include geographic data from the CDC in order to more directly account for the ACA Medicaid Expansion. Future analyses should also investigate heterogeneity in recommendation implementation and whether those infants at highest risk of pertussis mortality are being reached by this preventative strategy.

The thesis of Catherine Psaras is approved.

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2021

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Introduction

Pertussis Epidemiology

Pertussis, also known as whooping cough, is an infectious disease caused by the *Bordetella pertussis* bacteria that is transmitted through aerosolized droplets.[1] Pertussis is the most common vaccine preventable disease in children under 5 in the United States.[2] In 2010, the United States recorded its highest number of incident pertussis cases since 1959, at 27,550 cases and 27 deaths.[2] Though most pertussis transmission occurs among adults, the majority of pertussis mortality is concentrated in infants <2 months old.[3] This is because infants under <2 months old are too young to receive the diphtheria, tetanus, and pertussis (DTaP) vaccine.[4] The DTaP vaccine is a combination vaccine approved for use in children 2 months to 6 years old. The uppercase letters signify that the vaccine contains full strength doses of diphtheria, tetanus, and acellular pertussis vaccinations.[5] The Centers for Disease Control (CDC) recommends a five dose series with the first dose at two months, the second at four months, the third at 6 months, the fourth between fifteen and eighteen months, and the fifth between four and six years old.[6] Infants who are older than 2 months are also at elevated risk of pertussis infection and death from pertussis when their vaccine schedules have not yet been completed.[1] Of the infants <12 months old who contract pertussis, 50% are hospitalized.[7] Of those hospitalized, 68% have difficulty breathing, 23% develop pneumonia, 1.2% develop seizures, 0.4% develop encephalopathy, and 1% die.[7]

Pertussis Epidemics in the US (2005-2019)

There have been multiple pertussis outbreaks in the United States since 2005, mostly affecting young infants.[8] In 2010, a pertussis epidemic was declared in California, which eventually

resulted in 9,120 pertussis cases and 10 deaths. All of these deaths occurred in infants less than three months old and at least four of these deaths occurred in Los Angeles County.[4,9] In 2010, twenty-five deaths occurred in infants under one.[10] California announced another pertussis epidemic in June 2014 when reported pertussis incidence increased five-fold from months prior. Nearly ten-thousand cases occurred during this outbreak.[11]

In 2012, both the states of Washington and Vermont declared pertussis epidemics.[12,13] Between January and June 2012, Washington state observed a 1,300% rise in pertussis cases compared to the same time period in 2011.[12]

Maternal Vaccination Strategies

Maternal pertussis vaccination with the Tdap vaccine has been shown to protect both the mother and, through passive immunity, the newborn and is considered the primary pertussis prevention strategy to protect infants under two months-old.[1] The Tdap vaccine is used as a booster after initial DTaP vaccination prior to age seven.[5] The uppercase T signifies a full dose of the tetanus vaccine within the combination vaccine.[5] The World Health Organization (WHO) considers maternal pertussis immunization as the most cost-effective strategy to reduce both infant pertussis-related morbidity and mortality.[14] Other methods such as cocooning, a strategy where all those likely to have contact with the infant (i.e., parents and grandparents) are vaccinated, have had difficulty achieving high uptake and have had mixed reviews on effectiveness.[1,15] The US CDC currently recommends that pregnant women receive the vaccine during the 27th through 36th week of pregnancy and that this should be administered during every pregnancy.[16]

Pertussis Vaccine Efficacy

A CDC study on Tdap vaccine effectiveness found that maternal pertussis vaccination in the third trimester of pregnancy can prevent 78% of pertussis cases in infants under two months and is 90% effective at preventing pertussis-related hospitalizations in infants.[16] There has been concern that the passive immunity conferred to infants in utero may interfere with their own immune response to the DTaP immunization at two months of age.[17] However, the CDC continues to recommend maternal vaccination and infant pertussis vaccination at 2 months.[16]

Recommendations of CDC's Advisory Committee on Immunization Practices (ACIP)

Prior to the 2011 updates, the Advisory Committee on Immunization Practices (ACIP) of the CDC recommended the Tdap booster for unvaccinated postpartum mothers and family members or other caretakers who would be expected to have contact with the newborn.[18] In 2011, ACIP recommended the Tdap vaccine between weeks 27 and 36 in the third trimester of pregnancy for all women who have not previously been vaccinated in their lifetime.[18] In 2012, ACIP updated this recommendation to include all pregnant women due to waning immunity from initial vaccine administration early in life.[19] This recommendation is supported by the American College of Obstetricians and Gynecologists, the American College of Nurse-Midwives, the American Academy of Pediatrics, and the American Academy of Family Physicians.[16] The impact of these recommendations in the United States is currently unknown.

Despite these recommendations and a general increase in vaccine coverage over time, vaccine coverage as of 2016 was still considered low in the United States.[3] In a 2016 study that used data from 2007-2013 from the CDC's Vaccine Safety Datalink (VSD), 41.7% of women who had live

births were vaccinated during pregnancy in 2013.[20] By 2016, the CDC reports that this number increased slightly to 48.8%.[21] OBGYN physicians have noted vaccine price, need for repeated vaccination during each pregnancy, and perceived reduced need for the vaccine due to low pertussis incidence in the area as barriers to vaccinating pregnant women.[3]

Project Objective

The objective of this study is to examine the impact of the introduction of the 2011/2012 ACIP pertussis recommendation on pertussis-related morbidity and mortality among infants in the United States. Infants ≤12 months old are at the highest risk of serious complications and death from pertussis.[1] Maternal pertussis vaccination is effective in providing antibodies to young infants, preventing serious disease from pertussis, and preventing hospitalization and death among young infants.[16,22] However, evidence is scant on how effective the 2011/2012 recommendations were at reducing mortality infants, which is the ultimate goal of pertussis prevention programs. Since 2006, over 37,000 infants have contracted pertussis and 181 infants have died from pertussis. [10,23,24] Analysis on the effects of this recommendation will allow for assessment as to whether this recommendation has been successful in reducing infant morbidity and mortality due to this vaccine preventable disease.

Literature Review

Pertussis Vaccine History

Pertussis vaccines were first approved in the 1940's in the United States.[15] Original pertussis vaccines were pertussis whole cell (wP) vaccines and were very successful in reducing infant morbidity and mortality from pertussis.[15] In 1934, the US recorded 260,000 cases of pertussis,

which was the highest case number in any given year. By 1976, due to wP vaccines, this number decreased by over 99% to 1,010 cases.[25]

In the 1990's, acellular pertussis (aP) vaccines were introduced and found to have fewer side effects. This led aP vaccines to become the primary pertussis vaccine in use.[26] Subsequent studies however have shown that the aP vaccines are less effective than the wP pertussis vaccines due to more rapid waning immunity.[15] Waning immunity from the vaccine is partially responsible for outbreaks approximately every 3 to 5 years in the United States.[27]

Interrupted Time Series Analyses

Interrupted Time Series (ITS) analyses have become a popular method for analyzing the impact of population-level interventions.[28] ITS designs are quasi-experimental and are a unique observational design in that they compare outcomes in the same population pre- and post-treatment or intervention. The population acts as its own post-intervention control whereby the pre-intervention outcome trend (over time) is extrapolated to the post-intervention time period to predict the unobserved post-intervention counterfactual (potential) outcome trend that would have been observed had there been no intervention and which is then contrasted with the observed post-intervention (potential) outcome trend. This, in theory, protects against potential confounding caused by factors that do not vary or vary slowly between groups over time, which is a common source of bias in other observational study designs. Conversely, ITS designs do not inherently protect against confounders that vary over time, such as other historical events that occurred or changed concurrently with the intervention and may also affect the outcome of interest. This is also known as history bias.[29] This bias would also occur if there is a confounder or a risk factor for the outcome that is associated with the timing of the intervention.

The most basic form of an ITS contains one study population with equally spaced, serially collected data points before and after the intervention of interest. There are no minimums for the number of data points pre- and post- intervention that should be collected.[30] Power for ITS analyses depends on a number of factors including variability within the collected data, strength of the intervention effect, and confounding factors such as seasonality.[30] Power generally increases with increasing numbers of data points; however, it is not advised to use data points too far pre-intervention as they might not be representative of the immediate pre-intervention baseline trend.[30]

Though ITS designs are impervious to many classical sources of confounding, they are often plagued by overdispersion, autocorrelation, and sometimes time-varying confounding. Plans on how we will manage these issues are discussed further in the methods section.

Controlled Interrupted Time Series Analyses

As previously mentioned, history bias can occur in interrupted time series when an event unrelated to the study intervention occurs around the time of the study intervention and has a greater effect on the study outcome than the study intervention itself.[29] This makes it challenging to disentangle the effects of the intervention of interest from other co-occurring events. ITS designs can attempt to ameliorate this bias by including a control series, which is also called a controlled interrupted time series (CITS) design.

Lopez Bernal et. al (2017) classify the different types of control series into six groups: location-based, characteristics-based, behavior based, historical cohort, control outcome, and control time period.[30] Synthetic controls[31] and propensity score-weighted controls[32] are also other more computationally intensive controlled ITS methods. Synthetic controls have been most commonly used as a variation on location-based controls.[31] I will focus on the three types of controls from Lopez Bernal et. al (2017) that are most relevant to this study—location-based, behavior-based, and control outcome controls.

Location-based controls are a series of observations selected from a location where the confounding event would be expected to have an effect on the outcome, but not the intervention of interest. For example, a hypothetical study examining the impact of an indoor public smoking ban on rates of myocardial infarctions in California could compare myocardial infarction rates between California and Texas, a state that did not implement this during the study time period. This would account for possible national level co-interventions, administrative or diagnostic coding changes, and/or cultural or demographic shifts at a national level that could lead to changes in myocardial infarction rates over time.

When an intervention does not affect the behaviors of all individuals whom it was intended to affect, these unaffected individuals may be used as a control series. Ross-Degnan et. al (1993) used a behavior-based control while examining changes in analgesic prescribing practices after there were numerous reports of deaths related to Zomepirac, a non-steroidal anti-inflammatory drug..[33] Doctors who never prescribed Zomepirac were used as a control as their analgesic

prescribing practices, logically, would not be affected by the withdrawal of the medication from the market.

A control outcomes series would be a series of observations on a comparable outcome condition that would be expected to be affected by the confounding event, policy change, trend, or intervention, but not the intervention of interest. In a study on the impact of mandatory cycling helmet laws in Australia on head injuries, Walter et. al (2011) used limb injuries as a control because they would be affected by other trends in cycling but presumably not a mandatory helmet law. [34]

Interrupted Time Series Analyses of Public Vaccination Campaigns

Interrupted time series are a common method for examining the impacts of population level interventions such as public mass vaccination campaigns or national recommendations.[35–38] Outcomes were generally one of three types, case counts or incidence rates, hospitalizations or hospitalizations rates, and deaths or mortality rates. Model specification varied across different studies depending on the disease and outcome being studied. Several types of slope change can be used to encode assumptions about the shape of the expected trend. This would include assumptions about how long it would take to begin to see an effect of the intervention of the duration of the effect one would expect to find. This would account for differences between outcomes such as myocardial infarctions after smoking bans or the effects of increased preventative care use on chronic disease incidence. One would expect the first outcome to occur quite soon after the intervention while the latter would be expected to be more of a long-term change in trend.

