CAPSTONE PROJECT

A Systematic Review of the Impact of Maternal Tdap Vaccination on Infant Pertussis

by

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ABSTRACT

Introduction

Vaccines have been critical in reducing pertussis incidence worldwide. Despite high vaccine coverage rates, pertussis continues to be a global cause of morbidity and mortality in susceptible infants <3 months of age. Consequently, numerous countries have instituted comprehensive maternal pertussis immunization programs. However, published evidence supporting maternal vaccination effectiveness in infants has been limited to date.

Purpose

The purpose of this study was to conduct a systematic review of published literature from 2011 through 2019 to understand the real-world impact of maternal pertussis vaccination on reducing infant pertussis incidence, mortality, and morbidity. Relevant studies were identified from various databases using combinations of relevant keywords and were rated for inclusion by two independent researchers according to eight inclusion/exclusion criteria.

Results

The review included 19 studies for final synthesis. Results from 12 studies demonstrated 77–92% unadjusted and 69-91% adjusted vaccine effectiveness against pertussis incidence in infants <3 months of age compared to infants of unvaccinated mothers. Among the remaining studies, one asserted that infants of mothers vaccinated with Tdap had an overall 43% lower rate of pertussis diagnosis. Another study reported reduced pertussis-related infant mortality by 87% comparing pre and post maternal vaccination periods. Three additional studies demonstrated 72–94% unadjusted reduction in pertussis-related infant hospitalizations. However, maternal pertussis vaccine coverage rates were directly proportional to vaccine effectiveness and improved outcomes in susceptible infants. Kappa calculations demonstrated inter-rater

correlations of 1.0 for all included studies. Double coding protocol using Kappa analysis of two raters' study inclusion demonstrated the validity of the review process.

Conclusions

Findings from this systematic review supplement reviews including data on the presence of passive pertussis antibodies in infants of Tdap vaccinated mothers and endorse current maternal pertussis vaccination policy to protect infants <3 months of age. They also underscore the need to promote pertussis vaccination awareness to pregnant women.

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LIST OF ABBREVIATIONS

ACIP .....Advisory Committee on Immunization Practices

aP.....Acellular Pertussis

ATAGI .....Australian Technical Advisory Group on Immunisation

B. pertussis .....Bordetella pertussis

CDC .....Centers for Disease Control and Prevention

CDPH.....California Department of Public Health

DTaP .....Diphtheria, Tetanus toxoids & acellular Pertussis

DTP .....Diphtheria, Tetanus & Pertussis

ECDC.....European Centre for Disease Prevention and Control

HERO.....Health Education Research Online

JCVI .....Joint Commission on Vaccination and Immunisation

IRB.....Institutional Review Board

MeSH .....Medical Subject Heading

MDH .....Minnesota Department of Health

PHE.....Public Health England

PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Tdap .....Tetanus toxoid, reduced diphtheria toxoid & acellular pertussis vaccine

TDSHS.....Texas Department of State Health Services

US .....United States

UK.....United Kingdom

VPDT .....Vaccine-Preventable Disease Table

WHO.....World Health Organization

wP .....Whole Cell Pertussis

INTRODUCTION

Pertussis is a healthcare problem of global magnitude and affects people of all backgrounds and ages. Vaccines have been available for over 70 years and have effectively reduced the overall burden of pertussis disease (de Cellès, Magpantay, King, & Rohani, 2016). According to the World Health Organization (WHO, 2015), there were 16 million cases worldwide and approximately 195,000 children died globally from pertussis in 2008, despite 82% of infants receiving at least three doses of diphtheria, tetanus, and pertussis (DTP3) vaccines. Recent numbers from the WHO state that in 2016, there were 139,535 cases of pertussis reported despite high overall coverage rates of 80–90% (Figure 1). This number increased in 2018 to 151,074 cases and 89,000 deaths (WHO, 2019).

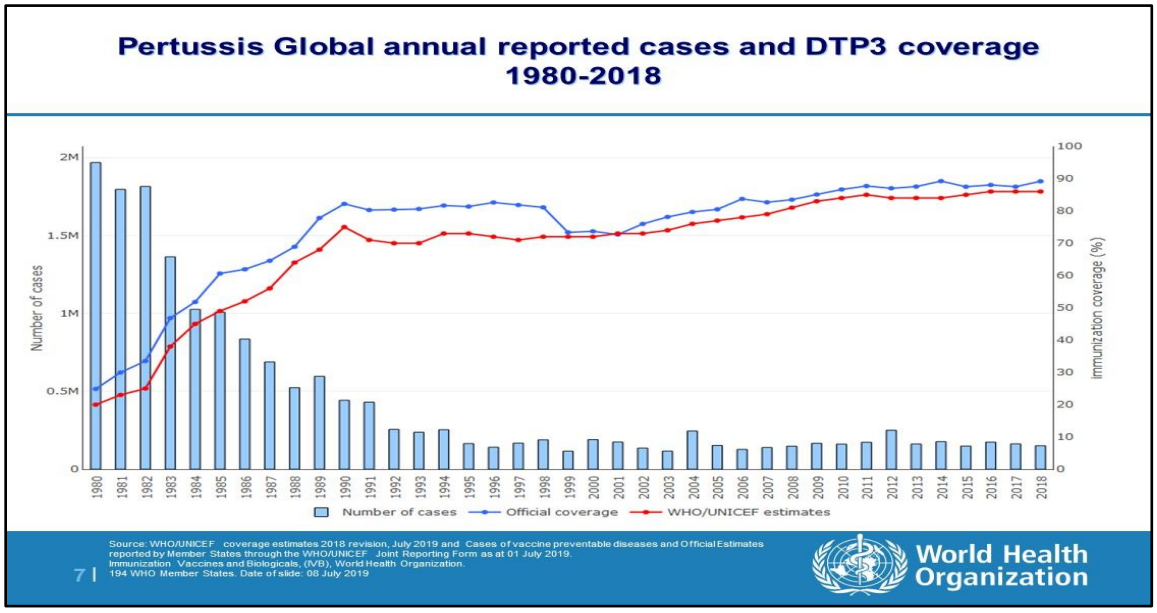

Figure 1. Graph of Annual Reported Cases of Pertussis and DTP3 Vaccine Coverage Rates From 1980 Through 2018. Reprinted from the WHO, 2019. Retrieved from *https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/*.

The data in Figure 1 support a sustained number of pertussis cases despite increasing vaccine coverage. In addition, it is believed that pertussis is grossly underreported, particularly in

developing countries, but also in developed countries (Schielke, Takla, von Kries, Wichmann, & Hellenbrand, 2018; Syed & Bano, 2015). According to a recent modeling study by Yeung, Duclos, Nelson, and Hutubessy (2017), an estimated 24.1 million cases occur worldwide with over 160,000 deaths annually, thereby demonstrating that reported figures and model-based numbers are vastly different.

The first goal of global immunization programs has been to reduce the risk of severe pertussis in infants (WHO, 2018). Infants are particularly at risk of more severe, life threatening disease from pertussis infection. According to Massieria, Martin, Krishnarajah, Becker, Buikema, and Tan (2017), in the United States, from 2005–2010, the overall pertussis incidence rate among infants <1 year of age was 117.7 per 100,000 person-years. The most vulnerable group of infants 3 months of age and under had the highest incidence rate for pertussis of 247.7 per 100,000 person-years, underscoring the need to protect this immune-naïve age group. In 2012, pertussis death in infants <1 year of age accounted for 16/20 or 80% of total pertussis deaths and 15 of those deaths were in infants under the age of 3 months (CDC, 2013a). Since then, maternal vaccination strategy was put in place to help protect immune-naïve infants. The most recent provisional data from the CDC show that pertussis deaths in infants under 1 year of age accounted for 4/10 or 40% of all pertussis deaths in 2018 (CDC, 2019). Further stratification for deaths in infants under 3 months of age was not done in 2018. Data from Europe, the United States, and United Kingdom, along with several other countries, underscore the fact that the burden of pertussis is greatest among infants under 12 months of age. Immune-naïve infants under 3 months of age are affected most severely by pertussis infection because they are too young to be actively vaccinated and have no naturally occurring circulating antibodies other than

those acquired passively through mother's breast milk or *in utero* (Wiley, Regan, & McIntyre, 2017).

In 2012, the number of cases reported in the United States reached a record high of 48,277. Case incidence per 100,000 population among the various age groups in 2012 were 126.65 in children under 12 months, 34.09 in children from 1–6 years, 58.52 in children from 7–10 years, 38.02 in adolescents 11–19 years, and 4.51 in adults 20 years and above (CDC, 2013a).

Pertussis Mortality

From 2008–2011, in the United States, 60 deaths (83%) out of the 72 pertussis-related deaths reported to the CDC were in infants under 3 months of age (CDC, 2015). Deaths during 2012 were highest among all infants compared to all other age groups, with 16 deaths in infants less than 1 year of age and 15 of those deaths in infants under 3 months who were too young to be immunized. Given that mortality was highest in the very young infants, the CDC further stratified pertussis age distribution in 2013 onward to include infants under 6 months and 6 through 11 months. Results of this stratification demonstrated that the highest incidence of pertussis occurred in infants under 6 months (Table 1) (CDC, 2017f). Deaths in infants, especially those under 3 months, continued to be the highest from 2012–2017, although there has been an overall decrease in the past three years (Table 2) (CDC, 2017f). This is likely due to greater maternal awareness of infant pertussis risks and higher maternal pertussis vaccine uptake.

Table 1. Pertussis Incidence Rates in the US Across Different Age Groups: 2012-2018

	2012 Per 100000 population	2013 Per 100000 population	2014 Per 100000 population	2015 Per 100000 population	2016 Per 100000 population	2017 Per 100000 population	2018 Per 100000 population
<6 months		**160.3**	**169.0**	**99.0**	**70.9**	**78.4**	**72.8**
6-11 months		45.3	44.4	37.2	31.9	37.1	32.7
***< 1year**	**126.65**	**102.77**	**106.68**	**68.10**	**51.41**	**57.75**	**52.73**
1-6 years	34.1	22.1	25.1	15.6	13.7	15.2	13.5
7-10 years	58.5	30.6	34.0	17.5	14.8	15.8	11.6
11-19 years	38.0	21.3	29,6	17.9	16.3	16.8	13.0
20+ years	4.5	2.6	2.2	1.9	1.7	1.7	1.4

* Calculated incidence of per 100,000 population for the ALL infants under 1 year of age cohort based on CDC provided cases and incidence.

Note: Pertussis incidence data from CDC, Pertussis surveillance and reporting. Centers for Disease Control and Prevention, Atlanta, GA. (2012-2018) Retrieved from https://www.cdc.gov/pertussis/surv-reporting.html.

Table 2. Age Distribution of Reported Pertussis Deaths in the US: 2012-2018

Year	Age	Deaths
2012	ALL	**2012 Total deaths: 20**
	Infants < 3 months	**15**
	Infants 3-11 months	1
	Children 1-4 years	2
	Adults >55years	2
2013	ALL	**2013 Total deaths: 13**
	Infants < 3 months	**12**
	Infants 3-11 months	0
	Children 1-4 years	1
	Adults >55years	0
2014	ALL	**2014 Total deaths: 13**
	Infants < 3 months	**8**
	Infants 3-11 months	1
	Children 1-4 years	2
	Adults >55years	2
2015	ALL	**2015 Total deaths: 6**
	<1year	**3**
	≥1 year	3
2016	ALL	**2016 Total deaths:7**
	<1year	**6**
	≥1 year	1
2017	ALL	**2017 Total deaths: 13**
	<1year	**9**
	≥1 year	4
2018	ALL	**2018 Total deaths: 10**
	<1year	**2**
	≥1 year	5

Note: Pertussis mortality data from CDC, Pertussis surveillance and reporting. Centers for Disease Control and Prevention, Atlanta, GA. (2012-2018) Retrieved from https://www.cdc.gov/pertussis/surv-reporting.html.

Similar to the United States, England and European nations also have data that demonstrate age adjusted mortality. Although the WHO has global vaccination coverage data (Figures 1 & 7), age-specific incidence and mortality surveillance data from Asia, the Middle East, and Africa are substantially lacking. Reported age-associated pertussis mortality rates in

England from 1998-2015 also show that infant deaths were consistently highest among those under 3 months of age (Figure 2).

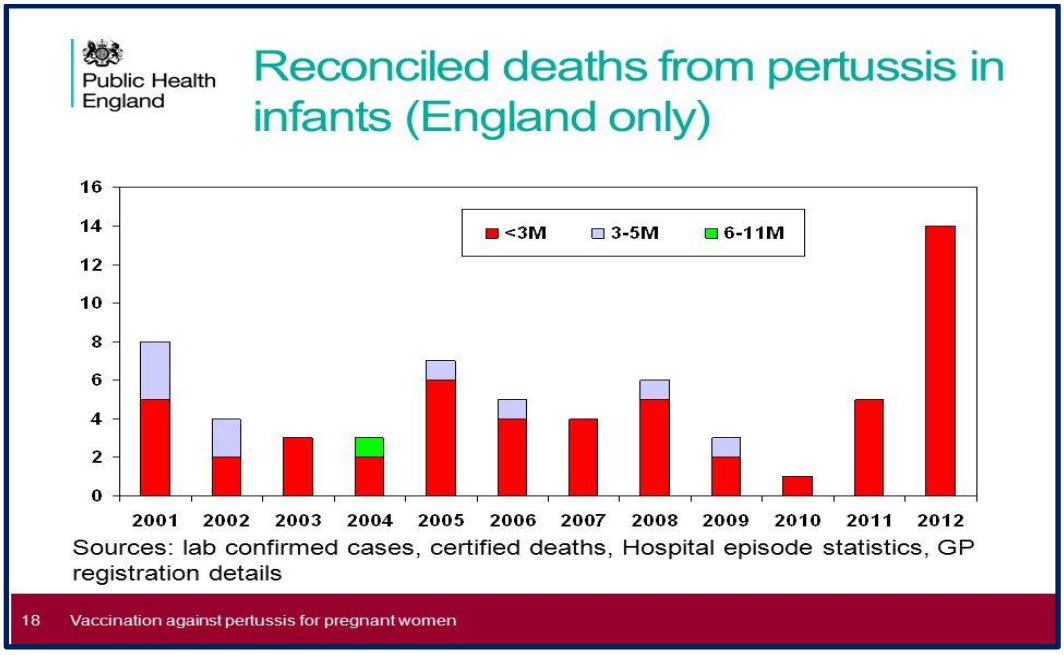

Figure 2. Graph of Reconciled Deaths from Pertussis in Infants from Laboratory Confirmed Cases of Pertussis – 2001-2012-England Reprinted from PHE, 2018. Retrieved from *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/703519/hpr1518_prtsss_ANN.pdf.*

The pertussis incidence, along with mortality rates among infants, highlight the need to control pertussis in immune-naïve infants globally. In the United States, maternal vaccination with each pregnancy started in 2012 after the Advisory Committee on Immunization Practices (ACIP) made that recommendation in 2011. Although full adoption of the recommendation takes time, this policy change of vaccinating pregnant women may have contributed to the lower mortality seen among unvaccinated or incompletely vaccinated infants. Indeed, actual and modeled prevalence data of pertussis between 1986 and 2011 indicate that introduction of acellular pertussis (aP) vaccines in 1996 effectively reduced the number of pertussis cases among

infants too young to be vaccinated by approximately 90%, thus providing evidence of herd immunity to pertussis by active pertussis vaccination programs (de Cellès et al., 2014).

Statement of the Problem

Unlike other vaccine preventable diseases, pertussis continues to persist and disproportionately affect very young infants. Despite robust, comprehensive vaccination programs, pertussis has not been eradicated and remains a global crisis among immune-naïve infants. Although all ages are affected, very young infants are most susceptible and are the highest risk for severe disease complications and potential death. Therefore, several countries have implemented strategies to reduce pertussis incidence and mortality rates among infants. In the United States, all infants were recommended to receive diphtheria, tetanus toxoids, and acellular pertussis (DTaP) at 2, 4, and 6 months of age, with booster doses administered at ages 15–18 months and again between 4–6 years of age. At least three doses are considered necessary for protection.

Although routine immunization for infants can potentially begin as early as 6 weeks of age, it requires several doses to elicit a full immune response. This leaves young infants unprotected as their adaptive immune systems are not capable of producing enough protective immunity against *Bordetella pertussis* (Winter et al., 2015). Immature immune systems in infants also contribute to disease severity and both earlier gestational age at birth and lower birth weight are predictors of death in pertussis cases (Winter et al., 2015). Therefore, young infants 3 months and younger are the most vulnerable to pertussis infection and potential mortality since they do not have any immunological protection during the first few months of life. Severity of disease also reduces with increasing age and even immunocompromised adults rarely report severe

pertussis disease, thereby contributing to the lower numbers in the elderly and overall underreported numbers.

Various strategies have been implemented to reduce the incidence of infant pertussis, especially in those under 6 months of age. In attempting to change pertussis outcomes in infants, a strategy of immunizing people in close proximity to infants (cocooning strategy) such as new mothers, siblings, grandparents, and caretakers, was recommended, but it had limited success. Countries like the United States and United Kingdom were among the first to implement the practice of immunizing pregnant women during each pregnancy as means of protecting newborns through passive transfer of maternal antibodies. Maternal immunization became standard practice in 2011 in the United States with the United Kingdom following the same policy implementation in 2012. Maternal pertussis immunization is now recommended with each pregnancy in several countries including New Zealand, Australia, Argentina, Belgium, Brazil, and Israel (ATAGI, 2019; Furuta, Sin, Ng, & Wang, 2017). However, there is a paucity of data on whether maternal immunization is correlated with reduced incidence of pertussis cases among very young infants and pertussis mortality rates in those respective infants during their first few months of life.

There is a need to understand whether vaccinating pregnant women during each pregnancy provides the best protection for very young infants and if it has reduced the burden of infant pertussis. It is necessary to review the data and determine if this strategy is effective. In addition, it is also important to understand whether policy changes have been successful at reducing the incidence of infant pertussis, morbidity, and mortality.

Purpose of Research, Research Questions

The purpose of this study was to conduct a systematic review on the impact of pertussis vaccination in pregnant women on infant pertussis incidence, mortality, and morbidity rates by evaluating published literature from 2011 through 2019. Although previous systematic reviews have been published, those reviews were either restrictive in the types of studies included, synthesized evidence on both vaccine safety and efficacy in the respective recipients (infants or pregnant women), focused on a limited number of years since the recommendation was made to vaccinate pregnant women against pertussis with every pregnancy, or was a compilation of various aspects of maternal pertussis vaccination in infants. Consequently, there was a need to undertake a more thorough systematic review with broader inclusion criteria on the types of studies. This review intended to capture more studies to provide recent data on the impact of maternal vaccination on infant outcomes by means of examining pertussis-related incidence, morbidity, and mortality as these relate to vaccine effectiveness in the past 9 years since most of recent data included in previously published systematic reviews do not include published literature from 2017-2019. The main objective of this systematic review was to synthesize the published literature to understand whether vaccinating women during each pregnancy against pertussis translates into reduced pertussis incidence, morbidity, and mortality in infants. An additional goal was to provide practitioners a comprehensive review of the data representing the effectiveness of maternal pertussis vaccination with every pregnancy to ensure greater awareness of the results of these newest policy recommendations.

This systematic review includes literature published from the last 9 years, January 2011 through December 2019, and it includes all varieties and combination of vaccines that include

the pertussis component given to pregnant women. The review addresses the following two questions (Q) with the accompanying hopeful outcomes (O):

Q1. What is the pertussis incidence range and associated morbidity among infants born to mothers vaccinated and to those mothers not vaccinated against pertussis during pregnancy?

O1. Hopeful outcome for this question as a result of the review will support that vaccinating pregnant women resulted in lower pertussis incidence in infants <1 year of age and particularly in infants under 3 months of age compared to infants born to unvaccinated mothers.

Q2. What is the pertussis-related mortality rate range among infants born to mothers vaccinated and to those mothers not vaccinated against pertussis during pregnancy?

O2. Hopeful outcome for this question as a result of the review will support the overall positive impact of gestational pertussis vaccination on number of pertussis-related deaths in infants <1 year of age and particularly in infants under 3 months of age compared to infants born to unvaccinated mothers.

LITERATURE REVIEW

Pertussis vaccines have been widely available since the 1950s (WHO, 2015). Despite the availability of vaccines and high coverage rates, epidemic cycles of pertussis continue to occur every 2–5 years. Pertussis is still a significant public problem. Most pertussis cases and deaths were in children, especially infants. The main aim of pertussis vaccination is to reduce the risk of severe disease in infancy by vaccinating at least 90% of infants with three doses (primary series) of the pertussis vaccine (WHO, 2019).

There have been two kinds of pertussis vaccines: whole-cell and acellular. The latter vaccine came to the market to resolve issues posed by the reactogenicity of the whole-cell vaccines, but acellular vaccines are significantly more expensive. Most developed countries have fully switched to the less reactogenic acellular vaccines. However, immunity neither from natural infection nor vaccination is long lasting and there has been a resurgence of pertussis. Several factors such as the evolution of bacteria virulence, waning immunity of vaccines, or insufficient vaccination boosters may have contributed to a pertussis resurgence (Kapil & Merkel, 2019; Melvin, Scheller, Miller, & Cotter, 2014; Warfel, Zimmerman, & Merkel, 2014). In addition, immunity from acellular vaccines does not seem to last as long as that induced by whole-cell vaccines. Both versions of pertussis vaccines act differently on the immune system (Th2 dominated response versus Th1 and Th17) (Kapil & Merkel, 2019). This means that with vaccines, booster doses are required with acellular vaccines.

In order to combat the resurgence of pertussis especially in the very young infants, several strategies such as additional boosters and immunizing close contacts of infants were put in place. The most recently implemented strategy is vaccinating pregnant women during their second or third trimester with pertussis-containing vaccines to elicit passive transplacental

immunity in newborn infants who are too young to be vaccinated. This review is a broad overview of pertussis globally and the strategies put in place to address the gaps in the persistence of pertussis. The United States and United Kingdom have been leaders in implementing strategies to help lower incidence, morbidity, and mortality of pertussis among the most vulnerable infant population by being the first to recommend and implement a maternal pertussis vaccination with each pregnancy. Similarly, other countries followed these strategies subsequently.

Previous Systematic Reviews

A total of five systematic reviews have been conducted over recent years regarding immunizing pregnant women with the pertussis vaccine and its impact in infants. These reviews primarily focused on efficacy and safety by means of serological findings and geometric mean titers in the infants after immunizing the respective mothers. There were not any studies that only looked at infant outcomes and vaccine effectiveness in the real-world setting post vaccination.

The first systematic review was published in 2017 by McMillan et al. and it focused only on the safety of maternal vaccination on the infant. It included published studies until May 2016. A total of 21 studies were included for synthesis. The review concluded that there were not any untoward effects on the infants of mothers vaccinated against pertussis while pregnant.

The second of five previous systematic reviews on maternal immunization against pertussis was done by Gkentzi et al. in 2017. The goal of that review was to broadly summarize the findings on antenatal vaccination globally with respect to national recommendations, coverage, immunogenicity, safety, and effectiveness of currently available vaccines. It included 47 published studies from four databases from January 2011 to May 2016. This review collectively summarized the respective findings from publications on maternal pertussis

immunization. There were only two studies included on effectiveness of maternal vaccination on infants. The study concluded that there was a large body of evidence supporting the safety, immunogenicity, and effectiveness of antenatal vaccination to reduce the morbidity and mortality in young infants prior to primary pertussis immunization series.

The third systematic review, conducted by Furuta et al. (2017), focused on the safety and efficacy of pertussis vaccination in pregnant women to protect their respective infants. This review was global in scope and included randomized controlled trials and observational studies. The study had very specific inclusion criteria that required at least one efficacy or safety outcome measure. The efficacy measures included pertussis infection or severe complications attributed to pertussis in infants up to 12 months of age or maternal and infant immune responses (serological findings in mothers' blood and infants' blood at delivery, in some studies at various intervals in infants' blood and also antibodies in mothers' colostrum). These included pertussis specific IgG and IgA antibodies to pertussis toxin, pertactin, and filamentous hemagglutinin/fimbriae. Safety measures included adverse events related to pertussis vaccines or obstetric/perinatal complications. The search time frame was not fully defined, but ended by May 16, 2016 for inclusion. This review specifically excluded cluster randomized trials and in doing so missed some key published literature demonstrating the impact of vaccinating pregnant women and its effect on reducing infant pertussis incidence, morbidity, and mortality. This review concluded that pertussis vaccination in pregnant women in middle or late pregnancy is associated with significantly higher antibody titers in both maternal and infant blood compared to no vaccination/placebo. In addition, the data did not reveal that maternal immunization was associated with increased safety risk for the mother or the infant.

The fourth systematic review was published in 2018 by Campbell et al., focusing again on a compilation of published literature on safety, immunogenicity, and effectiveness of maternal pertussis immunization. There were seven studies that focused on effectiveness (five more studies than Furuta et al.), which was likely due to the broader inclusion criteria for the types of studies and broader time frame (1940s through April 2017). This review synthesized a total of 46 studies for inclusion and concluded that the evidence supports vaccinating women during pregnancy provides efficient transplacental transfer of protective maternal antibodies in their respective infants.

Switzer, D'Heilly, and Macina (2019) published the fifth systematic review. This review was a pharmaceutical company sponsored study in which all authors were employees of Sanofi Pasteur. The review identified studies published from January 1995 through December 2018. Unlike earlier reviews, this publication focused only on the immunological and clinical benefits of maternal pertussis immunization. Forty studies were synthesized for inclusion. Maternal immune responses both in the mother and the respective infant was a key area of consideration for this review. Only 12 studies out of the 40 focused on effectiveness. This review concluded that based on published literature and the respective immunologic evidence presented, immunizing mothers during pregnancy protects infants prior to their first pertussis vaccination.

