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EXPLORATION OF CONTRIBUTING FACTORS IN THE RISE OF *BORDETELLA PERTUSSIS* INCIDENCE

BY
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Degree to be awarded: M.P.H.
Executive MPH

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M.P.H. Emory University, 2014
M.S. University of Maryland, 1992
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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
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2014

Abstract

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RISE OF *BORDETELLA PERTUSSIS* INCIDENCE

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Infectious diseases were once the leading cause of mortality in the United States. The discovery of vaccines, in addition to other public health advances, have reduced the impact of infectious diseases significantly; reducing the case count to zero for some of the diseases. Unfortunately, the incidence of many of these vaccine preventable diseases are on the rise again with many contributing factors. In this study, the pertussis outbreak in California in 2010 is used to explore contributing factors to the rise of cases.

Although the incidence of *Bordetella pertussis* is nowhere near where it was before the development of vaccines, there is reason to be concerned about the recent rise in incidence. The rate of pertussis incidence in 2012 was higher than any year since 1955 and 2014 is on track to be another record year with 17,325 cases reported from January 1st through August 16, 30% higher than the same period in 2013. There are many factors which contribute to the continued rise in incidence. Using the California 2010 Outbreak, this study will explore some of those factors including problems with diagnosis, efficacy of the current vaccines, changes in pertussis itself, potential waning of vaccine protection, vaccine uptake and exemptions, and the influence of providers. Each of these plays a role in contributing to pertussis incidence.

Length: The Abstract may not exceed one page, formatted according to the regular page formatting instructions (margins, spacing, font). The text itself cannot exceed 350 words (not counting the title etc.) The Abstract may be single-spaced.

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Definition of Terms

General Terms:

Infectious disease: illness that can be passed between people by means of an external agent or organism

Vaccine: biological or chemical substance which induces a protective immune response to a disease causing agent

Immunization/vaccination: introduction of a vaccine into a person for the purpose of inducing a protective immune response

Antigen: a substance that induces an immune response. Vaccines consist of one or more antigens

Antibodies: proteins created by an individual in response to an antigen

Vaccine efficacy: a measure of the reduction of disease incidence due to vaccination when compared to the incidence in an unvaccinated population. Vaccine efficacy is usually determined in randomized double blinded controlled prospective studies

Vaccine effectiveness: the ability of a vaccine to prevent disease by comparing the incidence of disease in vaccinated and unvaccinated populations. Vaccine effectiveness is usually differentiated from efficacy because the former is usually determined in observational studies in contrast to efficacy which is usually determined in randomized controlled prospective trials.

Index case: the first person to become infected with a particular disease in a community or outbreak

R_0: the basic reproductive number. The number of people to whom the average index case would transmit infection if all contacts were susceptible

Herd immunity threshold: the level of immunity needed in a population to protect those who are not immune (do not respond to vaccine, did not get vaccine, or did not receive all doses). This threshold is determined by the equation $(R_o\text{-}1)/R_o$

Vaccine dose: the amount of vaccine given at a particular time in a single immunization

Vaccine boost/booster: successive immunizations can increase the immune response to a vaccine, thus boosting the response. The current recommendations include boosting doses to improve the level of protection of the vaccine

Fully vaccinated: having received all doses that are recommended by the Advisory Committee on Immunization Practices (ACIP) for the age of the individual

Under vaccinated: having received less than the recommended doses for the age of the individual

Unvaccinated: having received no doses regardless of age

Outbreak: sudden increase of cases compared to the normal background rate

Pertussis specific terms:

Pertussis/whooping cough: disease caused by *Bordetella pertussis* bacterium, often named for the sound that is made by sick children (whoop)

Catarrhal stage: the first stage of a pertussis infection characterized by "flu-like" symptoms, runny nose, sneezing, low grade fever. Lasts one to two weeks.

Paroxysmal stage: violent coughing induced by thick mucosal secretions during the second stage of pertussis infection. The harsh intake of breath between the coughs causes the whoop for which the disease is known. Lasts two to four weeks, but may last up to 10 weeks.

Convalescent stage: third stage of pertussis infection, coughing still occurs but is much less violent, gradual recovery. Can last three to four weeks or up to several months.

Whole cell vaccine: formalin inactivated *B. pertussis* cells in suspension. First used in the 1930's.

DTP: designation for vaccine containing whole cell pertussis vaccine as well as vaccines for diphtheria and tetanus.

Acellular pertussis vaccine: vaccine made up of purified pertussis components rather than whole bacteria and indicated in vaccine formulations by lower case a.

DTaP: formulation of vaccine for pertussis, diphtheria and tetanus

Tdap: formulation of vaccine for tetanus, diphtheria, and pertussis with lower concentration of antigens to diphtheria and pertussis than the vaccine used for young children, DTaP

Components: parts of pertussis or other infectious agents used in vaccines

PT/pertussis toxin: exotoxin virulence factor produced by *B. pertussis* which is also involved in bacterial colonization and infection establishment.

FHA: filamentous hemagglutinin, a cell surface protein produced by *B. pertussis* which aids cell adherence

Pertactin: outer membrane protein produced by *B. pertussis* which aids adhesion specifically to tracheal epithelial cells

FIM: fimbriae, a cell surface protein produced by *B. pertussis* which aids cell adherence

Introduction

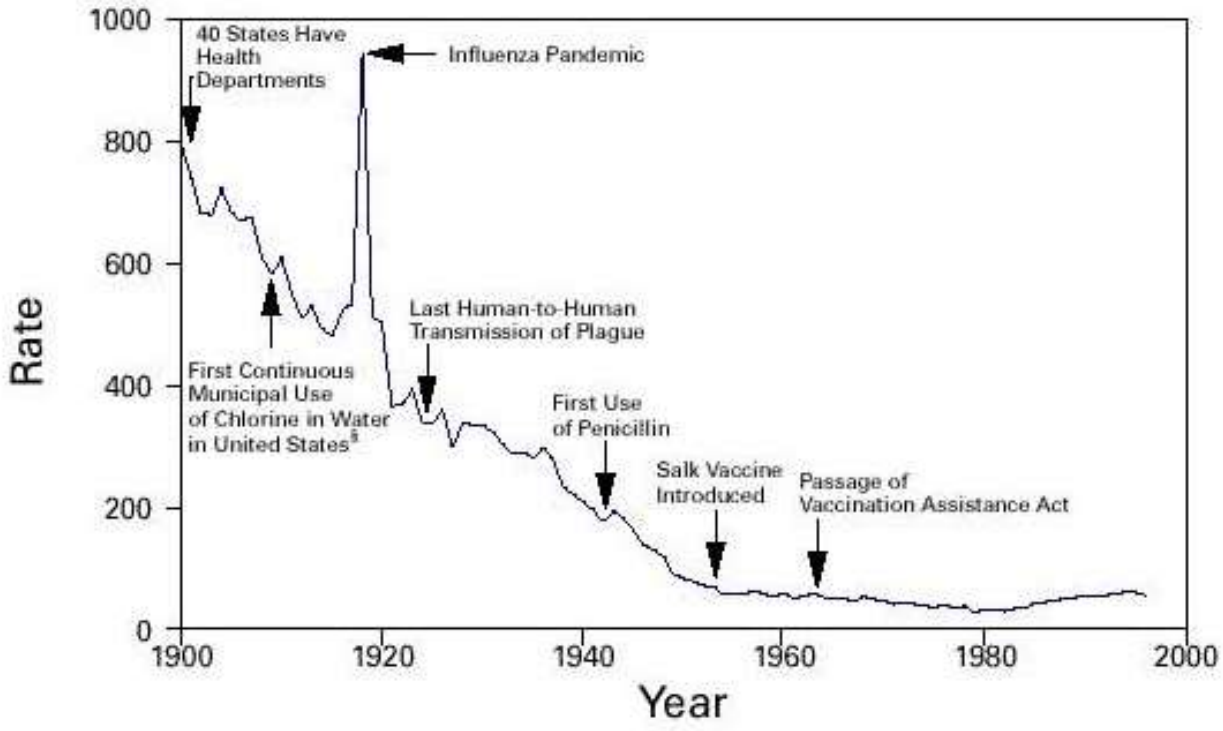
Before the advances of modern medicine, infectious diseases were the major cause of death for human beings. The first known descriptions of infectious diseases are from Hippocrates and Galen in Ancient Greece. (Kass, 1987) Attempts at prevention of infectious diseases were made through the ages, with the first wide-spread use of immunizations in the nineteenth century. (Andre, 2001; Bazin, 2003; Kass, 1987; Plotkin, 1999) These first immunizations were for smallpox, typhoid, cholera, plague and rabies.

In the twentieth century, the United States made tremendous inroads against infectious diseases with major strides in public health practices. (Centers for Disease Control and Prevention (CDC), 1999) This is thanks in part to the discovery of anti-infectious agents as well as preventive vaccinations, but must also be attributed to advances in sanitation and hygiene. The leading causes of death in 1900 were pneumonia, tuberculosis and gastrointestinal infections. (Centers for Disease Control and Prevention (CDC), 1999; Toro, 2012) Figure 1 shows the infectious diseases rate in the United States with several major public health advances marked. From the presence of state and later local health departments to the introduction of vaccines, the effect of these public health practices is dramatic.