When including a transition period, studies used segmented regression analyses to measure the change in the outcome.[38] To control for seasonality some studies included calendar month as a covariate[36] while other included Fourier terms.[37] Fourier terms are sine and cosine pairs that model waves with predefined period lengths that are useful for mathematically capturing repeating peaks and troughs with similar amplitudes in the data.[39] When using count data outcomes, generalized linear models with Poisson distributions and log-links (i.e. log-linear rate models) were used to estimate rate ratios comparing the outcome incidence or incidence trend in the post-intervention period versus the pre-intervention periods.[36]

Interrupted Time Series Analyses of Pertussis

Carrasquilla et. al (2020)[40] examined the impact of universal mass pertussis vaccination on pertussis morbidity and mortality in infants <12 months in Bogotá, Colombia in an ITS analysis. In response to a pertussis resurgence between 2010 and 2012 in Colombia, many public health strategies were combined into a national program to curtail this increase. The program was introduced in December of 2012 in Bogotá and became national in 2013. Carrasquila et. al (2020)[40] used a negative binomial regression with a year-long transition period and step change between the different study time periods. Overall, the authors found a substantially beneficial impact of the vaccination program on infant morbidity and mortality due to pertussis. The average monthly incidence of pertussis decreased 87.5% (95% CI: -93.17%, -77.30%) in the post program period compared to the pre-program period.[40]

Methods

Study Setting and Population

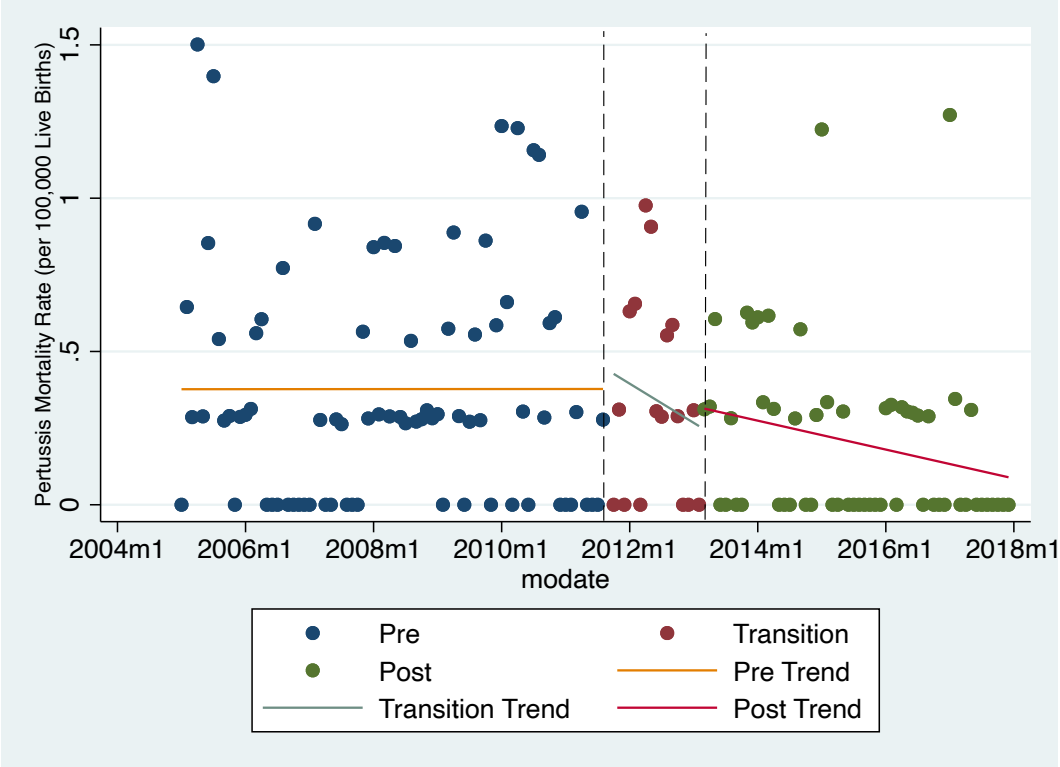
This study will examine changes in pertussis incidence and mortality in infants ≤2 months (newborns) and infants ≤1 year in the United States between January 2005 and December 2017. This study includes all pertussis cases diagnosed and reported to the CDC through the National Notifiable Disease Surveillance System (NNDSS) and cases of pertussis where infants died in the United States, regardless of citizenship or country of birth.

Data Sources

CDC Linked Infant Mortality Data

Period Linked Birth-Infant Death data are available through the CDC National Vital Statistics (NVS) program. Data are available from 1995 through 2017. The advantage of using this data source is the inclusion of mother's age at time of birth, number of prenatal visits, and month of prenatal care initiation. This assisted in restricting the potential effects of the Affordable Care Act (ACA) in a comparative ITS analysis. Data on the population at risk were extracted from the CDC NVS Natality files. Data from January 2005 through December 2017 were used in this analysis (Figure 1). This makes for a total of 156 time points (12 months × (2017 – 2005 + 1)). Deaths in this data are weighted to account for those records that could not be linked.

Figure 1: Pertussis-related mortality rates per 100,000 in infants <12 months, 2005-2017, n=155

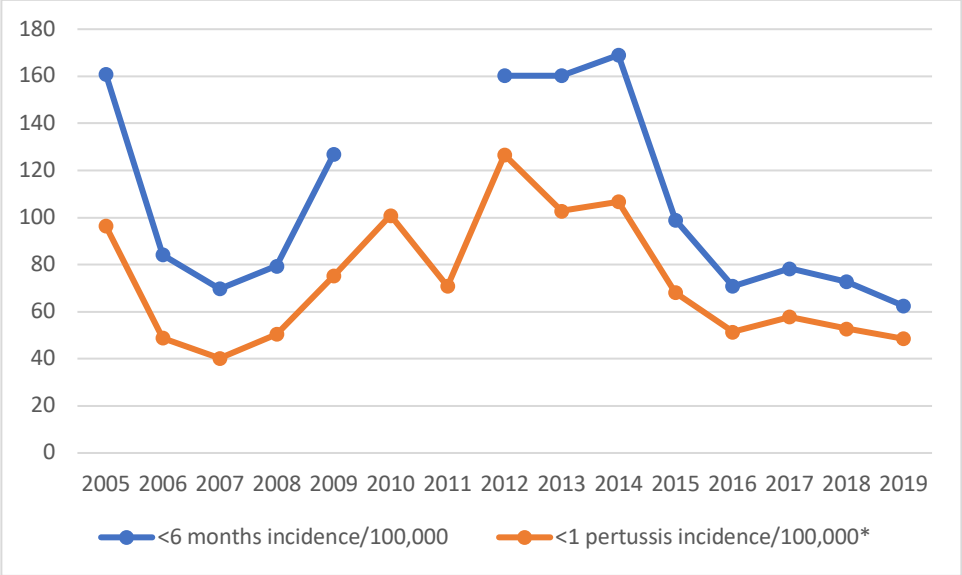


CDC Morbidity and Mortality Weekly Report (MMWR)

The CDC provides yearly pertussis incidence data for children under six months and under one year. These data are collected through the National Notifiable Disease Surveillance System (NNDSS). The NNDSS is a passive surveillance system that relies on case reporting to local and state health departments by patient care providers and laboratories.[41] State and local health departments then send deidentified data to the CDC where this data are ultimately published.[41] Case reporting is mandatory while case notification is not.[41] Data for children under six months are missing for 2010 and 2011 and were combined for 2012 and 2013. However, the incidence trend in 6-month-olds follows closely to that of 1-year-olds (Figure 2). Thus, it would be reasonable to believe the trend in the missing data would be similar to that of the known data of

1-year-olds in the same years. Incidence rates for 6-month-olds were thus interpolated for 2010 and 2011.

Figure 2: Pertussis incidence (per 100,000) in infants by age, 2005-2019



<6 Months Sources: 2005[42], 2006[43], 2007[44], 2008[45], 2009[46], 2012[47], 2013[47], 2014[48], 2015[49], 2016[50], 2017[51], 2018[52], 2019[53]
<12 Months Source: 2005-2019[54]

Pertussis Case Definition

The CDC notifiable disease case definition was used as the case definition for pertussis in this study. This includes all laboratory confirmed and clinically suspected cases of pertussis in the United States.[55]

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.

Analytical Strategies

Interrupted Time Series Design

Using an interrupted time series (ITS) design, we analyzed the impact of the 2011/2012 ACIP maternal pertussis vaccination recommendations. Using the ITS design allowed us to analyze the effects of the recommendation while also accounting for underlying trends in pertussis morbidity and mortality in the United States over the study period. We allowed for slope changes over three segments. The three segments are the preintervention period (January 2005-September 2011), transition period (October 2011-February 2013), and post intervention period (March 2013-December 2017). A transition period was assigned because the initial ACIP recommendation to vaccinate previously unvaccinated pregnant women was published in October 2011. This recommendation was then extended in February 2013 to include all pregnant women during every pregnancy regardless of previous vaccination status. We thus allowed for a transition window ending in February 2013. Dates of recommendation publishing in MMWR were used instead of dates of ACIP recommendation approval. These analyses were completed in Stata/IC 16.1[56] and UCLA Institutional Review Board (IRB) approval was waived as this study does not meet requirements to be considered human subjects research.

Model Parameters

The uncontrolled model is a segmented Poisson regression analysis containing parameters for time, a term for the number of months post the beginning of the transition period, a term for the number of months after beginning of the post intervention period, and an offset for the log of the number of live births in month *t* (Equation 1). This model is a combination of models from Wagner et. al (2002), Carrasquilla et. al (2020), and Kinlaw et. al (2017).[40,57,58]

Equation 1:

$$\log(Y_t) = \log(population) + \beta_0 + \beta_1 * time_t + \beta_2 * time\ since\ transition_t + \beta_3 * time\ since\ post_t + e_t$$

Y_t= number of pertussis deaths in month t

$Time_t$= continuous variable representing how many months elapsed since time=0 (Jan 2005)

Time since $transition_t$= time elapsed since beginning of transition period ($month_i$-Oct 2011)

Time since $post_t$= time elapsed since beginning of post intervention period ($month_i$-Feb 2013)

β_0= *baseline level of pertussis mortality in January 2005*

β_1= *estimated change in pertussis mortality per month prior to the transition period (Oct 2011)*

β_2= *estimated monthly change in pertussis mortality trend during transition period*

β_3= *estimated monthly change in pertussis mortality trend during post intervention period*

Time is segmented into three groups, pre-intervention, a transition period, and post-intervention. The length and presence of the transition window will be varied in sensitivity analyses. Conducting the analysis in this manner allows for the examination of a change in trend during the transition and post-intervention period. Step change terms were not included because gradual changes in morbidity and mortality were assumed post recommendation. This was similar to the model in Kinlaw et. al (2017).[58]

Comparative and Controlled Interrupted Time Series

Confounding Event: Affordable Care Act (2010)

The Affordable Care Act (ACA) was passed on March 23, 2010.[59] Starting in September 2010 all insurers were required to extend coverage to dependents of insured individuals up to the date

on which the dependent turns twenty-six.[60] It is important to note, however, that the extension of dependent coverage does not extend to the children of dependents and may in some circumstances not have covered the dependent individual's labor and delivery. Prior to the passage of the ACA, dependent children would age out of coverage at nineteen or twenty-two if they were full-time students. Nineteen- to twenty-five-year-olds were targeted for the coverage expansion because historically this group had high rates of being uninsured. Studies examining the impact of the coverage expansion have found three to six percentage point increases in coverage within this group post ACA.[60]

Studies have also shown that the ACA improved prenatal care and perinatal outcomes.[61] Dependent coverage expansion improved access to prenatal care for women ages 24-25 and decreased pre-term births in comparison to women ages 27-28, who would have been ineligible for the coverage expansion.[62] Some studies have also shown that Medicaid expansion due to the ACA improved access to prenatal standard of care for low-income women.[63] Overall, states that expanded Medicaid experienced greater reductions in infant mortality, particularly among black infants, than those states that did not expand Medicaid.[64]

Comparative and Controlled Interrupted Time Series

We included three versions of controls to account for potential confounding by the 2010 passage of the ACA. The first analysis was a comparative analysis, which was a stratified version of the original base analysis in this paper. Infant mortality will be stratified by maternal age, a proxy for being affected by the expansion of dependent coverage under the ACA. The second analysis stratified on adequacy of prenatal care and the third was a controlled ITS using deaths that occurred to infants whose mothers did not receive prenatal care.

