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Jerusha Elana Barton Date

The Changing Epidemiology of Pertussis in the Acellular Vaccine Era

By

Jerusha E. Barton
Master of Public Health

Epidemiology

_____

Walter A. Orenstein, M.D.
Faculty Thesis Advisor

_____

Saad B. Omer, M.B.B.S., M.P.H., Ph.D
Field Thesis Advisor

_____

Robert Bednarczyk, Ph.D
Committee Member

The Changing Epidemiology of Pertussis in the Acellular Vaccine Era

By

Jerusha E. Barton

B.A., Johns Hopkins University, 2012

Faculty Thesis Advisor: Walter A. Orenstein, M.D.
Field Thesis Advisor: Saad B. Omer, M.B.B.S., M.P.H., Ph.D

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Abstract

The Changing Epidemiology of Pertussis in the Acellular Vaccine Era

By Jerusha E. Barton

Pertussis remains endemic in the U.S., despite routine use of childhood pertussis-containing vaccines (DTP) in children since the 1940s. Although infants have the highest reported incidence rates compared to other age groups, incidence in adolescents and adults has been steadily increasing since the 1980s. In 1992, the Advisory Committee on Immunization Practices (ACIP) recommended that trivalent diphtheria-tetanus-acellular pertussis vaccines (DTaP) be substituted for the whole-cell formulation (DTwP) for doses four and five of the five-dose pertussis vaccine schedule, and in 1997, DTaP was recommended for all five doses. To combat increasing incidence in adolescents, the Advisory Committee on Immunization Practices (ACIP) recommended adolescents and adults receive a tetanus-diphtheria-acellular pertussis booster (Tdap) in 2006. To date, however, no study has been done in the U.S. on the rates of hospitalization across all age groups following the switch to acellular vaccines for routine infant immunization. We characterized the changing epidemiology of pertussis by examining the rates and rate differences of hospitalization across all age groups and infant subgroups in the acellular vaccine era.

Hospitalization records were obtained from the Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP). NIS and U.S. Census data were used to analyze national trends of hospitalizations due to pertussis. We calculated rates of pertussis hospitalizations for all ages during the years 1997-2011 and rate differences between the early acellular pertussis (aP) vaccine period (1997-2001) and the late aP period (2007-2011).

Hospitalization rates decreased significantly in infants between the early aP period (1997-2001) and the late aP period (2007-2011), but increased in all other age groups over the same period. Among infant subgroups, rates decreased significantly among infants 0-1 month of age and infants 2-6 months of age (-114.66 hospitalizations per 1,000,000 population (95% CI: -151.88, -77.45) and -22.03 hospitalizations per 1,000,000 population (95% CI: -43.00, -1.07), respectively).

Although the decreasing rates of infant hospitalizations are significant, rates of pertussis in infants are still high. Increasing rates of hospitalizations in non-infant age groups suggests ongoing transmission and susceptibility. This warrants research into new mitigation strategies across the lifespan.

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Introduction to Pertussis

Pertussis Epidemiology

Pertussis (commonly known as whooping cough) has reemerged as an important public health concern since current acellular pertussis vaccines (DTaP) replaced older whole-cell vaccines (DTwP). This vaccine-preventable disease (VPD) is among the most contagious diseases known, with a secondary attack rate (AR) as high as 80% among susceptible household[1], with an average of 15 secondary infections arising from a single case in a susceptible population[2]. Despite high childhood vaccination coverage, pertussis remains endemic in the U.S. today. The illness produced by *Bordetella pertussis* causes paroxysms of uncontrollable coughing, which is often so persistent that children "whoop" during inspiration and vomit after paroxysms. The force of the cough can crack ribs, break blood vessels, and lead to hernias; sequelae include pneumonia and seizures[3].

Unimmunized individuals are susceptible to pertussis infection. With the highest incidence of pertussis in infants, particularly infants younger than six months of age, pertussis has a unique epidemiology, with most children infected from close contact with adolescents and adults, not other children (e.g., in school settings)[14]. Infants have the greatest severity of disease and complications occur most frequently in this age group[5]. However, during recent upsurges and resurgences in pertussis incidence in the U.S. (i.e., 1999, 2004-2005, 2010), adolescents have accounted for a substantial proportion of cases. Although the

[1] Dr. Thomas Clark of the ACIP Pertussis Work Group has noted it was observed in the 1900s that transmission occurred from adults to naïve children [4. Clark TA. Changing Pertussis Epidemiology: Everything Old is New Again. *Journal of Infectious Diseases*. 2014;209(7):978-981.].

reasons for these resurgences are not clear, immunologic factors (e.g., low or absent herd effects, waning immunity) and societal events (e.g., the switch to acellular vaccines; increased surveillance, recognition, reporting, and laboratory/diagnostic capacity) may have played a role, and should inform future interventions.