Several individual states had nineteenth century mandates for compulsory vaccination, which was upheld in the United States Supreme Court in 1905 with a 7-2 decision in Jacobson v. Massachusetts. This decision stated that such laws were constitutional when “necessary for the public health or the public safety.” ("Jacobson v. Massachusetts," 1905) This ruling did leave room for certain individuals to claim medical exemptions when mandatory vaccinations would

be cruel or inhumane. A later decision added that a school could refuse entry for a student who did not receive required vaccinations. ("Zucht v. King," 1922) School mandates were slow in coming, and only after several outbreaks did all 50 states have mandates by 1980. (Salmon et al., 2006) All of the states allow medical exemptions and 48 allow religious exemptions. Some states also allow personal belief exemptions beyond religious. (Orenstein & Hinman, 1999; Salmon et al., 2006) The school immunization program has made a great impact on the infectious disease burden by incentivizing vaccination of one of the most vulnerable populations, children. (Orenstein & Hinman, 1999; Salmon et al., 2006)

Figure 1. Crude death rate for infectious diseases – United States 1900-1996 (per 100,000) (Centers for Disease Control and Prevention (CDC), 1999)



The result of these and other vaccination campaigns in the United States can be seen in table 1 comparing the average annual disease morbidity of the twentieth century to that of 2010. For example, measles annual average morbidity for the 20th century was 530,217, while for

2010, there were 61 reported cases. This is a reduction of cases of 99.99%. Pertussis, by contrast had a reduction of 89.4% of cases from the average 20th century year to 2010. Smallpox, diphtheria and paralytic polio had no cases in 2010 for a 100% decrease over the average morbidity of the twentieth century.

Table 1. Comparison of 20th Century Annual Morbidity & Current Morbidity

Disease	20th Century Annual Morbidity	2010 Reported Cases	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	21,291	89%
Tetanus	580	8	99%
Polio (paralytic)	16,316	0	100%
Measles	530,217	61	>99%
Mumps	162,344	2,528	98%
Rubella	47,745	6	>99%
Haemophilus influenzae (<5 years of age)	20,000 (est.)	270	99%

(Centers for Disease Control and Prevention (CDC), 2011a)

Another factor to consider in the reduction of infectious diseases burden is the herd immunity threshold. When a certain percentage of the community is successfully immunized (i.e., vaccinated and in whom a protective immune response was induced) against an infectious preventable disease, those who are unvaccinated or not successfully vaccinated have a measure of protection because the chains of person-to-person spread are broken. Hence the remaining susceptible individuals are protected by not being exposed to the infectious pathogen. The level of immunity needed for this effect is designated as the herd immunity threshold and varies by disease, mode of transmission, and vaccine efficacy. Herd immunity threshold is generally calculated using the simplified equation: $(R_0\text{-}1)/R_0$. (Diekmann, Heesterbeek, & Metz, 1990) The basic reproductive number, R_0, is the expected number of secondary cases, on average, produced by a single index case in a completely (100%) susceptible population. Once immune rates reach

high enough levels, the infection rate is significantly down due to a reduction in the susceptible population.

As an example, if R_0 for a given disease is four, then the herd immunity threshold is 75%. In this scenario, the average infected person could transmit to three susceptible others. If greater than 75% of the population were immune, the transmission would be to less than 1 person leading to ending transmission. If the immune portion of the population was less than 75%, the transmission would continue and sustain or increase the current level of infection. Characteristics of several vaccine preventable infectious diseases are listed in table 2. These characteristics include the method of transmission, basic reproductive number and herd immunity threshold.

Table 2. Characteristics of Selected Vaccine Preventable Diseases

Disease	**Transmission**	**R_0**	**Herd immunity threshold**
Diphtheria	Saliva	6-7	85%
Measles	Airborne	12-18	83 - 94%
Mumps	Airborne droplet	4-7	75 - 86%
Pertussis	Airborne droplet	12-17	92 - 94%
Polio	Fecal-oral route	5-7	80 - 86%
Rubella	Airborne droplet	5-7	80 - 85%
Smallpox	Social contact	6-7	83 - 85%

From (Centers for Disease Control and Prevention (CDC), 2003)

There are five main types of vaccines in modern use, live attenuated, inactivated, component, polysaccharide and recombinant. (Centers for Disease Control and Prevention (CDC), 2011c) Live attenuated vaccines are those which use weakened or altered forms of the infectious agent. Inactivated vaccines can be killed or replication-incompetent. Component vaccines are made of one or more purified components of the infectious agent. Polysaccharide vaccines are made up of the sugar chains which are seen on the surface of the infectious agent

and can be either the pure polysaccharides or conjugated with proteins. Recombinant vaccines are the result of genetic engineering. (Centers for Disease Control and Prevention (CDC), 2011c) As a general rule "the more similar a vaccine is to the disease-causing form of the organism, the better the immune response to the vaccine." (Centers for Disease Control and Prevention (CDC), 2011c) Unfortunately, these immune responses can be both beneficial and detrimental. Beneficial effects include prevention of disease, reducing the severity of disease, or blocking disease transmission. Detrimental effects can harm the individual receiving the vaccine.

Prior to the development of vaccines, *Bordetella pertussis* infection caused an estimated 270,000 cases and up to 10,000 deaths per year in the United States. Vaccines with their widespread use have dropped this incidence dramatically. However, the incidence of pertussis infection has been rising since the 1980's. The current vaccine recommendations have been changed and refined several times with the most recent recommendations being released in 2014. (Burns, Meade, & Messionnier, 2014; Centers for Disease Control and Prevention (CDC), 2013) Pertussis vaccines have also changed substantially as acellular vaccines have replaced whole cell vaccines. In initial studies, the acellular vaccines appeared to be as effective as whole cell vaccines without the severe side effects. However, recent resurgences of pertussis infections have raised concerns that the vaccines may have lost effectiveness over time (i.e., waning immunity) greater than with whole cell vaccines.

In this study, the California pertussis outbreak of 2010 will be used to explore potential contributing factors for the rise of pertussis incidence. In addition to the potential loss of vaccine effectiveness listed above, there are other contributing factors that show influence on the

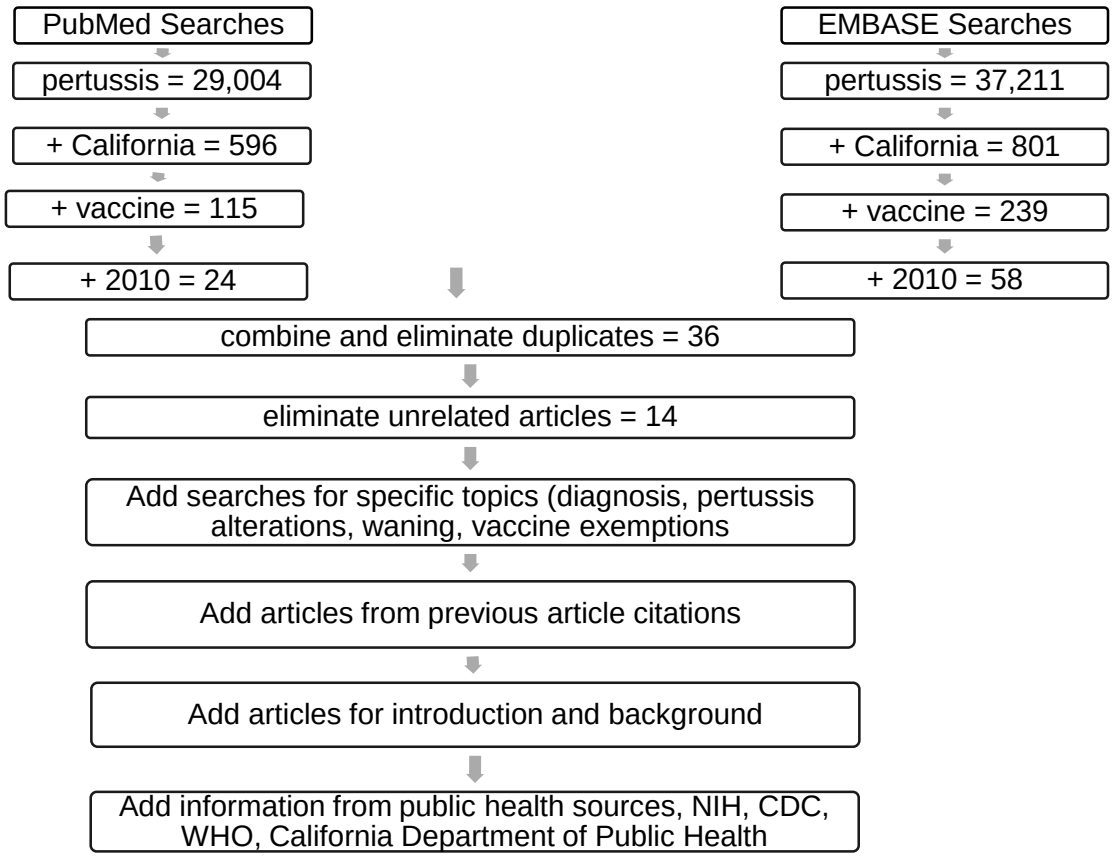
pertussis surge. The actual incidence of pertussis infection is likely to be much different than suspected due to problems with diagnosis and detection. The vaccine efficacy may have been misrepresented in the initial trials and may also be affected by the genetic variations in pertussis itself. There is evidence that the vaccine does not last as long as originally thought and instead protection wanes. Certainly, vaccine exemptions and non-compliance with vaccine recommendations contribute. The overall vaccination rate and corresponding population immunity level is below the herd immunity threshold. Additionally, pertussis is highly contagious in a susceptible population.

The more that is known about the contributing factors to the California 2010 pertussis outbreak, the more likely that future outbreaks can be reduced or prevented.