Maternal Age Stratified Analysis

Those deaths occurring in infants of mothers ages twelve through eighteen and twenty-six and up were considered unaffected by the ACA dependent coverage expansion. Those nineteen through twenty-five were considered affected by the ACA dependent coverage. The base model (Equation 1) was then run on each group separately. The pre-analysis logic was as follows. If both the ACA unaffected and affected models or just unaffected model show significant level and/or trend changes post intervention this would be supportive of a significant impact due to the ACIP recommendations. Any reduction found in the ACA non-eligible group, in theory, could not be due to the ACA dependent coverage expansion as they were not entitled to this. If the ACIP recommendation is associated with a reduction in pertussis morbidity and mortality in infants born to mothers ages 19-25 but not among the ACA ineligible group, this would be evidence that the reduction we are seeing is due to the ACA and not the ACIP recommendations.

Adequacy of Maternal Care Stratified Analysis

A previous study has found that the number of prenatal care visits attended is associated with increased likelihood of receiving the Tdap vaccine during pregnancy.[65] Linked Birth/Death and Natality data from the CDC contain information on the number of prenatal care visits attended by the infant's mother. In 2016, the WHO recommended a minimum of eight prenatal care visits.[66] Prior to this, the recommendation was at least four visits.[67] We will stratify the analysis based on number of attended visits fewer than 4 visits, between 4 and 7 visits, and 8 or more visits. We would expect to see a stronger decrease in the ≥8 visits group in comparison to the two lesser care groups.

Another form of this analysis was completed using the Adequacy of Prenatal Care Utilization (APNCU) Index levels as the stratifying variable. Index values for all pertussis deaths were calculated using the algorithm presented by Kotelchuk.[68,69] The SAS code provided in Alexander and Kotelchuck (1996)[69] was translated into Stata code. The index is on a scale from 1 to 4 with 1 being inadequate care and 4 being intensive/adequate+ care. The index is calculated based on the number of prenatal care visits attended in comparison to the expected number given gestational age at birth and the month of pregnancy in which prenatal care was initiated. Multiple imputation was implemented to account for missingness in one of the index variables. The month of prenatal care initiation variable's missingness decreased over time in the natality data due to staggered switches from the 1989 to 2003 birth certificate among states. This necessitated accounting for this missingness so that earlier pertussis mortality rates would not be artificially inflated by more complete natality data in the early years. Multiple imputation with chained equations were used to generate forty imputed data sets. The imputation analyses on the denominator data were completed using the Hoffman2 cluster at UCLA and a random sample of 1,000,000 births during the study period due to the large nature of the natality data.

Mothers Without Prenatal Care Visits as Controls (Behavior-Based Control)

In the Linked/Birth Death and Natality data from the CDC, there was a portion of mothers who did not attend any prenatal care visits and presumably would not have obtained or been offered the Tdap vaccine. Between 2005 and 2019, 1.3 percent of births, or nearly 78,000 births, occurred in mothers without prenatal care in the US.[70] Infant deaths in this population may serve as a control because we should not see a decline in pertussis mortality in this population at the time of the recommendations because they likely never obtained the vaccine. If there is a decline

in this population attributed to the recommendation time periods, this would be evidence that the declines in pertussis mortality we are observing may be due to broader changes in perinatal care.

The setup of this model differed slightly from the other models in order to incorporate the control series (Equation 2). The parallel lines trend assumption was checked by running a regression of time on the difference between the mortality rates in the intervention and control groups in the pre-recommendation period. A non-zero coefficient on the time parameter would be considered a violation of the assumption.

Equation 2:

$$D_{R_I - R_C} = \beta_0 + \beta_1 * time_t + \beta_2 * time\ since\ transition_t + \beta_3 * time\ since\ post_t + e_t$$

$D_{R_I - R_C}$= Difference in pertussis mortality rates between Intervention Group (prenatal care>0) and Control Group (no prenatal care)

$Time_t$= continuous variable representing how many months elapsed since time=0 (Jan 2005)

Time since $transition_t$= time elapsed since beginning of transition period ($month_i$-Oct 2011)

Time since $post_t$= time elapsed since beginning of post intervention period ($month_i$-Feb 2013)

β_0= *baseline difference in pertussis morality between the two groups in January 2005*

β_1= *estimated change in difference in pertussis mortalities between two groups per month prior to the transition period (Oct 2011)*

β_2= *estimated change in difference in pertussis mortalities between two groups per month during the transition period*

β_3= *estimated change in difference in pertussis mortalities between two groups per month during the post period*

Sensitivity Analyses

Multiple sensitivity analyses were completed. These included varying the length of the transition time period, examining trends in both ≤2-month-olds and ≤1-month olds, and addressing potential homoskedasticity violations.

Results

One-hundred-fifty-five deaths occurred during the study period (January 2005 – December 2017) (Table 1 and Figures 3-4). Ninety-nine deaths occurred during the pre-recommendation period (January 2005-September 2011), 18 deaths occurred during the transition period (October 2011-February 2013), and 38 deaths occurred during the post-recommendation period (March 2013 - Dec 2017).

Table 1: Characteristics of Pertussis Deaths in the USA (2005-2017)

	Pre* (2005 – 2011)	**Transition** (2011 – 2013)**	**Post*** (2013 – 2017)**	**Total (2005 – 2017)**
Deaths (N)	**N=99**	**N=18**	**N=38**	**N=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 (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%)	0 (0%)	4 (3%)
6 months	1 (1%)	0 (0%)	0 (0%)	1 (1%)
Maternal Age at Birth (Years)	26 (6)	29 (5)	26 (6)	26 (6)
Birthweight (grams)				
227 – 1499	6 (6%)	0 (0%)	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 (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 (0%)	4 (3%)
Missing	32 (32%)	2 (11%)	30 (79%)	64 (41%)
Number Prenatal Care Visits	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%

Data are presented as mean (SD) for continuous measures, n (%) for categorical measures, and % for imputed values.
**= (January 2005-September 2011)*
***= (October 2011-February 2013)*
****= (March 2013 - December 2017)*

Figure 3: Pertussis Mortality Rates in ≤2-month-olds between 2005 and 2017

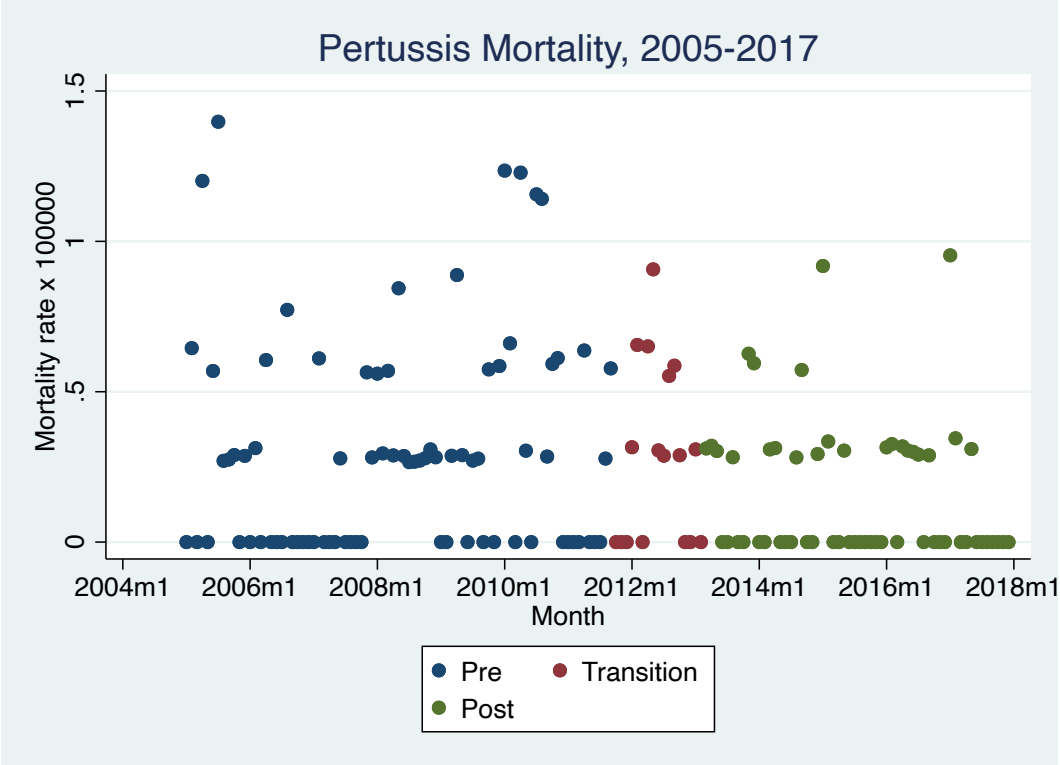
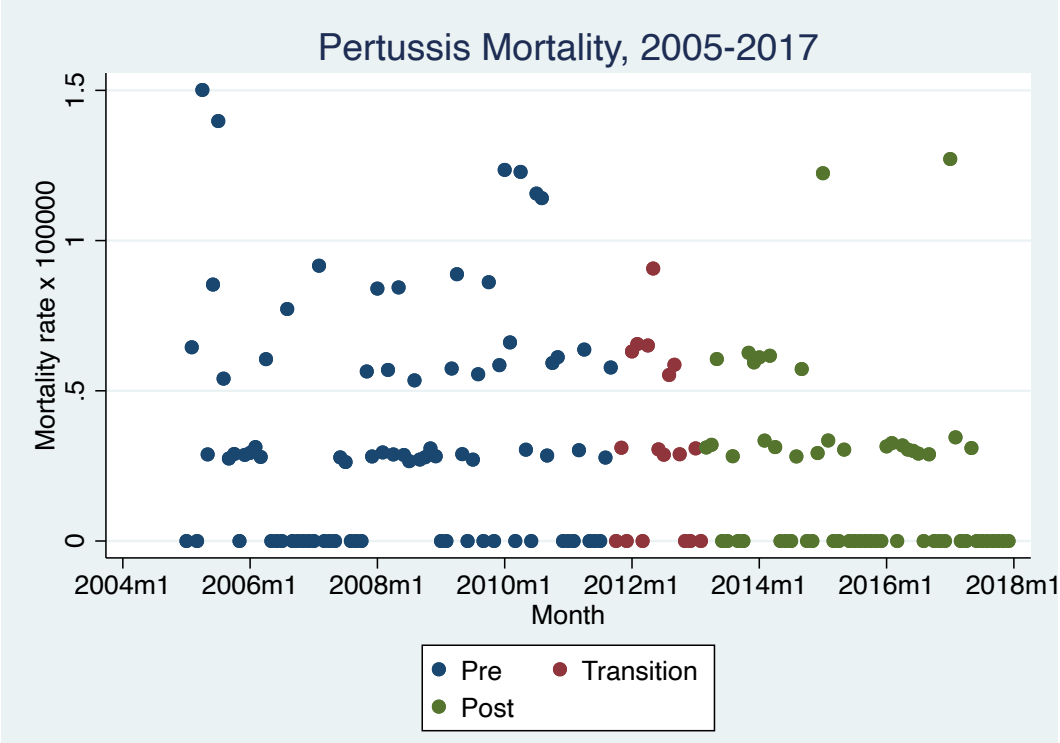