In summary, since the implementation of maternal pertussis vaccination recommendation with every pregnancy, there have been only five systematic reviews. The United States was the first country to recommend maternal pertussis vaccination with each pregnancy, irrespective of the receipt of pertussis vaccination in the past (CDC, 2013b). McMillan et al. (2017) only focused on safety through May 2016. The four other systematic reviews were broader covering, often covering safety, efficacy, and effectiveness. Furuta et al. (2017) and Gkentzi et al. (2017)

included data until May 2016, which is approximately four years since the recommendation in the United States. Furuta et al. (2017) included both safety and efficacy in which there was one study that included effectiveness data. Gkentzi et al. (2017) focused on synthesizing data with respect to national recommendations, maternal coverall, immunogenicity, safety, and effectiveness of current vaccines for pertussis. Only two effectiveness studies were included among the 47 studies in the entire review. The more recent reviews published by Campbell et al. (2018) and Switzer et al. (2019) had 5 and 6 years of data since the U.S. recommendation. Campbell et al. (2018) included data on safety, efficacy, and effectiveness from the 1940s through April 2017. The study included seven studies on effectiveness, whereas Switzer et al. (2019) covered the same data through December 2018 and included 10 studies that had vaccine effectiveness data. There were no systematic reviews completed that focused only on the effectiveness in infants and infant pertussis outcomes data to assess the real-world impact of the implementation maternal pertussis vaccination during every pregnancy on the most vulnerable infants.

Pertussis Disease and Epidemiology

Pathogenesis

Pertussis is a highly contagious respiratory infection caused by a bacterium called *Bordetella pertussis* (B. *pertussis*). A description of an illness like pertussis was recorded as early as the seventh century as “the cough of a 100 days” by a Chinese scholar named Yuanfang Chao (Liang, Salim, Wu, & Kilgore, 2016). Although there are records of outbreaks in Europe since the 16th century, it was not only until 1906 that the causative organism was identified and described as “a small ovoid Gram-negative bacterium” by Jules Bordet and Octave Genou. The bacterium was isolated 6 years later and taxonomically classified as *B. pertussis* (CDC, 2015).

Pertussis is also commonly known as “whooping cough” due to the gasping sounds patients make while taking deep breaths after becoming breathless following fits of violent uncontrollable coughing.

People with pertussis are most infectious during the catarrhal period and during the first 2 weeks after onset of the cough at approximately 21 days. Pertussis pathology is mediated primarily by pertussis toxin (PT) and is also believed to be secondarily mediated by an unidentified cough toxin (Cherry, 2013). The bacterium (*B. pertussis*) produces several biologically active and antigenic proteins that are mainly responsible for the clinical features. These include PT, filamentous hemagglutinin (FHA), agglutinogens like lipopolysaccharide endotoxin (LPS), adenylate cyclase toxin (ACT), pertactin (PRN), and tracheal cytotoxin (CDC, 2017e). These virulence factors interfere with innate immunity (Cherry, 2013; WHO, 2017). The tissue invasive properties of *B. pertussis* following attachment to respiratory epithelial cells include penetration of respiratory cells by ACT, release of PT that paralyzes the cilia, thereby impeding the clearance of pulmonary secretions, and inhibition of microbicidal and cytotoxic functions of neutrophils, tissue macrophages, monocytes, and natural killer cells (CDC, 2017e). Together, these virulence properties contribute to clinical disease through impairment of innate host defenses. FHA, LPS, and PRN are known to induce antibodies after infection or vaccination (CDC, 2017e; WHO, 2015, 2017).

Host, Transmission, and Clinical Features

B. pertussis only infects humans and is readily spread through aerosol droplet transmission (WHO, 2017). Unlike other common respiratory infections, pertussis is a non-inflammatory infection that is not accompanied by fever, but presents with paroxysms of cough, sometimes associated with vomiting as well as a whoop as the patient gasps for air after

coughing bouts and breathlessness (CDC, 2017b, 2017e; Cherry, 2013;; Moore et al., 2017; WHO, 2017). While healthcare providers can often diagnose pertussis by listening to the characteristic whoop and by asking about symptoms, not all cases, particularly babies, present with this characteristic cough. The gold standard in diagnosis is microbial cultural isolation of the organism from a swab taken from the nasopharynx during the first 2 weeks of cough, but this is not often done because patients can present with a cough without the whoop and other causes are suspected first. Alternatively, in developed countries, a polymerase chain reaction (PCR) test or serological testing (a blood sample can be tested for pertussis antibody) can diagnose disease, but these tests are cost prohibitive and time consuming, posing challenges for timely diagnosis and treatment, particularly in developing countries (CDC, 2017d). PCR is done by getting a sample of the patient's blood tested for genetic make-up of the pertussis bacteria. In addition, the optimal time to confirm diagnosis of pertussis after onset of cough varies according to the test used (CDC, 2017b, 2017d). This eventually contributes to the worsening of the disease and facilitates pertussis spread to others.

The incubation period for pertussis is typically between 7–10 days but can be as short as 4 days and as long as 21 days (CDC, 2017e). The course of the disease is divided into three distinct stages: the catarrhal, paroxysmal, and convalescence stages. The catarrhal stage is the period of infectiousness and is characterized by symptoms like the common cold, such as a runny nose, low-grade fever, and a mild occasional cough (CDC, 2017b, 2017e), making diagnosing disease at this stage difficult. This stage lasts for 1–2 weeks and the cough gradually worsens. Unfortunately, this stage is often under diagnosed because of its non-specific mild symptoms. Highlighting the high transmissibility of pertussis are data showing attack rates of 80% among susceptible household contacts when persons during the catarrhal period and the first 2 weeks

after cough onset (CDC, 2017b). As reported by CDC surveillance, 60 of 72 deaths (83%) from pertussis in the 2008–2011 time period occurred in children ≤3 months of age (CDC, 2017f).

The paroxysmal phase is characterized by bursts of rapid coughing spasms, difficulty expelling sputum, and a long inspiratory effort at the end with a high-pitched whoop. These paroxysms tend to be more frequent at night. Patients can even turn blue during the coughing bouts, and vomiting and severe exhaustion can result after a coughing bout. There may even be bouts of nonproductive paroxysmal coughing followed by periods of normalcy. The cough can last for extended periods of time (CDC, 2017e; WHO, 2017). The paroxysmal stage can last from 6–10 weeks and is the phase that is diagnostic for pertussis.

All patients have cough-associated apnea, but severity reduces with increasing age. However, apnea, a common clinical feature seen in infants, is not correlated with increased mortality. Also, infants infected with pertussis are too weak to have classical whoop and as such the cough is not easily recognized. Some features, such as seizures, increased white blood cells, and lymphocytosis are correlated with increased severity and are strong predictors of increased mortality (Winter et al., 2015). Leukocytosis is an effect of pertussis toxin and is a very important clinical feature seen in infected infants (Carbonetti, 2016).

The convalescence phase is a gradual recovery phase where the cough lessens and disappears in about 2–3 weeks. However, there can be other superimposed bacterial or viral infections that can lead to more paroxysms of coughing with hyperreactive airways. Full recovery can often take many months. In addition, concomitant secondary bacterial infection or viral infections can confuse the clinical picture by presenting with fever and inflammation (Cherry, 2013). Serious complications include secondary bacterial pneumonia, pulmonary

hypertension, convulsions and seizures in children from fever and lack of oxygen to the brain due to frequent coughing bouts, encephalopathy, and death (WHO, 2017; Cherry, 2013).

Incidence, Trends and Seasonality

Pertussis occurs worldwide in a cyclical nature, with peaks of disease occurring every 3–5 years, as illustrated in surveillance data from the U.S. CDC (Figure 3) (CDC, 2017f) and Public Health Service in England (Figure 4) (PHE, 2018). Pertussis affects all ages, races, and genders (Figures 3–5).

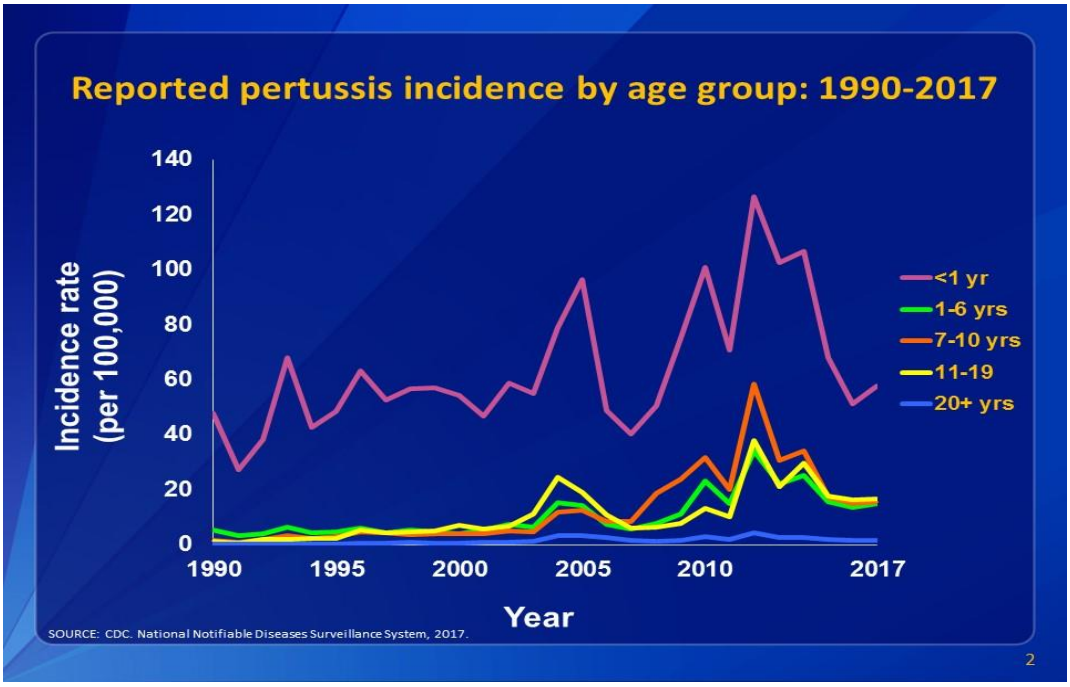

Figure 3. Graph of Pertussis Incidence by Age Group in the US: 1990–2017 .Reprinted from CDC, 2017. Retrieved from *https://www.cdc.gov/pertussis/images/incidence-graph-age-2017.jpg.*

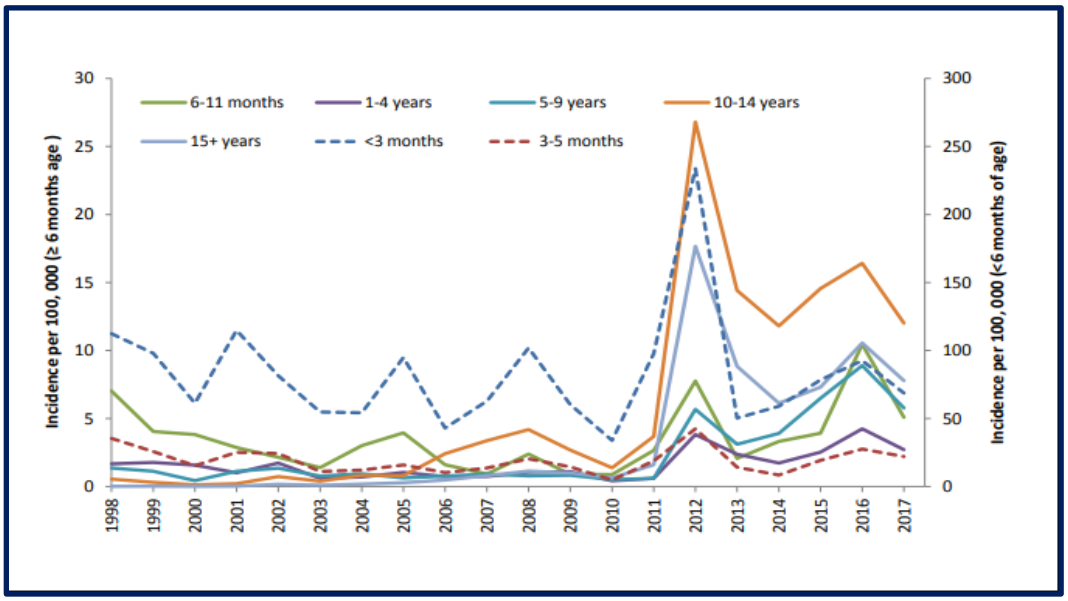

Figure 4. Graph of Laboratory Confirmed Pertussis Incidence Rates by Age Groups-1998–2017, England. Reprinted from PHE, 2018. Retrieved from *https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/703519/hpr1518_prtsss_ANN.pdf*.

The consistently highest reported incidence of pertussis among infants under 1 year of age in countries like the United States and England (Figures 3 and 4) and similar data provided to the European Centre for Disease Prevention and Control (ECDC) from 29 states of the European Union to the European Surveillance System (TESSy) in 2016 (Figure 5) highlight the need to control infant pertussis. Implementing mandatory maternal pertussis vaccination has been the most recent strategy to attempt to address this concern. This disease can be serious, especially in infants less than 1 year old, resulting in severe complications, including death. Adults and older children are typically not as badly affected, and sometimes due to the mild symptoms, the illness may even go undiagnosed (Teepe et al., 2015).

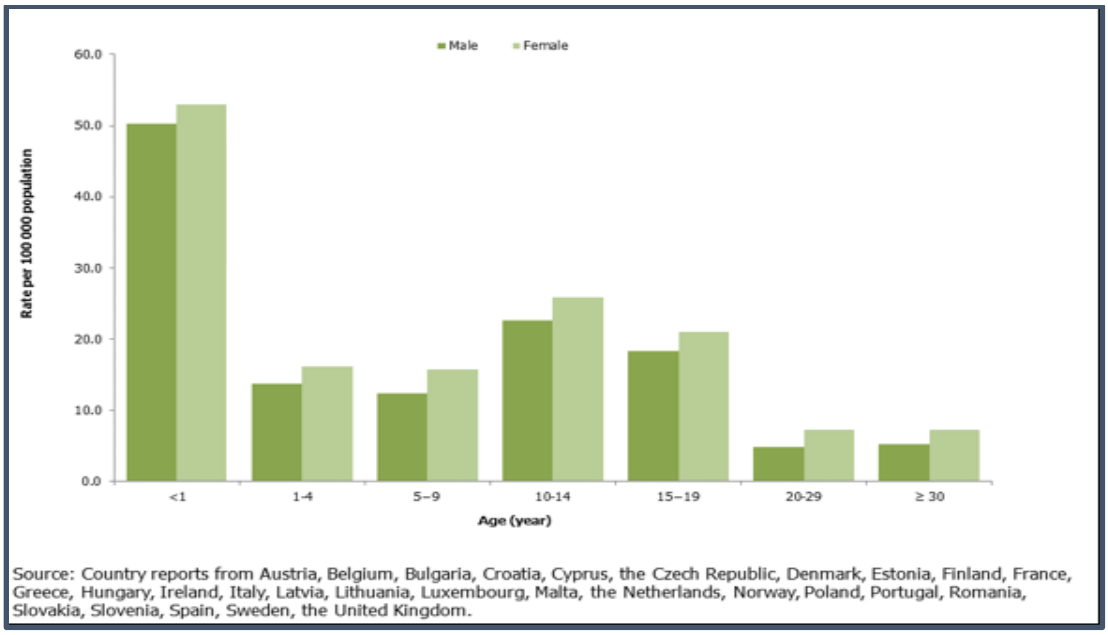

Figure 5. Graph of Reported Pertussis Cases, by Age and Gender, EU/EEA, 2014. Reprinted from European Centre for Disease Prevention and Control (ECDC), 2016. Retrieved from *https://ecdc.europa.eu/sites/portal/files/documents/Pertussis%20AER.pdf*

The incidence of pertussis exhibits no real pattern of seasonality, although increases in the number of cases are sometimes observed in summer and fall seasons in the United States (CDC, 2015). Seasonality is not consistent, seems to vary over time and place, and appears to be impacted by climatic conditions.

Some examples of pertussis seasonality are presented here. In one study examining reported pertussis cases from 1993–2007 in Toronto, Canada, a predominance of cases was noted in fall and winter (Fisman et al., 2011). A 2012 pertussis outbreak in Texas recorded its first case in late October (TDSHS, 2018). The Netherlands recorded its peak in August among infants and young children, while a November peak was observed among adolescents (de Greeff et al., 2009). In England, the seasonality of pertussis was followed over several decades from 1940–1985 (Fine & Clarkson, 1986), demonstrating that seasonality is not consistent. During the first 17 years, from 1940–1957, pertussis epidemics were noted in the early and middle months of the

year, unlike the second 17 years, from 1958–1975, where epidemics shifted to the end of the year from October through December. From 1976–1985, bimodal peaks in seasonality, in September and then again in February, were observed. Most recently in England, over the last 10 years, there was a predominance of cases in the second half of the year (PHE, 2018b). In African countries there is not any uniformity as to when cases take place. Senegal has bimodal peaks with one peak in the summer and a large epidemic was reported in the winter months (Préziosi et al., 2002). Kenya, conversely, demonstrated two large epidemics both in the winter months (Muller, Leeuwenburg, & Voorhoeve, 1984). Given the seasonal inconsistency of pertussis, vaccination provides the best protection to prevent or minimize disease. As pregnancies are often not planned and cannot be timed in a pre-emptive manner to coincide with anticipated seasonality, the public healthcare recommendations for vaccination of pregnant mothers will provide immune-naïve newborns some form of protection against this unpredictable disease.

Global Burden of Disease

Several challenges exist in estimating the true burden of pertussis globally. Most importantly, limited surveillance infrastructure hinders timely reporting of suspected pertussis cases (van der Zee, Schelkens, & Mooi, 2015). In developing countries, laboratory testing and molecular diagnostic tests such as PCR are not uniformly available, limiting the quality of reporting. Also, those countries only reporting laboratory confirmed cases are likely underreporting incidence of pertussis because clinically suspected cases are not always confirmed by laboratory testing (Cherry, 2016; Heininger, 2019). Finally, the lack of trained professionals, inconsistent clinical identification, and the lack of standardized case definitions of pertussis (CDC, 2014; WHO, 2014) have contributed to the underreporting of pertussis cases. It

has been suggested that pertussis rates may actually be three times greater than what is reported (Heininger, 2019; Kilgore, Salim, Zervos, & Schmitt, 2016).

In 1999, the global burden of pertussis was estimated at 48.5 million cases with approximately 295,000 deaths reported (Crowcroft, 1999). In 2008, there were 16 million cases reported with 195,000 deaths (Black, 2010). In 2013, 162,016 cases were reported, and in 2018, there were 151,074 reported cases (not including the United States and several other countries where these numbers were not captured) (WHO, 2019). In Latin America, there are wide differences in pertussis incidence, but surveillance data suggest that the greatest burden of disease is in the <1 year of age group (Gentile et al., 2019). From 2006 through 2015, pertussis cases increased in all age groups, but the most reported cases were in infants <1 year of age (Hozbor et al., 2019). During that period, the four Latin American countries with the highest incidence of pertussis in infants were Argentina, Chile, Costa Rica, and Uruguay.

In the United States, outbreaks usually occur every 2–5 years with the worst recent outbreak in 2012 with 48,277 cases (CDC, 2013a). In the following years, there were 28,639 pertussis cases in 2013; 32,971 in 2014; 20,762 in 2015; 17,972 in 2016; and 18,975 cases in 2017 (CDC, 2017c, 2017a, 2017f). Provisional pertussis data for 2018 reported 13,439 cases (CDC, 2019). This number is the lowest in the last 10 years and may be a result removing barriers and improving access to vaccination along with improved infant and maternal immunization.

Over the past decades, routine vaccination has dramatically reduced pertussis incidence. However, despite global pertussis vaccination coverage estimated at 85–90% coverage, there are still well over 150,000 cases occurring globally (Figure 1). Pertussis is also a leading cause of mortality in very young children in some developing countries in Africa such as Senegal and

Kenya having the highest reported mortality rates (Senegal: 13,100 in <2 years of age, 1986 data; Kenya: 5100 in <1 year of age, 1974–1977 data) (Chow, Khandaker, & McIntyre, 2016; de Cellès et al., 2016). In 2014, data from Brazil, another developing country, showed that infants had the highest incidence of pertussis disease at 175.20 per 100,000 persons with 97.6% (405/415) of all pertussis deaths being in infants <1 year of age (De Barros et al., 2019). Despite significant decreases in the number of pertussis cases, it is evident that pertussis continues to be a global health challenge. Similarly, in 2011, there was an outbreak in Argentina with 2,821 confirmed pertussis cases with the highest incidence and mortality in infants <1 year at 344/100,000 persons and 76 deaths (Romanin et al., 2014).

The disease has also re-emerged in many developed countries despite high vaccination rates, such as the United Kingdom, United States, and Australia. In the United Kingdom, there was a notable increase in pertussis activity in 2012 when there were 429 cases in infants under 3 months of age, the group in which pertussis disease continues to be the highest (PHE, 2014). During the 2012 pertussis epidemic in the United States, infants <1 year had the highest incidence of pertussis at 126.65/100,000 persons (Table 1) and infants under 3 months of age accounted for 15 out of a total of 20 deaths (Table 2) (CDC, 2013a). The highest incidence of pertussis is seen among unvaccinated and incompletely vaccinated infants as reported in the United States (Table 1) (CDC, 2017f) and the United Kingdom (PHE, 2014, 2018a, 2018b). According to the Australian Technical Advisory Group on Immunisation (2019), there are over 200 hospitalizations and at least one death in infants under 6 months of age every year in Australia. The Australian Government Department of Health in 2015 reported that there were 78 cases of children hospitalized with pertussis and 33 (42%) were infants under 3 months of age (McRae, Quinn, & Macartney, 2017). The highest annual pertussis rates were also consistently

seen in unimmunized and incompletely immunized vulnerable infants under 1 year of age in several European nations (Figure 5). Although pertussis is not discriminatory of persons, mortality rates among infants are the highest when compared to other age groups (Chow et al., 2016; Fedele & Stefanelli, 2017; Forsyth, Plotkin, Tan, & Von König, 2015; Gregory, 2005; WHO, 2015).

According to the Global Burden of Disease Study in 2013, infectious diseases attributed more than half of the 6.3 million deaths in children under the age of 5 years with estimated mortality ~400 per million live births (~56,000 deaths) due to pertussis in the first year of life (Liu et al., 2015). Pertussis documented cases accounted for a total of 2% of deaths (126,000) in 2013. Additionally, in data provided to the WHO from 15 high-income countries for the decade from 2003–2012, the average annual pertussis mortality rates per one million births ranged from 0.1 to 38.6, with the majority being between 3.0 and 10.0 deaths per million births (Chow et al., 2016).

Pertussis Resurgence

Following the introduction of wP vaccines in the 1940s, pertussis incidence gradually declined to eight per 100,000 population, for a total of 16,000 cases reported in 1960. This further declined to one per 100,000 population. Since widespread use of the vaccine began, incidence has decreased more than 75% compared to the pre-vaccine era. However, since the early 1980s, pertussis incidence has been gradually rising with an increasing number of reported cases. The reasons for the rise are not well understood and are believed to be multi-faceted.

Despite high vaccination rates and vaccine availability, pertussis incidence in the United States has steadily increased with an unprecedented number of 48,277 cases reported in 2012 (CDC, 2013a), the last peak year. The problem may be far greater than what has been observed,

since the CDC believes that many cases go unrecognized and unreported. In many instances, pertussis may be underdiagnosed and therefore, underreported, as it often presents with milder, less obvious symptoms in older children and adults (Kline, Lewis, Smith, Tracy & Moerschel, 2013). Both Seppa (2014) as well as Warfel et al. (2014) asserted that newer aP vaccines do not appear to protect from infection and transmission, despite successful vaccine efficacy trials conducted by sponsor pharmaceutical companies. Nationally, there has been an emergence of pertussis among vaccinated adolescents and adults. A similar trend was observed in several other developed nations that moved away from whole cell pertussis (wP) vaccines (Lapidot & Gill, 2016).

Several theories have been proposed to explain this resurgence, including the evolving virulence of *B. pertussis* to evade vaccine efficacy, waning immunogenicity of aP vaccines, insufficient administration of pertussis boosters in kids, and better surveillance and diagnosis due to heightened awareness (Saadatian-Elahi et al., 2016). Data from studies demonstrate that *B. pertussis* has gone through substantial genetic changes that appear to be occurring at a higher rate with aP vaccines compared to wP vaccines (Carbonetti, 2016). However, it is incontrovertible that the initial control once achieved with wP pertussis vaccines in the late 70s and early 80s is not what is being experienced today.

Outbreaks in the United States

In 2012, the United States saw the highest incidence of reported pertussis since the nadir of 1976. The state of Washington reported 2,520 cases from January 1 to June 16, 2012, which was a 1,300% increase from the same period a year earlier (CDC, 2012). Even though there was high vaccination coverage achieved, high rates of pertussis were still seen in 13–14-year-old adolescents. The fact that increased rates of pertussis were observed in 13–14-year old

adolescents who were fully vaccinated with acellular vaccines led to an inference that waning immunity could be the issue (Acosta et al., 2015). Similarly, in Minnesota, according to the Department of Health, there were 4,144 pertussis cases reported in 2012 (MDH).

In 2013, a pertussis outbreak was reported in Texas involving 3,985 cases (TDSHS, 2018). This was the highest annual number of cases in a year since 1959. The Texas Department of State Health Services identified several important reasons for this rise in pertussis cases, such as adults and adolescents experiencing waning immunity, and increased disease awareness among healthcare professionals, school nurses, parents, and the general public. Additionally, improved testing methods in laboratories and effective surveillance techniques were also important contributing factors.

During the 2014 pertussis outbreak in California, there were 11,213 cases with 458 hospitalizations and three fatalities. Infants from birth through 3 months of age comprised 61% of those hospitalized and all of the deaths (CDPH, 2015). However, in the 2010 outbreak in California, there were 9,120 cases reported with 10 infant deaths compared to only three infant deaths in the 2014 outbreak, suggesting that this infant mortality difference could be attributed to immunization of women during pregnancy (Sawyer & Long, 2015). During the 2010 outbreak, California had the highest reported incidence rates since 1958. The 2010 pertussis case fatality rate in infants <3 months of age in California was 1.3% (Winter et al., 2012). Klein, Bartlett, Rowhani-Rahbar, Fireman, and Baxter (2012) suggested that this 2010 outbreak could be the result of waning of immunity from the time the fifth dose of DTaP was administered, and that the risk of contracting pertussis therefore increased each year after that final dose by 42%. The authors of the Klein et al. (2012) study suggested that the way to overcome this short-lived

protection after the fifth DTaP dose was to develop new pertussis vaccines that would provide longer-lasting immunity.