Methodology

Using the available research, a systematic review was explored with the assistance of Amy Allison, Research Librarian, at the Woodruff Health Sciences Library, Emory University. The available data seemed to be divergent. There appeared to be small numbers of articles on several related topics. Given this, the choice was made to do a series of mini systematic reviews on the factors contributing to the California pertussis outbreak of 2010.

The search strategy followed the flow chart below:



Background

The respiratory illness commonly called Whooping Cough is caused by infection with *Bordetella pertussis;* which was first identified and isolated in 1906. (Centers for Disease Control and Prevention (CDC), 2011b) The earliest outbreak described in medical literature was by Guillaume de Baillou. He described a 1578 Paris epidemic which affected mostly infants and young children and had a high mortality rate. (Edwards & Decker, 2008) In this description, de Baillou used a common name for the illness suggesting that the disease emerged substantially before that time.

The aerobic gram negative bacterium is rod-shaped and small. (Faulkner et al., 2011) The cause of disease is thought to be primarily toxin driven leading to thick pulmonary secretions which are difficult to expel. The most severe disease occurs in young infants with narrow airways that can be plugged by the secretions. (Faulkner et al., 2011) Symptoms can vary from asymptomatic or mild cold-like illness to prolonged paroxysmal cough. (Centers for Disease Control and Prevention (CDC), 2010) The incubation period before the onset of symptoms typically ranges from seven to ten days although a range of four to twenty one days is not uncommon. (Centers for Disease Control and Prevention (CDC), 2011b) Rare cases have been seen with incubation periods as long as 42 days. (Faulkner et al., 2011) The first stage, or catarrhal stage, of the illness is cold-like and includes sneezing, runny nose, mild cough, and a low fever. (Centers for Disease Control and Prevention (CDC), 2011b) The second stage is the paroxysmal stage and is characterized by bursts of rapid coughs between which the patient may not be able to inhale. (Centers for Disease Control and Prevention (CDC), 2011b) The characteristic whoop occurs during the attempts to inhale, is more likely to occur in older infants

and children and is rarely seen in adults. (Centers for Disease Control and Prevention (CDC), 2010; Faulkner et al., 2011) The whoop is often not seen in young infants who lack the capacity to forcibly inhale against a partially closed glottis. (Edwards & Decker, 2013) The third stage is the convalescent stage which is gradual and may take from two weeks to several months. Individuals are generally contagious during the catarrhal stage and the first two weeks after cough onset.(Centers for Disease Control and Prevention (CDC), 2011b) Pertussis infection is required to be reported to state health departments throughout the United States, including all probable and confirmed cases. (Faulkner et al., 2011) These reports are eventually collected as part of the National Notifiable Diseases Surveillance System (NNDSS).

Before the development and widespread use of vaccines for pertussis, it is estimated that there were up to 270,000 cases and up to 10,000 deaths in the United States each year with the highest incidence in 1934. (Cherry, Brunell, Golden, & Karzon, 1988; "Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP)," 1997) The World Health Organization (WHO) estimates that there were 16 million cases and around 195,000 deaths of children worldwide in 2008. (World Health Organization (WHO), 2012) The WHO estimates that 95% of these cases took place in the developing world.

The early vaccines for pertussis were formalin inactivated whole cell vaccines (DTP) developed in the 1930's and in widespread use by the mid-1940's. The designation DTP is an indication that the vaccine contains three components pertussis, tetanus and diphtheria. CDC estimates that vaccination with whole cell pertussis vaccine was 70-90% efficacious after 3

doses. (Centers for Disease Control and Prevention (CDC), 2011b) Protection was estimated to last between 5 and 10 years. (Centers for Disease Control and Prevention (CDC), 2011b) A study on the efficacy of the whole cell vaccine determined that there was a reduction of 95% for severe illness (95% CI 66-99), 81% for paroxysmal cough (CI 65-89), and 64% for cases defined by a mild cough (CI 49-75). (Onorato, Wassilak, & Meade, 1992) While successful at reducing the number of cases, there were concerns about public perceptions of vaccine safety which were publicized in a book and on television in the early 1980s, which led to concerns about public acceptance of the vaccine with the potential for reduced vaccine coverage. (Centers for Disease Control and Prevention (CDC), 2011b; Gangarosa et al., 1998) Adverse reactions included milder symptoms of fever, erythema, tenderness, and irritability as well as more serious reactions including convulsions, hypotonic-hyporesponsive episodes and other neurological effects. (Hawken et al., 2012) In addition, there were allegations that whole cell pertussis vaccines caused permanent brain damage although these findings are now disputed. (Edwards & Decker, 2013) Other vaccines of the same time period had adverse effects including Guillain-Barré syndrome. Concerns about these proven and alleged adverse effects led to concerns that vaccination rates would decrease and lead to epidemics of disease. This had occurred in a variety of countries including the United Kingdom, Sweden, and Japan. ("Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP)," 1997) This led to the desire for development of alternative vaccines.

Acellular pertussis vaccines contain only components of pertussis and not the whole cell. There are no pertussis only acellular vaccines in the United States; only those combined with

tetanus and diphtheria toxoids. The current estimation by CDC is that acellular pertussis vaccines produced in the United States have approximately 85% efficacy. (Centers for Disease Control and Prevention (CDC), 2011b) There are different formulations recommended for pediatric vaccines (under age seven) versus the formulation for adolescents and adults. The pediatric formulation is called DTaP and is available under various brand names from the different vaccine manufacturers. (Centers for Disease Control and Prevention (CDC), 2011b) The formulation for adolescents and adults is designated Tdap and contains a reduced amount of the diphtheria and pertussis components compared with the tetanus component. (Centers for Disease Control and Prevention (CDC), 2011b) Tdap is currently approved for use starting at age 10 or 11, depending on the manufacturer. If the recommended dosing is followed, the efficacy of acellular pertussis vaccines is estimated to be 84-85% in children and 92% in adults when followed for 30 months. (Ward et al., 2005; Witt, Katz, & Witt, 2012b) Table 3 is a partial representation of the vaccines available in the United States. (Faulkner et al., 2011) Each vaccine is shown with the pertussis components that they contain, date of licensure and current use. All of the pertussis vaccines available in the United States contain pertactin which will be discussed later in this study.

The development of vaccines for pertussis in the 1930's and widespread use since the 1940's has dramatically reduced the number of cases in the United States. (Centers for Disease Control and Prevention (CDC), 2011b) In 1922, there were 150 cases reported per 100,000 people while in 1976 there were 0.5 cases per 100,000 people. (Faulkner et al., 2011) The numbers of cases began to rise again in the 1980's. (Centers for Disease Control and Prevention

(CDC), 2011b) In 2010, there were 27,550 reported cases of pertussis infection in the United States and 27 deaths. (Norton, 2012) This translates to 8.9 cases per 100,000 for 2010. Most of

Table 3. Selected Pertussis Vaccines

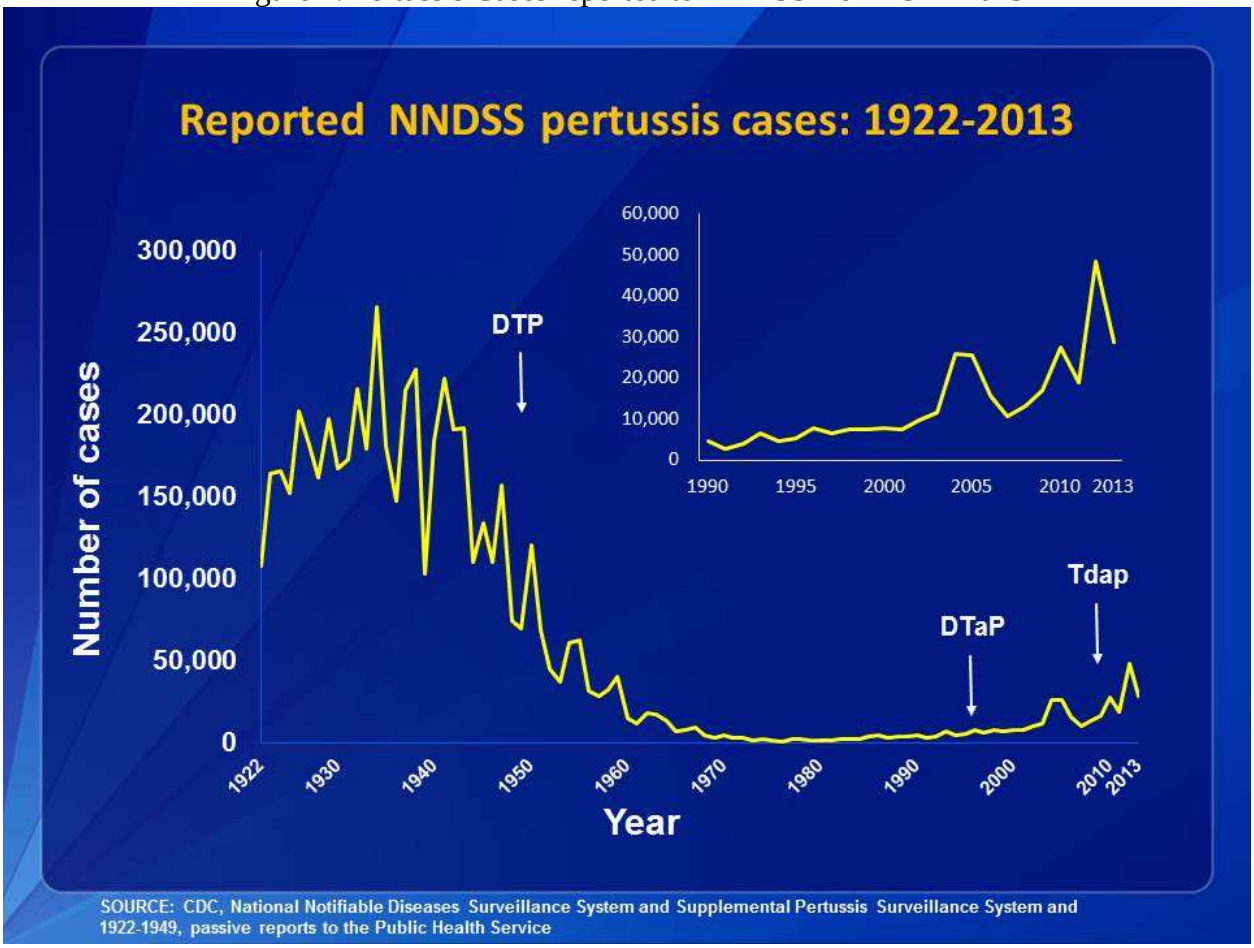
Pertussis-Containing Vaccines for Children	Brand	Pertussis components included	Licensed Date and Use
DTaP	INFANRIX®	PT, FHA, Pertactin	First licensed in 1991; used for all childhood doses
	DAPTACEL®	PT, FHA, Pertactin, FIM	
DTaP+IPV+HepB	PEDIARIX®	INFANRIX + HepB + IPV	Used for the first three doses
DTaP+IPV+Hib	PENTACEL™	PT, FHA, Pertactin, FIM	Approved in 2008; used for primary four-dose series
DTaP+IPV	KINRIX™	INFANRIX + IPV	Approved in 2008; used for booster dose at 4–6 years
Pertussis-Containing Vaccines for Adolescents and Adults			
Tdap	ADACEL®	PT, FHA, Pertactin, FIM	First available in 2005
	BOOSTRIX®	PT, FHA, Pertactin	
Other Vaccines			
Pertussis Only		Not available in the United States	
DT/Td	DECAVAC™ TENIVAC™	none	Do not contain pertussis; DT used for primary series when pertussis vaccination is contraindicated; Td used in persons aged ≥7 years