Figure 4: Pertussis Mortality Rates in ≤1-year olds between 2005 and 2017



Unadjusted Mortality Model

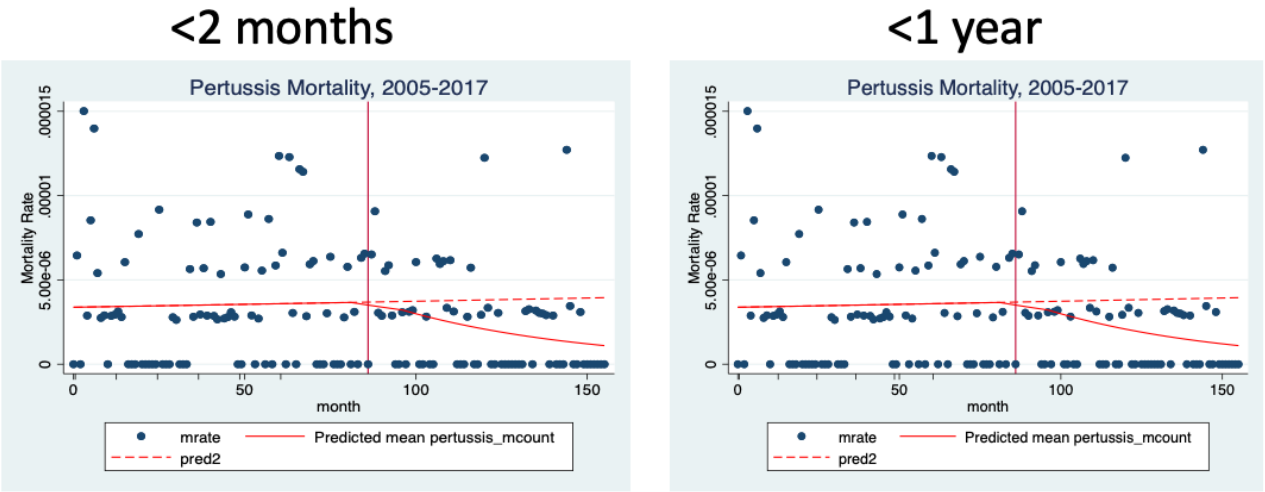
The results of the unadjusted mortality analyses are presented in Table 2 and Figure 5. In the uncontrolled interrupted time series analysis using the specification from Equation 1 and a quasi-Poisson regression, the mortality rate ratio (MRR) comparing the change in trend in the mortality rate in the post recommendation period 0.99 (95% CI: 0.94 – 1.05) among infants less than or equal to 2 months old. Among infants less than 1 year old, this remained the same (MRR: 0.99, 95% CI: 0.94 – 1.05). Estimates of precision were similar using Huber White robust standard errors to account for potential heteroskedasticity (Table 2).

Table 2: Model Parameter Estimates

	≤2 months (95% CI)		≤1 year (95% CI)	
Pertussis MRR** (e^{β})	Quasi-Poisson	NBR*	Quasi-Poisson	NBR*
Transition Period (October 2011-Feb 2013) vs Pre-Recommendations (Jan 2005-September 2011)	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.04)
Post-Recommendation (March 2013 - Dec 2017) vs Pre-Recommendations (Jan 2005-Oct 2011)	0.99 (0.93 – 1.05)	0.99 (0.93 – 1.05)	0.99 (0.93 – 1.06)	0.99 (0.94 – 1.05)

MRR= Mortality Rate Ratio
e^{β}= exponentiated beta coefficient from model
*= Negative Binomial Regression with Huber White Robust Standard Error Estimates to account for possible heteroskedasticity

Figure 5: Unadjusted ITS Analyses



*Mortality rates are per 100,000 live births

Quantity of Prenatal Care Visit Stratified Models

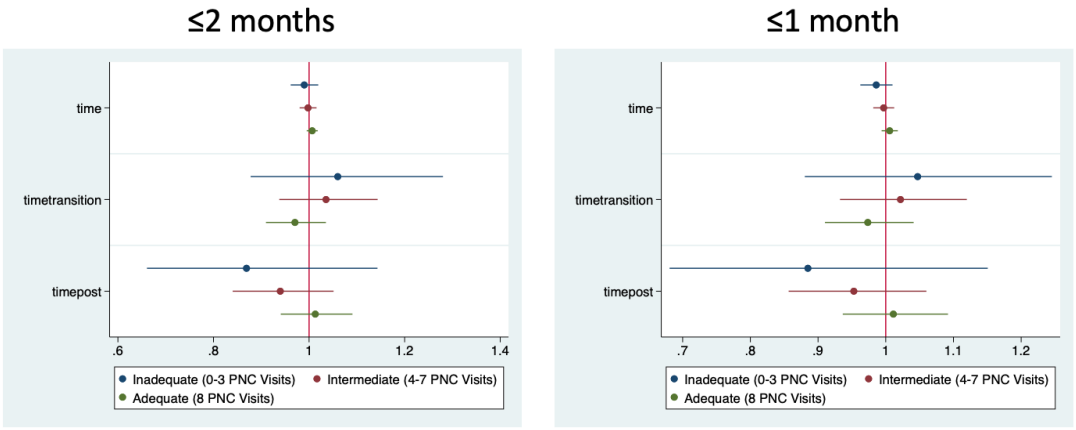
The results of the analyses stratified by number of prenatal care visits are presented in Table 3 and Figure 6. When using a stratified quasi-Poisson regression model to analyze the change in post recommendation trend among different levels of prenatal care visit quantities, no appreciable differences in trend in ≤2 month or ≤1-year infant pertussis mortality were found (Table 3). Examining the overall trends, in the transition period, there is decreasing mortality in the groups with more prenatal care and in the post period this trend reverses (Figure 8). With each month into the post recommendation period (March 2013 - Dec 2017), the estimated change in baseline mortality rate was 0.87 times that of the month prior in the inadequate group (95% CI: 0.88, 1.28), 0.94 times that of the month prior in the intermediate group (95% CI: 0.84, 1.05), and 1.01 times that of the month prior in the adequate group (95% CI: 0.94, 1.09).

Table 3: PCV Stratified Model Mortality Rate Ratio Estimates

	Inadequate Care (0-3 PNC Visits)		Intermediate Care (4-7 PNC Visits)		Adequate Care (8+ PNC Visits)	
	≤2mo	≤1yr	≤2mo	≤1yr	≤2mo	≤1yr
Time Trend (Monthly MRR)	0.99	0.99	1.00	1.00	1.01	1.01
	[0.96,1.02]	[0.96,1.01]	[0.98,1.02]	[0.98,1.01]	[1.00,1.02]	[0.99,1.02]
	(0.497)	(0.25)	(0.81)	(0.70)	(0.26)	(0.34)
Time since Transition Period Began (Monthly MRR)	1.06	1.05	1.04	1.02	0.97	0.97
	[0.88,1.28]	[0.88,1.25]	[0.94,1.14]	[0.93,1.12]	[0.91,1.04]	[0.91,1.04]
	(0.55)	(0.60)	(0.49)	(0.64)	(0.36)	(0.43)
Time since Post Period Began (Monthly MRR)	0.870	0.89	0.94	0.95	1.01	1.01
	[0.66,1.14]	[0.68,1.15]	[0.84,1.05]	[0.86,1.06]	[0.94,1.09]	[0.93,1.09]
	(0.32)	(0.36)	(0.28)	(0.38)	(0.73)	(0.78)
Months	156	156	156	156	156	156

PNC= Prenatal Care
Exponentiated coefficients
95% confidence intervals in brackets; p-values in parentheses.

Figure 6: PCV Stratified Model Parameter Estimates



Controlled ITS

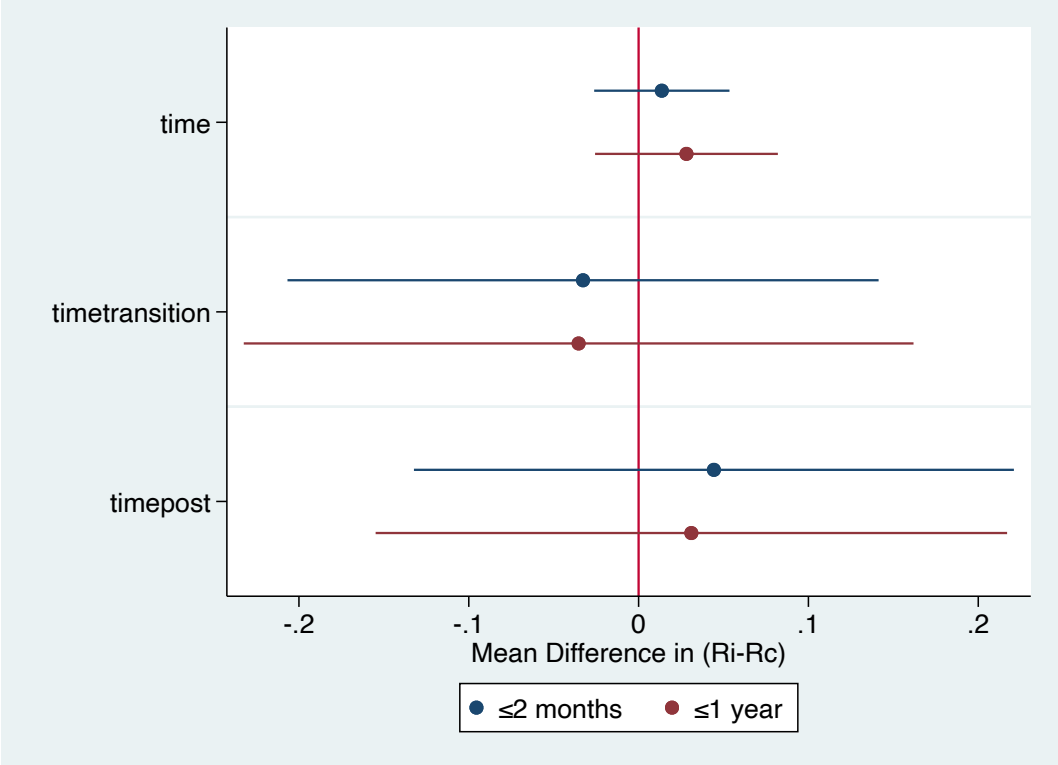
Results of the controlled interrupted time series analyses are presented in Table 4 and Figure 7. When using a controlled ITS using infant pertussis deaths that occurred to mothers without prenatal care, results from previous models in this paper changed little. The changes in trend in the mortality rate difference between the control and interventions groups were not convincingly different from zero in the post period ((≤2 months *timepost*: 0.04 95% CI: [[-0.13-0.22]; (≤1 year *timepost*: 0.03 95% CI: [-0.16,0.22]). The results of the test for parallel trend prior to the recommendation did not show persuasive evidence of differing trends (≤2 months: p=0.46, ≤1 year: p=0.32). Of note, there is evidence of a nonzero difference between the two groups at the beginning of the study period showing a lower mortality rate among those with prenatal care (RD_{2m}: -1.80, 95% CI [-3.94, 0.33]; RD_{2m}: -3.08, 95% CI [-6.18, 0.02]).

Table 4: Controlled ITS Risk Difference Estimates

	Model 1 (≤ 2 months)	Model 2 (≤ 1yr)
Mortality Rate Differences ($R_{intervention}$-$R_{control}$)		
Time	0.01 [-0.03,0.05] (0.50)	0.03 [-0.03,0.08] (0.31)
Time since transition	-0.03 [-0.21,0.14] (0.71)	-0.04 [-0.23,0.16] (0.73)
Time since post	0.04 [-0.13,0.22] (0.62)	0.03 [-0.16,0.22] (0.74)
Constant	-1.80 [-3.94,0.33] (0.10)	-3.08 [-6.18,0.02] (0.05)
Months	156	156
P-value on Parallel Trends Test*	0.46	0.32

95% confidence intervals in brackets; p-values in parentheses.
**= Coefficient on time in regression of mortality rate difference on time in pre-period*

Figure 7: Controlled ITS Mean Difference in Mortality Rate Difference Estimates



Ri= Mortality rate among those with prenatal care
Rc= Mortality rate among those without prenatal care

Adequacy of Prenatal Care Utilization (APNCU) Index Stratified Models

Results of the interrupted time series analyses stratified by APNCU level are presented in Table 5 and Figures 8-9. The morality rate ratio comparing the change in baseline trend from month to month in the post period showed a general increasing trend with increasing levels of adequacy of prenatal care. This remained the case in both ≤2-month-olds and ≤1-year-olds. However, none of these results reached statistical significance.