Pertussis Vaccines in the United States

Immunizations are considered the method of prevention for many infectious diseases, but controlling pertussis has been challenging for over 70 years. Pertussis is one of the most poorly controlled diseases that is vaccine preventable. In the United States, pertussis was first reportable in 1922, at which time there were 107,473 pertussis cases reported and 5,099 pertussis-related deaths (CDC, 1999; Clark, 2014). The CDC has recorded cases from 1922 through 2017, with the highest annual number of reported cases at 265,269 in 1935 and the lowest number of cases at 1015 in 1976 (CDC, 2017c). Provisional data for 2018 show a total of 13,439 cases (CDC, 2019). During the pre-vaccine era, the incidence of pertussis in the 1940s was about 157 per 100,000 population (CDC, 2017c; Cherry, 2012). According to the CDC, there were more than one million cases in the United States from 1940–1945. During that period, over 200,000 cases of pertussis were reported in certain years and approximately 4,000 deaths occurred annually (CDC, 2015; Roush, Murphy, & VPDT Working Group, 2007). According to the 1926 and 1929 Annual Report of the Surgeon General of the Public Health Service of the US, the average case fatality rate for pertussis during the pre-vaccine era was 4% (Kapil & Merkel, 2019).

Whole cell pertussis vaccines were first introduced in the United States in 1943 and were effective at reducing pertussis rates to all-time lows (Figure 6). Unfortunately, immunity from natural pertussis infection, as well as wP vaccines, was not permanent, lasting on average from 5–10 years (Cherry, 2013). Concerns about the safety of wP vaccines and its reactogenicity fueled the development of aP vaccines, which were first introduced in 1991 DtaP and 2007 (Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine -Tdap), respectively

(Figure 6). The complete replacement of wP with aP vaccines took place in 1997 (Guris, Strebel, Jafaari, Wharton, & Hadler, 1997), with the expectation that aP vaccines offered the same efficacy benefit with a better safety profile.

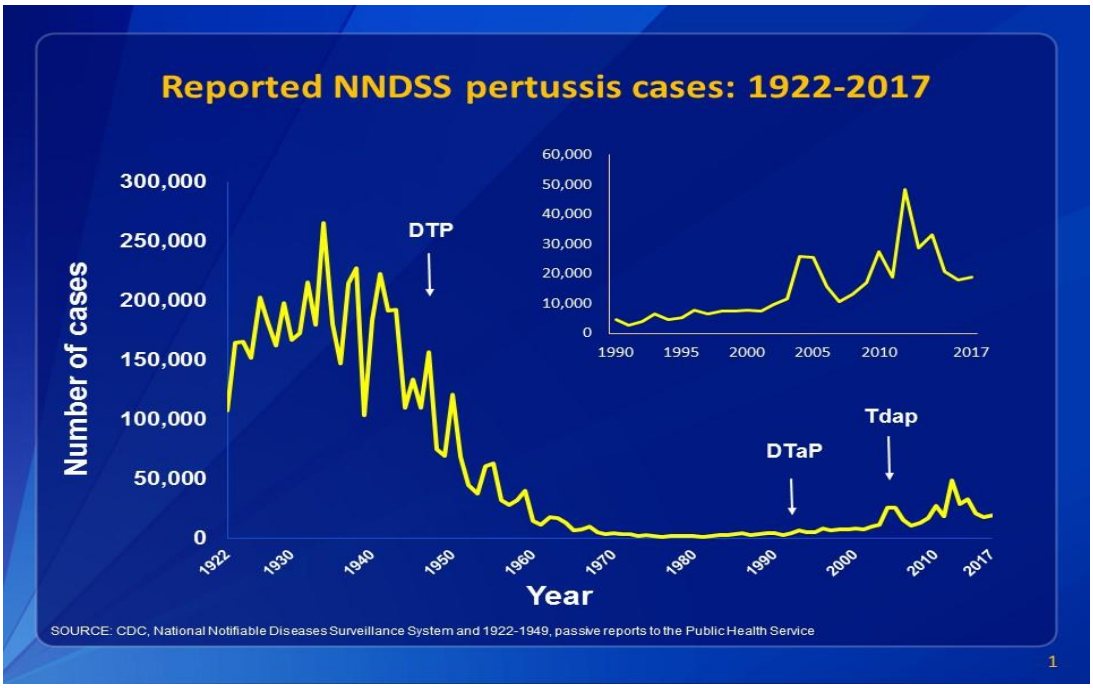

Figure 6. Incidence of Pertussis Cases Reported to the CDC in the US from 1922 Through 2017. Reprinted from the CDC, 2017. Retrieved from https://www.cdc.gov/pertussis/images/incidence-graph-2017.jpg.

Treatment Options in Infants

Pertussis in infants is often very severe and may result in hospitalization and even death. Unfortunately, there are not any proven effective treatments for reducing the symptoms of pertussis (Scanlon, Skerry, & Carbonetti, 2015). Antibiotics for the treatment of pertussis include the macrolides erythromycin, clarithromycin, and azithromycin in infants and children 1 month of age and older. For infants younger than 1 month of age, azithromycin is preferred for post exposure prophylaxis and treatment (CDC, 2017g). Ideally antibiotics should be administered during the incubation period or catarrhal phase of pertussis. If administered during the

paroxysmal phase, antibiotics do not have a significant impact on disease outcomes, but may eliminate the pertussis bacterium from the nasopharynx and thereby reduce transmission (WHO, 2015).

Recent evidence from a Swedish study suggests that macrolide antibiotics administered within the first 6 days in young infants was associated with a shorter duration of disease (Carlsson, Von Segebaden, Bergström, Kling, & Nilsson, 2015.). Antibiotics were also helpful at preventing further transmission. Overall options for protecting newborn infants are very limited. Some potential treatment options used, but not significantly beneficial, are antihistamines, steroids, and short acting beta-agonists (Wang et al., 2014). Another option is treatment of infants with intravenous anti-pertussis immunoglobulin (containing high titers of anti-PT antibodies), which has demonstrated some benefit in the past, but the option is extremely expensive and not sustainable or feasible for the larger population (Bruss et al., 1999; Carbonetti, 2016). There is little to no benefit to intervene with antimicrobial agents during the convalescent stage.

Vaccination Against Pertussis

Despite most developed countries having achieved infant pertussis coverage rates greater than 90% and the overall global DTP coverage being 86% (Figure 7), infant pertussis incidence and mortality rates are still high, thus indicating the critical need to achieve greater control of pertussis globally. Despite pertussis vaccines being available for over 70 years, pertussis continues to be a major public health problem (de Cellès, Magpantay, King, & Rohani, 2018). Since most cases of severe pertussis disease, complications, and death occur in infants during the first few months of life, immunizing pregnant women may be the best possible protection for young infants through transfer of protective maternal antibodies (CDC, 2017h). While this

strategy is somewhat new, the United Kingdom and the United States were the first to make recommendations to vaccinate women during each pregnancy in 2011 and 2012 respectively (JCVI, 2012; Sawyer, Liang, Messonnier, & Clark, 2013).

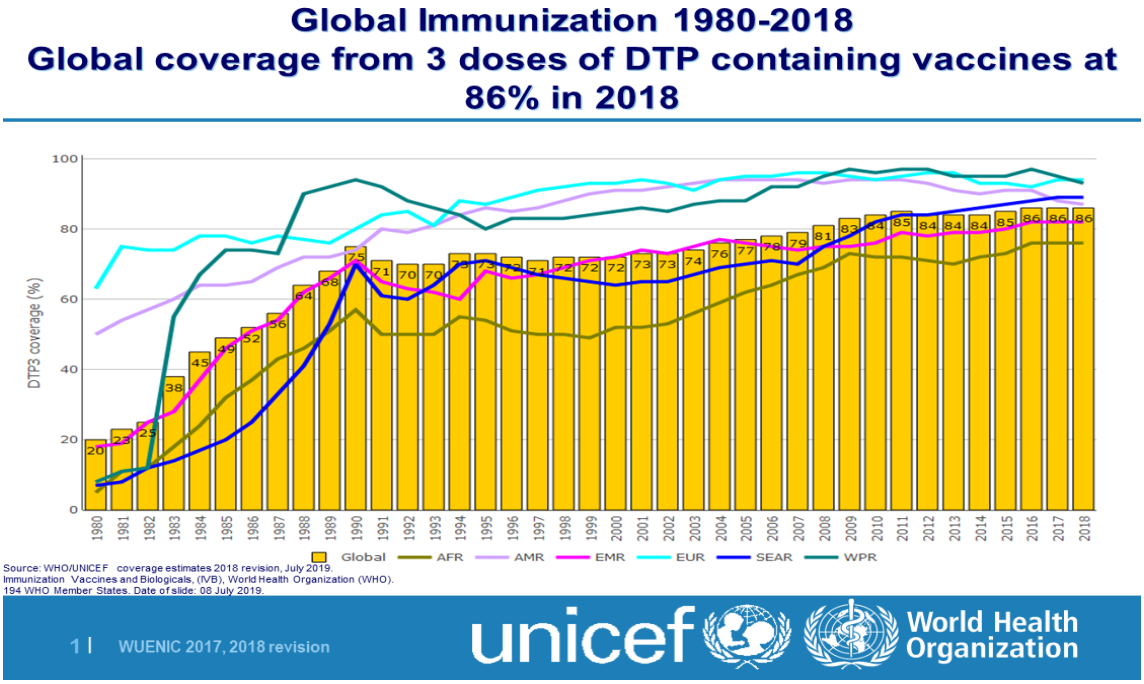

Figure 7. Global Immunization from 1980–2018. Global coverage of three doses of DTP containing vaccines at 86% in 2018. Reprinted from the WHO, 2019. Retrieved from *https://www.who.int/gho/immunization/en/.*

Vaccination Strategies to Protect Infants

The current ACIP recommendations for pertussis vaccination in the United States require that children receive the primary series of the DTaP vaccine at 2, 4, and 6 months of age, followed by booster doses at age 15–18 months, 4–5 years of age, and a dose of Tdap at 11–12 years of age (Liang et al., 2018). Active immunization and early diagnosis are crucial in the management of pertussis. Unfortunately, infants cannot be vaccinated until approximately six to eight weeks of age because their immune systems are too naïve and because the body takes time to elicit an immune response, thus making infants under 3 months the most vulnerable group. In

addition, waning immunity after childhood immunization has resulted in a larger number of vulnerable adolescents and adults who then become the source of infection, transmitting pertussis to immune-naïve, unvaccinated, or incompletely vaccinated infants. An aP vaccine, second booster dose (fifth), for adolescents has been recommended in most industrialized countries (Broder et al., 2006; Liang et al., 2018). This was implemented to help ease the burden in adolescents and reduce the source of adolescents spreading the bacteria to infants.

Several innovative strategic changes have been implemented over the years to address infant pertussis morbidity and mortality. The routine immunization schedule includes five doses of the DTaP vaccine before the age of 7. The first major change in recommended vaccination practice was switching to aP vaccines in 1997 in the United States and at various times in other industrialized countries in order purely to address any possible reactogenicity from wP vaccines in children. Controlled clinical trials with aP vaccines demonstrated a more favorable safety profile than wP vaccines (Weigl et al., 1997) while achieving approximately 70–90% vaccine effectiveness (Jurestzko et al., 2002). The United States completed a complete transition to aP vaccines from wP vaccines for all DTP primary series in infants in 1997. No new acellular vaccines have been studied or launched for use in infants since 1997. A recent statistical sensitivity analysis of pertussis vaccine effectiveness in Canada demonstrated that efficacy of aP vaccines wanes over time, decreasing from approximately 80% within 1 year of active vaccination to 50% by 4 years and <15% by 7 years of vaccination (Schwartz et al., 2016).

Despite active immunization programs, the highest annual pertussis cases are consistently seen in unimmunized and incompletely immunized vulnerable infants under 1 year of age (Forsyth et al., 2015) and mortality rates were the highest in infants compared to other age groups (Fedele & Stefanelli, 2017). Therefore, immunization strategies initially started focusing

on reducing pertussis exposure to newborns by immunizing those in close physical proximity to these infants (cocooning strategy) (CDC, 2017i; Forsyth et al., 2015). In 2006, the CDC recommended this immunization strategy to reduce the high pertussis rate in infants (CDC, 2012, 2016). However, immediate immunization of postpartum mothers and others in close contact with infants did not reduce pertussis illness in infants less than 6 months of age (Healy, Rench, Wooton, & Castagnini, 2015). These newborn infants still required more protection especially in the first 2 to 3 months of life.

For these reasons, the CDC focused on strategies that would help protect these very young immune-naïve infants. In 2011, the ACIP recommended a single dose of the Tdap in women previously not immunized with Tdap between 27 and 36 weeks of pregnancy (CDC, 2011). This strategy was thought to enhance infant protection via placental transport of maternal antibodies and secretory antibodies in breast milk. This recommendation was then amended in 2011 to include Tdap vaccination during each pregnancy irrespective of whether women were previously vaccinated (Sawyer et al., 2013), with the goal to optimize maternal antibody response and passive antibody transfer to each fetus. The reasoning behind this recommendation was the largest increase in pertussis cases in 60 years observed in 2012, when 2,269 of the 48,277 reported cases of pertussis occurred in infants younger than 3 months of age and 15 of those infants died (CDC, 2013a).

Maternal Vaccination

Vaccinating pregnant women rather than the initial cocooning strategy of immunizing immediate postpartum mothers appears to offer more by providing transplacental transfer of vaccine-induced antibodies from the mother to fetus (Swamy & Wheeler, 2014; WHO, 2015). Furthermore, unpublished CDC data showed that vaccinating pregnant women with Tdap from

27 through 36 weeks gestation was 80–91% effective (Liang et al., 2018). A decision analysis and cost-effectiveness study modeling vaccinating women during each pregnancy versus postpartum with or without cocooning was done in 2013 (Terranella, Asay, Messonnier, Clark, & Liang, 2013). According to the model, maternal Tdap vaccination could potentially reduce cases by 33% versus 20%, hospitalizations by 38% versus 19%, and deaths by 49% versus 16%.

Similarly, after experiencing a sharp rise in hospitalizations and deaths among unimmunized infants in 2012 (Figure 5), the United Kingdom introduced a similar program offering pertussis vaccinations to pregnant women in October 2012 (van Hoek, Campbell, Amirthalingam, Andrews, & Miller, 2013). The burden of infant disease has also been experienced by many other countries, which led to recommendations to immunize women during pregnancy in Argentina, Israel, New Zealand, Australia, Spain, and the United Kingdom (WHO, 2015).

Maternal Pertussis Vaccination Coverage Rates

Australia, Belgium, Canada, China, France, Germany, India, Mexico, the Netherlands, Poland, Spain, Slovenia, Switzerland, Turkey, the United Kingdom, and the United States all offer pertussis vaccination to pregnant women (Wilson, Paterson, Jarrett, & Larsen, 2015). In the United States and United Kingdom, routine pertussis vaccinations were offered to women during each pregnancy, given as part of Tdap vaccines since 2012 (CDC, 2013b; JCVI, 2012). Initially, in the United States, it was recommended only in pregnant women who were not immunized against pertussis earlier (CDC, 2011). However, the unprecedented number of cases in 2012 led to that improved strategy of prenatal immunization in the attempt to further protect infants. The United States and United Kingdom have had the recommendation in place for pertussis vaccination during each pregnancy for just over 7 years. In the United Kingdom, unlike the

United States, maternal pertussis vaccination coverage rates in excess of 70% during pregnancy were achieved after the national program was implemented (Amirthalingam et al., 2014). In the United States, according to an internet survey conducted by the CDC (Black et al., 2018), maternal Tdap immunization rates finally exceeded 50% coverage in pregnant women 6 years after the ACIP recommendation.

The CDC conducted an internet panel survey among women, between the ages of 18 and 49, who were pregnant any time after August 2017, to assess immunization coverage rates (Kahn et al., 2018b). Although 14,858 women opened the survey, only 2,342 were considered eligible and only 2,236 completed the survey. For Tdap maternal coverage estimation, a woman was considered to have received pertussis vaccination if she received a dose of Tdap during her pregnancy. The reported coverage was 396 of the 700 women (54.4%) who had live births and confirmed maternal immunization. Similar internet panel surveys in 2017, 2016, and 2015 reported 50.4% (Kahn et al., 2018a), 48.8% (Kahn et al., 2017), and 42.1% coverage (Black et al., 2017), respectively. The Tdap maternal vaccination coverage of 50.4% in 2017 represented a 1.6% increase from 2016 and a 6.7% increase from the 42.1% coverage in 2015 (Figure 8). Overall, each year has demonstrated some improvements in coverage rates since national implementation of maternal immunization.

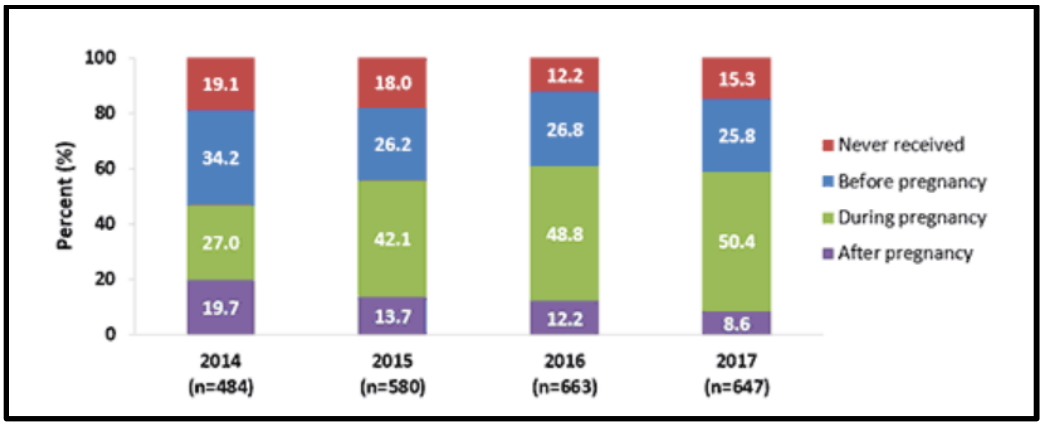

Figure 8. Graph of Tdap Vaccination Coverage Data Among Pregnant Women with Live Births, Internet Panel Surveys, United States, April 2014, April 2015, April 2016, & April 2017 from the CDC, 2017. Retrieved from https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/tdap-report-2017.html.

In the 2017 and 2016 surveys, several subcategories were included, such as age, race, and education, and respective coverage rates (Black et al., 2017; Kahn et al., 2018a). A total of 647 women who were pregnant any time from August 1, 2016 until the survey date in April 2017 were included in the analysis for 2017. A total of 663 women who were pregnant any time from August 1, 2015 until the survey in April 2016 were included in the 2016 survey analysis.

In the 2016 survey, higher level of education was associated with greater Tdap coverage. Women with more than a college education had the highest Tdap coverage during pregnancy at 52.5% compared to those with less than high school at 41.2%. However, this was different in the 2017–2018 survey, where women with some college education had the lowest coverage rate at 40.7% and those with less than high school was the second highest at 55.4%. The highest coverage (57.9%) was still the highest among women with more than a college degree.

Maternal Tdap coverage by race in 2015–2016 were as follows: Non-Hispanic White at 51.3%, Non-Hispanic Black at 42.7%, Hispanic at 44.6%, and Non-Hispanic other at 53.1% (Figure 9). In 2016–2017, Tdap coverage in pregnant women was the highest among Non-

Hispanic Whites at 57.8%, while Hispanics ranked the lowest at 37.9%, and Non-Hispanic Blacks and Non-Hispanic others declined to 40.8%, at 44.3% respectively (Figure 10). In both years, Blacks and Hispanics ranked the lowest. In 2017–2018, the distributions were similar. The age groups were divided into three groups: 18–24 years, 25–34 years, and 35–49 years. The 2016–2017 survey results demonstrated that ages 25–34 years had the highest coverage at 55.5%, the 18–24 years group was at 42.1%, and 42.4% was seen among women aged 35–49 years. Results in the 2017–2018 analysis were not much different and demonstrated that the 25–34 years age group had the highest coverage of 57.9%, followed in order by 50.6% in the 35–49 years group, and 49% in women 18–24 years of age.

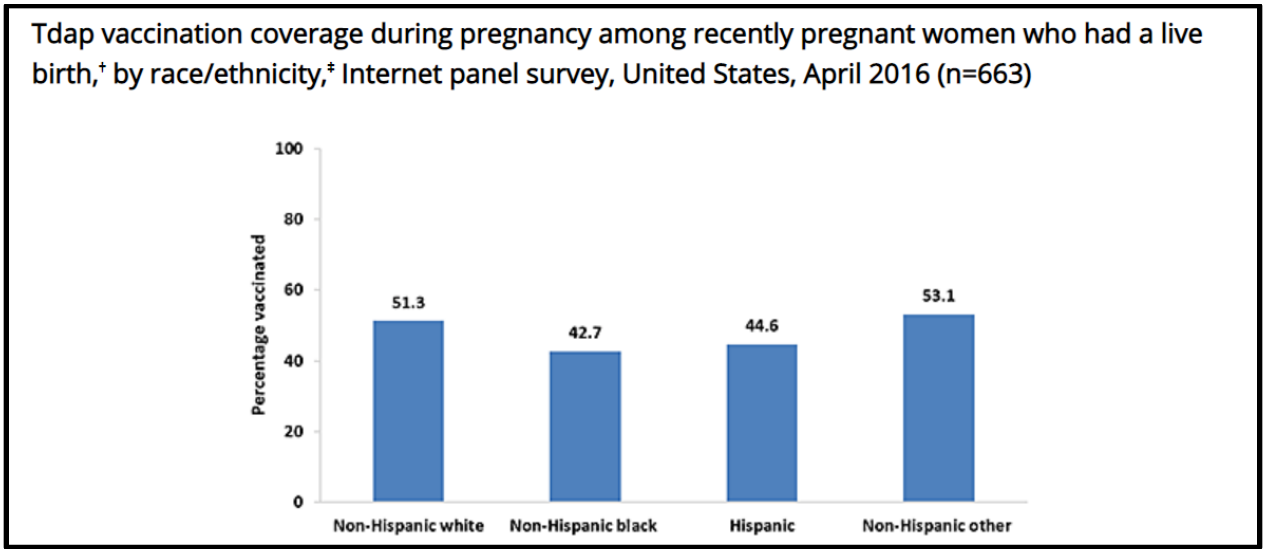

Figure 9. Graph of Tdap Vaccination Coverage Data Among Pregnant Women with Live Births by race/ethnicity, Internet Panel Surveys, United States, April 2016. Reprinted from the CDC, 2017. Retrieved from https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/tdap-report-2016.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fimz-managers%2Fcoverage%2Fadultvaxview%2Ftdap-report-2016.html.

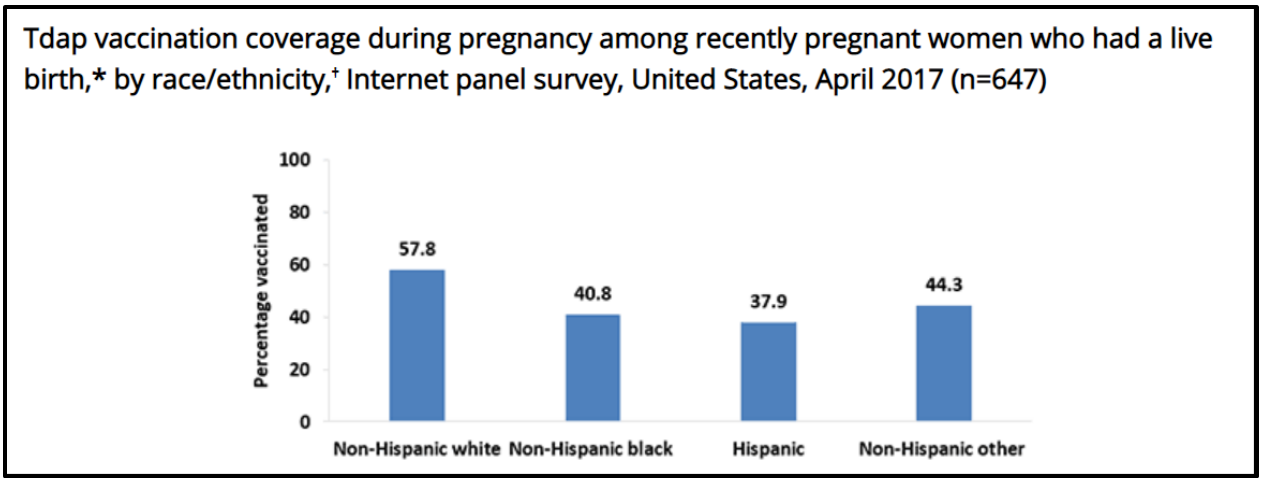

Figure 10. Graph of Tdap Vaccination Coverage Data Among Pregnant Women with Live Births by race/ethnicity, Internet Panel Surveys, United States, April 2017. Reprinted from the CDC, 2018. Retrieved from https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/tdap-report-2017.html#footnotes.

There were several reasons presented in each year's survey for not receiving the Tdap vaccination. The most common theme across 2014–2017 that ranked the highest was a lack of awareness or not knowing that they should get Tdap vaccination during pregnancy (Black et al., 2017; CDC, 2016; Kahn et al., 2018a). In the 2017–2018 survey, the reason that was most commonly stated was the misunderstanding that they already got the Tdap vaccine in a previous pregnancy and did not think they needed it again (Kahn et al., 2018b). The next section will discuss maternal barriers to immunization more in detail.

Maternal Vaccination – Barriers, Promoters, and Interventions

Maternal and child health and survival has improved significantly over recent years, especially with respect to maternal vaccination (Wilson, Paterson, Jarrett, & Larson, 2015). However, despite the availability of vaccinations and programs dedicated to increasing maternal vaccination, there is still a great deal of improvement that can be made (Wilson et al., 2015). Several barriers to improving vaccination rates exist with any population (Yuen & Tarrant, 2014), but achieving high vaccination coverage in pregnant women remains more challenging.

For example, although the rate of prenatal Tdap vaccination increased from 0.0% in 2010 to 44.4% in the United States in 2014, still less than half of pregnant women were receiving this vaccination (Butler et al., 2017). It was further observed that among the high percentage of pregnant women who were not vaccinated, the majority were younger women, women who had other children, and women who lived in Southern United States (Butler et al., 2017). Understanding why these trends exist and creating interventions specific to these target populations and the challenges they face in receiving vaccinations could be key in improving maternal vaccination rates.

From a review of 155 articles regarding vaccination during pregnancy, several challenges to improving rates of prenatal vaccination have been reported, including those from both the patients and the healthcare workers (Wilson et al., 2015). Barriers from the patient perspective included lack of insufficient understanding of vaccine safety and efficacy, conflicting recommendations from others including social networks, communities, and healthcare workers, and inadequate access and affordability of vaccines (Larson, 2015; Wilson et al., 2015).