Prior to the introduction of vaccines to prevent pertussis, pertussis was counted among the universal childhood diseases, accounting for a significant proportion of morbidity and mortality among children. Between 1940 and 1945, more than 1 million cases of pertussis were reported in the U.S., with an average of 175,000 cases per year (incidence ~150 cases per 100,000 population)[1,6].

Initially, pertussis vaccines were comprised of killed, whole-cell *B. pertussis* cells, combined with diphtheria and tetanus toxoids (DTwP). Following the introduction of DTwP, pertussis incidence gradually declined, dropping as low as 15,000 reported cases in 1960 (incidence ~8 per 100,000 population) and hitting an historic nadir in 1976, with 1,010 cases reported[1,4]. The annual reported incidence of pertussis had been reduced by 99% by 1970. Yet, during the 1980s, the numbers of reported cases increased annually, from 1,730 in 1980 to 4,157 in 1989, reaching an average of 2,900 reported cases per year (~1 per 100,000 population) between 1980-1990[1]. Throughout the 1980s, an average of eight pertussis-associated fatalities were reported annually, a figure close to what is reported today (on average ~10 deaths per year[3]). It is unclear whether the increase in reported cases reflects a true increase in incidence or an improvement in pertussis reporting[7].

During the period 2001–2003, infants younger than one year of age had the highest average annual pertussis incidence (55.2 cases per 100,000 population); incidence in the first six months of age was even higher (98.2 per 100,000 population)[1]. Of the cases for which age was reported in 2004, 10% occurred among infants younger than six months who were too young to have been fully vaccinated. This age group had the highest reported rate (136.5 per 100,000 population), compared to older infants aged six to eleven months (31.8 per 100,000 population)[8]. As of 2007, the case-fatality ratio (CFR) in infants under six months of age was estimated to be 0.5%[9].

While infants represent the highest incidence of cases and highest proportion of deaths, the most recent data suggest that adolescents are contributing significantly to the burden, particularly in the recent pertussis epidemics of 2004 and 2012[10]. In 2005, infants younger than six months of age had the highest reported rate of pertussis (160.81 per 100,000 population), but adolescents aged 10--19 years and adults 20 years or older had the greatest number of reported cases (60%))[11]. As pertussis is frequently missed in adolescents and adults, the aforementioned numbers most likely underestimate the true burden of the disease in these older age groups. In 2004, it was estimated that between 600,000 and 900,000 cases occur in adolescents and adults every year[2].

In 2012, 48,227 cases of pertussis were reported in the U.S., the highest recorded burden since 1955[12]. The average annual incidence in the U.S. in 2012

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[2]Offit PA, DeStefano F. Vaccine safety. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th edition, Elsevier Saunders, Philadelphia, 2013. Page 1471.

was 13.4 cases per 100,000[13]. Compared to the 1,010 cases seen in 1976, this is astonishing given the high vaccination coverage in age-eligible children (2012 National Health Interview Survey (NHIS): DTP3+ coverage, 96.0%; and DTP4+ coverage, 85.0% in 19-35 months-old infants[6,10,14]).

Rates vary by state, but have been as high as 100 cases per 100,000 population. Recently, California and Washington have been particularly hard-hit, both states having endured notable epidemics within the last decade. With the exception of California, every state reported an increase in pertussis cases from 2011 to 2012. Many states observed a threefold increase in the number of reported cases, as compared with 2011. 18 pertussis-related deaths were reported in 2012, 13 of which were in children younger than three months of age[13].

Although the reasons for the resurgence are not clear, immunologic factors and societal events surrounding the vaccine may have played a role. This includes the possibility that the switch from whole-cell to acellular pertussis vaccines in the 1990s may be changing the epidemiology of the disease[6]. At the same time, the timing of the resurgences follows the traditional periodicity of the disease, with inter-epidemic years ranging from three to five years[4]. Pertussis does not have a distinct seasonality, although cases appear to increase during the summer and fall months[1], a pattern that may be exacerbated during outbreak years, when there is increased pertussis transmission.

Bordetella pertussis **Microbiology and Pathogenesis**

B. pertussis is a small, aerobic, gram-negative, fastidious coccobacillus that requires special media for isolation[1]. Although infections can be induced in

animals in a laboratory setting, animals are not known to be reservoirs of pertussis. *B. pertussis* is unable to survive for long periods in the environment[5].