Table 5: Pertussis Mortality Rate Ratio Estimates by APNCU Index Level

	Inadequate Care (APNCU=1)		Intermediate Care (APNCU=2)		Adequate Care (APNCU=3)		Adequate+ Care (APNCU=4)	
	≤2mo	≤1yr	≤2mo	≤1yr	≤2mo	≤1yr	≤2mo	≤1yr
Time Trend (Monthly MRR)	0.99	0.99	1.00	1.00	1.01	1.01	1.01	1.01
	[0.97, 1.00]	[0.97, 1.00]	[0.99, 1.02]	[0.94, 1.13]	[0.98, 1.03]	[0.99, 1.03]	[0.99, 1.04]	[0.99, 1.03]
	0.14	0.07	0.89	1.00	0.59	0.42	0.30	0.35
Time since Transition Period Began* (Monthly MRR)	1.04	1.03	0.99	1.03	0.96	0.96	0.94	0.94
	[0.94, 1.15]	[0.94, 1.13]	[0.88, 1.11]	[0.93, 1.14]	[0.85, 1.08]	[0.85, 1.07]	[0.84, 1.04]	[0.85, 1.04]
	0.45	0.55	0.85	0.47	0.51	0.42	0.23	0.23
Time since Post Period Began* (Monthly MRR)	0.93	0.94	1.01	0.96	0.99	1.01	1.05	1.05
	[0.82, 1.06]	[0.84, 1.06]	[0.88, 1.17]	[0.86, 1.08]	[0.85, 1.15]	[0.88, 1.15]	[0.94, 1.18]	[0.94, 1.18]
	0.27	0.32	0.84	0.47	0.86	0.92	0.39	0.38
Months	156	156	156	156	156	156	156	156

Figure 8: Pertussis Mortality Rate Ratio Estimates by APNCU Index Level (≤2 months)

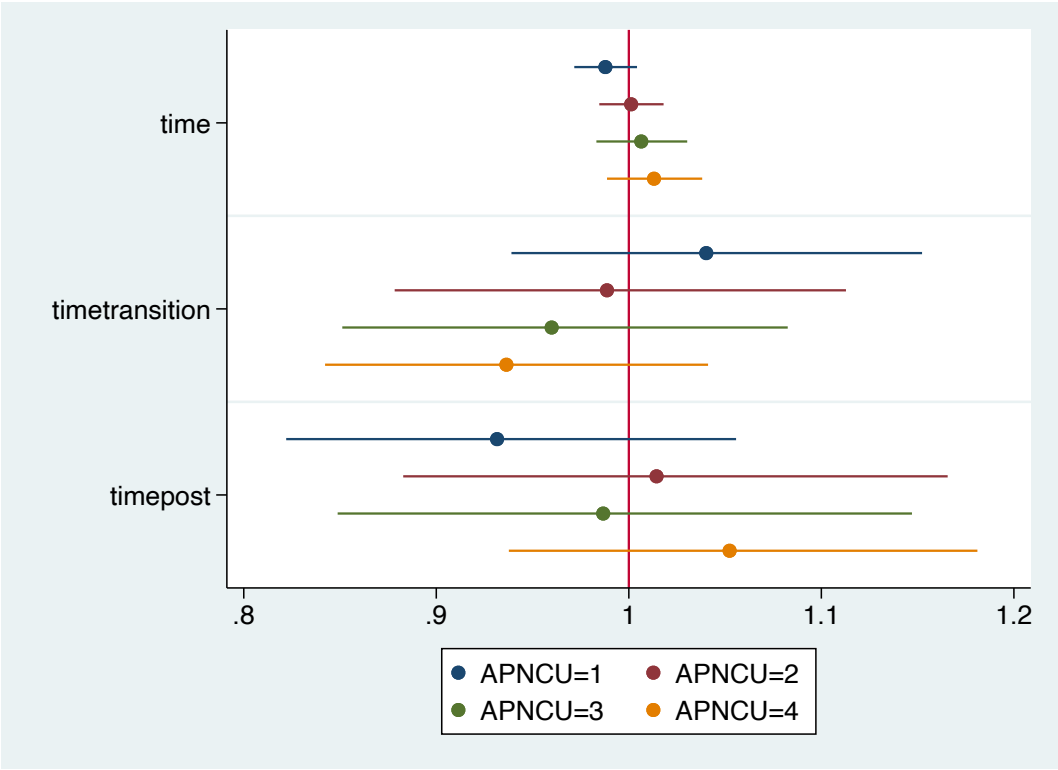
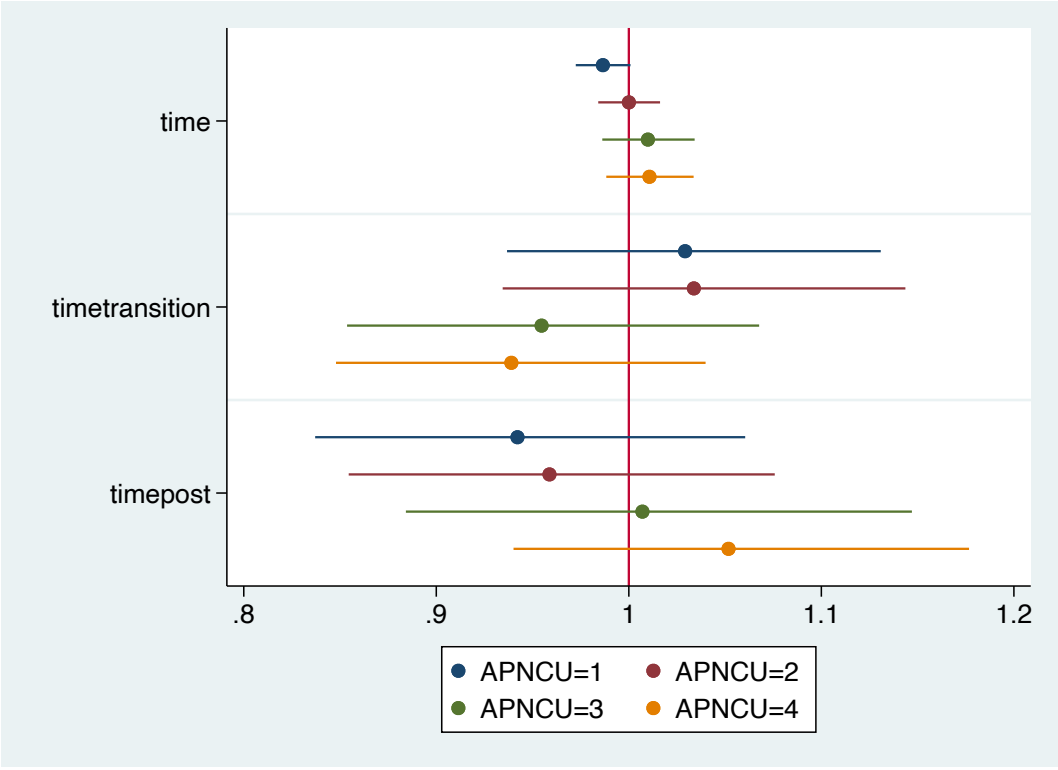


Figure 9: Pertussis Mortality Rate Ratio Estimates by APNCU Index Level (≤1 year)



Maternal Age Stratified Models (Primary Models)

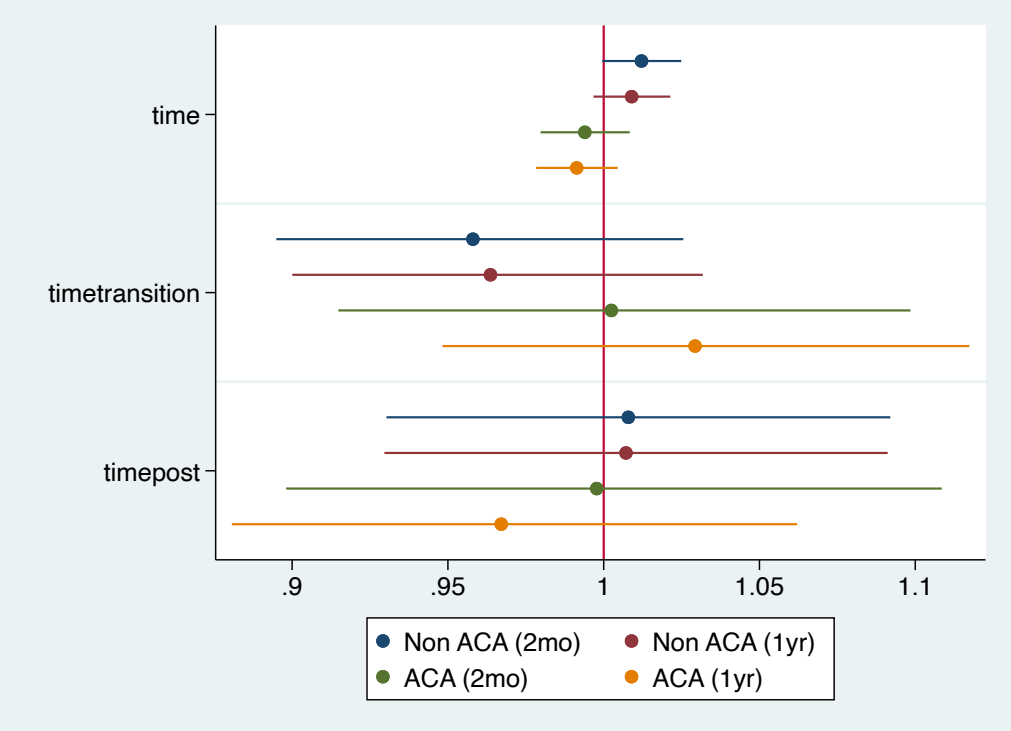
The results of this analysis are presented in Table 6 and Figure 10. When stratified by maternal ACA dependent coverage expansion eligibility at birth, no appreciable differences in trend were found in infant pertussis mortality after the guideline changes. There may be slight evidence that baseline time trends between maternal ACA eligible and ACA non-eligible differ. The baseline trend in pertussis mortality over time appears to be slightly increasing for the non-ACA group and decreasing over time for the ACA eligible group.

Table 6: Mortality Rate Ratio Estimates Stratified by Maternal ACA Dependent Coverage Expansion Eligibility at Birth

	Non-ACA (2mo)	Non-ACA (1yr)	ACA (2mo)	ACA (1yr)
Mortality Rate Ratios				
time	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)
timetransition	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)
timepost	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

Exponentiated coefficients
95% confidence intervals in brackets; p-values in parentheses.

Figure 10: Mortality Rate Ratio Estimates Stratified by Maternal ACA Dependent Coverage Expansion Eligibility at Birth



Sensitivity Analyses

Varying Timing

Results from this sensitivity analysis are presented in Table 7 and Figures 11-12. When using the months that the recommendations were passed instead of published in the primary model (Maternal Age Stratification), results were little changed.