It is important to note that reports of these barriers also differed across ethnicities and income levels, with reports of access and affordability issues being more common in ethnic minorities and low-income individuals (Wilson et al., 2015). According to a Belgian study in 2015, a survey of 250 women revealed that foreign women and women with lower levels of education are also more at risk of not being vaccinated (Laenen, Roelants, Devlieger, & Vandermuelen, 2015). From the healthcare workers' points of view, barriers to maternal vaccination have included a lack of sufficient training and reimbursement as well as increased workload (Wilson et al., 2015).

A review of published literature from 2005 to 2015 conducted by MacDougall and Halperin (2016) identified that safety concerns were the most commonly cited barriers for patients and healthcare providers. In addition, other barriers to achieving high maternal vaccination rates included perception of poor vaccine effectiveness, lack of knowledge on disease burden, decreased perceived risk of disease, inadequate time, social norms, family influence, and religion (MacDougall & Halperin, 2016). There were also systemwide barriers noted such as insufficient staffing, inadequate facilities, issues on vaccine purchase and storage, and challenges or lack of reimbursement for vaccination. A high level of knowledge about the vaccine, increased perceived risk of the disease, disease severity and susceptibility, a desire to protect their babies and themselves, and trust in recommendations by authorities were all predictive of improved vaccine uptake during pregnancy. Therefore, promoters of maternal immunization included safety information on vaccine use in pregnant women and a strong national recommendation urging all pregnant women to get vaccinated. According to MacDougall and Halperin's review (2016), certain evidence-based interventions such as reminders to pregnant women through text messaging, chart reminders for healthcare reminders, and standing orders facilitated improvement in maternal vaccination uptake. Additional patient and physician education have also had a positive impact in increasing maternal vaccination uptake.

According to the most recent CDC-sponsored internet panel survey of 297 women who did not receive Tdap vaccine conducted by the CDC in 2017–2018, the most common barrier to vaccination among women between ages 18–49 was a lack of awareness on the need to get vaccinated (45.1%), wherein 31.6% did not receive the vaccine during pregnancy because they were vaccinated previously, and 13.5% did not know they were supposed to get the vaccine

during each pregnancy (Kahn et al., 2018b) (Figure 11). The second most common reason for not receiving the vaccine was safety concerns about risks to the baby.

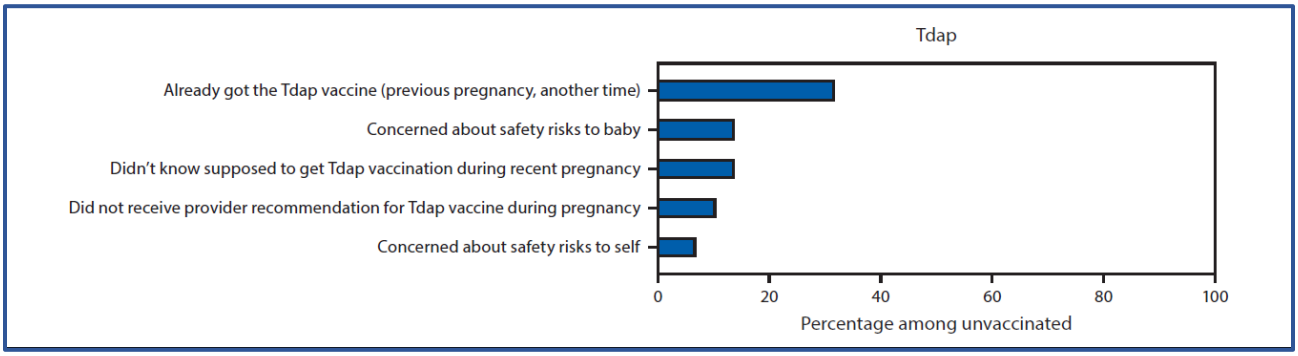

Figure 11. Graph of Reasons for Not Receiving Tdap, US, April 2018 from Kahn et al., 2018b. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6188122/.

While there are challenges to increasing vaccination in pregnant women, there are guidelines and interventions in place that aim to encourage pregnant women to be vaccinated. The ACIP created two recommendations for Tdap vaccinations during pregnancy, the second of which was created in October of 2012 and recommended that the Tdap vaccine should be administered during each pregnancy between 27 and 36 weeks 6 days gestation (Butler et al., 2017). This was then later approved by the CDC as well. Several other interventions have attempted to increase prenatal vaccination as well, including health communication messages and communication strategy training for physicians (Wilson et al., 2015). These were cursory interventions and did not consider the reasons why specific barriers to vaccination exist in different populations of pregnant women.

Other interventions for which further evaluation of effectiveness is needed include patient reminder systems, clinic-based interventions, and education on vaccine safety (Butler et al., 2017). These interventions are slightly more specific, but in order to make the greatest impact on vaccination rates among pregnant women, it is necessary to have a comprehensive understanding

of the different populations' and individuals' beliefs and ideas towards vaccination. Wilson et al. (2015) suggested doing this by conducting ethnographies of communities, holding interviews and focus groups for individuals, and understanding socio-political influences on vaccination. Given the need for improvement, the National Institute of Health has made strides towards increasing maternal vaccination by hosting and participating in meetings and workshops with several other partner organizations including the Department of Health and Human Services and its individual divisions, the WHO, and nonprofit organizations (Rubin, Koso-Thomas, Isaacs, Piper, Read, & Nesin, 2015). While this is a good start to advancing maternal vaccination, significant efforts are still needed to make the desired difference.

SUMMARY OF LITERATURE REVIEW

Despite the success of childhood vaccination programs with pertussis-containing cellular or acellular vaccines globally, the incidence of pertussis remains a public healthcare problem across both developed and developing countries. This is particularly important with respect to the risk for pertussis-associated morbidity and mortality in infants less than 1 year of age and infants less than 6 months of age who have no natural immunity to *B pertussis.*

Because treatment options for pertussis in immune-naïve infants, including antimicrobial or passive immunologic therapy, are limited, programs for maternal vaccination during the second or third trimester of pregnancy have been introduced in recent years. These programs have further reduced the incidence of neonatal pertussis, but barriers to vaccination, including suboptimal vaccination rates, limited success with cocooning vaccination strategies, awareness of and education on the importance of gestational vaccination, concern with vaccine safety, and underreporting of pertussis cases, continue to present gaps in further reduction in infant pertussis incidence and negative disease outcomes.

Although several systematic reviews have been published on the efficacy (immunogenicity) and safety of pertussis vaccination on both mother and infant disease outcomes, there is a need to undertake a more thorough systematic review focusing on real-world effectiveness. Previous reviews excluded certain kinds of studies (i.e., nonrandomized clinical studies) or they focused on safety outcomes. Also, earlier reviews had limited years of published literature since the recommendation to vaccinate all pregnant women against pertussis was made. Some reviews were not double coded to add validity to the studies selected. This review intends to include all studies that vaccinated pregnant women against pertussis and evaluated infant outcomes and it will be double coded. This systematic review synthesized published data from January 2011–December 2019 with broader study inclusion criteria as defined in this research paper. While post vaccination response rates have been suggested to be used as surrogate markers of protection (Olin, Hallander, Gustafsson, Reizenstein, & Storsaeter, 2001), there are not any agreed upon correlates of protection for pertussis (Plotkin, 2008; Switzer, D'Heilly, & Macina, 2019). This is particularly the case because of the waning immunity seen with aP vaccines. Therefore, extrapolation of data from serological evidence of persisting antibody geometric mean concentrations to conclude that infants are protected against pertussis is not possible. Consequently, it would not be possible to access the impact of preventing infant pertussis by vaccinating all pregnant mothers from only serological findings. Most systematic reviews of the past have focused mainly on immune responses. This review focused on vaccine effectiveness and infant outcomes such as incidence, mortality, and morbidity to better understand the impact maternal immunization has against pertussis.

METHODOLOGY

This research project was a systematic review of published literature regarding the impact of maternal vaccination against pertussis on infant outcomes by conferring passive immunity to newborns. The general belief is that infants of mothers vaccinated during pregnancy are better protected against pertussis than infants of mothers who are not vaccinated. The project aimed to answer three primary research questions.

Does the current literature on vaccinating women against pertussis during each pregnancy translate into:

1. Reduced pertussis incidence in infants?
2. Reduced pertussis morbidity in infants?
3. Reduced pertussis mortality in infants?

Relevant publications in the PubMed, Google Scholar, Clinicaltrials.gov, and Radford University McConnell Library electronic databases were identified by using the portal of Radford University McConnell Library. The time frame for the literature search was January 1, 2011 through December 31, 2019. These searches rendered all relevant published literature and key reports like Morbidity and Mortality Weekly Reports (MMWR) from the CDC. Because this project was a systematic review of existing data, neither sample size calculations nor Institutional Review Board approval was required. No human subject testing was conducted.

PubMed search strategies used index words, Medical Subject Heading (MeSH) terms, free text keywords, and phrases (Table 3). To maximize results in Radford University's McConnell Library and Google Scholar, search strategies included keywords in various combinations and as phrases. The search was limited to publications with abstracts in peer-

reviewed, academic journals written in English, but global in scope. In addition, only human studies were evaluated.

Table 3: Search Strategy Terms, Keywords, Phrases, and MesH Terms

Databases	Keywords/Free text/Phrases/ "MeSH terms"
PubMed McConnell Library Google Scholar ClinicalTrials.gov	1. Maternal vaccination impact on infant pertussis cases 2. Maternal pertussis vaccination infant outcomes 3. Maternal pertussis vaccination infant effectiveness 4. Maternal Tdap vaccination infant pertussis cases 5. Study maternal pertussis vaccination impact on infant pertussis cases "vaccine effectiveness" 6. Study maternal pertussis vaccination impact on infant pertussis cases "infant outcomes"

The study selection process was recorded according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines. A flow chart of the selection process is shown in Figure 12.

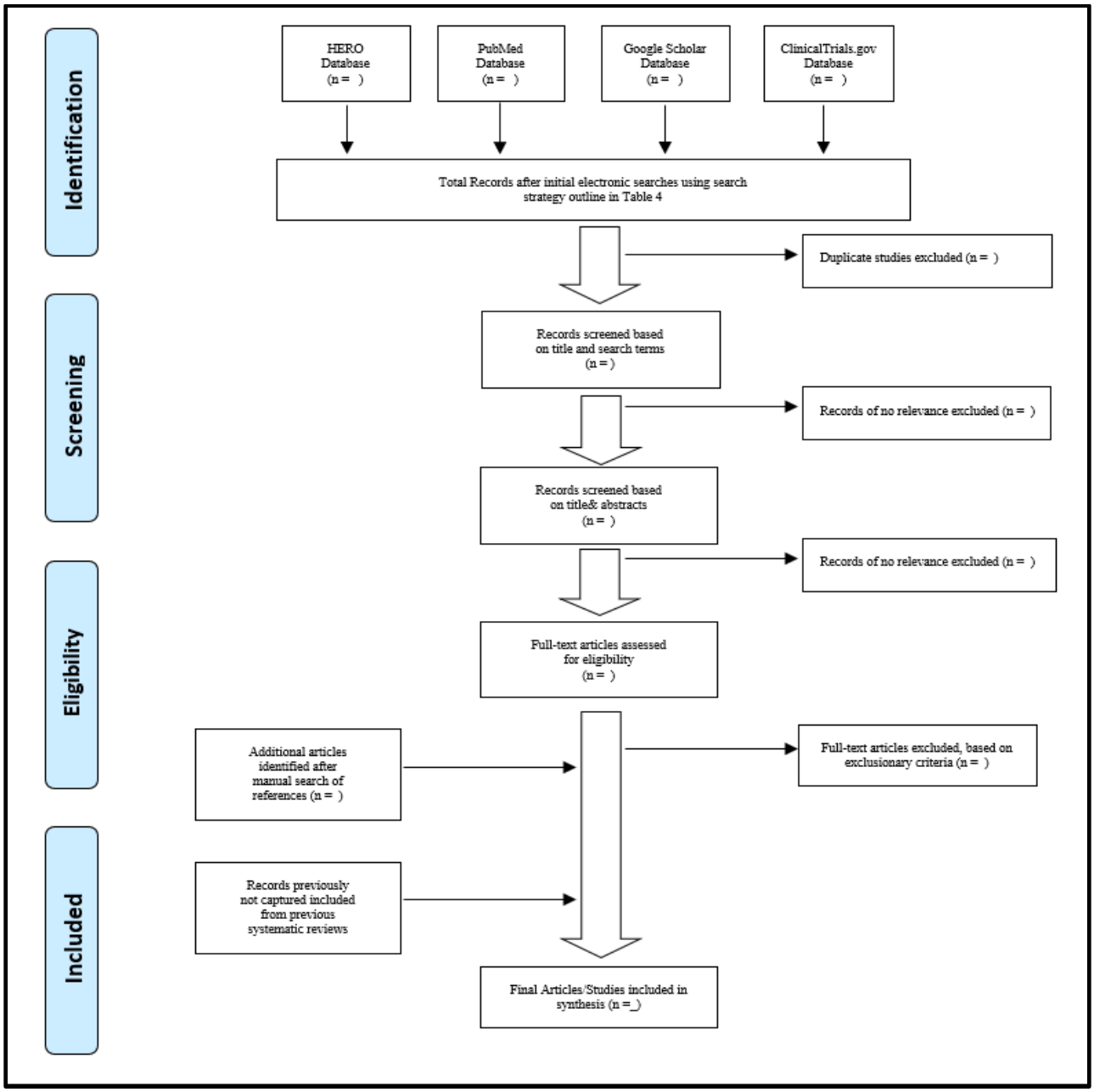

Figure 12. Systematic Review Process and Flow Adapted from PRISMA Flow Diagram by Moher, Liberati, Tetzlaff, & Altman, 2009.

The number of records identified during the initial electronic searches of each database were recorded, and duplicate publications were excluded. Next, the title of each publication was assessed, and articles with irrelevant titles were excluded. The next review step was to assess the abstracts of publications with relevant titles; publications whose abstracts lacked an

effectiveness, or an outcomes component were excluded. Abstracts of relevant publications were then reviewed to determine eligibility for inclusion or exclusion. In addition, after all the review-eligible studies were identified, the references sections of these publications were assessed manually to maximize the capture of relevant studies for evaluation. Finally, the references sections of previously conducted systematic reviews on maternal pertussis vaccination and its effect on infant pertussis were screened manually for any potentially missed relevant studies involving maternal vaccination and infant pertussis effectiveness. All publications that were identified and met the inclusion criteria were included to the final studies in the synthesis of data.

All relevant publications were compiled, and the characteristics and outcome data of the studies were entered into a table. Study characteristics included (but were not limited to) study title, authors of the publication, country of study, type of study and design, objectives, duration of study, sites, sample sizes of both maternal and infants included, test group, control group/comparator, participants/comparators, interventions (vaccine used), and infant effectiveness outcomes including incidence, morbidity, mortality, and other effectiveness outcomes included (Table 4).

Table 4: Data Extraction Table

Study Title & Link	Authors, Country/ Countries of Study	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Participants & Comparators	Interventions	Infant Outcomes				Biases/ limitations
				Mothers	Infants						I	M_1	M_2	O	

I= incidence, M_1=morbidity, M_2=mortality, O=other outcomes

In particular, details such as study centers and hospitals involved in the published study were included under “Study Setting.” Data included under “Participants” included mean age of mothers, infants’ age range, gestational age of infant when mother was immunized, infant sex, severity of condition, pertussis diagnostic criteria, study inclusion and exclusion criteria, and

comparators. Interventions included the type of pertussis vaccine used, length of exposure, and comparator used. Outcomes included prespecified objectives such as infant pertussis incidence, morbidity and mortality, and other outcomes such as pertussis-related hospitalizations that are directly involved with infant outcomes and vaccine effectiveness.

By using the data collected, each study was summarized to highlight how—in that study—vaccinating mothers against pertussis during pregnancy affected their infants. Based on the quality of data gathered and assessed during this systematic review, conclusions and recommendations regarding the value of vaccinating all pregnant women against pertussis were made, with the aim of stipulating the benefits and drawbacks of various immunization strategies in terms of infant pertussis incidence, morbidity, and mortality.

Types of Studies for Inclusion and Exclusion

This systematic review included all randomized controlled trials, interventional trials, trials that are not strictly randomized, and non-randomized trials, such as observational, cluster-randomized, and case studies. Included studies in this review were published between January 2011 through December 2019. In addition, the study population had pregnant women who received pertussis or pertussis-containing vaccines. If studies were observational studies, maternal pertussis vaccination policy must have been in effect. Those studies that had comparator groups were also included for this review. This test population was compared with mothers who received placebo, no vaccination, or a different pertussis or pertussis-containing vaccine during pregnancy. In addition, all relevant studies had at least one infant outcome endpoint, such as pertussis infection in infants 12 months of age and younger, complications due to pertussis (measured as number of hospitalizations), mortality due to pertussis in infants, and vaccine effectiveness measure. Studies without infant outcomes or with only maternal outcomes,

infant safety outcomes, studies with only immunogenicity data in terms of antibodies/geometric mean titers, as well as commentaries, systematic reviews, meta-analyses, modelling studies, theoretical papers, studies on vaccine uptake, vaccine perception studies, health economic studies, and opinions and letters to the editor were excluded. The target population is comprised of infants and/or can include mother–infant pairs.

Coding

A coding protocol (Appendix 1) was used to review selected studies. In order to ensure data extraction accuracy, double coding was conducted by the primary author and another study team member independently. Each member completed data extraction separately and then answered questions with either "Yes" or No" for inclusion and exclusion criteria. This process was tested by using the Kappa coefficient (Statistics Solutions, 2019) to measure inter-rater reliability. Cohen's kappa coefficient (two raters) (Appendix 3) was used to determine data reliability percentage (McHugh, 2012).

RESULTS

The researchers conducted a systematic review of literature in the English language, following the PRISMA framework, to identify studies reporting infant pertussis outcomes in response to maternal pertussis vaccination. An initial search yielded 18,220 records through database searching from January 1, 2011 through December 31, 2019. This number was later reduced to 2,881 with the addition of specific key words (Figure 13). These records were further reduced to 2,714 after de-duplication. One completed study that looked at the effectiveness of vaccinating mothers against pertussis in young infants, according to clinicaltrials.gov, was excluded because the study had not been published yet. Initial review of titles resulted in the exclusion of 2,618 records, leaving 96 records for abstract review assessment for eligibility. Another 72 records were further excluded for the lack of required inclusion criteria of maternal pertussis vaccination and infant pertussis outcomes. Twenty-four records were selected and assessed using the coding protocol and tool (Appendix 4). Five more records were additionally excluded for the lack of necessary inclusion criteria. Finally, 19 peer-reviewed full-text publications were included for analysis and synthesis within this systematic review.

Double coding was conducted for 24 studies. Inter-rater reliability for each of the included 19 studies was “almost perfect” at a kappa value of 1.0. Perfect alignment was achieved among both the raters on all screening questions for each study (Table 5). There were five studies that both raters decided should be excluded from the review. Inter-rater reliability for these studies is also provided in Tables 6 and 7. Perfect alignment was not reached for three out of the five excluded studies. There was one question for these three studies that the raters originally did not align on, lending to a moderate inter-rater reliability with kappa of 0.6. The

raters had perfect alignment for the remaining two excluded studies, achieving an “almost perfect” inter-rater reliability with a kappa of 1.0.

Figure 13: **Study Flow Diagram of Database Searches from January 1, 2011 through December 31, 2019**
(Adopted &Modified PRISMA Flow Chart)

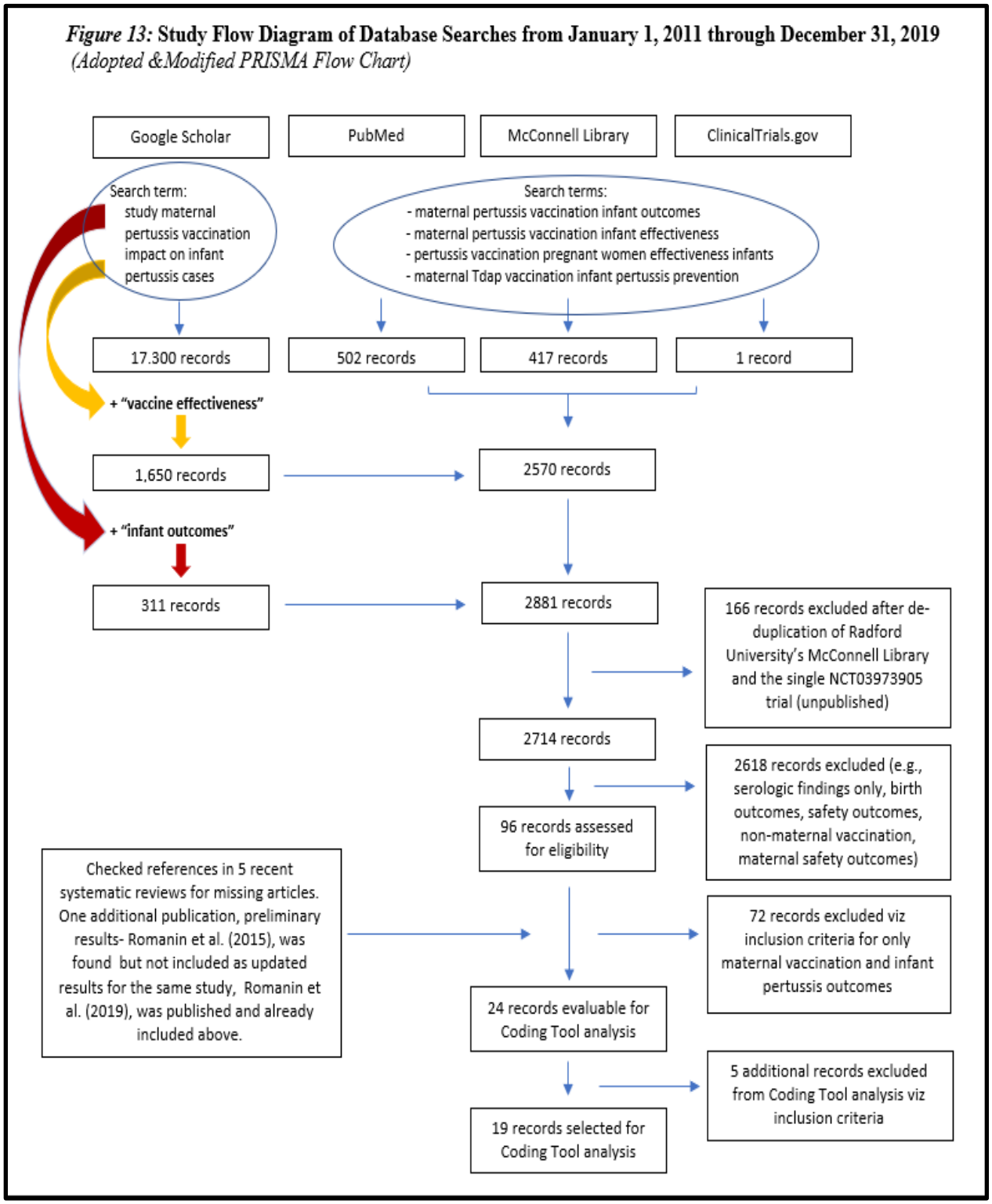

Table 5: Kappa Calculations for Included Studies

Kappa Calculation for 19 Studies Included in the Review *(Both raters agreed on all inclusion and exclusion criteria for each of the 19 studies). Data for these tables can be found in Appendix 4.*

	Inclusion criteria present & exclusion criteria absent in study	Inclusion criteria absent & exclusion criteria present in study	Subtotal
Inclusion criteria present & exclusion criteria absent in study	8	0	8
Inclusion criteria absent & exclusion criteria present in study	0	0	0
Subtotal	8	0	8

Observed agreement = (A+D)
*Expected agreement = (((A+B) *(A+C)) +((C+D) *(B+D)))/(A+B+C+D)*
Kappa = ((Observed agreement) – (Expected agreement))/((A+B+C+D) – (Expected agreement))

Observed agreement: (8+0) =8
Expected agreement= ((8)(8) +(0)(0)/8=64/8=8
Kappa= 8-8/8-8= 1

*Calculations were not repeated 19 times because the figures/sums for study were the same.

The inter-rater reliability had a value of kappa at 1 for all included studies.

****

Table 6: Kappa Calculations for Three Excluded Studies

Kappa Calculation for 3 out of the 5 studies. *Data for table found in Appendix 4.*

	Inclusion criteria present & exclusion criteria absent in study	Inclusion criteria absent & exclusion criteria present in study	Subtotal
Inclusion criteria present & exclusion criteria absent in study	6	1	7
Inclusion criteria absent in studies& exclusion criteria present in study	0	1	1
Subtotal	6	2	8

Observed Agreement: (6+1) =7
Expected agreement= ((7)(6) +(1)(2)/8= 44/8=5.5
Kappa= (7-5.5)/ (8-5.5) =0.6

Calculations were not repeated three times (one of each study of the three excluded) because the figures/sums for study were the same.

For three of the excluded studies the inter-rater reliability was moderate with a kappa of 0.6.

Table 7: Kappa Calculation for Two Excluded Studies *(Data for table found in Appendix 4)*

	Inclusion criteria present & exclusion criteria absent in study	Inclusion criteria absent & exclusion criteria present in study	Subtotal
Inclusion criteria present & exclusion criteria absent in study	6	0	6
Inclusion criteria absent & exclusion criteria present in study	0	2	2
Subtotal	6	2	8

Observed Agreement: (6+2) =8
Expected agreement= ((6)(6) +(2)(2)/8= 40/8=5
Kappa- 8-5/8-5=1

Calculations were not repeated two times (one of each study of the two excluded) because the figures/sums for study were the same.

For two of the excluded studies the inter-rater reliability had a kappa of 1.0.
****

All 19 studies included in this review included women who were vaccinated during pregnancy and reported on some infant outcome pertaining to pertussis, such as confirmed cases, hospitalizations, respiratory infections, or deaths. Most studies were retrospective cohorts or case studies. There were also epidemiologic surveillances and one prospective observational study. Studies that only reported on efficacy through serologic geometric antibody mean concentrations were excluded. There were not any randomized controlled trials included for synthesis in this systematic review. All studies focused on infant outcomes/vaccine effectiveness in a real-world setting demonstrating the impact the maternal pertussis vaccination on infants too young to get vaccinated. Among the 19 studies, two were published in 2014, four in 2016, five in 2017, five in 2018, and three studies were published in 2019. There were seven studies in the United States, three from the United Kingdom, three from Argentina, two from Spain, one from Brazil, Colombia, Australia, and New Zealand. Given that the United States was the first to implement the maternal pertussis vaccination policy, it is no surprise that they had the most data around

vaccine effectiveness and infant outcomes. Findings from each study are summarized in this section.