Adapted from (Centers for Disease Control and Prevention (CDC), 2011b; Edwards & Decker, 2013; Faulkner et al., 2011)

the deaths occurred in infants under the age of one year. (Norton, 2012) California reported 9,159 of these cases and ten infant deaths. (The Associated Press, 2012) This was the highest number of cases in California since 1947 when 9,394 cases were reported. (California Department of Health, 2014a) After a widespread vaccination campaign, including translation of vaccine and disease information materials into Spanish, California's numbers improved greatly with over 70% fewer reported cases and no deaths in 2011. (The Associated Press, 2012) Other countries have also experienced this resurgence of cases. (Clark, Messonnier, & Hadler, 2012)

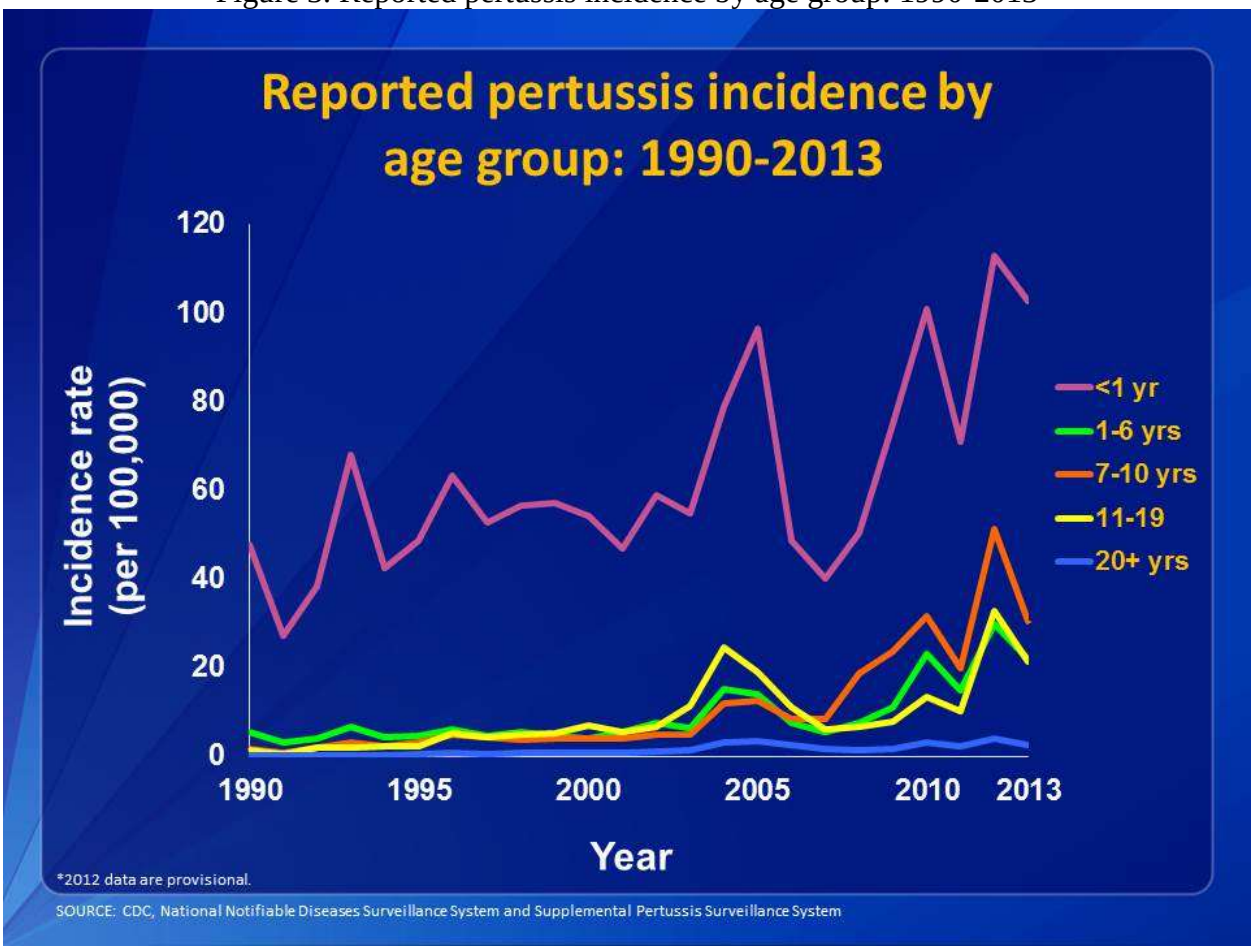
The number of cases in 2012, 48,277, was the highest in the United States since 1955. (Centers for Disease Control and Prevention (CDC), 2014; Stobbe, 2013) Figure 2 shows the total number of pertussis cases reported to NNDSS. Also shown on figure 2 are the introductions of DTP, DTaP and Tdap. Figure 3 shows the incidence from 1990-2013 for the United States broken down by age group. Table 4 shows the increase in reported pertussis cases in California and the United States in recent years. The pertussis numbers include both probable and confirmed cases. A probable case is a clinically diagnosed case without laboratory confirmation.

Figure 2. Pertussis Cases reported to NNDSS from 1922-2013



(Centers for Disease Control and Prevention (CDC), 2012b)

Figure 3. Reported pertussis incidence by age group: 1990-2013



(Centers for Disease Control and Prevention (CDC), 2012b)

Table 4. Recent Pertussis Case Reports for the United States and California

Report Year	United States	California
2007	10,454	590
2008	13,278	534
2009	16,858	869
2010	27,550	9159
2011	18,719	3016
2012	48,277	1023
2013	28,639	2537
Data from (California Department of Health, 2014a; Centers for Disease Control and Prevention (CDC), 2012b, 2014)		

The Healthy People 2020 goals for pertussis are under the vaccine preventable disease arm. (U.S. Department of Health and Human Services, 2012)

1. 2500 cases or less in children under 1 year of age (baseline set with an average of 2,777 cases in this age group between 2004 and 2008, goal is 10% reduction)
2. 2,000 cases or less in adolescents aged 11-18 years (baseline set with an average of 3,995 cases in this age group between 2004 and 2008, goal is 50% reduction)

Unfortunately, these goals have had set backs in more recent years as there were 3206 cases in infants under one year old in 2009. (Faulkner et al., 2011) Part of this has to do with the disease reservoir and how it is spread, and part has to do with vaccine compliance. Pertussis is considered endemic, meaning that it is always in the environment. (Centers for Disease Control and Prevention (CDC), 2011b) There do not appear to be animal or insect hosts or vectors. It is passed from person to person through contact with respiratory droplets. (Edwards & Decker, 2008) New cases are getting the disease from close contact with those who are already infected. Besides vaccination, the best potential to limit disease spread is early diagnosis and treatment. (Faulkner et al., 2011) Additionally, pertussis incidence goes through cyclic peaks, one such peak occurred in 2005 and another in 2010. (Edwards & Decker, 2013; Faulkner et al., 2011) These peaks were higher than previous years since 1959. The totals for 2012 exceeded all previous years since 1955. (Centers for Disease Control and Prevention (CDC), 2014; Stobbe, 2013)

The current vaccine recommendations for children aged 0-6 years include three primary immunizations followed by two boosters. These recommendations with the age of each

immunization are shown in table 5 for childhood vaccination. (Adapted from (Advisory Committee On Immunization Practices (ACIP), 2011))

Table 5. Current Pertussis Vaccine Recommendations for Children

Dose	Age	Year acellular vaccine recommended
Primary 1	2 months	1997
Primary 2	4 months	1997
Primary 3	6 months	1997
First Booster (fourth dose)	15-18 months	1992
Second Booster (fifth dose)	4-6 years	1992

("Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP)," 1997)

Additionally, the Advisory Committee on Immunization Practices (ACIP) has included recommendations since 2005 for a single dose of Tdap for individuals 11-18 years of age who have completed the childhood schedule, preferably between ages 11-12. (Centers for Disease Control and Prevention (CDC), 2011d) Adults 19-64 are also recommended to have the single dose regardless of the last tetanus shot. Until recently, ACIP recommended that adults who are aged 65 and older who have close contact with children under twelve months of age receive a single dose. This was changed in June 2012, to include all adults regardless of age or contact with children. (Centers for Disease Control and Prevention (CDC), 2012c) Children aged 7 through 10 who have not received all of the five doses listed above are not considered fully vaccinated. Those not fully vaccinated should receive one dose of Tdap then follow the regular schedule. (Centers for Disease Control and Prevention (CDC), 2011d) Those not vaccinated at all should receive three doses beginning with Tdap followed by two doses of Td. The most recent addition to the recommendations was to add a Tdap vaccination in the third trimester of every pregnancy to attempt to protect infants until they can be vaccinated. (Burns et al., 2014; Centers for Disease Control and Prevention (CDC), 2013). Vaccination during the third

trimester maximizes the amount of antibody which can be transferred transplacentally to the developing fetus.