Table 7: Sensitivity Analysis of MRR using Recommendation Passage Date

	Non-ACA (2mo)	Non-ACA (1yr)	ACA (2mo)	ACA (1yr)
Monthly MRR				
Time	1.01 [1.00,1.03] (0.07)	1.01 [1.00,1.02] (0.17)	0.99 [0.98,1.01] (0.46)	0.99 [0.98,1.01] (0.21)
Time since Transition	0.97	0.97	1.00	1.03

Period Began	[0.91,1.03] (0.35)	[0.91,1.04] (0.41)	[0.92,1.09] (1.00)	[0.95,1.11] (0.51)
Time since Post Period Began	0.99 [0.92,1.07] (0.85)	1.00 [0.93,1.07] (0.89)	1.00 [0.91,1.10] (0.99)	0.97 [0.89,1.06] (0.51)
Months	156	156	156	156

Exponentiated coefficients
95% confidence intervals in brackets; p-values in parentheses.
MRR= Mortality Rate Ratio
Non-ACA: pertussis infant deaths among mothers ages 12-18 and 26+ years old
ACA: pertussis infant deaths among mothers ages 19-25

Figure 11: Sensitivity Analysis of MRR using Recommendation Passage Date (≤2 months)

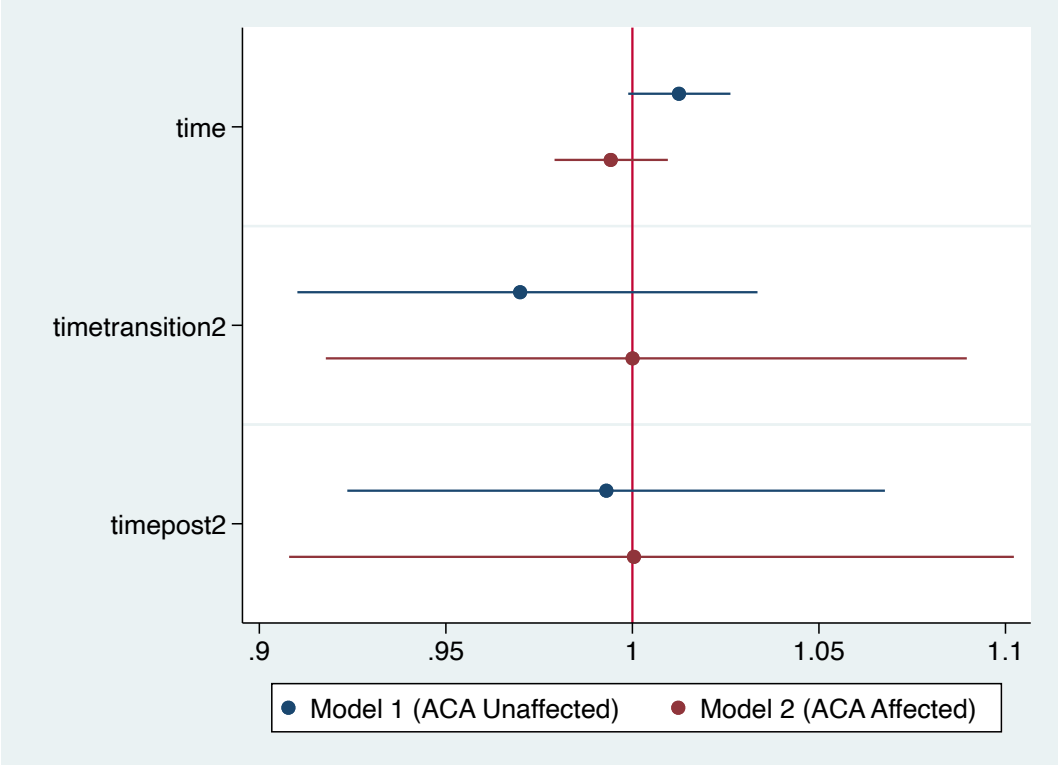
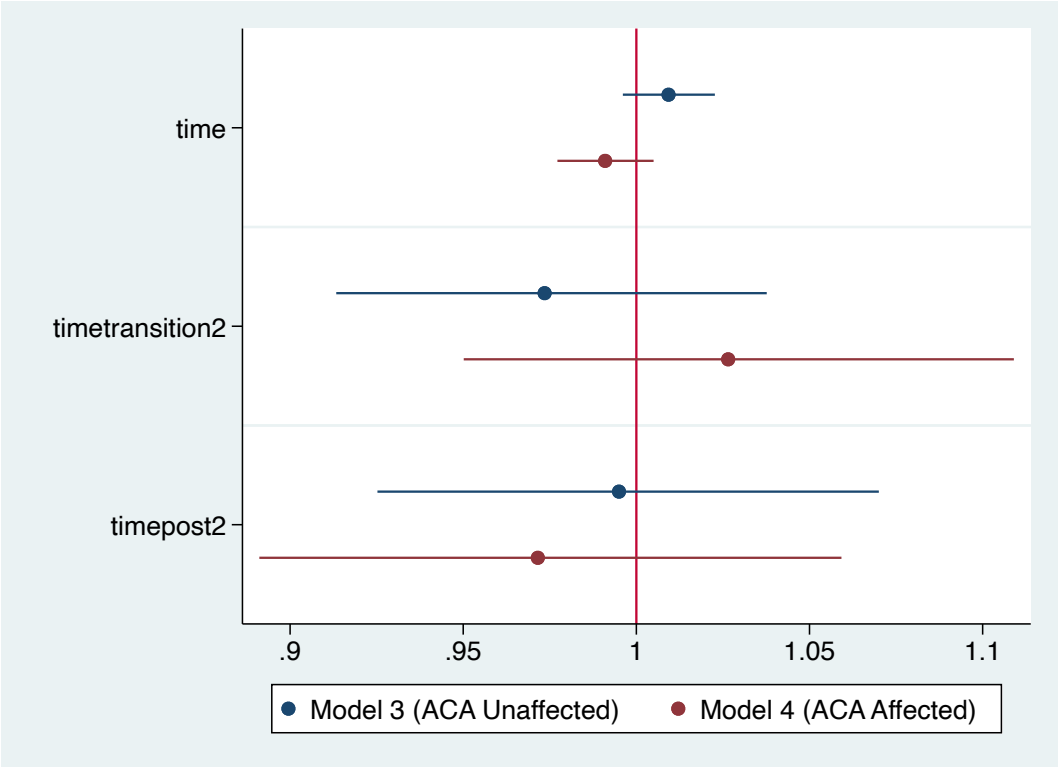


Figure 12: Sensitivity Analysis of MRR using Recommendation Passage Date (≤1 year)



No Transition

Results from this sensitivity analysis are presented in Table 8 and Figure 13. When excluding the use of a transition period in the primary model (Maternal Age Stratification), the non-ACA dependent coverage expansion group demonstrated a decrease in trend in the post period (timepost MRR_{2mo}: 0.96 [95% CI: 0.94 - 0.99]; timepost MRR_{1yr}: 0.97 [95% CI: 0.94 - 0.99]). The ACA dependent coverage expansion affected group did not show this same trend (*timepost* MRR_{2mo}: 1.00 [95% CI: 0.97 - 1.03]; *timepost* MRR_{1yr}: 1.00 [95% CI: 0.97 - 1.03]). Further illustrations of this trend can be found in Figures 14-16.

Upon further review of a scatterplot of time vs mortality rate of ≤2-month-olds of non-ACA dependent coverage expansion eligible mothers, a further analysis using natural cubic splines

was completed. There is a spike in mortality rates, which peaked around month 50 of the study period (March 2009). There appears to be a decreasing trend starting from month 50 prior to the beginning of the post period in month 98 (March 2013). When a natural cubic spline was added to the model providing flexibility for the pre-trend to better fit the data, the protective effect of the post-period disappears (Table 9, Figures 17-18).

Table 8: Sensitivity Analysis of MRR without Transition Period

	Non-ACA (2mo)	Non-ACA (1yr)	ACA (2mo)	ACA (1yr)
MRR				
Time	1.01 [1.00,1.02] (0.15)	1.00 [1.00,1.01] (0.33)	0.99 [0.98,1.01] (0.28)	0.99 [0.99,1.00] (0.26)
Time since Post Period Began	0.96 [0.94,0.99] (0.01)	0.97 [0.94,0.99] (0.02)	1.00 [0.97,1.03] (0.98)	1.00 [0.97,1.03] (0.91)
Observations	156	156	156	156

Exponentiated coefficients
95% confidence intervals in brackets; p-values in parentheses.
MRR= Mortality Rate Ratio
Non-ACA: pertussis infant deaths among mothers ages 12-18 and 26+ years old
ACA: pertussis infant deaths among mothers ages 19-25

Figure 13: Sensitivity Analysis of MRR without Transition Period

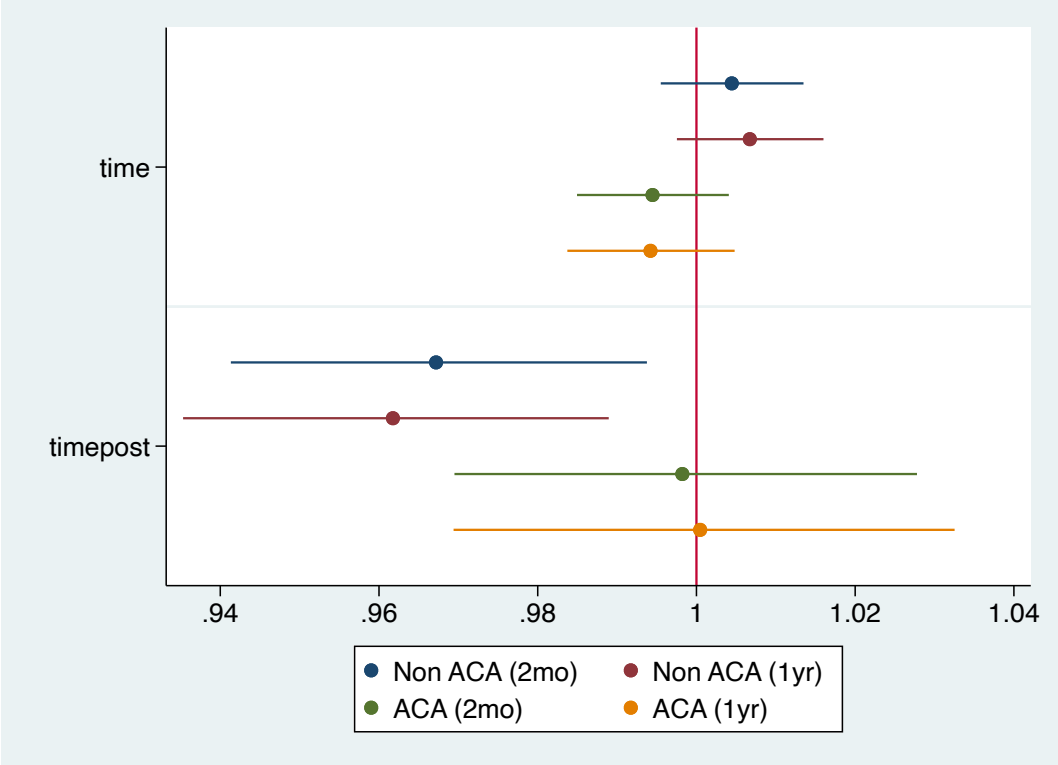


Figure 14: Sensitivity Analysis of Maternal Age Stratified MRR without Transition Period (≤2 months, 2005-2017)