Dabrera et al. were the first to publish a case control study in February of 2014 with data from England and Wales. The primary aim of the study was to measure pertussis vaccine effectiveness per the rate of maternal vaccination among infant pertussis cases versus a no pertussis control infant cohort. The study took place from October 2012 through July 2013 and included 58 confirmed infant pertussis cases (PCR/Culture positive for *B. pertussis*) and 55 controls among infants less than 8 weeks of age. Of the 58 infant pertussis cases, 10 cases (17%) were in infants of women who were vaccinated during pregnancy. Among the 55 controls, 39 mothers (71%) were vaccinated during pregnancy. The unadjusted odds ratio (OR) for the rate of maternal pertussis vaccination was significantly lower in mothers of pertussis-positive infants than in mothers of pertussis-negative infants (OR: 0.09; 95% confidence interval [CI], 0.03–0.23]), yielding an unadjusted vaccine effectiveness of 91% (95% CI, 84–95%) and of 93% (95% CI, 82–95%) when adjusted for sex, geographical area, and birth period. No statistically significant difference was observed for hospital stay among the pertussis cases from mothers who were or were not vaccinated during pregnancy.

Amirthalingam et al. were the next to publish in October of 2014 regarding the effectiveness of maternal pertussis vaccination in infants in England. This study included data from January 1, 2008 through September 3, 2013. Of note, after the resurgence of pertussis in 2012 in England, the government implemented the maternal pertussis immunization program. This made the period of interest for this study as October 1, 2012 through September 3, 2013. During this time frame, there were 26,684 women who had a live birth in the Clinical Practice Research Link Datalink and the average pertussis vaccine coverage was 64%. There were 82

laboratory confirmed pertussis cases in infants under 3 months of age at onset of disease. Vaccine effectiveness was calculated as 91% in infants younger than 3 months of age (95% CI, 88–94%). When analysis and calculations were restricted to infants under 2 months of age, vaccine effectiveness was 90%.

Amirthalingam et al. published an additional follow-up study in 2016 to determine sustained effectiveness of vaccinating pregnant women against pertussis to protect their infants too young to be immunized. This study included births from October 1, 2012 through August 31, 2015, a time period in which maternal pertussis vaccination was in place. There were 72,781 live births during this period. Maternal vaccine coverage for pertussis was between 50–62% from 2012 through December 2013 with coverage being as high as 78% in January 2013 and 70% from January through August of 2015. In this retrospective study, 243 infant pertussis cases were eligible for inclusion and 35 of these cases were born to mothers who were vaccinated during pregnancy. Once again, vaccine effectiveness calculated for infants under 3 months was 91% (95% CI, 88–94%). and for those infants under 2 months was 90% (95% CI, 86–93%).

Winter, Cherry, and Harriman (2016) conducted a retrospective cohort study of infant pertussis hospitalization parameters and death using data from the CDPH of infants <63 days of age, born from January 2011 through December 2015. There were 752 live births, of which the respective maternal vaccination status was known for 420 live births; 49 mothers received Tdap vaccination during pregnancy and 371 mothers did not receive the vaccine. Infants of mothers who received Tdap versus no maternal Tdap during pregnancy demonstrated that hospitalizations, duration of hospital stays, intensive care unit (ICU) admission, and deaths were all lower in the infants of mothers who received Tdap vaccine during pregnancy—Hospitalization: 43% vs. 73% ($p < 0.001$), Relative Risk (RR): 0.47 (95% CI, 0.35–0.63);

duration of hospital stay: 3 days vs. 6 days ($p = 0.02$); ICU admission: 13% vs. 30% ($p = 0.01$), RR: 0.80 (95% CI, 0.70–0.91); and death: 0 vs. two ($p > 0.99$). Vaccine effectiveness for preventing hospitalization was 72.3% (unadjusted) or 58.3% (adjusted), whereas vaccine effectiveness for preventing hospitalization in infants of mothers who received Tdap in the third trimester was 75.4% (unadjusted) or 52.1% (adjusted).

Winter, Nickell, Powell, and Harriman (2016) also conducted a retrospective cohort study with 2013–2014 CDPH data to assess overall maternal pertussis vaccine effectiveness and with respect to timing of gestational vaccination (third trimester vs. postpartum) on the number of reported pertussis cases in the respective infants ≥12 weeks of age and infants <8 weeks of age. According to the CDPH, in 2013 and 2014, there were a total of 994,971 live births in California with a gestational age ≥27 weeks and a birth weight ≥500 g. Only 74,791 of the total live births had a recorded Tdap vaccine dose administered during the pregnancy or within 14 days after delivery. However, 287 mother-infant pairs were excluded for having a gestational age <27 weeks or a birth weight of <500 g, leaving the remaining 74,504 mothers as the included cohort for this study. A total of 42,941 (58%) were vaccinated during pregnancy and 31,563 (42%) were vaccinated within 14 days of delivery. During 2013–2014, CDPH reported a total of 1,562 pertussis cases in infants <12 months of age. In the cohort for this study (74,504), there were 119 pertussis cases at <1 year of age (an incidence of 1.6 cases per 1000 births). Of these, 35 (29%) cases were ≤12 and 25 cases (21%) were <8 weeks of age. The study demonstrated that infants born to mothers vaccinated with Tdap during pregnancy were less likely to have pertussis at <8 or ≤12 weeks of age (both were $p = .01$). However, there was no statistical difference observed in the risk of pertussis among all infants <1 year of age ($p = 0.11$) compared with infants born to women vaccinated postpartum. Additionally, infants born to mothers receiving maternal Tdap

vaccination during 27–36 weeks gestation were less likely to have pertussis at ≤12 weeks of age compared with infants whose mothers received Tdap during pregnancy but outside of 27–36 weeks gestation (77% received Tdap from 27–36 weeks gestation, 14% in the first or second trimester, and 9% after 36 weeks gestation but before delivery – OR: 0.22; 95% CI, .08–.63). The overall adjusted vaccine effectiveness of Tdap vaccination at 27–36 weeks gestation was 85% for preventing pertussis in infants <8 weeks of age and 72% in infants ≤12 weeks of age, compared with postpartum Tdap vaccine administration within 14 days of delivery. Data were adjusted for maternal and infant covariates such as mother's ethnicity, number of prenatal visits, prior births, payer, mother's country of birth, infant's birth weight, and gestational age.

Vizzoti et al. (2016) conducted a retrospective epidemiologic surveillance study to determine if there was any impact on infant outcomes in Argentina after the implementation of the maternal Tdap vaccination policy in February 2012, following a record year of pertussis cases and fatalities in 2011. The study analysis was done on cases identified from January 2010 through December 2013. The greatest reported incidence and mortality were among infants <2 months of age. According to the Argentinian Ministry of Health, maternal Tdap vaccination coverage reached 50.9% in 2012 and increased to 67.2% in 2013. Maternal Tdap vaccination resulted in an overall statistically significant 51% decrease in reported pertussis cases among infants <2 months of age in areas of high maternal vaccination coverage, defined as greater than 50%, relative to areas of low (≤50) vaccination coverage (95% CI, 67–35%; p = 0.001). The number of deaths also decreased by 87% from 76 fatalities in 2011 to 10 deaths (0.9 per 100,000) in 2013.

Khodr, Bukowinski, Gumbs, and Conlin (2017) assessed the association between timing of maternal Tdap vaccination during pregnancy and acute respiratory infection (ARI) including

pertussis in infants <2 months of age by conducting a retrospective cohort study. The rationale for the study was that pertussis is a respiratory infection that can be misdiagnosed and often unidentified. This study included 99,434 infants born to active duty military women from 2006 through 2013. Data was secured from the Department of Defense Birth and Infant Health Registry. Infants of Tdap vaccinated mothers anytime during pregnancy compared to unvaccinated mothers were 9% less likely to be diagnosed with an ARI at <2 months of age (RR: 0.91; 95% CI, 0.84–0.99). This risk was additionally lowered by 17% if mothers received Tdap between 27 and 36 weeks of pregnancy (RR: 0.83; 95% CI, 0.74–0.93).

Baxter, Bartlett, Fireman, Lewis, and Klein (2017) studied the effectiveness of maternal pertussis vaccination for protecting infants <2 months of age and in the first year of life followed through the primary DTaP vaccination series. Researchers carried out a retrospective cohort study of infants born from 2010–2015 in Kaiser Permanente Northern California Hospitals. The study cohort included 148,981infants in which the mothers of 68,168 (45.8% of the cohort population) infants received Tdap during the pregnancy or at least 8 days prior to delivery. There were 17 pertussis cases among infants <2 months of age and 110 pertussis cases in infants <1 year group (only 103 were followed up for the 12 months). Out of the 17 cases, only one case was from a mother vaccinated during pregnancy. Among the full cohort of 148,981, vaccine effectiveness at protecting infants <2 months of age against pertussis was 91.4% and 69% during the entire first year of life. More specifically, vaccine effectiveness was 87.9% before infants had any DTaP doses. The study also looked at vaccine effectiveness between doses until completion of the primary DTaP series (81.4% between doses 1 and 2, 6.4% between doses 2 and 3, and 65.9% after three DTaP doses).

Bellido-Blasco, Guiral-Rodrigo, Míguez-Santiyán, Salazar-Cifre, and González-Morán (2017) carried out a 1-year (March 1, 2015 to February 29, 2016) prospective case-control study in the Valencian community of Spain to assess the effectiveness of maternal pertussis vaccination on their infants <3 months old. There were 22 pertussis cases and 66 matched controls from same clinical practices and maternity wards. Among the 22 cases, 18 were hospitalized. Only five of the infant pertussis cases were from vaccinated mothers. In the remaining 17 cases, mothers were not vaccinated. In 41 of the 66 controls, mothers were vaccinated. In this study, all women had their pertussis vaccination between 28 and 36 weeks of gestation and 15 to 89 days before delivery. The unadjusted OR of vaccinating women during pregnancy to prevent pertussis in infants <3 months was 0.080 (95% CI, 0.017–0.371), making vaccine effectiveness 92%. The adjusted vaccine effectiveness was close at 90.9%. Sub-studies demonstrated vaccine effectiveness of 95.4% ($p = 0.022$) for maternal vaccination (with artificial breastfeeding) and 96.7% ($p = 0.005$) for vaccination and breastfeeding.

Skoff et al. (2017) evaluated the impact of maternal Tdap vaccination on the prevention of pertussis in infants <2 months of age. This case-control study used data from six U.S. Emerging Infection Program Network states ranging between January 1, 2011 and December 31, 2014. A final cohort of 240 cases and 535 controls were included in the evaluation. Among the cases, 17 (7.1%) mothers were vaccinated with Tdap in the third trimester of pregnancy and 90 (16.8%) mothers among controls. Vaccine effectiveness for maternal Tdap vaccination in the third trimester of pregnancy at preventing pertussis in infants <2 months was 77.7%. Vaccine effectiveness was 90.5% against hospitalizations. However, vaccine effectiveness was only 4.9% when mothers were vaccinated in the postpartum period.

Reynolds, Grant, Thornley, and Hale (2017) did a retrospective surveillance study in New Zealand from April 1, 2015 through March 31, 2016 on the number of infant pertussis cases. New Zealand introduced vaccinating pregnant women in 2011 as a response to recent pertussis epidemics. Data was secured from the Auckland Regional Public Health Service. During that time frame, there were 18 confirmed pertussis cases in infants aged <20 weeks. Most of the cases (16) were in infants ≤12 weeks. Fifteen of the 18 cases (83.3%) were in infants of unvaccinated mothers, whereas three cases (16.7%) were in infants born to Tdap-vaccinated mothers. This demonstrated that there was low maternal vaccine uptake in the Auckland region.

The U.S. based, case-control study by Sukumaran et al. (2018) was included in this analysis for one reason. The study included respiratory hospitalizations as infant outcomes in the first 6 months of life, specifically those defined by ICD-9 code 033, which is a pertussis case. There were 413,034 infants included in the evaluation from January 1, 2004 through December 31, 2013. At least one or more hospitalizations were identified in 25,222 infants and 157 infants died. There were 4,644 (18.4%) hospitalizations due to respiratory causes of which 105 (2.2%) had an influenza ICD-9 code (487, 488), and 137 (3%) had a pertussis ICD-9 code (033.0, 033.9). Among the 157 deaths, 14 (9%) had a respiratory cause of death, albeit not due to influenza or pertussis per laboratory and medical record review. The authors did find a protective association between vaccinating mothers with Tdap during pregnancy and infant respiratory hospitalizations. According to the study, the odds of maternal Tdap vaccination were significantly lower in infants hospitalized due to respiratory causes (adjusted OR: 0.79; 95% CI, 0.67–0.94; p= .007) versus controls not requiring hospitalization.

A matched case-control study was conducted between August 16, 2015 and August 17, 2016 in New South Wales, Australia by Saul et al. (2018). There were 117 pertussis cases and

117 controls recruited. The overall adjusted vaccine effectiveness estimate was non-significantly protective for infants <6 months old at 39% (OR: 0.61; 95% CI, 0.34–1.12). Adjusted vaccine effectiveness was higher for infants <3 months old at 69% (OR: 0.31; 95% CI, 0.11– 0.87) and against hospitalization at 94% (OR: 0.06; 95% CI, 0.01–0.41).

Gentile et al. (2018) carried out a retrospective epidemiologic surveillance study comparing incidence of confirmed pertussis, related hospitalization, and mortality in infants <3, <6, and <12 months of age born to mothers prior to maternal Tdap vaccination strategy implementation (2003–2011) and after (2013–2016). All confirmed pertussis cases were from "Ricardo Gutierrez" Children's Hospital between December 1, 2003 and December 31, 2016 in Argentina. There were a total 1,046 suspected cases, but only 337 were confirmed and only 308 cases were included in the analysis. A total of 237 cases were from infants of unvaccinated mothers and 71 cases in infants of mothers vaccinated during the pregnancy. Cases in the pre-maternal vaccination period were younger (3 months) compared to cases in the post-maternal pertussis vaccination period (9 months) ($p = 0.001$). The study also showed a statistically significant decrease in the pertussis hospitalization rate (22.3 [pre] vs. 11.6 [post]) (86.9% vs. 67.6%; $p < 0.001$) when comparing the pre-maternal vaccination group to the post-maternal vaccination group. In addition, the mortality rate in the pre-maternal vaccination group (14 cases) was 5.9%, while there were no deaths in the post-maternal vaccination group ($p = 0.036$).

Becker-Dreps et al. (2018) conducted a nationwide observational cohort study in the United States of pregnant women and their infants (defined in this study as age ≤18 months) delivered between June 2010 and December 2014. Researchers used commercial insurance claims data to identify women that received Tdap during their pregnancies, and hospitalizations and outpatient visits for pertussis in their infants (≤18 months). Comparisons were made between

infants of mothers who received Tdap during their pregnancy and infants of unvaccinated mothers. Out of 1,079,034 live births recorded between 2010 and 2014, a total of 675,167 (62.6%) were successfully matched to a newborn. Therefore, 675,167 mother–infant pairs were in the study cohort. A total of 90,445 (13.4%) women received prenatal Tdap defined as vaccinated during pregnancy but >2 weeks prior to delivery. A postpartum vaccinated group included 36,470 (5.4%) women who were vaccinated with Tdap on the day of or within 7 days after giving birth, along with 5,872 (0.9%) women who were vaccinated in the 2 weeks prior to delivery. For infants of mothers vaccinated prenatally with Tdap, the rate of overall diagnosed pertussis was 43% lower (Hazard Ratio (HR) = 0.57; 95% CI, 0.35–0.92), and the rate of inpatient only diagnosed pertussis hospitalization was 68% lower (HR = 0.32; 95% CI, 0.11–0.91) compared with infants whose mothers did not receive prenatal or postpartum Tdap. Pertussis rates were especially lower for infants whose mothers received Tdap during the third trimester (≥27 weeks gestation until 2 weeks prior to delivery). Reductions in rates of pertussis were not seen in infants of mothers vaccinated with Tdap at <27 weeks of gestation (HR for pertussis = 1.10). When evaluating prenatal Tdap effectiveness by timing of immunization, infants whose mothers received prenatal Tdap ≥27 weeks experienced 58% (HR = 0.42; 95% CI, 0.23–0.78) lower rates of pertussis and 70% (HR = 0.30; 95% CI, 0.09–0.97) lower rates of inpatient only pertussis compared with infants of unvaccinated mothers.

Hincapié-Palacio et al. (2018) conducted a cohort study from eight randomly selected hospitals in Medellin and nine municipalities in the metropolitan area of Antioquia, Colombia from December 2015 through April 2016. While the researchers focused more on serological findings, they also reported on infant pertussis cases and deaths. A total of 1,005 mothers, 805 in cohort 1 and 200 in cohort 2, were enrolled. A total of 745 (74.13%) vaccinated and 260

(25.87%) unvaccinated mothers were included in the study. Twenty-five (12.50%) mothers of cohort 2 were not vaccinated at the time of delivery. A total of 896 (719 in cohort 1 and 177 infants in cohort 2) children (89.15%) were followed from birth through their first 6 months. There were two confirmed infant pertussis cases from the maternal Tdap vaccinated group and no confirmed infant pertussis cases from unvaccinated mothers. Seven infants died (0.70%), of which five were vaccinated mothers and two were unvaccinated mothers, but death certificates did not list pertussis as cause of death. While there were 21 probable pertussis cases according to mothers or relatives, they were not confirmed clinically or by laboratory criteria. Samples were not taken from any infants for ethical and cultural reasons. Therefore, vaccine effectiveness of vaccination could not be estimated due to the lack of confirmed pertussis cases in infants of unvaccinated mothers.

Uriarte, Rodríguez, Sancristobal, and Agirre (2019) focused on pertussis in infants under 3 months of age in Bizkaia, Basque Country in Spain. The researchers did a retrospective case study for the incidence of pertussis in infants <3 months of age born to Tdap-vaccinated (27–36 weeks gestation) mothers from February 1, 2015 through January 31, 2016. This was specifically done after the recommendation was made that all pregnant women should get vaccinated against pertussis. During this period, pertussis vaccination coverage among pregnant women aged 18–50 years was 93.7%. There was a total of 1,035 cases of pertussis across all age groups and 19 cases in infants <3 months. Twelve cases out of the 19 cases in infants had mothers who were vaccinated during pregnancy. Uriarte et al. calculated vaccine effectiveness of 89%, based on number of reported cases in infants from vaccinated mothers/dTap coverage rates in pregnant women.

Romanin et al. (2019) conducted a matched case-control study in Argentina to assess the effectiveness of maternal Tdap in preventing pertussis among infants aged <2 months. The study took place from September 2012 to March 2016 over two time periods (September 24, 2012 to March 31, 2014; December 1, 2014 to March 31, 2016) to achieve the required sample size. The final analyses only included 71 case patients and 300 controls. In this cohort of 371, there were 269 women who were considered as vaccinated while the remaining 102 were considered as unvaccinated. It was observed that 35 (49%) of the 71 case patients and 234 (78%) of the 300 controls had mothers who were vaccinated during the current pregnancy. The overall adjusted vaccine effectiveness of maternal Tdap was estimated to be 80.7% (OR: 0.19; 95% CI, 52.1–92.2). Similar effectiveness was found whether Tdap was administered during the second or third trimester of pregnancy.

Fernandes et al. (2019) conducted a case-control study that included infants <2 months of age from three metropolitan cities in Sao Paulo, Brazil to study the effectiveness of maternal pertussis vaccination in protecting newborn infants. The data was gathered from February 1, 2015 through July 31, 2016. A total of 42 pertussis incident cases and 249 controls were included in the analysis. Out the total 291 infants <2 months of age in this cohort, 151 infants (8/42 cases and 143/249 controls) had mothers who were vaccinated during pregnancy. There were 106/249 infant controls whose mothers were not vaccinated. There were 34 cases that occurred in infants whose mothers were not vaccinated against pertussis during pregnancy. This resulted in an unadjusted OR for vaccination in pregnancy of 0.17, and therefore, an unadjusted vaccine effectiveness of 82.6%.

Detailed data from the studies described are included in Table 8: Studies Included in the Systematic Review: Data Extraction Table.

Effectiveness Measures

Twelve studies reported on effectiveness measures. The range of adjusted vaccine effectiveness of preventing pertussis in infants less than 8 weeks to less than 3 months of age provided in 11 studies included in this review was 69–91.4% (unadjusted: 77.7–92%). Data particularly addressing studies with vaccine effectiveness detailed are listed in Table 9. One study looked at effectiveness in terms of severity of pertussis cases (Winter, Cherry, & Harriman, 2016) demonstrating that hospitalizations, duration of hospital stays, ICU admission, and deaths were all lower in the infants of mothers who received Tdap vaccine during pregnancy. Vaccine effectiveness at preventing hospitalizations was 72.3% (unadjusted) or 58.3% (adjusted). In infants of mothers who received Tdap in the third trimester, vaccine effectiveness was 75.4% (unadjusted) or 52.1% (adjusted).

Outcome Measures

There were also seven other studies included in this review that focused on infant outcomes such as incidence, morbidity, and mortality. Two of these studies (Gentile et al., 2018; Vizzoti et al., 2016) looked at pre-maternal pertussis vaccination strategy period versus post strategy implementation period. Both studies showed significantly lower numbers of pertussis cases and deaths post policy implementation. In addition, Gentile et al. (2018) showed a lower hospitalization rate due to pertussis in the post maternal vaccination implementation period. Another two studies (Becker-Dreps et al., 2018; Reynolds et al., 2017) also demonstrated lower rates of pertussis cases among the infants of vaccinated mothers versus unvaccinated cases. Becker-Dreps et al. (2018) also demonstrated a lower rate of hospitalization by 63% among infants of vaccinated mothers and the percentage was 70% if the mother was vaccinated in the third trimester. Two studies looked at respiratory infections in infants under 2 months of age

(Khodr et al., 2017 & Sukumaran et al., 2018). Both studies demonstrated a protective association of vaccination of pregnant women against pertussis and the hospitalizations due to respiratory infections. The last study reporting outcome measures of pertussis cases and deaths was by Hincapié-Palacio et al. (2018). The primary objective of this study focused on serological findings in maternal antibodies and infant umbilical cord antibodies along with the occurrence of pertussis in infants in the first 6 months of age. However, the study had several limitations. There were no cases of pertussis among infants of unvaccinated mothers. Vaccine effectiveness and attack rates could not be calculated. Infant samples could not be collected for ethical reasons and pertussis was not confirmed among infants that died, particularly those that had respiratory disease.

Study Findings Relating to Research Questions

In light of the lack of validated surrogate endpoints for assessing maternal vaccine effectiveness, such as threshold levels of specific anti-pertussis antibodies associated with infant protection from infection, this review chose to evaluate the impact of maternal vaccination on infants according to objectives identified earlier (page 9) as two research questions. Research question one asked "What is the pertussis incidence range and associated morbidity among infants born to mothers vaccinated and to those mothers not vaccinated against pertussis during pregnancy?," and question two, "What is the pertussis related mortality rate range among infants born to mothers vaccinated and to those mothers not vaccinated against pertussis during pregnancy?"

Regarding *Research Question 1*, 12 of the 19 studies included in this systematic review reported on maternal pertussis vaccine effectiveness, with 11 of these reporting the calculated percent reduction in pertussis case incidence and one study assessing the severity of pertussis

cases in infants born to Tdap-vaccinated mothers versus those from unvaccinated mothers. Two of the 12 studies provided relative vaccine effectiveness data on pertussis-related hospitalization (Skoff et al. 2017 and Saul et al. 2018) and two studies provided comparative percentages of pertussis-related hospitalization between vaccinated and unvaccinated mother/infant pairs (Dabrera et al. 2014 and Gentile et al. 2018).

Taken together, data from studies reporting vaccine effectiveness represent a robust examination of the impact of maternal pertussis vaccination on infant pertussis incidence and morbidity, given the sheer number of mother/infant pairs across the various retrospective and case-control studies that yielded dozens or hundreds of confirmed infant pertussis cases from vaccinated and unvaccinated mothers. The range of adjusted vaccine effectiveness of preventing pertussis in infants less than eight weeks to less than 3 months of age provided in the 11 aforementioned studies was 69–91.4% (unadjusted: 77.7–92%). In terms of actual cases numbers, maternal pertussis vaccination was associated with a reduction in pertussis incidence to 17–22% relative to unvaccinated infants: one of 17 cases (Baxter et al., 2017), 10 of 58 cases (Dabrera et al., 2014), and 8 of 42 cases in infants <2 months of age (Fernandes et al., 2019); 5 of 22 cases in infants <3 months of age (Bellido-Blasco et al. 2017); and 3 of 18 cases in infants <20 weeks of age (Reynolds, 2017). Other studies calculated vaccine effectiveness on the basis of recorded maternal vaccine coverage (screening method).

The single study assessing vaccine effectiveness in terms of severity of pertussis cases (Winter, Cherry, & Harriman, 2016) demonstrated that hospitalizations, duration of hospital stays, ICU admission, and deaths were all lower in the infants of mothers who received Tdap vaccine during pregnancy. Vaccine effectiveness at preventing hospitalizations was 72.3% (unadjusted) or 58.3% (adjusted). In infants of mothers who received Tdap in the third trimester,

vaccine effectiveness was 75.4% (unadjusted) or 52.1% (adjusted). Case-control studies by Skoff et al. (2017) and Saul et al. (2018) demonstrated maternal vaccine effectiveness against pertussis-related hospitalization of 90.5% and 94%, respectively, while the retrospective surveillance study by Gentile et al. (2018) showed a significant ($P < 0.001$) reduction in pertussis-related hospitalization incidence following implementation of the maternal vaccination program in Argentina. In contrast, the study by Dabrera et al. (2014) failed to show any demonstrable reduction in pertussis-related hospitalization according to maternal vaccination coverage data.