As mentioned earlier, vaccination with the acellular vaccines is considered to be approximately 85% efficacious after 4 doses. Protection is not necessarily complete. Many studies have been performed on the efficacy of the different acellular pertussis vaccines. (Edwards & Decker, 2013) The results of these studies are widely varied due partly to the different vaccines tested but also due to the differences between the case definitions used in the studies. The overall data show that acellular vaccines increase protection with each successive dose; however the single dose protection (~15-20%) is significantly lower than that of whole cell vaccine. (Edwards & Decker, 2013)

As mentioned previously, unvaccinated or under vaccinated members of a community can gain a measure of protection in a community where the vaccination rate leads to a population immunity level that surpasses the herd immunity threshold. R_0, the number of secondary cases expected from a single index case, for pertussis is estimated to be 12-17 (Centers for Disease Control and Prevention (CDC), 2003). Pertussis is highly infectious and as a result the herd immunity threshold is very high, 92-94% (Centers for Disease Control and Prevention (CDC), 2003). Vaccination coverage for children 19-35 months in the United States and California in 2009 and 2013 is in table 5. (Centers for Disease Control and Prevention (CDC), 2010, 2012a) The 2009 numbers are shown as the year before the California outbreak and because there was a big push for vaccinations after the state epidemic declaration in June 2010 which would skew the 2010 results. (California Department of Health, 2012)

Table 5. Pertussis Vaccination Coverage for the United States and California for 2009 and 2013

	USA, 2009	California, 2009	USA, 2013	California, 2013
3+ doses	95.0%	93.8%	94.1%	91.7%
4+ doses	83.9%	79.7%	83.1%	83.1%

Incomplete protection, high levels needed for herd immunity, and high transmission rates are all of concern to those hoping to reduce the spread of pertussis. There may be an additional complication brought on by the current vaccination schedule. For those following the standard recommendations, the second booster is given at 4-6 years of age. If the booster is given at age 4, there will be a minimum of 7 years before the next recommended immunization given from ages 11-18. As described previously, the duration of protection from the whole cell vaccine was estimated to be 5- 10 years. Data presented in studies on the duration of protection for the acellular vaccines varied widely by vaccine formulations (2-6 years). (Edwards & Decker, 2013) Recent studies that will be presented below have suggested that the duration may be shorter than expected. While the burden of disease remains with infants, the largest increase in incidence of pertussis in the United States in recent years has been in 7-10 year olds. (Guris et al., 1999; Rittle, 2010; Ward et al., 2005; Winter et al., 2012; Zepp et al., 2011)

Rohani and Drake have suggested five reasons for the increase in pertussis incidence based on trends seen in individual states in the United States. (Rohani & Drake, 2011) They propose the following:

1. Higher notification rates due to increased physician awareness and improved diagnosis
2. Potential nucleic acid changes in B. pertussis causing reduced vaccine efficacy
3. Lower efficacy of acellular vaccines (as opposed to the whole cell vaccines)

4. Waning immunity from acellular vaccines and reduced and waning infection acquired immunity
5. Population demographics including expansion, vaccine uptake and vaccine exemptions.

In the following series of mini reviews, these potential contributing factors will be explored using the California 2010 outbreak as a case study.

Problems with Detection/Diagnosis

In addition to vaccine protection, detection of cases and mitigation of contagion would help to reduce the spread of pertussis. Early diagnosis and treatment may be harder to accomplish than thought. As mentioned earlier, symptoms can vary from asymptomatic or mild cold-like illness to prolonged paroxysmal cough. (Centers for Disease Control and Prevention (CDC), 2010) It can be difficult for patients, families or even physicians to appropriately separate pertussis symptoms from other common ailments. Individuals are infectious during the catarrhal stage and the beginning or the paroxysmal stage thus potentially increasing the likelihood of others becoming infected. (Edwards & Decker, 2013; Faulkner et al., 2011) Since adolescents and adults are less likely to whoop, diagnosis is often missed or delayed. Infected individuals may not know to avoid those who are susceptible such as infants and the unvaccinated or under vaccinated.

In addition to the problem of controlling disease spread, there may be a problem with the reporting of cases. Halperin proposes that cases were significantly undercounted in clinical practice when compared to the cases detected in clinical trials. (Halperin, 2005) To estimate background rates, Halperin reviewed incidence of pertussis in controls in vaccine clinical trials reported in 1996 and 2005. (Greco et al., 1996; Gustafsson, Hallander, Olin, Reizenstein, & Storsaeter, 1996; Ward et al., 2005) Halperin estimated the background incidence in controls to be 370 cases per 100,000 person-years; this translates to approximately 1 million cases per year in the US. This is significantly higher than the 27,550 cases reported in 2010, which would be 8.9 cases per 100,000 (considering the US population in 2010 was approximately 309 million). Other studies have suggested that up to 500% of the actual cases may be underreported meaning

that the actual numbers could be six times the currently reported cases. (Cherry, 2005; Shapiro, 2012; Winter et al., 2012) Even if these estimates were off ten-fold, this would take the incidence rates back to those reported before the vaccines were in use.

Another group, led by Cornia, believe that in the non-outbreak setting, pertussis diagnosis is often missed in agreement with Halperin. (Cornia, Hersh, Lipsky, Newman, & Gonzales, 2010) Cornia and colleagues looked at three prospective studies and examined the symptoms that are classically associated with pertussis including posttussive emesis, posttussive syncope, paroxysmal cough and inspiratory whoop. Cornia suggests that less severe and even some severe cases of infected adolescents and adults may be routinely missed when classic symptoms are not present and even when one or more symptoms are present. Additionally, when clinicians obtain a sample for PCR screening, they may be using the wrong sampling method. Swabs may be toxic to pertussis or interfere with PCR. (Cornia et al., 2010) The conclusions of the study included the recommendation for laboratory testing of more cases based on the overall clinical impression especially during outbreak situations. When the classic symptoms are not present, even the suggestion to test may not come to mind. Additionally, the clinician must decide which of the many respiratory illnesses to be tested. It is not cost effective to test everyone for all possibilities. Additional lines of questioning including exposure to other ill individuals are needed to help reduce the possibilities.

In a study of laboratory confirmed cases from the California 2010 outbreak, Chan and colleagues, noted that the most commonly reported sites of exposure were the home setting (58.6%) and school (36.4%). (Chan et al., 2012) Since diagnosis is usually made after the

infected individual becomes contagious, this would make it difficult to mitigate spread because many susceptibles have already been exposed by the time a diagnosis is confirmed. (Chan et al., 2012; Cornia et al., 2010) Additionally, the peak of infections for infants, young children and adults was in the summer while for adolescents it was in the fall. Chan suggests this indicates adults and young siblings may be the source of infection of infants. (Chan et al., 2012) Since infants are too young to be fully vaccinated and are therefore highly susceptible, earlier knowledge of the infection could have provided better protection and potentially reduced the number of infant deaths during the outbreak

A retrospective cohort study looked at delayed diagnosis from another viewpoint. This study looked at 501 PCR positive cases in Kaiser Permanente Southern California from July to December 2010. (Taylor et al., 2014) These cases had a high uptake of vaccinations with 93% of 4-6 year olds having 4 or 5 vaccinations and 38% of 11-18 year olds having a Tdap booster. In addition to the classic pertussis symptoms, wheezing was added. Twenty nine percent of the patients were evaluated two or more times before a pertussis diagnosis was reached. Ninety five percent of patients with wheezing were assumed to have asthma exacerbation while less than half of these patients had previously diagnosed asthma. Those treated for asthma were diagnosed with pertussis later than those not treated, averaging 2-3 days later. (Taylor et al., 2014) Questioning the patient regarding a previous history of asthma along with potential exposures would help to reduce the delay in diagnosis when wheezing is present.

It may seem that problems with detection or diagnosis of pertussis infection would reduce the overall incidence, but that does not take into account the effect of the undiagnosed on the

population. Individuals who are not aware that they have pertussis instead of a cold or other respiratory illness, may continue to go to school or work and increase the incidence by infecting others.