B. pertussis produces several biologically active products that are responsible for the clinical disease, including pertussis toxin (PT), filamentous hemagglutinin (FHA), agglutinogens, adenylate cyclase, tracheal cytotoxin, and pertactin. Acellular pertussis vaccines used in the U.S. at one time or another included 1) PT alone, 2) PT and FHA, 3) PT, FHA, and pertactin, and 4) PT, FHA, petactin, and agglutinogens. Clinical trials have demonstrated that acellular vaccines that contain at least PT could produce substantial levels of at least short-term protection against laboratory-confirmed pertussis[15]. On the other hand, concerns have been raised with regard to duration of immunity. However, the formal correlates of protection have not been established[1,16,17]. It is known that natural pertussis infection may not lead to life-long immunity[1,4].

Pertussis is predominantly a toxin-mediated disease. The coccobacilli attach to the cilia of the respiratory epithelial cells and produce toxins that paralyze the cilia. The resulting inflammation in the respiratory tract interferes with the routine clearing of pulmonary secretions. Historically, *B. pertussis* was not thought to invade the tissues; however, recent studies have shown the bacteria to be present in alveolar macrophages[1].

Related species include *B. parapertussis* and *B. bronchoseptica*. *B. bronchoseptica* is a zoonotic pathogen that rarely causes difficult-to-treat respiratory infections in humans. *B. parapertussis* infection results in a milder form of pertussis. A similar, acute clinical syndrome characterized by a self-limited, reactive respiratory syndrome has been reported in association with

viruses, particularly adenoviruses. The cough in such instances, however, typically lasts fewer than 28 days[5].

Characteristics of Pertussis Disease

Pertussis interferes with the normal transfer of mucus from the airway to the mouth, causing attacks of coughing[5]. The incubation period is commonly seven to 10 days, with a range of four to 21 days, and rarely can be as long as 42 days[1]. The time-course of the disease is divided into three stages. The catarrhal stage lasts about two weeks and is characterized by symptoms similar to the common cold, namely coryza, sneezing, low-grade fever, and a mild, occasional cough, which becomes progressively more frequent and severe. Pertussis cases are most infectious during this stage, before the eponymous whoop is even present, and for about two weeks following the onset of cough (i.e., approximately 21 days)[1]. Infectiousness declines quickly after this period. Patients are no longer infectious after five days of treatment with the appropriate antibiotics[5].

Most cases of pertussis are suspected and diagnosed during the paroxysmal stage, which begins 10-14 days post-infection. Paroxysms are characterized by numerous, violent coughs resulting from a difficulty to expel thick mucus and end with a long, inspiratory effort. Inspiration is frequently accompanied by the characteristic, high-pitched whoop, although some infants and adults may not whoop between paroxysms. Patients may become cyanotic following a paroxysm, and children and infants appear very ill and distressed. Paroxysms are often followed by exhaustion and post-tussive vomiting; may be

more frequent at night, with an average 15 attacks per 24 hours; may be brought on by external stimuli, such as cold air, eating, drinking, crying, and laughing. During the first week or two weeks of the paroxysmal stage, attacks increase in frequency. The attacks then remain at the same level for two to three weeks before gradually decreasing. Individuals are well between paroxysms, and those with partial immunity may experience less severe symptoms. The paroxysmal stage usually lasts one to six weeks, but may persist up to 10 weeks[1,5].

Recovery is gradual during the convalescent stage. The cough becomes less paroxysmal and disappears in two to three weeks[18]. A typical illness lasts six to 12 weeks in total, although paroxysms may occur for months with subsequent respiratory illness[1,5].

The Council of State and Territorial Epidemiologists (CSTE) in June 1997 approved the following clinical case definition: A cough illness lasting at least 2 weeks with one of the following: paroxysms of coughing, inspiratory “whoop,” or posttussive vomiting; and without other apparent cause (as reported by a healthcare professional)[18].

B. pertussis may infect children, adolescents, and adults partially protected by the vaccine or prior natural infection, but may cause milder disease than what is typically seen in infants and young children. Pertussis infection in these groups may be asymptomatic or may present with a mild cough illness. Classic pertussis with a persistent cough (i.e., lasting more than 7 days) may also occur in these groups. As noted earlier, inspiratory whoop is not common[1].