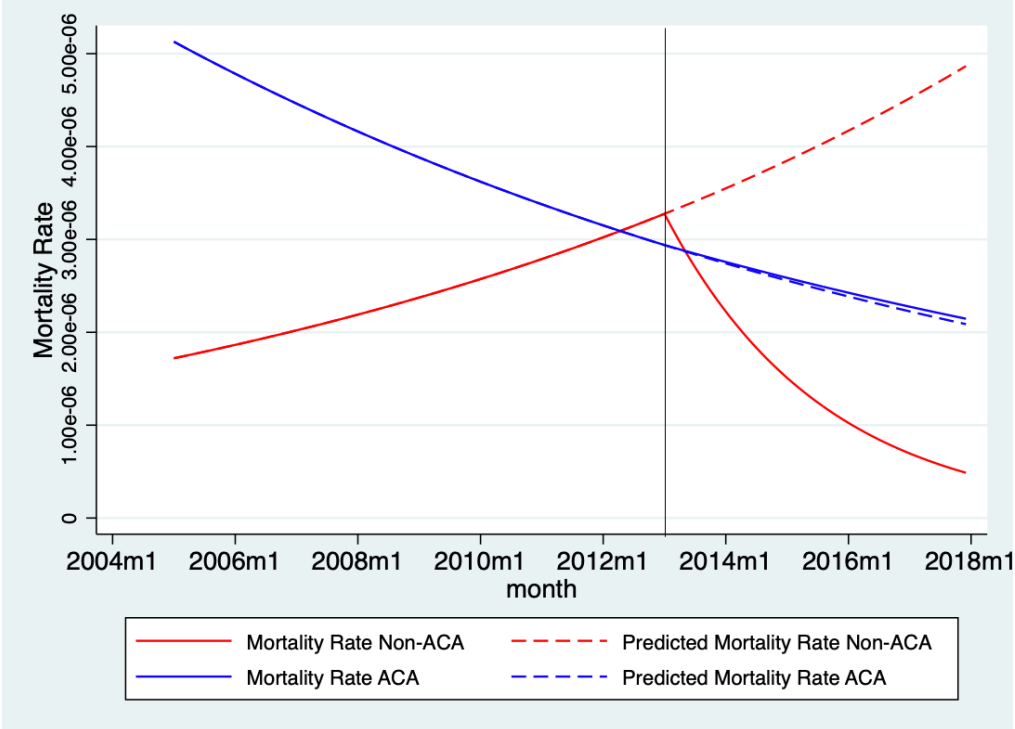


Figure 15: Pertussis Mortality Rates Among Infants Born to Mothers Ages 12-18 and 26+ Years Old (≤2 months, 2005-2017)

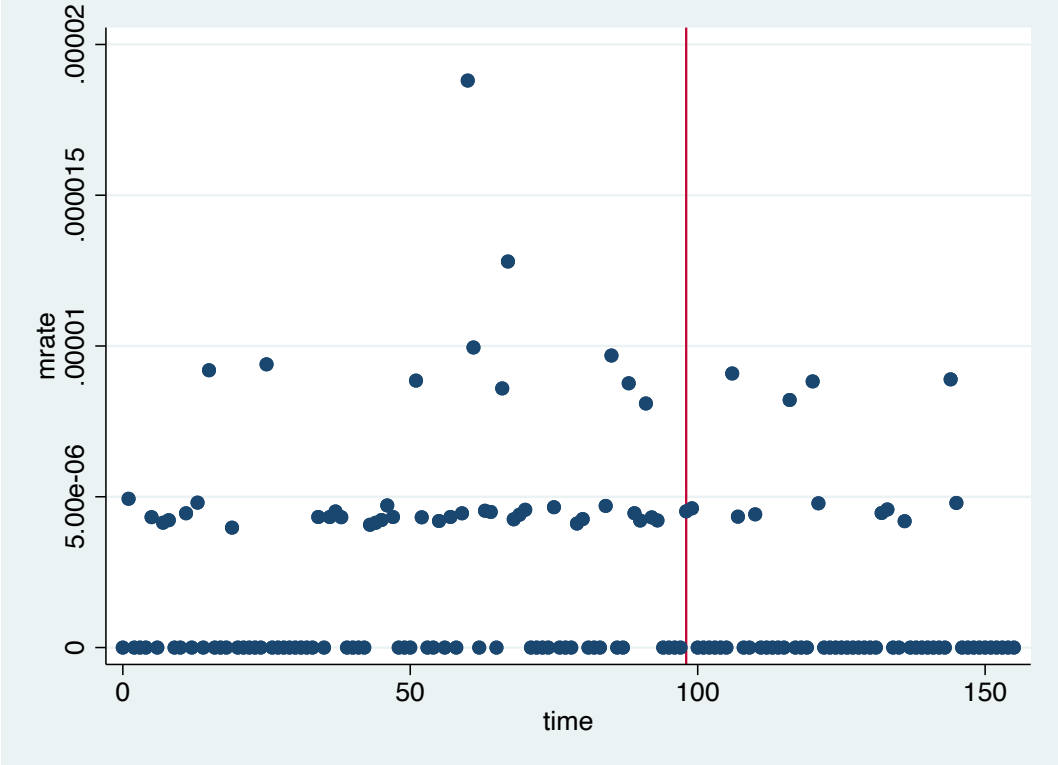


Figure 16: Pertussis Mortality Rates Among Infants Born to Mothers Ages 19-25 Years Old (≤2 months, 2005-2017)

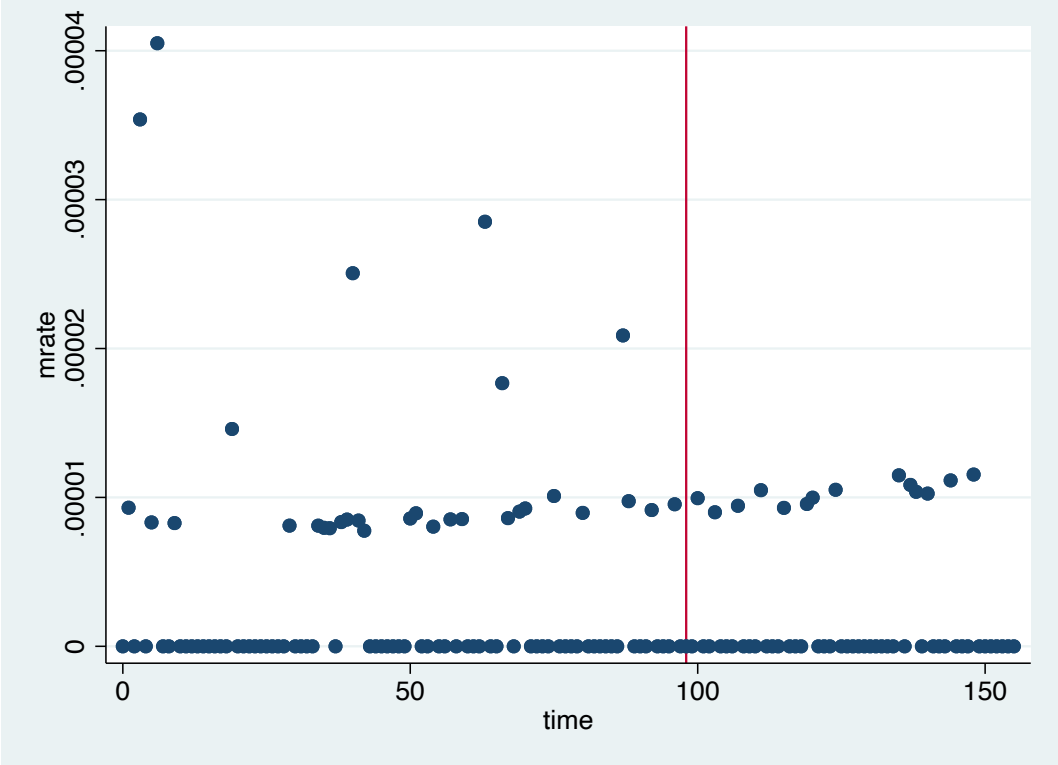
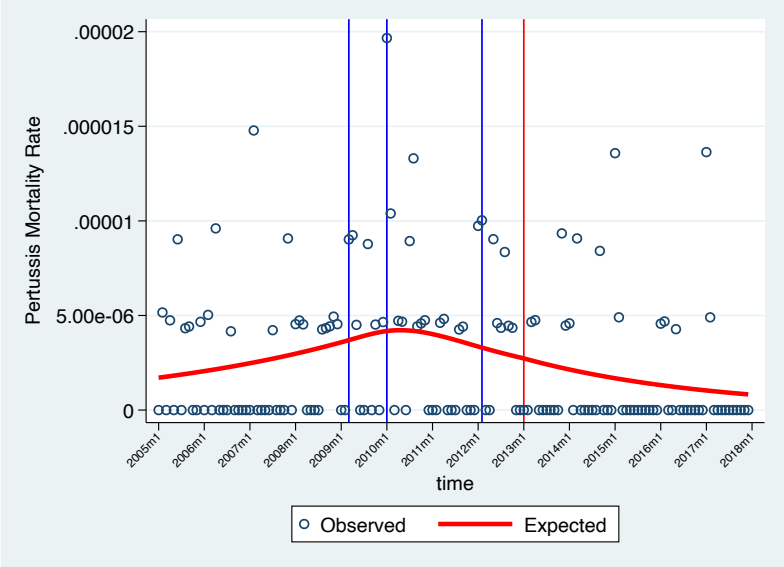


Table 9: Sensitivity Analysis of MRR without Transition Period with Splines

	Non-ACA (2mo)	ACA (2mo)
MRR		
time	1.016	0.990
	[0.998,1.033]	[0.973,1.007]
	(0.077)	(0.237)
timepost	0.997	0.982
	[0.950,1.046]	[0.930,1.038]
	(0.902)	(0.530)
Observations	156	156

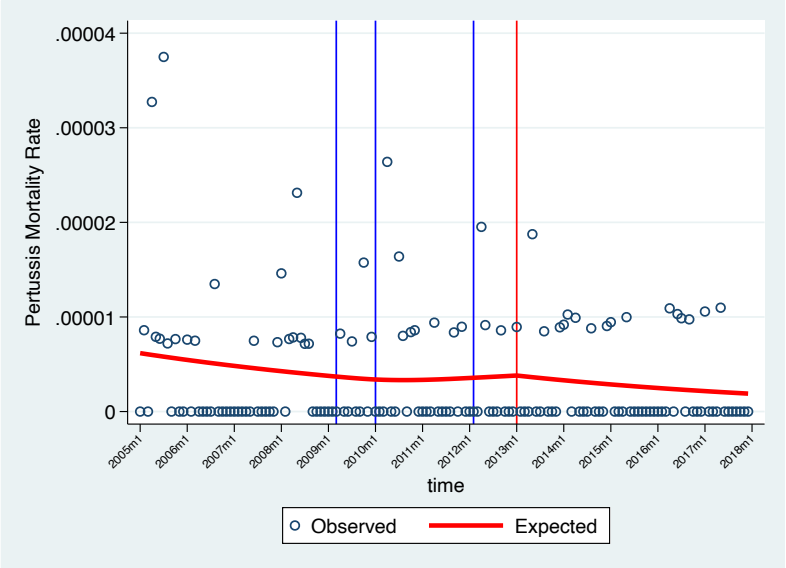
MRR= Mortality Rate Ratio
Exponentiated coefficients
95% confidence intervals in brackets; p-values in parentheses.

*Figure 17: Pertussis Mortality Rates Among Infants Born to Mothers Ages 12-18 and 26+ Years Old (≤2 months, 2005-2017) **



*Location of knots of natural cubic spline marked in blue. Post period marked in red.

*Figure 18: Pertussis Mortality Rates Among Infants Born to Mothers Ages 19-25 Years Old (≤2 months, 2005-2017) **



*Location of knots of natural cubic spline marked in blue. Post period marked in red.

Unadjusted Incidence Model

The results of the pertussis incidence ITS analyses are presented in Table 10 and Figure 19. When examining mean pertussis incidence rate differences in baseline trend per year, conclusions from the mortality analyses were little changed. There was no appreciable difference in the point estimates, however interpreting the overall trend there appears to be a slight increase in the transition period and a slight decrease in the post period in comparison to the pre period time trend.