Efficacy of Acellular Pertussis Vaccines/Changes in Pertussis

There are many possible reasons why pertussis vaccines may lose effectiveness or "fail". Cherry proposes the following list of reasons for presumed pertussis vaccine failure: (Cherry, 2012b)

1. Over expectation of efficacy because of case definition.

   The case definition during early efficacy trials included laboratory confirmation and ≥21 days of paroxysmal cough. (Cherry, 2012b) This very limited case definition excludes cases with fewer symptoms or asymptomatic cases. By limiting the definition to only severe cases, asymptomatic or individuals with minor illness were not counted thus potentially inflating the efficacy in the early trials. Additionally, both the acellular and whole cell vaccines were more efficacious against more severe disease. (Onorato et al., 1992; Ward et al., 2005)

2. Inflated estimates of efficacy because of observer bias.

   Different efficacy studies had differing case definitions, different requirements for timely reporting and varied experience of those who obtained the data. (Cherry, 2012b) Additionally, Cherry cites a study in Germany where the investigators were expected to call the parents every two weeks. Any child with a cough for more than 7 days was to be evaluated by the investigators. It was revealed that during the study only one third of the investigators stuck to the protocol. (Cherry, 2012b) Other studies may have called the subjects once a month or every 6-8 weeks asking the parents to be the observer. Recall and observer bias may have added to the inaccuracy.

3. Other *Bordetella* species are the cause of similar cough illnesses.

Of specific interest are false positive cases due to *B. parapertussis*. (Cherry, 2012a, 2012b) These would seem like vaccine failure unless the specific PCR primers are used to separate the species.

4. Lack of initial potency.

   One lot of whole cell vaccine is known to have had reduced potency. More may exist. (Cherry, 2012b)

5. Decay in antibody over time.

   Potential vaccine failure over time has been and is being explored and is discussed below. (California Department of Health, 2014a; Klein, Bartlett, Rowhani-Rahbar, Fireman, & Baxter, 2012; Misegades, Winter, et al., 2012; Witt et al., 2012b)

6. Incomplete antigen package.

   Some vaccines contain only one or two pertussis components: however, those in current use in the United States are 3 and 5 component vaccines. (Ausiello & Cassone, 2014; Misegades, Winter, et al., 2012) These vaccines have increased in use over time, as previously licensed 1 and 2 component vaccines are no longer in the US market but are still in use in Europe. Ausiello suggests that the recipients of the 3-5 component vaccines should not develop disease or as severe disease as recipients of the 1 or 2 components vaccines. (Ausiello & Cassone, 2014)

7. Incorrect balance of antigens in the vaccine.

8. Genetic changes in B. pertussis.

   Genetic changes in B. pertussis have been documented through the years. (Guiso, 2009) Circulating strains differ from those used to create the vaccines. This could

> adversely affect the potency of the vaccine. Recent strains that do not express pertussis toxin or pertactin were isolated from infected patients. (Bouchez et al., 2009) In this study, both the pertussis toxin negative and pertactin negative strains could cause lung infections in mice but the pertussis toxin negative strain could not cause a lethal infection. Pertussis toxin is a component in all of the pertussis containing vaccines in the table above. Pertactin is in all of those vaccines. Removing one or both of these increases the potential for an incomplete antigen package.

In a recent study comparing whole cell vaccine to acellular vaccine in baboons, whole cell vaccine not only prevented illness but also prevented colonization of pertussis stopping the transmission cycle. (Warfel, Zimmerman, & Merkel, 2014) By contrast, acellular vaccine only prevented severe symptoms and allowed colonization and transmission. The acellular vaccines used in the study were Daptacel (4 component) and Infanrix (3 component). T-cell response alterations may play a large role in the protection differences. Whole cell vaccine T-cell responses matched those of previously infected animals while acellular vaccine responses matched those of naïve animals. (Warfel et al., 2014) Whole cell vaccine stimulates a T helper 17 (Th17) response and T helper 1 (Th1) memory, while the acellular vaccine stimulates a Th1/Th2 response. (Warfel et al., 2014) The Th17 response is also seen after natural infection which leads to longer immunity before waning. Since the majority of individuals infected with pertussis do not know that they are infected due to lessened or no symptoms, a vaccine which reduces transmission is more desirable.

Many groups have suggested the need for new or better vaccines.(Ausiello & Cassone, 2014; Burns et al., 2014; Cantey, Sanchez, Tran, Chung, & Siegel, 2014; Cherry, 2012b; Clark et al., 2012; Klein et al., 2012; Misegades, Martin, Messonnier, & Clark, 2012; Mooi, Van Der Maas, & De Melker, 2014) Ausiello suggests that the choices are to revise the existing vaccines or create new less reactogenic whole cell vaccines. (Ausiello & Cassone, 2014) Revising the existing vaccines could be done either by adding new or alternative components or by adding adjuvants which stimulate the desired T-cell responses. Making whole cell vaccines less reactogenic may be more difficult. A third option is to make entirely new vaccines, essentially returning to the drawing board. (Ausiello & Cassone, 2014) Unless new vaccines are already in the research pipeline, they will not help to reduce incidence in the short term. (Burns et al., 2014) More research is needed on the vaccine efficacy and ways to improve both the initial efficacy and the long term immunity. Breaking the transmission cycle also needs to be included as a characteristic of an improved vaccine.

Potential Waning of Vaccine Protection

An issue that affects the spread of pertussis is that immunity to pertussis wanes regardless of whether the immunity was acquired by vaccination or natural infection. (Centers for Disease Control and Prevention (CDC), 2011b; Edwards & Decker, 2008; Faulkner et al., 2011; Halperin, 2005) Active surveillance in Germany showed that of 79 symptomatic adults with pertussis, 34% previously had pertussis as children. (Edwards & Decker, 2008) As mentioned earlier, the current increase in burden of disease in the US is shifting from young children to older children and adolescents. (Guris et al., 1999; Rittle, 2010; Ward et al., 2005; Zepp et al., 2011) The shift is suspected to be partly due to waning vaccine induced immunity and partly due to delay or non-compliance with the vaccination schedule. The effects of waning immunity in adults are documented. (Centers for Disease Control and Prevention (CDC), 2011b; Edwards & Decker, 2008; Faulkner et al., 2011; Halperin, 2005) Similar effects in older children and adolescents were not previously well documented. The studies by Klein, Misegades and Witt, discussed below, have shown immunity waning with each year after the fifth childhood dose of pertussis vaccine.

The first look at waning immunity in adolescents and pre-adolescents was presented by Baxter et al at the IDSA conference in 2011. (Baxter, Bartlett, Rowhani-Rahbar, Fireman, & Klein, 2011) Baxter and colleagues conducted a retrospective case-control study at Kaiser Permanente Northern California (KPNC) and looked at cases during the California pertussis outbreak in 2010. Table 6 shows the cases and controls included in the study and the criterion for inclusion.

Table 6. Retrospective Case-Control Study at KPNC

Cases	Confirmed PCR+ cases
Control 1	Matched PCR- controls
Control 2	Matched from KPNC population

There were three major conclusions of Baxter's study. 1. DTaP waned from 90% effective to less than 50% in five years. 2. Tdap did not appear to wane, however most study subjects received the vaccine within 3 years of the outbreak. 3. The majority of study subjects received vaccinations according to the recommendations. Those who did not follow the recommendations had higher rates of pertussis infection. (Baxter et al., 2011) This poster presentation was the first glimpse into the waning of immunity during the California 2010 outbreak.

The California 2010 outbreak has provided fertile ground for research studies. The number of confirmed, probable and suspected cases was the highest seen in the state since 1947. (California Department of Health, 2014a) The case count is shown in table 7: (Winter et al., 2012)

Table 7. California Department of Health Pertussis Cases for 2010

Cases	% of Cases	classification	Method of confirmation
5482	60	Confirmed	82% PCR
			6 % cell culture
			12% epidemiologically linked to confirmed case
1706	19	Probable	
1966	22	Suspected	
Total: 9154	100		
Deaths	10		

The case definitions used followed the 2010 guidelines from the Council of State and Territorial Epidemiologists and are as shown in table 8 for this study:

Table 8. Case definitions used by the California Department of Health

Confirmed	a cough illness and a respiratory specimen from which *B pertussis* was isolated in culture or	
	a cough illness of at least 2 weeks in duration along with either:	a respiratory sample from which PCR testing detected *B pertussis* nucleic acid or
		known contact with a case confirmed by either culture or PCR testing
Probable	cough illness of at least 2 weeks but was not laboratory-confirmed and not linked epidemiologically to a laboratory-confirmed case	
Suspected	having a cough illness of any duration along with:	PCR detection of *B pertussis*–specific nucleic acid or
		direct epidemiologic linkage to a confirmed case and at least 1 of the following: paroxysms of coughing, inspiratory "whoop," or post-tussive vomiting

Adapted from (Winter et al., 2012)

There was a marked increase in cases among 7-10 year olds; however, the group that remained at highest risk of severe disease and death was infants too young to be fully vaccinated against pertussis. (Winter et al., 2012) Of strong interest is the finding that 79% of the cases aged 7-10 had received all five doses of vaccine as recommended by ACIP. (Winter et al., 2012) This finding indicated that being fully vaccinated did not confer absolute protection against infection.

Recent studies have delved deeper into the causes of the magnitude of the California outbreak. Baxter, Klein and colleagues further studied the population at KPNC with an expansion of their retrospective case-control study. (Klein et al., 2012) Table 9 shows the numbers and criterion for the cases and controls.