Five of the 19 studies included in this systematic review provided data on the protective capacity of maternal pertussis vaccination during different gestational periods. Collectively, results from these studies supported vaccination during the third trimester of pregnancy as the optimal period for eliciting production and prepartum passive transfer of protective anti-pertussis antibodies to newborn infants. Thus, in the retrospective cohort study by Winter, Nickell, Powell, and Harriman (2016), vaccine effectiveness against pertussis case incidence was 85% in infants <8 weeks of age and 72% in infants ≤12 weeks of age when mothers were vaccinated between 27 and 36 weeks of pregnancy, as compared with postpartum vaccination. Maternal vaccination at any time during pregnancy also increased vaccine effectiveness to 64% and 53% in infants <8 weeks and ≤12 weeks of age, respectively, compared with postpartum vaccination. Data from this study also suggested that vaccination during the early third trimester (27–31 weeks gestation) may be more effective than vaccination at >31 weeks gestation in reducing risk of infant pertussis. Similarly, Skoff et al. (2017) found that vaccine effectiveness against pertussis-related hospitalization decreased to only 4.9% when mothers were vaccinated in the postpartum period, compared with 90.5% effectiveness when mothers received Tdap during the third

trimester. Data from the study by Khodr et al. (2017) provided indirect evidence for greater risk reduction (17%) of acute respiratory infections in infants born to mothers vaccinated with Tdap between 27 and 36 weeks of gestation, while Becker-Dreps et al. (2018) demonstrated 58% lower rates of infant pertussis and 70% lower rates of inpatient infant pertussis when mothers were vaccinated at or after 27 weeks of gestation, compared with no vaccination. In contrast to these findings, Romanin et al. (2019) did not find any difference in infant pertussis case incidence when Tdap was administered to mothers during either the second or third trimester of pregnancy.

Regarding *Research Question 2*, "What is the pertussis related mortality rate range among infants born to mothers vaccinated and to those mothers not vaccinated against pertussis during pregnancy?," three studies included in this systematic review provided data supporting vaccine effectiveness against pertussis-related mortality. Epidemiologic data from Vizzoti et al. (2016) demonstrated that infant pertussis-related mortality decreased by 87% in the year following implementation of a maternal pertussis vaccination program; pertussis-related mortality was greatest in infants <2 months of age. No cases of pertussis-related mortality were found in infants born to vaccinated mothers (n = 49) in the retrospective cohort study by Winter, Cherry, and Harriman (2016), compared with two deaths reported in the infant cohort (n = 371) from unvaccinated mothers (difference not statistically significant). However, in the retrospective surveillance study by Gentile et al. (2018), maternal pertussis vaccination resulted in a statistically significant ($p = 0.036$) decrease in infant pertussis-related mortality (no deaths) compared with 14 infant deaths during the period prior to implementation of the Tdap maternal vaccination program in Argentina.

Biases and Limitations of Included Studies

Across the 19 studies included in the final coding analysis, a number of biases and limitations were detailed in the included published reports. However, none of the included studies had financial support from pharmaceutical companies. Therefore, the risk of that bias is low. Nonetheless, the following biases and limitations reported include:

- Low number of reported pertussis cases
- Possible misclassification of pertussis deriving from reliance on clinical criteria in the absence of laboratory (e.g., PCR) confirmation or inaccurate recall of vaccination status in patient surveys
- Heterologous classification of respiratory infections
- Ascertainment bias: milder pertussis cases being missed
- Selection biases: for example, data gathered from insured populations of individuals, which could theoretically translate into better health outcomes than the general population
- No ability to accurately calculate vaccine effectiveness based on lack of pertussis cases or data on maternal vaccination status
- Observational study impact on possible intergroup (i.e., vaccinated vs. none) variability
- Low coverage rate of maternal vaccination
- Reliance on statistical tools to estimate vaccine effectiveness in retrospective analysis
- Unmatched cases analysis using historical controls as comparators or lack of unvaccinated controls

- No available data on maternal vaccination status (despite the maternal pertussis vaccination policy being in place), so could not calculate actual vaccine effectiveness
- Possible influence of post-birth infant pertussis vaccination on outcomes
- Possible influence of seasonal pertussis incidence on outcomes in limited time frame (e.g., 12 months) studies
- Limitations of claims-based analyses include the possibility of misclassification
- Impact of mothers' antibody status prior to getting vaccinated
- Confounders like mother's educational status, access to healthcare, maternal age, and cohabitating school children with pertussis exposure

Table 8: Studies Included in Systematic Review: Data Extraction Table

Study Title & Link	Authors	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Infant Outcomes				Biases/ limitations	Other notable findings
				Mothers	Infants				Incidence	Mortality	Morbidity	Other Outcomes		
A Case-Control Study to Estimate the Effectiveness of Maternal Pertussis Vaccination in Protecting Newborn Infants in England and Wales, 2012–2013	Dabrera G, Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al.	Case-control study of maternal pertussis vaccine effectiveness (case incidence and hospitalization stay) in England and Wales of infants born between 22 October 2012 and 11 July 2013; measured VE (=1-OR for vaccination status)	Cases from multiple sites reported to Public Health England		58 pertussis cases vs 55 consecutive control infants (no pertussis) from same practices	9 months	58 pertussis cases	55 controls	The unadjusted odds ratio for vaccination in pregnancy was 0.09 (95% CI, .03–.23), giving an unadjusted vaccine effectiveness of 91% (95% CI, 77%–97%)		No statistically significant difference between these 2 groups in terms of length of hospital stay, according to the rank-sum test (P =0 .58).		Unmatched cases analysis; second analysis of two was done by questionnaire only	
Effectiveness of maternal pertussis vaccination in England: an observational study	Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al.	Prospective, observational study to assess the maternal Tdap vaccine effectiveness, assessed by screening method (number of pertussis cases from vaccinated mothers/estimated vaccine coverage rates)	Laboratory-confirmed pertussis cases and hospital admissions reported to Public Health England	26,684 women included in the Clinical Practice Research Datalink with a livebirth between Oct 1, 2012 and Sept 3, 2013 (after vacc program began)		69 months	Number of confirmed pertussis cases among 26,684 women included in the Clinical Practice Research Datalink with a livebirth between Oct 1, 2012 and Sept 3, 2013 (after vaccination program began)				Vaccine effectiveness based on 82 confirmed cases in infants born from Oct 1, 2012, and younger than 3 months at onset was 91%. Vaccine effectiveness was 90% in infants younger than 2 months		none listed	
Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction	Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, Andrews N.	Retrospective statistical analysis of Tdap maternal Tdap vaccination (dT5aP/IPV or dT3aP/IPV vaccine at <1 wk to >=8 wks pre-birth) on pertussis incidence ibn infants <3 months of age (screening method)	520 English general practices (CPRD) for confirmed pertussis cases from ImmForm and national CPRD database for vaccine coverage		72,781 live births	35 months	243 pertussis cases		Overall vaccine effectiveness of 91% (95% CI, 88-94%) in infants <3 months and 90% (95% CI, 86-93%)nfor infants <2 months of age	Estimated vaccine effectiveness for death was 95% (95% CI, 79-100%)			Small infant numbers in those receiving post-birth vaccinations may preclude conclusions around the potential imm. Blunting effect of maternal immunization	Calculated vaccine effectiveness decreased comparatively in infants born to vaccinated mothers (at least 7 d pre-birth) relative to number of sequential post-birth vaccinations
Effectiveness of Prenatal Tetanus, Diphtheria, and Acellular Pertussis Vaccination on Pertussis Severity in Infants	Winter K, Cherry JD, Harriman K	Retrospective cohort study on risk of pertussis severity (symptoms reduction), clinical course, and hospitalizaion in infants born to Tdap-vaccinated mothers vs non-vaccinated mothers (n=49 and 371, resp.)	CDPH Center for Health Statistics for the mother and infant and California Immunization Registry (CAIR) Tdap immunization records		Infants born to Tdap-vaccinated mothers vs non-vaccinated mothers (n=49 and 371, resp.)	5 years (most enrolled between 2014 and 2015)	49 infants born to Tdap-vaccinated mothers	371 infants born to non-vaccinated mothers			Infants born to vaccinated mothers were less likely to have paroxysmal cough (RR, 0.41; 95% CI, .25–.68), apnea (0.66; .47–.91), cyanosis (0.53; .39–.73), or whoop (0.78; .62–.99); the frequency of posttussive vomiting was similar between groups; also: lower risk of hospitalization (RR, 0.5; 95% CI, .4–.6) or ICU admission (0.8; .7–.9).		Misclassification of Tdap immunization based on immunization recall bias	

Table 8- Cont'd: Studies Included in Systematic Review: Data Extraction Table

Study Title & Link	Authors	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Infant Outcomes				Biases/ limitations	Other notable findings
				Mothers	Infants				Incidence	Mortality	Morbidity	Other Outcomes		
Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis.	Winter, K., Nickell, S., Powell, M., & Harriman, K.	Retrospective cohort study comparing incidence of pertussis in infants <8 and <=12 wks of age born to mothers vaccinated with Tdap at <=27 wks, 27-36 wks and >36 wks gestation, and those vaccinated within 14 days postpartum	California Immunization Registry	6092 mother/infant pairs (<=27 wks vacc.), 32,445 (27-36 wks vacc.), 3681 (>36 wks), and 31,563 (postpartum vacc.)		24 months	Mother/infant pairs from mothers vaccinated with Tdap during pregnancy	Mother/infant pairs from mothers vaccinated with Tdap postpartum	Adjusted vaccine effectiveness of 85% in infants <8 weeks of age and 72% in infants or ≤12 wks of age (both P = .01) for third trimester vaccination, compared to postpartum vaccination				Lack of an unvaccinated comparison group; retrospective surveillance study	Pertussis incidence was significantly greater in Infants <8 and <12 wks of age, born to mothers vaccinated during the second trimester
Impact of a maternal immunization program against pertussis in a developing country	Vizzotti C, Juarez MV, Bergel E, Romanin V, Califano G, Sagradini S, et al.	Retrospective epidemiologic surveillance study comparing incidence of pertussis-confirmed cases in infants <2, <6, and <12 months of age born to mothers prior to and after implementation of the maternal Tdap vaccination program in February 2012 (from 2010 to 2013); a Bayesian structural time-series model was used (no Tdap vaccination status known) to estimate pertussis incidence and mortality in high-coverage (proxy vaccinated) vs low-coverage (proxy non-vaccinated) regions	24 juristictions across Argentina Health Surveillance System		6865 pertussis cases and 134 case fatalities	4 years	Pertussis cases in high vaccine coverage states	Pertussis cases in low vaccine coverage states	Significant 51% (95% CI [-67%, -35%]; p = 0.001) reduction in calculated pertussis incidence in infants <2 months of age and 44% (95% CI [-66%, -24%]; p = 0.001) reduction in illness in infants 2-6 months of age	2.9 deaths per 100,000 pertussis-related cases in 2011 and 0.9 deaths per 100,000 in 2013 (estimated vaccine effectiveness=87%)		60% reduction in overall number of pertussis cases from 2821 cases (2011)to 1112 (2013)	No available data on maternal vaccination status, so could not calculate actual vaccine effectiveness; effect of disease seasonality on incidence reduction not known	
Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections	Khodr ZG, Bukowinski AT, Gumbs GR, Conlin AMS	Retrospective cohort study assessing association between maternal Tdap vaccination during pregnancy and infant actute respiratory infection (ARI, including pertussis) at <2 months of age	Active duty military women in the Department of Defense Birth and Infant Health Registry from 2006 through 2013		99, 434 infants	8 years	5726 infants from Tdap-vaccinated mothers of 99, 434 total infants		15 of 12,983 ARI cases were pertussis - 14 in infants from non-vaccinated mothers and 1 from Tdap-vaccinated mother (first trimester)			Tdap vaccination during 27 and 36 weeks of pregnancy had significantly lower rate of ARI vs infants from non-vaccinated mothers and mothers vaccinated pre-pregnancy	Heterogenous definition of ARIs; no breastfeeding data collected; could not confirm clinical cases with laboratory findings	
Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis	Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP	Retrospective cohort study assessing effect of maternal Tdap vaccination on infant (<2 months of age) pertussis incidence	Kaiser Permanente Northern California		148,981 newborns	6 years	68,168 infants from Tdap-vaccinated mothers	79,292 infants from non-vaccinated mothers	Estimated vaccine effectiveness of 91.4% at <2 months of age and 69.0% during first year of life after adjustment for the effects of DTaP vaccination				none listed	

Table 8- Cont'd: Studies Included in Systematic Review: Data Extraction Table

Study Title & Link	Authors	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Infant Outcomes				Biases/ limitations	Other notable findings
				Mothers	Infants				Incidence	Mortality	Morbidity	Other Outcomes		
The Impact of the U.S. Maternal Tdap Vaccination Program on Preventing Pertussis in Infants <2 Months of Age: A Case-control Evaluation	Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, et al.	Case-controlled study assessing effect of maternal Tdap vaccination on infant (<2 months of age) pertussis incidence based on percentage of Tdap maternal vaccination >=14 days before delivery	6 Emerging Infections Program Network (EIP) sites		240 cases and 535 controls were included in vaccine effectiveness analysis	48 months	240 pertussis cases	535 non-pertussis infants	Multivariable vaccine effectiveness estimate for Tdap administered during the third trimester of pregnancy was 77.7% (48.3% – 90.4%); vaccine effectiveness increased to 90.5% (65.2 – 97.4%) against pertussis-related hospitalized cases.				none listed	
A case–control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016	Bellido-Blasco J, Guiral-Rodrigo S, Miguez-Santiyan A, Salazar-Cifre A, Gonzalez-Moran F	Observational, case-controlled, stats models study to assess maternal vaccine effectiveness on pertussis incidence in newborns <3 months of age vs healthy controls	Territory of the Valencian Community (5 million inhabitants)		22 pertussis cases and 66 matched controls from same clinical practices and maternity wards	12 months	22 pertussis cases	66 matched controls (same practice as cases)	Vaccine effectiveness of 95.4% (P=0.022) for maternal vaccination (artificial breastfeeding) and 96.7% (P=0.005) for vaccination and breastfeeding; level of education and presence of children under 15 years-old in the home were also significant for statistical OR.				Observational study impact on possible intergroup (ie vaccinated vs none) variability	
Low uptake of maternal vaccination in notified pertussis cases aged less than 20 weeks	Reynolds G, Grant N, Thornley S, Hale M	Retrospective surveillance study of number of infant pertussis cases (2015-2016)	Auckland Regional Public Health Service		18 confirmed pertussis cases	12 months			15 of 18 cases (83.3%) in infants were born to non-Tdap-vaccinated mothers; 3 cases (16.7%) were in infants born to Tdap-vaccinated mothers				none listed	
Infant Hospitalizations and Mortality After Maternal Vaccination	Sukumaran L, McCarthy NL, Kharbanda EO, Vazquez-Benitez G, Lipkind HS, Jackson L, et al.	Matching case-control study assessing incidence of infant hospitalization and mortality during first 6 months of life, as stratified by vaccine type (any influenza vaccine +- Tdap), any Tdap vaccine +- influenza, and both influenza and Tdap vaccines in the same pregnancy	8 CDC-integrated health care organizations		413,034 infants from 500,447 pregnancies	10 years				157 infant deaths	25,222 infant hospitalizations	No association between infant hospitalization or death and maternal influenza or Tdap vaccinations	Data from an insured population, which could translate to better health outcomes than the general population.	

Table 8- Cont'd: Studies Included in Systematic Review: Data Extraction Table

Study Title & Link	Authors	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Infant Outcomes				Biases/ limitations	Other notable findings
				Mothers	Infants				Incidence	Mortality	Morbidity	Other Outcomes		
Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study	Saul N, Wang K, Bag S, Baldwin H, Alexander K, Chandra M, et al.	Matching case-control study assessing incidence of infant hospitalization and mortality during first 6 months of life	Public health unit staff in each local health district (LHD, the administrative divisions of the state health service)	117 infants aged <6 months at symptom onset, with laboratory or physician definitive evidence of pertussis	117 controls	12 months	117 infants aged <6 months at symptom onset, with laboratory definitive evidence of pertussis	117 controls	Overall vaccine effectiveness estimate was nonsignificantly protective for infants <6 months old (Vaccine effectiveness 39%, 95% CI -12 to 66%). Higher vaccine effectiveness was observed for infants <3 months old (VE 69%, 95% CI 13–89%)		Estimated vacine effectiveness of 94%, (95% CI, 59–99%) against hospitalization		none listed	Maternal dTap vaccination was highly effective at preventing severe disease in infants, but less effective at preventing less severe disease
Bordetella pertussis (Bp) disease: Before (2003–2011) and after (2013–2016) maternal immunization strategy in a pediatric hospital	Gentile A, del Valle Juarez M, Lucion MF, Martínez AC, Romanin V, Areso S, Mistchenko A	Retrospective epidemiologic surveillance study comparing incidence of pertussis-confirmed/related hospitalization/mortality in infants <3, <6, and <12 months of age born to mothers prior to (2003-2011) and after (2013-2016) maternal Tdap vaccination implementation periods	R. Gutiérrez Children's Hospital, Buenos Aires, Argentina		308 of 337 confirmed pertussis cases total (237 pre-vacc period and 71 post-vacc period)	13 years	237 pertussis cases during pre-vaccination policy years	71 pertussis cases during post-vaccination policy years			Post-vaccine policy period cases were older (3 vs 9 months, $p < 0.001$) and required less hospitalization (86.9% vs 67.6%, $p < 0.001$); hospitalization rates correlated directly correlation with lethality rate increases during pre-vaccinepolicy period but not in post-vaccine policy period		No available data on maternal vaccination status, so could not calculate actual vaccine effectiveness.	
Effectiveness of Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination in the Prevention of Infant Pertussis in the U.S.	Becker-Dreps S, Butler AM, McGrath LJ, Boggess KA, Weber DJ, Li D, et al.	Nationwide observational cohort study	Truven Health Analytics insurance claims/encounters database	90,445 of 675,167 (13.4%) Tdap-vaccinated pregnant women (>2 weeks prior to delivery) and 16,273 women at <27 gestation; postpartum-vaccinated group included 5,872 (0.9%) women vaccinated in the 2 weeks prior to delivery and 36,470 (5.4%) women vaccinated at delivery or within 7 days after delivery.		54 months	90,445 of 675,167 (13.4%) Tdap-vaccinated pregnant women (>2 weeks prior to delivery) and 16,273 women at <27 gestation; postpartum-vaccinated group included 5,872 (0.9%) women vaccinated in the 2 weeks prior to delivery and 36,470 (5.4%) women vaccinated at delivery or within 7 days after delivery.	542,380 unvaccinated control mother/infant pairs	The rate of pertussis was 43% lower (HR=0.57, 95% CI=0.35, 0.92), and the rate of inpatient-only pertussis was 68% lower (HR=0.32, 95% CI=0.11, 0.91) in infants from Tdap-vaccinated mothers vs controls (no pre- or post-natal Tdap vaccination)				Possibility for misclassications and mismatching from insurance database records	Tdap vaccination at <27 wks gestation was associated with no reduction in pertussis incidence; however, at >27 wks vacc 70% reduction in inpatient pertussis incidence
Effect of maternal immunization against pertussis in Medellin and the metropolitan area, Colombia, 2016-2017.	Hincapié-Palacio D, Hoyos MC, Ochoa J, Montoya N, García D, Osorio E; Pertussis Working Group	Case cohort study on serologic responses in mothers' and infants' (cord blood) samples and pertussis case incidence	8 randomly selected hospitals in Medellin and metropolitan area of Antioquia, Colombia	805 mothers immunized recruited during labor and 200 mothers recruited during the prenatal care before immunization and followed until delivery <<this needs clarification>>	896 infants through 6 months of age	1 year (2015-16 stated in abstract)	896 infants through 6 months of age from either 745 Tdap-vaccinated mothers or 260 non-vaccinated mothers		Two cases of pertussis (incidence of 1.99 per 1000) born to Tdap-vaccinated mothers with low anti-PT IgG antibody titers	7 total infant deaths: 5 from Tdap-vaccinated mothers and 2 from non-vaccinated mothers			No estimation of vaccine effectiveness due to no pertussis cases in non-vaccinated mother/infant pairs	

Table 8- Cont'd: Studies Included in Systematic Review: Data Extraction Table

Study Title & Link	Authors	Type of Study & Design	Study Sites	Sample sizes		Study Duration	Test Group	Control Group	Infant Outcomes				Biases/ limitations	Other notable findings
				Mothers	Infants				Incidence	Mortality	Morbidity	Other Outcomes		
Effectiveness of dTpa vaccination during pregnancy in preventing whooping cough in infants under 3 months of age. Bizkaia, Basque Country, Spain.	Uriarte P S, Rodríguez S S J, Sancristobal I G, Agirre N M	Retrospective case study for population incidence of pertussis in infants <3 months of age born to dTap-vaccinated (27-36 wks gestation) mothers	Basque Microbiological Information System		1035 reported pertussis cases (2015-2016)	12 months			Calculated vaccine effectiveness of 89%, based on number of reported cases in infants from vaccinated mothers/dTap coverage rates in pregnant women				Screening study design using maternal vaccine coverage rates as denominator; vaccination of infants at 2 months of age may have affected incidence rates	
Maternal Vaccination in Argentina: Tetanus, Diphtheria, and Acellular Pertussis Vaccine Effectiveness During Pregnancy in Preventing Pertussis in Infants <2 Months of Age	Romanin V, Acosta AM, del Valle Juarez M, Briere E, Sanchez SM, Cordoba BL, et al.	Matched case-controlled study to assess the effectiveness of maternal Tdap vaccination in preventing pertussis among infants aged <2 months	Six reference hospital sites in 4 provinces (Buenos Aires, Neuquén, Tucumán, and Salta)		Seventy-one case patients and 301 matched controls	i	71 (PCR-confirmed) pertussis cases	300 controls included in the final analyses (286 controls for analysis by trimester of vaccination)	Adjusted vaccine effectiveness of Tdap during pregnancy was 80.7% (95% confidence interval [CI], 52.1%–92.2%); adjusted vaccine effectiveness was 77.6% (95% CI, 39.1%–91.8%) for Tdap given during the second trimester and 82.7% (95% CI, 46.4%–94.4%) for Tdap given in the third trimester				Misclassification and selection biases may result in over or underestimation of vaccine effectiveness	
The effectiveness of maternal pertussis vaccination in protecting newborn infants in Brazil: A case-control study.	Fernandes EG, Sato APS, Vaz-de-Lima LRA, Rodrigues M, Leite D, de Brito CA, et al.	Observational, unmatched, case control study assessing effectiveness of Tdap maternal vaccination in preventing infant pertussis incidence	São Paulo State, Brazil information database		Forty-two cases (<8 wks of age at pertussis onset) and 248 controls (a 1:4-6 ratio)	18 months	42 PCR-confirmed pertussis cases in infants <8 wks of age	248 healthy infants historical controls	Unadjusted vaccine effectiveness of 82.6% (95% CI, 60.8-92.3%) including mothers of 8 cases (19.1%) and 143 controls (57.4%) vaccinated during pregnancy; same vacccine effectiveness after adjusting for maternal age and monthly home income				Low number of cases prohibiting assessment of vaccine effectiveness at different gestational age; 30% loss rate of controls enrollment; records possible source of vaccine status misclassification; no pertussis severity data collected, and only a regional study	

Table 9: Studies with Vaccine Effectiveness Data			
Study Author(s) & Year	***Unadjusted (Incidence)***	***Adjusted (Incidence)***	***Other***
Dabrera et al., 2014	infants < 8 weeks: 91%		
Amirthalingam et al., 2014		infants <3 months: 91% infants <2 months: 90%	
Amirthalingam et al. 2016		infants <3 months: 91% infants <2 months: 90%	
Winter, Cherry, & Harriman, 2016 (Pertussis severity assessment only)			Preventing hospitalizations in pertussis cases: 72.3% (unadjusted) or 58.3% (adjusted) 75.4% (unadjusted) -In infants of mothers who received Tdap in the third trimester or 52.1% (adjusted)
Winter, Nickell, Powell, & Harriman, 2016	infants <8 weeks: 85% infants ≤12 weeks: 72%		
Baxter et al., 2017		infants ≤2 months: 91.4%	
Bellido-Blasco et al., 2017	infants <3 months: 92%.	infants <3 months: 90.9%	Preventing pertussis: 95.4% (maternal vaccination & artificial feeding) 96.7% (mothers vaccinated & breast feeding)
Skoff et al., 2017	infants <2 months: 77.7%.		Hospitalizations: 90.5%
Saul et al., 2018		infants <3 months: 69%	Hospitalizations: 94%
Uriarte et al., 2019	infants <3 months: 89%		
Romanin et al., 2019		infants <2 months: 80.7%	
Fernandes et al., 2019	infants <2 months: 82.6%		

SUMMARY OF SYSTEMATIC REVIEW FINDINGS

Within the group of 19 studies synthesized for this systematic review, 12 studies reported vaccine effectiveness measured as either calculated pertussis case incidence or severity of pertussis-related hospitalization. Results of studies focusing on vaccine effectiveness are listed in Table 9. Six of the 12 studies assessing pertussis vaccine effectiveness were case-control studies and six were retrospective surveillance studies. Three of these 12 studies (Skoff, 2017; Winter, Cherry, & Harriman, 2016; Winter, Nickell, Powell & Harriman, 2016) also assessed the effectiveness of maternal pertussis vaccination during the third trimester versus at any time during pregnancy or postpartum. Only one study (Bellido-Blasco, 2017) utilized a prospective case-control study design.

The range of adjusted vaccine effectiveness of preventing pertussis in infants <8 weeks to <3 months of age that were provided in 11 of the 12 studies was 69–91.4%, with similar unadjusted vaccine effectiveness of 77.7–92%. One study looked at vaccine effectiveness in terms of severity of pertussis cases (Winter, Cherry, & Harriman, 2016), which demonstrated that hospitalizations, duration of hospital stays, ICU admission, and deaths were all lower in the infants of mothers who received Tdap vaccine during pregnancy. Vaccine effectiveness at preventing hospitalizations was 72.3% (unadjusted) or 58.3% (adjusted). In infants of mothers who received Tdap in the third trimester, vaccine effectiveness was 75.4% (unadjusted) or 52.1% (adjusted). Collectively, 11 studies addressed the research question on incidence. Whereas, only one of the 12 studies addressed the research questions on morbidity and mortality in infants of mothers vaccinated against pertussis during pregnancy demonstrating that those respective infants had decreased severity of disease in terms of reported pertussis-related hospitalizations.