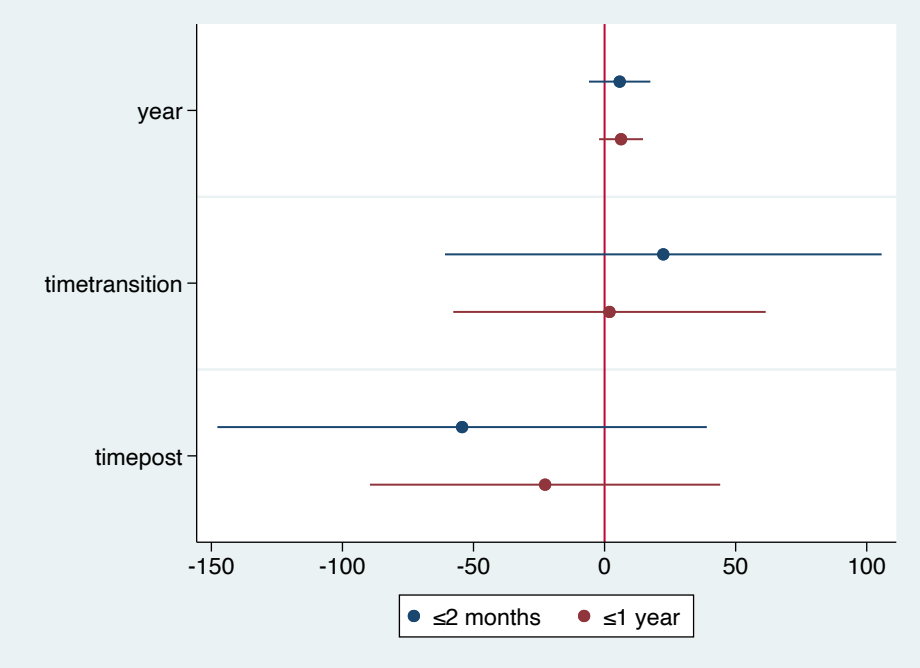
Table 10: Pertussis Mean Difference Estimates (per 100,000 live births)

	Model 1 (≤ 2 months)	Model 2 (≤ 1yr)
Time	5.76 [-5.94,17.46] (0.29)	6.29 [-2.08,14.66] (0.12)
Time since transition	22.40 [-60.88,105.69]	1.87 [-57.72,61.47]

	(0.56)	(0.95)
Time since post	-54.35 [-147.71,39.00] (0.22)	-22.69 [-89.49,44.11] (0.46)
Years	13	13

95% confidence intervals in brackets; p-values in parentheses.

Figure 19: Pertussis Mean Difference Estimates (per 100,000 live births)



Model Diagnostics

Overdispersion

Because Poisson models were used, potential overdispersion was assessed. Overdispersion occurs when the variance of the outcome counts is greater than the expected count. Underdispersion was possible, but unlikely. If overdispersion is not addressed, standard errors may be underestimated and confidence intervals around model estimates will be too narrow. We implemented quasi-Poisson regression; the method referenced by Lopez Bernal et. al (2017) and Bhaskaran et. al (2013) if overdispersion is present.[30,39] There were many months with zero

pertussis deaths in all forms of the analyses. A zero-inflated negative binomial regression was considered a candidate model as we could assume that months with zero pertussis deaths and those with >0 deaths are governed by different mechanisms—months where outbreaks are present vs. months where no outbreaks are present. However, the zero inflated models were little improved over the quasi-Poisson models because indicators for being a declared pertussis epidemic year were not sufficiently predictive of zero inflation.

Autocorrelation

Autocorrelation is important to assess in any time series analysis. The conventional regression model assumes that the error terms for each observation are unrelated to one another. This is unlikely when examining adjacent data points and/or seasonality. Pertussis incidence and mortality are not distinctly seasonal in the United States.[71] Nonetheless, autocorrelation was examined in the models. Autocorrelation was checked by visually inspecting plots of residuals and autocorrelation function plots.[28]

Discussion

Model Results

Mortality

In this study including 155 infant pertussis deaths between 2005 and 2017, no appreciable differences in infant pertussis mortality were found post the 2011/2012 ACIP maternal pertussis recommendation changes in comparison to the pre-period (Jan 2005-September 2011) in the primary analyses. This result was robust to limiting infant age at death to less than 2 months. The result was also robust to differing models to account for potential confounding by the effects of the introduction of the ACA. These results would suggest that though maternal pertussis vaccination is increasing in the US, there has not been a convincing accompanying change in

infant pertussis mortality. Another possibility could also be that we did not have the power to detect a convincing change in infant pertussis mortality. Though there was a positive finding in the two-term analysis using the maternal age stratified model, viewing the results of this study holistically our data do not strongly support an appreciable change in pertussis mortality trend post ACIP recommendations. Maternal pertussis vaccination has been shown to be effective for reducing infant pertussis morbidity when analyzing individual level data.[3,72] Heterogeneity of guideline implementation and/or failure to reach those mothers who would have infants at highest risk of pertussis mortality may be an explanation for the lack of change in mortality found in this study. According to an internet survey commissioned by the CDC, women ages 25 to 34, 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.[73] Low birth weight, Hispanic ethnicity, and low maternal education have all been associated with increased risk of infant pertussis mortality in the United States.[74] We were not able to look at these subgroups individually due to lack of data and adequate power.

In most adjusted models, with increasing prenatal care, a proxy for probability of receiving the Tdap vaccine during pregnancy, a slight decrease in trend in comparison to pre-period trend was noted during the transition period. This then reversed during the post-period. In the post-period, increasing prenatal care was associated with a slight increase in trend in comparison to pre-period trend. This, however, was not the case with the APNCU analyses. The APNCU adds an additional level of information as it adjusts the levels of care for when prenatal care was initiated and adjusts for the expected number of prenatal care visits given the gestational age of the

newborn at birth. The controlled ITS and PCV stratified analyses were simply stratifying by quantity of prenatal care visits. These measures would differ where there are a number of infant deaths that occurred to mothers with an adequate number of visits as defined by the World Health Organization, but whose prenatal care was initiated after the first trimester of pregnancy. The difference in these results would suggest that these cases were driving the potential difference between the transition and post periods. The APNCU is a stronger measure of adequate prenatal care utilization than the crude number of prenatal care visits attended as thus would provide more sound evidence in favor of this model's findings.

It is unexpected that the APNCU stratified analyses would show an increasing trend in pertussis mortality over time as adequacy of prenatal care utilization increased. It is not unexpected that the Adequate+ group would have high pertussis mortality rates. This may be an artifact of the relatively small number of cases in each group.

Though multiple imputation was used, results of the APNCU analyses should be interpreted with caution as the variable indicating the month in which prenatal care was initiated, the variable differentiating the APNCU from the CITS and PCV models, was 25% missing in the original data from the CDC.

Comparison to Previous Literature

Previous literature employing individual level data have found decreases in infant pertussis mortality among women receiving the Tdap vaccine.[3] This study is different from these previous studies as we are examining ecological time trends after a recommendation. Though there has

been an increase in maternal pertussis vaccination, this may not have targeted those infants at highest risk of pertussis mortality.

In a more similar analysis, an ITS study using data from Mexico examining mortality, hospitalizations, and incidence found reductions in incidence and hospitalizations, but not infant mortality when using a negative binomial regression model. Opposingly, Carrasquila et. al (2020) found a decrease in infant pertussis mortality after the introduction of a maternal pertussis vaccination program in Colombia in 2012/2013. However, maternal pertussis vaccination was implemented within a wider set of programs which included lowering the age of DTap eligibility from 2 months to 6 weeks old. This menu of programs in tandem with the implementation of maternal pertussis vaccination may have led to this decrease. It is also worth noting that the infant pertussis mortality rate was much higher in Colombia in the pre-program period at 5.8 deaths per 100,000 persons possibly providing more power to detect a difference. The pre-period pertussis mortality rate in the United States of 0.35 per 100,000 live births.

Incidence

There were no appreciable differences found in the pertussis incidence rates in <1-year olds and under 6-month-olds in the US. These results should be interpreted with great caution as they do not account for the passage of the ACA in 2010 and the subsequent rollout of programs associated with the policy.

Comparison of Study Findings to Boulet et. al (2019)

In an ITS analysis using Truven Health Analytics Marketscan Commercial data from 2009 through 2017, Boulet et. al[75] found a 48% decrease in the rate of pertussis hospitalization (RR:

0.52; 95% CI, 0.31-0.89) after the 2012 ACIP recommendation. They did not, however, find a change in trend and did not use a transition period between the two recommendations. Other than differences in model specification, there are multiple explanations for the possible differences between the Boulet et. al results and the results from this study. The first is that pertussis incidence and mortality were examined in the present study. The trend for hospitalizations may differ with respect the recommendation effects. This study also included all pertussis deaths that occurred in the US between 2005 and 2017. Boulet et. al used a dataset consisting of privately insured individuals. It is possible, and further maybe likely, that the US population that is privately insured has better access to prenatal care, and thus the vaccine, than those who are not.[76] A previous study has found that privately insured women are more likely to receive the Tdap vaccine during pregnancy than publicly insured women.[65]

Strengths

This study has numerous strengths. The study population is representative of the United States population unlike studies limited to commercial databases or other smaller databases. All pertussis deaths captured by the National Vital Statistics center are included in the analyses. We were also able to include monthly data from multiple years pre and post the recommendation due to the detail of the publicly mortality available data from the National Center of Health Statistics.

This study was also able to account for many different facets of the Affordable Care Act, 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 for four separate models to be utilized in exploring potential confounding due to the ACA. The maternal age-stratified analysis was able to

examine the effects of the dependent coverage expansion policy under the ACA. The prenatal care stratified and controlled analyses were able to examine both the dependent care coverage and Medicaid expansion policies as both would be expected to affect pertussis mortality through their effects on prenatal care.

Limitations

Residual Confounding due to Medicaid Expansion

Starting in 2005, geographic mortality data was withheld from the CDC public use due to a privacy policy change within the National Center for Health Statistics, thereby precluding a comparison of states that expanded Medicaid and those without to account for potential time-varying confounding from the ACA. The prenatal care-controlled and stratified analyses should be able to ascertain this to some level. However, given more time, we would undertake the CDC micro-data application process and obtain this data for future analyses.

2010 California Recommendation

In response to a pertussis epidemic, the California state department of public health in July 2010 issued a recommendation that pregnant women receive the Tdap vaccine. This may have muddied the effects of the subsequent 2011/2012 recommendations by ACIP. California as a populous state accounted for nearly 14% of pertussis cases in the US in 2017.[77] Given more time we would undertake the CDC micro-data application process and obtain this state-level data. This would allow for sensitivity analyses including and excluding California.

Power

There is little information on power analysis in interrupted time series studies. As explained previously, power in ITS study designs depend on a range of factors and there is no accepted

number of time points.[28] Though, it is generally accepted that the more relevant time points included the better. This study was hindered by the relatively low number of pertussis mortality events in the US. This compounded with the need to stratify and adjust for various variables to disentangle the effects of the ACA from the ACIP recommendation further challenged the power this model needed. It is possible that there was a change in pertussis mortality trend post recommendation, but this model was underpowered to find it. Potential evidence for this is the positive finding in the two-term maternal age stratified analysis in the adequate care group. When fewer terms were used in the model, confidence intervals were narrower, and a convincing difference was found.

Conclusion

This study examined the effects of the 2011/2012 ACIP Maternal Pertussis Recommendations on infant pertussis morbidity and mortality in the United States between 2005 and 2017. Unadjusted and adjusted analyses were used to account for possible confounding effects due to the Affordable Care Act passage in 2010. No appreciable differences were found in both infant pertussis morbidity and mortality in the post-recommendation as compared to the pre-recommendation period. Future analyses should include geographic data from the CDC in order to more directly account for the ACA Medicaid Expansion. Future analyses should also investigate heterogeneity in recommendation implementation and whether those infants at highest risk of pertussis mortality are being reached by this preventative strategy.

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