Table 9. Retrospective Case-Control Study at KPNC (Expanded)

Cases	277 cases aged 4-9	PCR +
Control 1	3318 controls	PCR -
Control 2	6086 matched controls	General population

The first set of controls was PCR-negative for both B. pertussis and B. parapertussis and had received their fifth dose of pertussis vaccine before the negative test result. The second set of

controls was members of the same health plan who were matched for sex, age, ethnicity and membership of the same clinic at the time of testing of cases. The exclusion criterion of no previous PCR-positive result was used for all controls. The chance of becoming PCR-positive increased with age as shown in table 10: (Klein et al., 2012)

Table 10. Proportion of PCR+ by age in KPNC Study

Age	% PCR +
6	4.5
8	12.2
10	18.5

The average time since fifth dose for PCR-positive cases was 1699 days while the time for PCR-negative was 1028 days ($P<0.001$). (Klein et al., 2012) Controls received their fifth dose significantly later than cases. A 42% increase in the odds of pertussis infection was associated with each year following the fifth dose of DTaP. (Klein et al., 2012) This finding indicates a waning of immunity over time following the fifth dose of vaccine. Klein also suggests that there was a drop off of infection rate in ages 12-15 corresponding with the switch-over from whole cell to acellular vaccines. (Klein et al., 2012) The recommendations to stop using whole cell vaccine were put in place in 1997. Children 12-15 years old during the outbreak may have received one or more doses of the whole cell vaccine before the switch-over.

Witt and colleagues conducted a similar study using the population at San Rafael Kaiser Permanente (SRKP). (Witt et al., 2012b) Noting that the highest incidence at SRKP was among 8-12 year olds, Witt set out to determine causes. The population at SRKP had a high immunization rate of 89%. (Witt et al., 2012b) In this study, the researchers chose to look at vaccine effectiveness using the following calculation:

$$VE = 1 - \frac{PCV}{1-PCV} \times \frac{1-PPV}{PPV}$$

VE=vaccine effectiveness
PCV=proportion of cases vaccinated
PPV=proportion of total population vaccinated (Witt et al., 2012b)

This equation comes from earlier work describing a simple way to estimate vaccine effectiveness. (Farrington, 1993) This equation is in turn based on the relative risk of disease being equal to 1-VE, which is also equal to the odds ratio of vaccination in a selected population. (Farrington, 1993) Using this method of calculation, Witt obtained the vaccine effectiveness for age groups within the study as shown in table 11.

Table 11. Vaccine Effectiveness by Age Group in SRKP Study

Age group	Effectiveness	95% CI
2-7 years	41%	21-54
8-12 years	24%	0-40
13-18 years	79%	23-84
2-18 years	51%	44-58

Due to the vaccine effectiveness drop in the 8-12 year old group, Witt comes to the conclusion that the current acellular pertussis vaccine schedule is insufficient to prevent outbreaks and recommends more boosters either as part of the schedule or as outbreak control. (Witt et al., 2012b) As mentioned earlier, there is no currently approved pertussis only vaccine in the United States. (Faulkner et al., 2011) To be able to give extra pertussis doses without excessive doses of tetanus and diphtheria toxoids, a monovalent pertussis vaccine would be needed.

The following issue of the journal had three commentaries on Witt's article along with a response from the authors. The first commentary was from CDC researchers, Misegades and colleagues and questions the vaccine effectiveness results. (Misegades, Martin, et al., 2012) The first question raised involves under vaccinated individuals. These are children who have not received the recommended number of doses for their age group. The under vaccinated children

were included with the unvaccinated. Another concern raised is that the age groupings in the data presentation would cross dosing recommendations and, therefore, the group would differ in vaccinated status within the group. (Misegades, Martin, et al., 2012) Guiso of the Pasteur Institute wrote the second commentary questioning again both the inclusion of under vaccinated and the age grouping as well as other methods involving the PCR testing technology used. (Guiso, 2012) The third commentary came from Sheridan and colleagues from Queensland. (Sheridan, Ware, Grimwood, & Lambert, 2012) Sheridan stated that the results may be skewed because the age categories include individuals who may have received whole cell vaccines in the oldest group (aged 13-18 in 2010). Witt mentioned that they did not have manufacturer's information on the vaccines received prior to 2002. (Sheridan et al., 2012; Witt et al., 2012b) The other two groups are of the correct age (12 and under in 2010) to have received only acellular vaccines. Witt's response states that the numbers of fully unvaccinated children were so low that the confidence intervals were severely skewed which is why they included the under vaccinated children in this group. (Witt, Katz, & Witt, 2012a) Table 12 is adapted from their data which excludes under vaccinated children from both the cases and controls: (Witt et al., 2012a)

Table 12. Vaccine Effectiveness by Age Group in SRKP Study (Under Vaccinated Excluded)

Age, years	% Effectiveness	95% CI
2–7	64	-61 to 92
8–12	-33	-230 to 47
13–18	56	-49 to 87
Overall	23	-48 to 60

Additionally, Witt defends their preference for using odds ratios to estimate vaccine effectiveness stating that this is the method preferred by the World Health Organization when the vaccination rates are high. (Witt et al., 2012a) In response to both the age category question and the question of whole cell vaccine use in the oldest category, Witt acknowledges the concerns

have validity. The authors revisited their data regarding vaccines used and determined that 22% of cases and 27% of the overall population studied had received at least one dose of whole cell vaccine. (Witt et al., 2012a) They state that this difference is not statistically significant and should not affect their results. Since whole cell vaccine may have been used for any child over the age of 12, this argument is suspect. The vaccine effectiveness for children in the older categories would be affected by those who had received whole cell vaccine.

Misegades and colleagues expanded the study population to look across the 15 California counties involved in the 2010 outbreak. (Misegades, Winter, et al., 2012) This retrospective case-control study was confined to children ages 4-10 with cases including suspected, probable and confirmed. The case definition used was the same as in the California Department of Health study described in table 8. Controls, 3 per case, were selected from the same clinics which treated the cases. Medical records and immunization registries were used for vaccination records. Data showed that 7.8% of the cases and 0.9% of the controls had not received any pertussis vaccines. (Misegades, Winter, et al., 2012) Incomplete vaccination (less than 5 doses but at least one dose) or vaccinations that did not follow the recommended guidelines were exclusionary criteria. Odds ratios (OR) were calculated using logistic regression and vaccine effectiveness was estimated with VE = (1-OR) x 100%. The reference for the odds ratios were the unvaccinated or those who had received no vaccine doses. Vaccine effectiveness for the fully vaccinated was 88.7% as shown in table 13.

Table 13. Odds ratios for vaccine effectiveness in 15 county study

# doses	OR	VE
0	1 (reference)	1 (reference)
5	0.11	88.7%

Misegades found waning immunity as did Witt, but not as extreme. (Misegades, Martin, et al., 2012) Their explanation is the exclusion of under vaccinated individuals who skew the data. (Misegades, Martin, et al., 2012; Misegades, Winter, et al., 2012) Partially vaccinated children may have some measure of protection depending on the level of under vaccination. Including these individuals in the unvaccinated group would lead to underestimation of vaccine effectiveness by reducing the attack rate in the unvaccinated group. Misegades further breaks down their vaccine effectiveness by time since the fifth dose. (Misegades, Winter, et al., 2012) This data shows a reduction in effectiveness over time as shown in table 14.

Table 14. Vaccine effectiveness with respect to time since 5th dose

Time since fifth dose	Effectiveness
No doses, 0	1 (reference)
< 12 months	96.1%
12-23 months	95.3%
24-35 months	92.3
36-47 months	87.3
48-59 months	82.8
>60 months	71.2

The conclusion is that as time increases since last DTaP dose, the odds of contracting pertussis increases, however, the efficacy is well within the pre-licensing rates based on 3 doses of 59-89%. (Misegades, Winter, et al., 2012) Misegades suggests that moving the fifth dose later might shift the burden of disease to a younger population rather than to solve the issue of waning immunity in pre-adolescents. "However, a recommendation to delay the fifth DTaP dose until 6 years of age or later may unintentionally increase the burden of disease between the fourth and fifth doses of the childhood series, and implementation would likely be programmatically challenging because many states' school entry immunization requirements for pertussis are built around the current DTaP schedule." (Misegades, Winter, et al., 2012)

Regardless of the method used for testing, each of the groups above showed that the vaccine protection wanes over time. Given that the current recommendation schedule assumes vaccine protection between dose and boosters, it would seem that something needs to change. Whether the dosing schedule needs to be revisited, a change in the vaccine, its components or a potential adjuvant is needed or a whole new vaccine is needed remains to be seen. More research is needed to determine the best course of action.