Seven other studies included in this review focused on infant outcomes including pertussis case rates, morbidity, and mortality, but did not provide statistically calculated vaccine effectiveness. The study designs of these seven studies had a large degree of heterogeneity. Nonetheless, the data from these studies addressed both research questions (incidence, morbidity, and mortality) posed in this review. Two of these studies (Gentile et al., 2018; Vizzoti et al., 2016) assessed the impact of pre-maternal pertussis vaccination strategy periods versus post strategy implementation periods. Both studies showed significantly lower numbers of pertussis cases and deaths post policy implementation. In addition, Gentile et al. (2018) showed a lower hospitalization rate due to pertussis in the post maternal vaccination implementation period. Another two studies (Becker-Dreps et al., 2018; Reynolds et al., 2017) also demonstrated lower rates of pertussis cases among the infants of vaccinated mothers versus cases from unvaccinated mothers. Becker-Dreps et al. (2018) found a 63% lower rate of hospitalization among infants of vaccinated mothers, and the percentage was 70% if the mother was vaccinated in the third trimester, but no reduction in pertussis rates among infants born to mothers receiving Tdap at <27 weeks of gestation. Two studies looked at respiratory infections in infants <2 months of age (Khodr et al., 2017 & Sukumaran et al., 2018). Both studies demonstrated a protective association of vaccinating pregnant women against pertussis and hospitalizations due to respiratory infections. The last study reporting outcome measures of pertussis cases and deaths was by Hincapié-Palacio et al. (2018). The primary objective of this study focused on serological findings in maternal antibodies and infant umbilical cord antibodies along with the occurrence of pertussis in infants in the first 6 months of age. However, that study had several limitations. There were no cases of pertussis among infants of unvaccinated mothers and vaccine effectiveness and attack rates could not be calculated. Infant samples could not be collected for

ethical reasons and pertussis was not confirmed among infants that died, particularly those that had respiratory disease.

In summary, implementation of maternal pertussis vaccination across multiple countries has provided adjusted vaccine effectiveness of 69–91.4% against pertussis incidence in infants <3 months of age or younger, and reduced pertussis-related hospitalizations as well. In addition, two studies included in this review clearly demonstrated the benefits of a recommended maternal pertussis vaccination program for reducing infant pertussis case rates. Taken together, these results support the effectiveness of maternal pertussis vaccination in reducing pertussis incidence in young infants and provide further evidence that vaccination of pregnant women during the third trimester is particularly impactful.

DISCUSSION

Recommendations for vaccination against infant pertussis have gone through many changes since the first whole cell vaccines were introduced in the early 1950s, including additional booster doses after the initial vaccination series to reduce the incidence of adolescent pertussis, and the cocooning strategy to reduce the risk for incidental transmission of pertussis and subsequent disease. Despite these recommendations and implementation, infant pertussis continues to be a global healthcare problem in developed countries and particularly in developing countries. In part, the persistence of infant pertussis arises from the demonstrated inability of the cocooning strategy of vaccinating all persons in close contact with newborns, to prevent infant pertussis.

Because the earliest documented age at which infants can be actively vaccinated against pertussis is at least 6 weeks but more often at 2 months of age, infants less than 3 months of age are known to be the most vulnerable group at risk of pertussis and its complications. Given the documented resurgence of pertussis in the past decade, many countries have implemented the policy of vaccinating all pregnant women against pertussis irrespective of their previous pertussis vaccination status. The strategy of maternal vaccination is to provide protective antibody concentrations to the fetus in utero with the expectation that passive transfer of enough antibodies to infants would translate into definitive reductions in infant pertussis morbidity and mortality during the first 3 months of life. The United States was the first to implement this strategy, followed by the United Kingdom in late 2012.

To date, there have been a number of safety and efficacy studies (Campbell et al., 2019; Furuta et al., 2017; Gkentzi et al., 2017; McMillan et al., 2017; Switzer et al., 2019) demonstrating the safety of maternal vaccination on pregnant mothers and their respective

infants as well as robust maternal antibody responses to vaccine antigens and effective transplacental transfer of anti-pertussis antibodies to the fetus to higher geometric mean concentrations in fetal cord blood compared to maternal blood. Given the lack of validated clinical endpoints for measuring maternal pertussis vaccination, our study results provide real-world evidence on vaccine effectiveness that corroborate serologic findings demonstrating maternal production and placental transfer of protective anti-pertussis antibody levels to susceptible infants.

This systematic review was unique in that it is the first to synthesize the impact of maternal pertussis vaccination during each pregnancy by evaluating only those studies reporting vaccine effectiveness measured as infant pertussis outcomes such as confirmed case incidence and pertussis-related morbidity and mortality. These outcomes were the focus of the two research questions for this systematic review, namely, whether or not maternal pertussis vaccination provides clinically meaningful reduction in the risk for pertussis case incidence in the most susceptible infants and associated morbidity and mortality. The goal was to have real-world evidence on the benefits of maternal vaccination on neonatal infant outcomes. Furthermore, the review also captured substantially more published reviews than previous systematic reviews and provided additional evidence that vaccinating pregnant mothers yielded meaningful prevention against pertussis disease in infants too young to be immunized or able to elicit a full immune response to an injected vaccine. In this systematic review, there was a total of 12 studies out of the 19 included studies that specifically addressed vaccine effectiveness (Table 9). However, only 11 of those studies provided data on calculated vaccine effectiveness in preventing pertussis disease in young infants. In providing an answer to the first research question (page 9), the collective data synthesized in this review strongly support vaccinating pregnant women against

pertussis in their third trimester, whereby around 77.7–92% (unadjusted) pertussis cases can be prevented in infants less than 3 months of age. This is especially evident in light of the robustness and greater trial homogeneity on vaccine effectiveness from the large retrospective cohort studies and various case-control studies directly comparing pertussis case incidence in infants from vaccinated versus unvaccinated mothers. While only one study among those selected for synthesis demonstrated vaccine effectiveness at reducing the severity of disease in terms of reported pertussis-related hospitalizations, data from several other outcomes studies provided supporting evidence for the value of maternal vaccination coverage in reducing pertussis case incidence, pertussis-related hospitalization, mortality, and overall incidence of acute respiratory infections.

While conducting the systematic review, multiple case-control and retrospective cohort studies published in the recent scientific literature that have not been described in previous systematic reviews were identified. Thus, the Futura et al. (2017) review mentioned only the single study by Dabrera et al. 2015 study included in our review, while Campbell et al. (2018) mentioned six studies on vaccine effectiveness published through 2017. A more recent systematic review by Switzer et al. in 2019 mentioned 10 studies published through 2018 that were included in our systematic review. The systematic reviews by Gkentzi et al. (2017) included only two effectiveness studies. McMillan et al. (2017) only reported on studies regarding safety of pertussis vaccines and did not include any data on effectiveness. Hence our review is the most current assessment of relevant studies on maternal pertussis vaccine effectiveness measured as reduction in disease incidence and pertussis-related morbidity and mortality.

There were some limitations to this systematic review given the heterogeneity in study designs across the various studies included in this systematic review. Since none of the included studies were randomized controlled studies, then reliance on retrospective surveillance data and case-control studies results could affect assessment of vaccine effectiveness in infants born to vaccinated mothers. Available data on the impact of maternal vaccination against pertussis-related infant mortality were particularly sparse among the included studies, an observation likely resulting from the low infant pertussis mortality rates in the various countries following implementation of maternal vaccination programs and the overall low mortality compared with other infant respiratory diseases. Nevertheless, the available data support the value of maternal pertussis vaccination in reducing infant mortality.

Another potential study limitation is that most of the mothers vaccinated were likely primed during their youth with wP vaccines, but it is unknown whether there was any effect of that on the infant outcomes. In addition, lack of accurate information on maternal vaccination status would negatively affect outcomes data. Sample sizes were small in some studies included, which can impact its external validity. Researchers may have overlooked some published literature by limiting the search to only English language papers. A selection bias in the studies chosen could also be a limitation as the researchers/authors of this study were not blinded. However, clear pre-defined selection criteria and the double coding conducted minimized this bias.

Furthermore, observational studies or retrospective analysis of cases over a limited time frame could be influenced by seasonal occurrence of pertussis in neonates; however, this may not be a significant limitation to our study results since analysis of pertussis cases over at least 12 months should offer a reasonable time frame to evaluate vaccine effectiveness. Some studies

presented data from a single site or region, which may or may not translate into expected outcomes over larger areas or a general population. One may also anticipate that the results of the included studies could have been affected by prior maternal vaccination status (i.e., a maternal booster effect), community/household environment, or specific strain virulence of circulating *B. pertussis*. This study did not include published articles on outcomes in infants born to vaccinated mothers and following the primary pertussis vaccination series, since the focus was to ascertain the direct effect of maternal pertussis vaccination on those infants most susceptible to pertussis disease prior to initiation of the primary pertussis vaccinations.

However, the strength of this review was the strict predefined study protocol with clearly defined inclusion and exclusion criteria, the double coding conducted and the coding protocol to avoid selection bias, and the numerous databases searched. The overall strong kappa of 1.0 for studies included in this review demonstrated the strength of the coding protocol. The importance of this value demonstrates the extent to which the studies included within this review were correct representations of the inclusion and exclusion criteria. Several data points were extracted directly from the paper and transcribed into the data extraction tool by both raters, allowing for a high degree of alignment and resulting in a high kappa score.

One goal of this study was to determine what real-world evidence exists in support of or against a maternal pertussis immunization strategy to protect the most vulnerable infants. While the studies were not similar in design, duration, sample sizes, time frames or geographies, the studies were concordant with the review outcomes, advocating the maternal vaccination strategy to help protect infants less than 3 months of age. Vaccinating mothers is the best possible protection for infants too young to be vaccinated. Meanwhile, continued epidemiology monitoring is essential to detect any shifts in pattern or age distribution of pertussis, particularly

in response to this maternal vaccination strategy. Therefore, more studies are needed to characterize the continued impact of this strategy to determine if there is any evolution of the disease.

In the United States, there is clear evidence regarding the impact of maternal pertussis vaccination on young infants as demonstrated by the declining trend in infant pertussis incidence (Table 1) and mortality (Table 2) since maternal vaccination policy implementation. Results of this study also demonstrated that the maternal pertussis vaccine coverage rate is directly proportional to real-world impact on infants. However, maternal pertussis vaccination uptake in the United States has been slow (Black et al., 2018) compared with the United Kingdom (Amirthalingam et al., 2016). For that reason, every effort should be made to continue to raise awareness among pregnant women around pertussis disease in infants and the vital importance of prenatal vaccination during the optimal gestational time periods.

Regarding initiatives to increase maternal pertussis vaccination rates, a 2019 systematic review by Mohammed et al. of published literature on strategies to improve maternal pertussis vaccination provided insight into the barriers for vaccination and practices that have successfully increased maternal vaccination coverage. As mentioned in the study conclusions, the greatest barriers to maternal pertussis vaccination are pregnant women's misperceptions about the risk of pertussis in young infants, and the effectiveness and safety of vaccination during pregnancy. Similarly, this systematic review recognized that vaccine effectiveness was directly related to maternal vaccination uptake, specifically in the third trimester of pregnancy. The authors pointed to the success of standing orders for administering pertussis vaccines to pregnant women by attending midwifes, best practice alerts for vaccination reminders in antenatal healthcare settings, and increased vaccine coverage in offices that stock pertussis vaccines.

Despite improvements in maternal pertussis vaccine coverage in countries with national vaccination recommendations, the persisting low coverage rates of maternal pertussis vaccination even in populations of informed women in developed countries like the United States speak to the need for increasing patient education on the risks for significant morbidity or death among susceptible infants, and increasing healthcare provider involvement in ensuring pregnant women receive their vaccination at the optimal gestational time period. According the most recent published internet panel survey results (Murthy et al., 2020), one of the main reasons for the lack of Tdap vaccination in the United States is the misconception that the respective subjects (pregnant women) felt they already received the vaccine (32.5%) and do not need it again. The second most common reason (14.7%) was that patients did not realize they were supposed to get the Tdap vaccine. These issues, both the misconception and the lack of awareness, need to be addressed to improve vaccine uptake. The demonstrated lower vaccine coverage rates in minority populations and individuals or groups resistant to vaccination in general also point to the need for increasing educational awareness of disease risk and benefits of vaccination through distribution of easily understood and accessible patient literature for women from culturally and linguistically diverse backgrounds. Among antenatal healthcare providers, greater awareness of information from reviews like this study can support the national recommendations for maternal vaccination during discussions with pregnant women and provide a rationale for stocking vaccines in antenatal healthcare offices. Moreover, performance metrics should be put in place among obstetricians on discussing pertussis and recommending vaccination to their patients. These should require documentation for reimbursement of discussions of pertussis vaccination with pregnant women during antenatal visits and recommending vaccination in the third trimester for reimbursement. Discussions should address

concerns and help reassure mothers-to-be that getting vaccinated would not harm their unborn baby and will actually help protect their baby against pertussis during the months that the baby is ineligible for vaccines. Furthermore, both obstetricians and family practitioners should have supply of the Tdap vaccine in stock to offer their third trimester pregnant patients. Obstetricians and family practitioners should also be incentivized for getting 90% or more of their pregnant patients vaccinated with Tdap in the third trimester. This can be achieved by the government reducing reimbursement for vaccinations if rates of 90% are not achieved. These metrics could form the basis for review of best practices across different antenatal healthcare facilities on the best ways to inform pregnant women on the value of pertussis vaccinations. Medicaid and managed care companies could send print material to all pregnant women on pertussis vaccination. Issues of limited access to vaccines relating to cost or reimbursement could be addressed through discussions and negotiations with vaccine manufacturers, insurance payers, pharmacy managers, and patient advocacy groups aimed at providing affordable vaccine coverage to individuals with limited or no current insurance. Direct-to-consumer advertising and television campaigns should be designed to proactively encourage pregnant women to get vaccinated against pertussis to protect their infant babies. For example, company-sponsored print and media advertising campaigns and television initiatives have increased awareness for vaccines in recent years. Examples include adult vaccination against shingles and pneumococcal pneumonia, flu vaccination, and early teenage vaccination against human papillomavirus. Hence, greater media coverage of pertussis risks presented in different languages could help drive awareness around pertussis in young infants, waning immunity to pertussis vaccines and need for revaccination during each pregnancy, and the importance of maternal vaccination to protect vulnerable, at risk, young infants. Such efforts will likely help reach the underserved populations

as most people will likely have televisions. Achieving maternal pertussis coverage rates of 90% and above with every pregnancy should be a priority in order to continue lower infant pertussis rates along with its morbidity and mortality.

CONCLUSIONS

This systematic review adds to the body of evidence on the impact of maternal pertussis vaccination to help protect the most vulnerable infants less than 3 months of age and underscores the importance of this strategy in the prevention of pertussis and its complications in these young infants. Previously conducted review findings stressed that high concentrations of vaccine induced antibodies were consistently seen in women immunized during the third trimester of pregnancy and passive transplacental transfer of antibodies was seen in fetal cord blood. However, there was a gap in the number of effectiveness studies included versus studies addressing immunogenicity and safety studies. Studies synthesized bridge the gap and addressed the research questions in the review. Infants of vaccinated mothers (third trimester) had lower pertussis incidence, morbidity, and mortality compared to infants of unvaccinated mothers. The goal of protecting young infants remains a priority. Importance should be placed on promoting maternal immunization through education of primary care providers as well as pregnant women to increase uptake of Tdap vaccination during every pregnancy. Currently, recommendations are in place for women to be vaccinated with every pregnancy. However, many pregnant women remain unvaccinated against pertussis during subsequent pregnancies. Therefore, more work needs to be done to emphasize the importance of repeat vaccinations in subsequent pregnancies for prevention of infant pertussis and to reassure women on vaccine safety for both mothers and infants. Continued increases in vaccine uptake are necessary to help ensure that vulnerable young infants are protected from pertussis and its complications. More effective vaccines with greater duration of immunity are much needed, but until then, maternal pertussis immunization with every pregnancy is integral to help prevent infant pertussis cases, morbidity, and mortality in infants under 3 months of age.

REFERENCES

Acosta, A. M., DeBolt, C., Tasslimi, A., Lewis, M., Stewart, L. K., Misegades, L. K., ... Patel, M. (2015). Tdap vaccine effectiveness in adolescents during the 2012 Washington State pertussis epidemic. *Pediatrics*, *135*(6), 981-989.

Amirthalingam, G., Andrews, N., Campbell, H., Ribeiro, S., Kara, E., Donegan, K., ... Ramsay, M. (2014). Effectiveness of maternal pertussis vaccination in England: An observational study. *The Lancet*, *384*(9953), 1521-1528.

Amirthalingam, G., Campbell, H., Ribeiro, S., Fry, N. K., Ramsay, M., Miller, E., & Andrews, N. (2016). Sustained effectiveness of the maternal pertussis immunization program in England 3 years following introduction. *Clinical Infectious Diseases*, *63*(suppl_4), S236-S243.

Australian Technical Advisory Group on Immunisation (ATAGI). (2019). *The Australian immunisation handbook* (10th ed.,2018 update). Canberra: Australian Government Department of Health. Retrieved from https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/pertussis-whooping-cough

Baxter, R., Bartlett, J., Fireman, B., Lewis, E., & Klein, N. P. (2017). Effectiveness of vaccination during pregnancy to prevent infant pertussis. *Pediatrics*, *139*(5), e20164091.

Becker-Dreps, S., Butler, A. M., McGrath, L. J., Boggess, K. A., Weber, D. J., Li, D., ... Layton, J. B. (2018). Effectiveness of prenatal tetanus, diphtheria, acellular pertussis vaccination in the prevention of infant pertussis in the US. *American Journal of Preventive medicine*, *55*(2), 159-166.

Bellido-Blasco, J., Guiral-Rodrigo, S., Míguez-Santiyán, A., Salazar-Cifre, A., & González-Morán, F. (2017). A case–control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016. *Eurosurveillance*, *22*(22).

Black, C., Ding, H., Kahn, K., Ball, S., Fink, R., Devlin, R., ... Greby, S. (2017). Tdap and influenza vaccination among women with a live birth, internet panel survey, United States, 2015–2016. *In Open forum Infectious Diseases* (Vol. 4, No. Suppl 1, p. S457). Oxford University Press.

Bordet, J., & Gengou, O. (1906). Le microbe de la coqueluche. *Annales de l'Institut Pasteur*, *20*, 731-741.

Broder, K. R., Cortese, M. M., Iskander, J. K., Kretsinger, K., Slade, B. A., Brown, K. H., ... Srivastava, P. U. (2006). Preventing tetanus, diphtheria, and pertussis among adolescents; use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP).

Bruss, J. B., Malley, R., Halperin, S., Dobson, S., Dhalla, M., Mciver, J., & Siber, G. R. (1999). Treatment of severe pertussis: a study of the safety and pharmacology of intravenous pertussis immunoglobulin. *The Pediatric Infectious Disease Journal*, *18*(6), 505-511.

Butler, A. M., Layton, J. B., Li, D., Hudgens, M. G., Boggess, K. A., McGrath, L. J., ... Becker-Dreps, S. (2017). Predictors of low uptake of prenatal tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis immunization in privately insured women in the United States. *Obstetrics and Gynecology*, *129*(4), 629.

California Department of Public Health (CDPH). (2015). *Vaccine-preventable surveillance in California-2014 annual report*. Retrieved from

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/VPD-AnnualReport2014.pdf#search=2014%20pertussis%20rates

Campbell, H., Gupta, S., Dolan, G. P., Kapadia, S. J., Singh, A. K., Andrews, N., & Amirthalingam, G. (2018). Review of vaccination in pregnancy to prevent pertussis in early infancy. *Journal of Medical Microbiology, 67*(10), 1426-1456.

Carbonetti, N. H. (2016). Bordetella pertussis: New concepts in pathogenesis and treatment. *Current Opinion in Infectious Diseases, 29*(3), 287.

Carlsson, R. M., Von Segebaden, K., Bergström, J., Kling, A. M., & Nilsson, L. (2015). Surveillance of infant pertussis in Sweden 1998–2012; severity of disease in relation to the national vaccination programme. *Eurosurveillance, 20*(6), 21032.

Centers for Disease Control and Prevention (CDC). (2011). 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 month---Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR. Morbidity and Mortality Weekly Report*, *60*(41), 1424. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm

Centers for Disease Control and Prevention (CDC). (2012). Pertussis epidemic--Washington, 2012. *MMWR. Morbidity and Mortality Weekly Report, 61*(28), 517.

Centers for Disease Control and Prevention (CDC). (2013a). *2012 Final pertussis surveillance report.* Retrieved from https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2012.pdf

Centers for Disease Control and Prevention (CDC). (2013b). 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. *MMWR. Morbidity and Mortality Weekly Report, 62*(7):131-135.

Centers for Disease Control and Prevention (CDC). (2014). *Pertussis/whooping cough (Bordatella pertussis) 2014 case definition*. Retrieved from https://wwwn.cdc.gov/nndss/conditions/pertussis/case-definition/2014/

Centers for Disease Control and Prevention (CDC). (2015). *Epidemiology and prevention of vaccine-preventable diseases* (13th ed.). J. Hamborsky, J & A. Kroger, A, & Wolfe, S. (Eds.).U.S. Department of Health & Human Services, Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/vaccines/pubs/pinkbook/index.html

Centers for Disease Control and Prevention (CDC). (2016). *Vaccines and preventable diseases: Diphtheria, tetanus and pertussis recommendation.* Retrieved from https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html

Centers for Disease Control and Prevention (CDC). (2017a). *2016 Final pertussis surveillance report.* Retrieved from https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2016.pdf

Centers for Disease Control and Prevention (CDC). (2017b). "Chapter 10: Pertussis." *Manual for the surveillance of vaccine-preventable diseases.* Retrieved from https://www.cdc.gov/vaccines/pubs/surv-manual/chpt10-pertussis.html

Centers for Disease Control and Prevention (CDC). (2017c). *Pertussis cases by year (1922-2017).* Retrieved from https://www.cdc.gov/pertussis/surv-reporting/cases-by-year.html

Centers for Disease Control and Prevention (CDC). (2017d). *Pertussis (whooping cough). Diagnosis confirmation.* Retrieved from https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html

Centers for Disease Control and Prevention (CDC). (2017e). *Pertussis (whooping cough). Disease specifics*. Retrieved from https://www.cdc.gov/pertussis/clinical/disease-specifics.html

Centers for Disease Control and Prevention (CDC). (2017f). *Pertussis (whooping cough). Surveillance and reporting.* Retrieved from https://www.cdc.gov/pertussis/surv-reporting.html

Centers for Disease Control and Prevention (CDC). (2017g). *Pertussis (whooping cough). Treatment.* Retrieved from https://www.cdc.gov/pertussis/clinical/treatment.html

Centers for Disease Control and Prevention (CDC). (2017h). *Pregnancy and whooping cough. Rationale: Why vaccinate pregnant women?* Retrieved from https://www.cdc.gov/pertussis/pregnant/hcp/rationale-vacc-pregnant-women.html

Centers for Disease Control and Prevention (CDC). (2017i). *Pregnancy and whooping cough. Surround babies with protection*. Retrieved from https://www.cdc.gov/pertussis/pregnant/mom/protection.html

Centers for Disease Control and Prevention (CDC). (2018). *2017 Final pertussis surveillance report.* Retrieved from https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2017.pdf

Centers for Disease Control and Prevention (CDC). (2019). *2018 Provisional pertussis surveillance report.* Retrieved from https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2018-508.pdf

Cherry, J. D. (2012). Epidemic pertussis in 2012—the resurgence of a vaccine-preventable disease. *New England Journal of Medicine*, *367*(9), 785-787.

Cherry, J. D. (2013). Pertussis: Challenges today and for the future. *PLoS Pathogens, 9*(7), e1003418.

Cherry, J. D. (2016). Pertussis in young infants throughout the world. *Clinical Infectious Diseases, 63*(suppl_4), S119-S122.

Chow, M. Y., Khandaker, G., & McIntyre, P. (2016). Global childhood deaths from pertussis: A historical review. *Clinical Infectious Diseases, 63*(suppl 4), S134-S141.

Clark, T. A. (2014). Changing pertussis epidemiology: Everything old is new again. *The Journal of Infectious Diseases, 209*(7), 978-981.

Dabrera, G., Amirthalingam, G., Andrews, N., Campbell, H., Ribeiro, S., Kara, E., ... Ramsay, M. (2014). A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013. *Clinical Infectious Diseases*, *60*(3), 333-337.

de Barros, E. N. C., Nunes, A. A., Abreu, A. D. J. L. D., Furtado, B. E., Cintra, O., Cintra, M. A., & Coelho, E. B. (2019). Pertussis epidemiological pattern and disease burden in Brazil: An analysis of national public health surveillance data. *Human Vaccines & Immunotherapeutics*, (just-accepted).

de Cellès, M.D., Magpantay, F. M., King, A. A., & Rohani, P. (2016). The pertussis enigma: reconciling epidemiology, immunology and evolution. *Proceedings of the Royal Society B: Biological Sciences*, *283*(1822), 20152309.

de Cellès, M. D., Magpantay, F. M., King, A. A., & Rohani, P. (2018). The impact of past vaccination coverage and immunity on pertussis resurgence. *Science Translational Medicine*, *10*(434), eaaj1748.

de Cellès, M. D., Riolo, M. A., Magpantay, F. M. G., Rohani, P., & King, A. A. (2014). Epidemiological evidence for herd immunity induced by acellular pertussis vaccines. *Proceedings of the National Academy of Sciences*, *111*(7): E716-E717.

de Greeff, S. C., Dekkers, A. L., Teunis, P., Rahamat-Langendoen, J. C., Mooi, F. R., & de Melker, H. E. (2009). Seasonal patterns in time series of pertussis. *Epidemiology & Infection*, *137*(10), 1388-1395.

European Centre for Disease Prevention and Control (ECDC). (2016). *Annual epidemiological report 2016- Pertussis.* Stockholm. Retrieved from https://ecdc.europa.eu/sites/portal/files/documents/Pertussis%20AER.pdf

Fedele, G., & Stefanelli, P. (2017). Pertussis in infants and the resurgence of a vaccine preventable disease: What to do? *Annali dell'Istituto superiore di sanita*, *53*(2), 100-103.

Fernandes, E. G., Sato, A. P. S., Vaz-de-Lima, L. R., Rodrigues, M., Leite, D., de Brito, C. A., ... de Castilho, E. A. (2019). The effectiveness of maternal pertussis vaccination in protecting newborn infants in Brazil: A case-control study. *Vaccine 37*(36), 5481-5484.

Fine, P. E., & Clarkson, J. A. (1986). Seasonal influences on pertussis. *International Journal of Epidemiology*, *15*(2), 237-247.

Fisman, D. N., Tang, P., Hauck, T., Richardson, S., Drews, S. J., Low, D. E., & Jamieson, F. (2011). Pertussis resurgence in Toronto, Canada: A population-based study including test-incidence feedback modeling. *BMC Public Health, 11*(1), 694.