Although disease may be milder in older age groups, those who are infected may transmit pertussis to susceptible people, including unimmunized or

incompletely immunized infants. In households with multiple pertussis cases, older people are often the source of infection for infants. Pertussis is transmitted person-to-person through close, direct contact. Those who are susceptible to pertussis contract the disease either through contact with infectious respiratory droplets or by contact with airborne droplets of infectious respiratory secretions. Transmission via fomites occurs infrequently[1]. The infectious dose is unknown. Asymptomatic chronic carriage of *B. pertussis* is uncommon and those who may be asymptomatic carriers are unlikely to be a significant source of infection as they are not coughing[5].

Surveillance

The Supplemental Pertussis Surveillance System (SPSS), was introduced in 1979, with the cooperation of the Council of State and Territorial Epidemiologists (CSTE), to provide additional information on pertussis epidemiology, health impact, and vaccine and antibiotic usage and efficacy. Since its introduction, state participation has increased, as demonstrated by the growing percentage of patients who have been reported to both the National Notifiable Disease Surveillance System[3] (NNDSS) and SPSS. Individual case report forms were submitted for 88% of patients who have been reported both to the NNDSS and to SPSS in 1985, compared with 20% of patients in 1979[19]. SPSS was incorporated into NNDSS in 1996[20,21].

[3] NNDSS is the passive surveillance system maintained by CDC. It collects information on cases of notifiable diseases throughout the U,S. and the territories and publishes summary data, as well as supplemental reports, in the publicly available Morbidity and Mortality Weekly Report (MMWR).

SPSS and NNDSS receive reports on a disproportionate number of pertussis patients who are hospitalized, laboratory-confirmed, or have classic clinical disease. Because a substantial proportion of the reported cases have laboratory confirmation and/or classic clinical manifestations, reporting error is not likely to be a major problem, although reporting of non-pertussis cases as pertussis may still occur. However, pertussis surveillance, like other passive surveillance, suffers from low sensitivity, as under-diagnosis and underreporting are common, given the differing presentation of disease in older age groups. Pertussis surveillance systems provide estimates of the minimum incidence of pertussis, the maximum rates of disease complications, and the health impact of the disease, as well as comparisons of the trends in disease epidemiology and the utility of prevention and control measures[21].

Cases are expected to occur in all communities; a period of several years in which no cases are reported from a jurisdiction likely reflects failures to diagnose and/or report disease rather than an absence of disease. The level of diagnostic testing being undertaken can be evaluated by reviewing the number of pertussis diagnostic tests (e.g., cultures or PCR results) submitted by a jurisdiction[18].

Transmission

Pertussis is transmitted person-to-person through close, direct contact. Those who are susceptible to pertussis contract the disease either through contact with infectious respiratory droplets or by contact with airborne droplets of infectious respiratory secretions; transmission via fomites occurs infrequently[1]. Although the infectious dose is unknown, Pertussis is described as being highly

infectious. Previous reports of household contact studies estimated attack rates ranging between 58% and 100%[22]. Unfortunately, differences in case definitions and incomplete vaccination history and antibiotic therapy limit the interpretation of these findings. The average AR for unvaccinated children was 76% (range, 64%–86%) in prospective studies of household contacts of confirmed index cases[22]. Community ARs are difficult to quantify, but classroom contact studies found ARs to vary, ranging from 0% to 36%[22]. Like most respiratory diseases, transmission of pertussis requires repeated or prolonged exposure and/or close contact.

B. pertussis infection in vaccinated children, adolescents, and adults may cause milder disease than what is typically seen in infants and young children. Under-recognition of atypical disease in older children, adolescents, and adults likely maintain a reservoir of infection in those age groups (Taylor 2014). Pertussis infection in these groups may be asymptomatic or may present with a mild cough illness. Classic pertussis with a persistent cough (i.e., lasting more than 7 days) may also occur in these groups. As noted earlier, inspiratory whoop is not common in older individuals infected with pertussis[1].

Although disease may be milder in older age groups, older individuals who are infected may transmit pertussis to susceptible people, including unimmunized or incompletely immunized infants, and likely play a substantial role in bringing infections into households where the index case was an infant[23]. In households with multiple pertussis cases, older people are often the source of infection for young infants. Asymptomatic chronic carriage of *B. pertussis* is uncommon and those who may be asymptomatic carriers are unlikely to be a

significant source of infection as they are not actively coughing[23]. In households with multiple pertussis cases, older people are often the source of infection for children. Asymptomatic chronic carriage of *B. pertussis* is uncommon and those who may be asymptomatic carriers are unlikely to be a significant source of infection as they are not actively coughing[5].