Vaccine Uptake/Vaccine Exemptions/ Provider Influence

While vaccine efficacy and potential waning of immunity contributed to the severity of the California 2010 outbreak. Other factors are likely to have contributed as well. One such factor is the rise of a susceptible population of unvaccinated or under vaccinated. While the entire burden of transmission cannot be laid on this factor, a susceptible population adds to transmission with the addition of potential asymptomatic carriers and ill individuals. California's overall non-medical or personal belief exemption (NME) rate in 2010 was 2.33%, however, there is a clustering effect as some schools report rates of up to 84%. (Atwell et al., 2013) In 2010, California only required one form to receive a non-medical or personal belief exemption. In 2014, the California legislature expanded this to require an additional form certifying that a health care practitioner has informed parents about vaccines and diseases. (California Department of Health, 2014b)

Providers themselves are not always compliant with vaccinations. In a poster presented at the APIC 39th Annual Educational Conference & International Meeting, the changes in compliance due to a declared epidemic were examined. (Gornick, Santos, Patel, & Singh, 2012) Prior to the state declaring a pertussis epidemic, 67% of staff and 50% of attending physicians had received Tdap boosters at the Children's Hospital of Orange County. This facility had 133 cases and one death. After the epidemic declaration the compliance went up to 92% of staff and 82% of attending physicians. While not hitting their 95% goal, this improvement showed a significant rise in awareness. (Gornick et al., 2012)

Another study looked at vaccine providers specifically. (Silvaggio et al., 2014) The state of California passed a law in September 2010, requiring all incoming seventh and twelfth graders to have the Tdap booster based on the ACIP recommendations at the time. (California Department of Health, 2014c) The law created pressure on vaccine providers that Silvaggio and colleagues wanted to explore. Providers expressed the most concern about patient messaging, increased patient load, and vaccine availability. Increased demand for vaccines was seen for about 70% of providers. In addition to compliance with the law about adolescent vaccinations, providers were asked whether they discussed the pertussis vaccine with adult patients. Only 50% reported this to be routine. (Silvaggio et al., 2014)

In the study by Chan, discussed earlier, 986 laboratory confirmed cases from the California 2010 outbreak were examined. (Chan et al., 2012) Of these cases, 69 (7%) children old enough for immunization were completely unimmunized with 55 personal belief exemptions, 12 claiming to follow delayed vaccination schedules and one child had a medical exemption. Of the 986 cases, 91-95% in each age group over 6 months had received at least one dose of vaccine. Illness in those who are under-vaccinated is not unexpected given that the acellular vaccines are estimated to be 85% efficacious after 4 doses. (Edwards & Decker, 2013)

Atwell and colleagues looked at the geographic clustering of NME between 2005 and 2010 and 2010 onset pertussis cases in California. (Atwell et al., 2013) The study identified 39 statistically significant clusters of high NME rates and two statistically significant pertussis case clusters. The pertussis case clusters were in Central California and San Diego County. The study showed association between the NME and case clusters given that NME clusters were 2.47 times

more likely to be in a case cluster. Factors of affluence also associated with these clusters. The authors suggest that large numbers of intentionally unvaccinated individuals in a community can contribute to outbreaks stating "The contribution of NMEs to the changing epidemiology of pertussis should be acknowledged and explored in future studies along with other contributing factors…" (Atwell et al., 2013)

A matched case control study looked at children 3 to 36 months of age with 72 laboratory confirmed cases and 288 matched controls (4 each). (Glanz et al., 2013) Table 15 shows the cases and controls in the study with how many were under vaccinated and how many were hospitalized.

Table 15. Matched case-control study exploring under vaccinated effects

	Total	Under vaccinated	Hospitalized
Cases	72	34 (47.22%)	12 (16.67%)
controls	288	64 (22.22%)	
Adapted from (Glanz et al., 2013)			

Children who should have more vaccines according to the recommendations were considered under vaccinated. The odds ratios of becoming a laboratory confirmed case versus those who are up-to-date on the recommendations were calculated. The risk of being a case when a child was under vaccinated by three doses was 18.56 times more likely than the matched fully vaccinated. The risk for a child under vaccinated by 4 doses was 28.38 times more likely. The overall risk for a child under vaccinated by 1, 2, 3, or 4 doses was 4.36. (Glanz et al., 2013) These data suggest a significantly higher rate of incidence in under vaccinated children in the study which was conducted across several states. Since the full vaccination data for all of the cases in the California 2010 outbreak is not available, the effect of under vaccination cannot be determined. (Winter et al., 2012) However, the contribution of under vaccination cannot be ignored.

Pertussis is highly contagious and the increase in the susceptible population due to under vaccination or lack of vaccination contributes to the rise in pertussis incidence. Vaccination rates in the United States and especially those in California are not enough to reach the herd immunity threshold needed to protect susceptible individuals. Prior to the 2014 law, it was very easy for Californians to obtain non-medical exemptions. Now it is harder, but certainly not impossible. Increased awareness due to an outbreak seems to raise vaccine uptake in health care workers but not necessarily the general public. Increased mandates including the 2010 California law regarding seventh and twelfth graders helped to increase vaccination rates. However, there will still be those individuals who will question the need or refuse outright.

Discussion and Conclusion

Despite nearly 80 years of vaccination, *Bordetella pertussis* remains a problem in the United States. The recent steady rise in incidence has been taking even larger jumps in the past few years. The most susceptible population remains infants who are too young to be vaccinated. This study explored some of the contributing factors in the rise of incidence. Problems in detection and diagnosis can lead to infected individuals not aware that they are spreading pertussis. There is a possibility that the diagnosis rates could be off by a very large factor. The current acellular pertussis vaccines may not have the efficacy that was determined in the early clinical trials. Additionally, the pertussis organism may be changing over time and may lack critical factors such as pertactin that is in vaccines, designed to induce an immune response against pertactin. There is good evidence the vaccine protection wanes over time with an increased chance of infection as protection wanes. Vaccination rates are lower than desired and vaccine exemption rates may be on the rise. Additionally, vaccine exemptions and incidence clusters associate geographically.

The incidence of pertussis is considerably lower than it was in the pre-vaccine era with an estimated 10-fold drop from 1934 (270,000 cases) to 2010 (27,550). However, what was once a great success story with cases of less than an average of 1800 per year (1973-1982), is now nearly 13 times higher with case counts of over 23,000 (2004-2013). This recent resurgence had led to a major increase in the burden of disease including the highest case count since 1954 in 2012 with 48,277 cases. More research is needed both to elucidate the contributing factors in the incidence rise and to find ways to bring down incidence. Here are some suggestions:

1. Problems with detection/diagnosis

   Clinician awareness and education is needed to encourage better and longer lines of questioning to parse out diagnosis. During a known outbreak, it is easier to suspect or decide to test. It is much harder before an outbreak is declared or when there are other potential health issues involved.

2. Efficacy of acellular pertussis vaccines/Changes in pertussis

   Steps can be taken to improve the existing vaccines including adding or changing components. Additionally, adjuvants could be added to move the response into a more desired direction such as a Th17 response. The whole cell vaccine could be revisited with an effort for less reactogenicity. A new vaccine formulation could be developed with the best of both types of vaccines. The circulating strains of pertussis should be characterized to aid in the production of new or better vaccines.

3. Potential waning of vaccine protection

   The new or improved vaccines discussed above are a long term solution. In the more immediate future, the current vaccination schedule should be revisited with the recent data on waning vaccine protection. This change in schedule may require the addition of boosters with pertussis only vaccines not currently approved for use in the United States.

4. Vaccine uptake/Vaccine exemptions/Provider influence

   Vaccine uptake is down and exemptions are on the rise. Providers are our first line of education for patients and their families. The providers need better training on overcoming objections especially when those objections may be their own. Awareness campaigns need to be directed at both providers and the public. Recently vaccine

advocacy has been primarily reactive. It is time to be proactive and show that public health officials believe their own data on the safety and benefits of approved vaccines.

Of the four suggestions above, lessons can be learned that apply to all vaccinations and vaccination campaigns. Problems with detection and diagnosis occur often. The level of training needed to be an infectious disease specialist is different from that of the pediatrician or internist. Yet, it is expected that all three specialties will be able to diagnose patients who come to them with symptoms. The reduction in the burden of infectious disease means that outside of an outbreak, many vaccine preventable diseases might not be seen often, and therefore, not recognized. It is necessary to recognize the infections for what they are to stop a few cases from turning into an outbreak.

Many of the modern vaccines have not changed much since their introduction. It may be time to revisit and reanalyze several of these to assess their current effectiveness. It may also be necessary for new vaccines to be created to replace those that have lost effectiveness. This would also apply to those vaccines which no longer last as long and wane earlier than expected. The Advisory Committee on Immunization Practices already meets routinely to discuss changes in vaccine recommendations. These discussions are based on the research available.

The effect on vaccine uptake and vaccine exemptions is occurring across the immunization spectrum. The lack of serious consequences makes it easy for individuals and parents to think a disease is no longer a threat. Asking someone who currently has young children what they think of vaccine preventable diseases is very different from asking someone

old enough to remember a time before vaccines. Vaccines have been around long enough for there to be fewer and fewer people in the United States who remember what a threat infectious disease could truly be.

"If there is a shot available, just get it. Don't delay." Naomi Burns Rapoza 3/30/1918-6/23/2013 (My grandmother)

Future Research

There are many factors which contribute to the rise in infectious diseases. This study explored a few that can be found in the literature. Many contributing factors may not have been published, and therefore, not available for this study. It would be very beneficial for future studies, if more data were published or otherwise available for analysis. This would include both positive or definitive data and more ambiguous or negative data.

California's 2010 outbreak has been well researched as a good case study. The rise in cases in recent years has not only been occurring in outbreak situations. A potential study to look at these and more contributing factors could be run in a smaller state which has a significantly lower population and case count. Since all confirmed and suspected cases of pertussis are required to be reported to the state, it would be ideal to track all cases reported within a 5 year time period to take account of the cyclic nature of pertussis. The choice of a smaller case count is so that more attention can be paid to the gathering of case information. A smaller state population would make it easier to track all of the cases. This tracking would include contacting the case or parents of the case for additional information regarding vaccination status with confirmation from medical records, if necessary. Additionally, information would be gathered about the potential exposures to and from contacts. Family dynamics and illness status would also be collected. Ideally, healthy matched controls would be obtained either from the school, community or medical facility. Exemption rates for the attended schools would add to the knowledge base. This study could add additional insight into the underlying factors by looking at the state as a whole, where most of the studies presented in the review above looked at the populations who sought care at specific medical centers. This study would need to be funded as

there is a significant time involved for both for the length of the study and the time needed to collect and analyze the data.

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