Forsyth, K., Plotkin, S., Tan, T., & Von König, C. H. W. (2015). Strategies to decrease pertussis transmission to infants. *Pediatrics*, *135*(6), e1475-e1482.

Furuta, M., Sin, J., Ng, E. S., & Wang, K. (2017). Efficacy and safety of pertussis vaccination for pregnant women–a systematic review of randomised controlled trials and observational studies. *BMC Pregnancy and Childbirth*, *17*(1), 390.

Gentile, A., Bricks, L., Ávila-Agüero, M. L., Kfouri, R. A., Torres, J. P., Ulloa-Gutierrez, R., ... Sarti, E. (2019). Pertussis in Latin America and the Hispanic Caribbean: A systematic review. *Expert Review of Vaccines*, *18*(8), 829-845.

Gentile, A., del Valle Juarez, M., Lucion, M. F., Martínez, A. C., Romanin, V., Areso, S., & Mistchenko, A. (2018). Bordetella pertussis (Bp) disease: Before (2003–2011) and after (2013–2016) maternal immunization strategy in a pediatric hospital. *Vaccine*, *36*(11), 1375-1380.

Gkentzi, D., Katsakiori, P., Marangos, M., Hsia, Y., Amirthalingam, G., Heath, P. T., & Ladhani, S. (2017). Maternal vaccination against pertussis: A systematic review of the recent literature. *Archives of Disease in Childhood-Fetal and Neonatal Edition*, *102*(5), F456-F463.

Gregory, D. S. (2006). Pertussis: A disease affecting all ages. *American Family Physician*, *74*(3), 420-426.

Guris, D., Strebel, P. M., Jafari, H., Wharton, M., & Hadler, S. C. (1997). Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/00048610.htm

Healy, C. M., Rench, M. A., Wootton, S. H., & Castagnini, L. A. (2015). Evaluation of the impact of a pertussis cocooning program on infant pertussis infection. *The Pediatric Infectious Disease Journal*, *34*(1), 22-26.

Heininger, U. (2019). Pertussis and other Bordetella infections of the respiratory tract. In *Kendig's disorders of the respiratory tract in children* (9th ed., pp. 528-534).

Hincapié-Palacio, D., Hoyos, M. C., Ochoa, J., Montoya, N., García, D., Osorio, E., & Pertussis Working Group. (2018). Effect of maternal immunization against pertussis in Medellin and the metropolitan area, Colombia, 2016–2017. *Vaccine*, *36*(27), 3984-3991.

Hozbor, D., Ulloa-Gutierrez, R., Marino, C., von Koenig, C. H. W., Tan, T., & Forsyth, K. (2019). Pertussis in Latin America: Recent epidemiological data presented at the 2017 Global Pertussis Initiative meeting. *Vaccine*, *37*(36), 5414-5421.

Joint Committee on Vaccination and Immunisation (JCVI). (2012). Joint Committee on Vaccination and Immunisation: Minutes of meeting held October 2012. Retrieved from https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/229171725721

Kahn, K. E., Black, C. L., Ding, H., Fiebelkorn, A. P., Liang, J. L., Ahluwalia, I. B., & Greby, S. M. (2017). Pregnant women and Tdap vaccination, internet panel survey, United States, April 2016. Retrieved from https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/tdap-report-2016.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fvaccines%2Fimz-managers%2Fcoverage%2Fadultvaxview%2Ftdap-report-2016.html

Kahn, K. E., Black, C. L., Ding, H., Fiebelkorn, A. P., Havers, F., D'Angelo, D., … Greby, S. M. (2018a). Pregnant women and Tdap vaccination, Internet panel survey, United States, April 2017. Retrieved from https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/ pubs-resources/tdap-report-2017.html

Kahn, K. E., Black, C. L., Ding, H., Williams, W. W., Lu, P. J., Fiebelkorn, A. P., … Devlin, R. (2018b). Influenza and Tdap vaccination coverage among pregnant women - United

States, April 2018. *MMWR. Morbidity and Mortality Weekly Report*, *67*(38), 1055-1059. Retrieved from https://www.cdc.gov/mmwr/volumes/67/wr/mm6738a3.htm

Kapil, P., & Merkel, T. J. (2019). Pertussis vaccines and protective immunity. *Current Opinion in Immunology*, *59*, 72-78.

Khodr, Z. G., Bukowinski, A. T., Gumbs, G. R., & Conlin, A. M. S. (2017). Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections. *Vaccine*, *35*(42), 5603-5610.

Kilgore, P. E., Salim, A. M., Zervos, M. J., & Schmitt, H. J. (2016). Pertussis: Microbiology, disease, treatment, and prevention. *Clinical Microbiology Reviews*, *29*(3), 449-486.

Klein, N. P., Bartlett, J., Rowhani-Rahbar, A., Fireman, B., & Baxter, R. (2012). Waning protection after fifth dose of acellular pertussis vaccine in children. *New England Journal of Medicine, 367*(11), 1012-1019.

Laenen, J., Roelants, M., Devlieger, R., & Vandermeulen, C. (2015). Influenza and pertussis vaccination coverage in pregnant women. *Vaccine, 33*(18), 2125-2131.

Lapidot, R., & Gill, C. J. (2016). The Pertussis resurgence: Putting together the pieces of the puzzle. *Tropical Diseases, Travel Medicine and Vaccines*, *2*(1), 26.

Larson, H. J. (2015). Maternal immunization: The new "normal" (or it should be). *Vaccine, 33*(47), 6374-5.

Liang, Y., Salim, A. M., Wu, W., & Kilgore, P. E. (2016). Chao Yuanfang: Imperial physician of the Sui Dynasty and an early pertussis observer? *Open Forum Infectious Diseases, 3*(1). Oxford University Press.

Liang, J. L., Tiwari, T., Moro, P., Messonnier, N. E., Reingold, A., Sawyer, M., & Clark, T. A. (2018). Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United

States: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR. Morbidity and Mortality Weekly Report, 67*(2), 1-44. Retrieved from https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm

Liu, L., Oza, S., Hogan, D., Perin, J., Rudan, I., Lawn, J. E., ... Black, R. E. (2015). Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: An updated systematic analysis. *The Lancet, 385*(9966), 430-440.

MacDougall, D. M., & Halperin, S. A. (2016). Improving rates of maternal immunization: Challenges and opportunities. *Human Vaccines & Immunotherapeutics, 12*(4), 857-865.

McHugh, M. L. (2012). Interrater reliability: The kappa statistic. *Biochemia medica, 22*(3), 276-282.

McMillan, M., Clarke, M., Parrella, A., Fell, D. B., Amirthalingam, G., & Marshall, H. S. (2017). Safety of tetanus, diphtheria, and pertussis vaccination during pregnancy. *Obstetrics & Gynecology*, *129*(3), 560-573.

McRae, J., Quinn, H. E., & Macartney, K. (2017). Surveillance (PAEDS) annual report 2015: Prospective hospital-based surveillance for serious paediatric conditions. *Communicable Diseases Intelligence*, *41*(3). Retrieved from https://www1.health.gov.au/internet/main/publishing.nsf/Content/94C5388875219E11CA2581FE0003EB5F/$File/CDI4103-m.pdf

Melvin, J. A., Scheller, E. V., Miller, J. F., & Cotter, P. A. (2014). Bordetella pertussis pathogenesis: current and future challenges. *Nature Reviews Microbiology*, *12*(4), 274-288. http://dx.doi.org/10.1038/nrmicro3235

Minnesota Department of Health (MDH). (2012). *Infectious disease epidemiology, prevention and control division 2012 annual report.* Retrieved from https://www.health.state.mn.us/about/org/idepc/reports/2012.pdf.

Mohammed, H., McMillan, M., Roberts, C. T., & Marshall, H. S. (2019). A systematic review of interventions to improve uptake of pertussis vaccination in pregnancy. *PloS One, 14*(3).

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264-269.

Moore, A., Ashdown, H. F., Shinkins, B., Roberts, N. W., Grant, C. C., Lasserson, D. S., & Harnden, A. (2017). Clinical characteristics of pertussis-associated cough in adults and children: a diagnostic systematic review and meta-analysis. *Chest*, *152*(2), 353-367.

Muller, A. S., Leeuwenburg, J., & Voorhoeve, A. M. (1984). Pertussis in a rural area of Kenya: Epidemiology and results of a vaccine trial. *Bulletin of the World Health Organization, 62*(6), 899.

Murthy, N. C., Black, C., Kahn, K. E., Ding, H., Ball, S., Fink, R. V., ... Fiebelkorn, A. P. (2020). Tetanus, diphtheria, and acellular pertussis and influenza vaccinations among women with a live birth, internet panel survey, 2017-2018. *Infectious Diseases: Research and Treatment, 13*, 1-9. https://doi.org/10.1177/1178633720904099

Olin, P., Hallander, H. O., Gustafsson, L., Reizenstein, E., & Storsaeter, J. (2001). How to make sense of pertussis immunogenicity data. *Clinical Infectious Diseases, 33*(Supplement_4), S288-S291.

Plotkin, S. A. (2008). Correlates of vaccine-induced immunity. *Clinical Infectious Diseases*, *47*(3), 401-409.

Préziosi, M. P., Yam, A., Wassilak, S. G., Chabirand, L., Simaga, A., Ndiaye, M., ... Simondon, F. (2002). Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. *American Journal of Epidemiology, 155*(10), 891-896.

Public Health England (PHE). (2014). *Confirmed pertussis in England and Wales: Data to end in December 2012*. Retrieved from https://webarchive.nationalarchives.gov.uk/20140714090247/http://www.hpa.org.uk/hpr/archives/2013/news0513.htm

Public Health England (PHE). (2018a). Laboratory confirmed cases of pertussis (England): annual report for 2017. *Health Protection Report, 12*(15). Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/703519/hpr1518_prtsss_ANN.pdf

Public Health England (PHE). (2018b). Laboratory confirmed cases of pertussis (England): July -September 2018. *Health Protection Report, 12*(45). Retrieved from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/764970/hpr4518_PRTSSS.pdf

Reynolds, G., Grant, N., Thornley, S., & Hale, M. (2017). Low uptake of maternal vaccination in notified pertussis cases aged less than 20 weeks. *The New Zealand Medical Journal (Online), 130*(1449), 72.

Romanin, V., Acosta, A. M., Juarez, M. D. V., Briere, E., Sanchez, S. M., Cordoba, B. L., ... Skoff, T. H. (2019). Maternal vaccination in Argentina: Tetanus, diphtheria, and acellular pertussis vaccine effectiveness during pregnancy in preventing pertussis in infants < 2 months of age. *Clinical Infectious Diseases, 70*(3), 380-387.

Romanin, V., Acosta, A. M., Juarez, M. D. V., Briere, E., Sanchez, S. M., Cordoba, B. L., ... & Skoff, T. H. (2019). Maternal Vaccination in Argentina: Tetanus, Diphtheria, and Acellular Pertussis Vaccine Effectiveness During Pregnancy in Preventing Pertussis in Infants< 2 Months of Age. *Clinical Infectious Diseases*, *70*(3), 380-387.

Romanin, V., Agustinho, V., Califano, G., Sagradini, S., Aquino, A., Juarez Mdel, D., ... Lara, C. (2014). Epidemiological situation of pertussis and strategies to control it: Argentina, 2002–2011. *Archivos Argentinos de Pediatria*, *112*(5), 413-420.

Roush, S. W., Murphy, T. V., & Vaccine-Preventable Disease Table (VPDT) Working Group. (2007). Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *Jama*, *298*(18), 2155-2163.

Rubin, F. A., Koso-Thomas, M., Isaacs, M. B., Piper, J., Read, J., & Nesin, M. (2015). Maternal immunization efforts of the National Institutes of Health. *Vaccine*, *33*(47), 6380-6387.

Saadatian-Elahi, M., Plotkin, S., Mills, K. H., Halperin, S. A., McIntyre, P. B., Picot, V., ... Johnson, D. R. (2016). Pertussis: Biology, epidemiology and prevention. *Vaccine*, *34*(48), 5819-5826.

Saul, N., Wang, K., Bag, S., Baldwin, H., Alexander, K., Chandra, M., ... Conaty, S. (2018). Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study. *Vaccine*, *36*(14), 1887-1892.

Sawyer, M., Liang, J. L., Messonnier, N., & Clark, T. A. (2013). 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. *MMWR. Morbidity and mortality weekly report*, *62*(7), 131.

Sawyer, M. H., & Long, S. S. (2015). Tdap in every pregnancy: Circling the wagons around the newborn. *Pediatrics, 135(6*), e1483-e1484.

Scanlon, K. M., Skerry, C., & Carbonetti, N. H. (2015). Novel therapies for the treatment of pertussis disease. *Pathogens and Disease, 73*(8), ftv074.

Schielke, A., Takla, A., von Kries, R., Wichmann, O., & Hellenbrand, W. (2018). Marked underreporting of pertussis requiring hospitalization in infants as estimated by capture-recapture methodology, Germany, 2013-2015. *Pediatric Infectious Disease Journal*, *37*(2), 119.

Schwartz, K. L., Kwong, J. C., Deeks, S. L., Campitelli, M. A., Jamieson, F. B., Marchand-Austin, A., … Crowcroft, M. S. (2016). *Canadian Medical Association Journal, 188*(16), E399-E406.

Skoff, T. H., Blain, A. E., Watt, J., Scherzinger, K., McMahon, M., Zansky, S. M., ... Martin, S. W. (2017). 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. *Clinical Infectious Diseases*, *65*(12), 1977-1983.

Seppa, N. (2014). Whooping cough bounces back: Replacement vaccine is not so great at protecting kids. *Science News*, *185*(8), 22-26.

Statistics Solutions. (2019). Data analysis plan templates: Kappa coefficients. Retrieved from https://www.statisticssolutions.com/kappa-coefficients/

Sukumaran, L., McCarthy, N. L., Kharbanda, E. O., Vazquez-Benitez, G., Lipkind, H. S., Jackson, L., ... Kawai, A. T. (2018). Infant hospitalizations and mortality after maternal vaccination. *Pediatrics*, *141*(3), e20173310.

Syed, M. A., & Bana, N. F. (2014). Pertussis. A reemerging and an underreported infectious disease. *Saudi Medical Journal, 35*(10), 1181-1187.

Swamy, G. K., & Wheeler, S. M. (2014). Neonatal pertussis, cocooning and maternal immunization. *Expert Review of Vaccines*, *13*(9), 1107-1114.

Switzer, C., D'Heilly, C., & Macina, D. (2019). Immunological and clinical benefits of maternal immunization against pertussis: A systematic review. *Infectious Diseases and Therapy*, 1-43.

Teepe, J., Broekhuizen, B. D., Ieven, M., Loens, K., Huygen, K., Kretzschmar, M., ... Coenen, S. (2015). Prevalence, diagnosis, and disease course of pertussis in adults with acute cough: a prospective, observational study in primary care. *British Journal of General Practice*, *65*(639), e662-e667.

Terranella, A., Asay, G. R., Messonnier, M. L., Clark, T. A., & Liang, J. L. (2013). Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: A decision analysis. *Pediatrics, 131,* e1748–56. doi:10.1542/peds.2012-3144

Texas Department of State Health Services (TDSHS). (2018). *Pertussis*. Retrieved from https://www.dshs.texas.gov/idcu/disease/pertussis/

Uriarte, P. S., Rodríguez, S. S. J., Sancristobal, I. G., & Agirre, N. M. (2019). Effectiveness of dTpa vaccination during pregnancy in preventing whooping cough in infants under 3 months of age. Bizkaia, Basque Country, Spain. *Heliyon*, *5*(2), e01207.

Van Hoek, A. J., Campbell, H., Amirthalingam, G., Andrews, N., & Miller, E. (2013). The number of deaths among infants under one year of age in England with pertussis: Results of a capture/recapture analysis for the period 2001 to 2011. *Eurosurveillance*, *18*(9), 20414.

van der Zee, A., Schellekens, J. F., & Mooi, F. R. (2015). Laboratory diagnosis of pertussis. *Clinical Microbiology Reviews, 28*(4), 1005-1026.

Vizzotti, C., Juarez, M. V., Bergel, E., Romanin, V., Califano, G., Sagradini, S., ... Manzur, J. (2016). Impact of a maternal immunization program against pertussis in a developing country. *Vaccine, 34*(50), 6223-6228.

Wang, K., Bettiol, S., Thompson, M. J., Roberts, N. W., Perera, R., Heneghan, C. J., & Harnden, A. (2014). Symptomatic treatment of the cough in whooping cough. *Cochrane Database of Systematic Reviews, 9*, CD003257-CD003257.

Warfel, J. M., Zimmerman, L. I., & Merkel, T. J. (2014). Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proceedings of the National Academy of Sciences*, *111*(2), 787-792.

Weigl, J. A., Bock, H. L., Clemens, R., Zepp, F., Habermehl, P., Beutel, K., ... Laukamp, S. (1997). Safety and efficacy of acellular pertussis vaccines: The Mainz study and other recent studies. *Annals of the Academy of Medicine, Singapore*, *26*(3), 320-325.

Wiley, K., Regan, A., & McIntyre, P. (2017). Immunisation and pregnancy – who, what, when and why? *Australian Prescriber*, *40*(4), 122-124. http://doi.org/10.18773/austprescr.2017.046

Wilson, R. J., Paterson, P., Jarrett, C., & Larson, H. J. (2015). Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. *Vaccine*, *33*(47), 6420-6429.

Winter, K., Cherry, J. D., & Harriman, K. (2016). Effectiveness of prenatal tetanus, diphtheria, and acellular pertussis vaccination on pertussis severity in infants. *Clinical Infectious Diseases*, ciw633.

Winter, K., Harriman, K., Zipprich, J., Schechter, R., Talarico, J., Watt, J., & Chavez, G. (2012). California pertussis epidemic, 2010. *Journal of Pediatrics, 161*(6), 1091-1096.

Winter, K., Nickell, S., Powell, M., & Harriman, K. (2016). Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis. *Clinical Infectious Diseases*, ciw634.

Winter, K., Zipprich, J., Harriman, K., Murray, E. L., Gornbein, J., Hammer, S. J., ... Cherry, J. D. (2015). Risk factors associated with infant deaths from pertussis: A case-control study. *Clinical Infectious Diseases, 61*(7), 1099-1106.

World Health Organization (WHO). (2014). WHO strategic advisory group of experts (SAGE) pertussis working group background paper. Retrieved from https://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_FINAL4_web.pdf

World Health Organization. (2015). Pertussis vaccines: WHO position paper. *Weekly Epidemiological Record, 35*(90), 433-460. Retrieved from http://www.who.int/wer/2015/wer9035.pdf?ua=1

World Health Organization. (2017). The immunological basis for immunization series: Module 4: Pertussis-update 2017. Retrieved from https://www.who.int/immunization/documents/WHO_IVB_ISBN9789241513173/en/

World Health Organization (WHO). (2018). Pertussis. Retrieved from https://www.who.int/immunization/diseases/pertussis/en/

World Health Organization (WHO). (2019). Immunisations, vaccines & biologics. Pertussis. Retrieved

fromhttps://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis/en/

Yeung, K. H. T., Duclos, P., Nelson, E. A. S., & Hutubessy, R. C. W. (2017). An update of the global burden of pertussis in children younger than 5 years: A modelling study. *Lancet Infectious Diseases*, *17*(9), 974-980.

Yuen, C. Y. S., & Tarrant, M. (2014). Determinants of uptake of influenza vaccination among pregnant women–a systematic review. *Vaccine*, *32*(36), 4602-4613.

Appendix A: Coding Protocol

1. Articles selected using the search strategy need to be read completely to ensure that it meets all inclusion criteria.
    a. Inclusion Criteria
        i. Date: Literature published between January 2011 through December 2019
        ii. Language: English
        iii. Type of Publication: Peer-reviewed
        iv. Study design: randomized controlled trials, interventional trials, trials that are not strictly randomized, and non-randomized trials, such as observational, cluster-randomized, and case studies
        v. Studies must have at least one infant pertussis outcome/vaccine effectiveness endpoint

    b. Exclusion Criteria
        i. No editorials, commentaries, opinion papers, systematic reviews, or letters to the editor will be included
        ii. Studies with only maternal vaccination outcomes or only maternal or infant safety outcomes
        iii. Studies that only have maternal or infant serological outcomes

2. After completing full review of each article, determine if the publication is still eligible.
    a. If yes, identify if there are any companion article to search and evaluate.
    b. If no, document the reason for not including the study.

3. Each coder needs to complete the coding sheet for each article reviewed.
    a. A table for each study will be completed with rater 1 and rater 2 information for all inclusion and exclusion criteria and calculations completed
    b. Calculate the kappa coefficient (Appendix 2)

4. After completing the coding both raters should discuss the articles which had discrepancies between the raters.
    a. Discuss the concerns
    b. Go over the articles again
    c. Do not change the initial answers
    d. Repeat a version 2 of the coding table for the articles that were inconsistent
    e. If inconsistencies persist, a new line for coding should be determined and included

5. After completing the reconciliation of the articles, the author should fill out the final data extraction tables.

6. Document any issues and concerns that may cause a bottleneck in coming to consensus.

Appendix B

Kappa Coefficient Table and Formulae

		RATER 1		
RATER 2		Inclusion criteria present & Exclusion criteria absent in study	Inclusion criteria absent & Exclusion criteria present in study	Subtotal
	Inclusion criteria present & Exclusion criteria absent in study	A	B	A+B
	Inclusion criteria absent & Exclusion criteria present in study	C	D	C+D
	Subtotal	A+C	B+D	A+B+C+D

Observed agreement = (A+D)
Expected agreement = (((A+B) *(A+C)) +((C+D) *(B+D)))/(A+B+C+D)
Kappa = ((Observed agreement) – (Expected agreement))/((A+B+C+D) – (Expected agreement))

Adapted from* Data analysis plan templates: Kappa coefficients. *Statistics Solutions, 2019

Appendix C

Interpretation of Cohen's kappa*

Value of Kappa	Level of Agreement	% of Data that are Reliable
0–.20	None	0–4%
.21–.39	Minimal	4–15%
.40–.59	Weak	15–35%
.60–.79	Moderate	35–63%
.80–.90	Strong	64–81%
Above.90	Almost Perfect	82–100%

***Table taken from** Interrater Reliability: The Kappa Statistic. McHugh, 2012. Reprinted from *Biochemia Medica*, *22*(3), 276-282. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900052/

Appendix D- Ratings for Studies Selected for Analysis

Studies for Analysis to Select for Inclusion/Exclusion in the Review- Rater One/Rater Two (19 Selected for Inclusion)									
Study Title	Is the study peer reviewed?	Is the study in English?	Does the publication date fall in the Jan 2011-June 2019 period?	Was maternal vaccination policy in place or Were pregnant women vaccinated in the study?	Were infant outcomes measured/reported?	Was the study type either a trial, observational, cohort, or case study?	Exclusion criteria absent? The study was not a theoretical paper, opinion paper, letter to editor, commentary, or systematic review or metanalyses?	Exclusion criteria absent? -The study did not only include only maternal outcomes or only infant safety or infant serological immune responses.	**Agreement**
The effectiveness of maternal pertussis vaccination in protecting newborn infants in Brazil: A case-control study.	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Maternal Vaccination in Argentina: Tetanus, Diphtheria, and Acellular Pertussis Vaccine Effectiveness During Pregnancy in Preventing Pertussis in Infants <2 Months of Age	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Infant Hospitalizations and Mortality After Maternal Vaccination	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Effectiveness of maternal pertussis vaccination in preventing infection and disease in infants: The NSW Public Health Network case-control study	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Effectiveness of Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination in the Prevention of Infant Pertussis in the U.S.	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Effect of maternal immunization against pertussis in Medellin and the metropolitan area, Colombia, 2016-2017.	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
A case–control study to assess the effectiveness of pertussis vaccination during pregnancy on newborns, Valencian community, Spain, 1 March 2015 to 29 February 2016	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
The Impact of the U.S. Maternal Tdap Vaccination Program on Preventing Pertussis in Infants <2 Months of Age: A Case-control Evaluation	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Effectiveness of Vaccination During Pregnancy to Prevent Infant Pertussis	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**
Effectiveness of Prenatal Tetanus, Diphtheria, and Acellular Pertussis Vaccination on Pertussis Severity in Infants	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**8 out of 8**

Effectiveness of maternal pertussis vaccination in England: an observational study	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
A Case-Control Study to Estimate the Effectiveness of Maternal Pertussis Vaccination in Protecting Newborn Infants in England and Wales, 2012–2013	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Effectiveness of dTpa vaccination during pregnancy in preventing whooping cough in infants under 3 months of age. Bizkaia, Basque Country, Spain.	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis.	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Bordetella pertussis (Bp) disease: Before (2003–2011) and after (2013–2016) maternal immunization strategy in a pediatric hospital	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Tetanus, diphtheria, and acellular pertussis vaccination during pregnancy and reduced risk of infant acute respiratory infections	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Impact of a maternal immunization program against pertussis in a developing country	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8
Low uptake of maternal vaccination in notified pertussis cases aged less than 20 weeks	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	8 out of 8

Studies for Analysis to Select for Inclusion/Exclusion in the Review- Rater One/Rater Two (5 Studies Excluded)									
Study Title	Is the study peer reviewed?	Is the study in English?	Does the publication date fall in the Jan 2011-June 2019 period?	Was maternal vaccination policy in place or Were pregnant women vaccinated in the study?	Were infant outcomes measured/reported?	Did the study type a trial, observational study, or case study?	Exclusion criteria absent? The study was not a theoretical paper, opinion paper, letter to editor, commentary, or systematic review or metanalyses?	Exclusion criteria absent? -The study did not only include only maternal outcomes or only infant safety or infant serological immune responses.	**Agreement**
Hospitalisation of preterm infants with pertussis in the context of a maternal vaccination programme in England.	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**N/Y**	**Y/Y**	**Y/Y**	**N/N**	**7 out of 8**
Maternal and infant outcomes among women vaccinated against pertussis during pregnancy	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**N/N**	**Y/Y**	**Y/Y**	**N/N**	**8 out of 8**
Pertussis vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age.	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**N/N**	**Y/Y**	**Y/Y**	**N/N**	**8 out of 8**
Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**N/Y**	**Y/Y**	**Y/Y**	**N/N**	**7 out of 8**
Maternal Tdap vaccination and risk of infant morbidity	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**N/Y**	**Y/Y**	**Y/Y**	**N/N**	**7 out of 8**