Several studies have reported that parents (20%–48%) and siblings (19%–53%) were common sources of pertussis for infants for whom a source was identified, although the primary source of infection could not be identified in 47%–60% of infant index cases and diagnosis of the index case was not always laboratory-confirmed. A study conducted in the Netherlands predicted that 40%of infants cared for by mothers with pertussis will be infected. The probability that the infant will become infected decreases to 15% in households where the father is identified as the source case; and to 20% in households where another person is identified as the source case[24]. Wendelboe et al estimated that household members are responsible for 73%-82% of pertussis transmission to infants. Parents contributed between 48%–55%; siblings, 16%–21%; and non-household close contacts, 18%–29%. A source case was identified for an additional 16.5% of index cases when transmission from asymptomatically infected contacts was assumed possible[25]. In a separate study, Wendelboe et al investigated whether the 47%–60% of transmission (i.e., index cases with no identified source case) was due to casual contact in the community or transmitted from unidentified close contacts. This study estimated that about one in three infant pertussis cases is infected through casual contact[2]. These findings contradict the dogma that asymptomatic “carriers” do not transmit pertussis.

Baptista et al found that infection was introduced into households by adults (parents, uncles and aunts, and grandparents), whether primary or co-primary cases, in ~25% of the household outbreaks included in the study. 43% of all secondary cases occurred in households where the co-/primary case was an adult. 80% of the primary and co-primary cases were between 19—39 years of age. All adults diagnosed with pertussis in this study were identified through the investigation of pertussis diagnoses in children in the same household. A fifth of all adults in these households had pertussis during the household outbreaks; of these, approximately 50% acquired pertussis in the household. The secondary AR among adults was 12.6%. That 20% of cases were adults suggests that undiagnosed pertussis is not rare among adults, particularly those with a prolonged cough[23].

Complications and Hospitalization

Severe disease is infrequent in healthy, vaccinated persons. Infants, particularly those who have not received the primary vaccination series against pertussis, are at risk for complications and mortality. Pneumonia is the most common complication in all age groups. Seizures and encephalopathy are rare and generally only reported in young infants. Death is rare and most likely to occur in young, unvaccinated infants, although fatalities are occasionally reported among older children and adults with serious underlying health conditions[18].

As the severity of disease is greatest among infants, complications occur most frequently in this age group. Secondary bacterial pneumonia, which may be caused by *B. pertussis* or by other organisms, is the most frequent complication

and the cause of most pertussis-related deaths. Less common complications include seizures and encephalopathy as a result of hypoxia from coughing or a result of the intoxication[1,5]. Minor complications include otitis media, nosebleeds, anorexia, dehydration, and small conjunctival hemorrhages as a result of forceful coughing[1,5]. Complications resulting from the pressure effects of severe paroxysms include pneumothorax, epistaxis, subdural hematomas, hernias, and rectal prolapse[1].

Approximately 20%-50% of infants with pertussis are admitted to the hospital[5,26]. Approximately one patient in every 400 infant hospitalizations dies as a result of either pneumonia or brain damage[5]. During the period 1997–2000, data indicate that pneumonia occurred in 5.2% of all reported pertussis cases and among 11.8% of infants younger than 6 months of age. In 2004 through 2008, 111 deaths from pertussis were reported to the CDC; children 3 months of age or younger accounted for 92 (83%) of these deaths[1].

Severity of disease is dependent on age, immune status (prior immunization or infection), and probably extent of exposure and virulence of organism[27], although adolescents and adults may develop complications, such as difficulty sleeping, urinary incontinence, pneumonia, rib fracture, pneumothorax, inguinal hernia, aspiration, pneumonia, seizures, and otitis media[1,28]. Although the current lack of population-based data makes it hard to measure the level of risk of complications in adult age groups, case reports describe a variety of problems, including pneumothorax, inguinal hernia, aspiration, hearing loss, fractured ribs, and carotid artery dissection. Severe paroxysmal cough is expected to increase the risk of fractures, particularly in the ribs, in patients with

osteoporosis and the risk of intracranial bleeding in elderly patients, particularly those on anticoagulants. Seizures and encephalopathy occur in less than 1% of patients. Complications are reportedly more frequent in adults than in adolescents (28% versus 16%)[28].

Despite severe underreporting, pertussis-related hospitalization does occur in adults and adolescents. Of the cases reported, 1.4%–7.5% of individuals 10–19 years of age and 3.5%–5.7% of individuals over 20 years of age required hospitalization. In one study, the mean duration of hospitalization for all ages was seven days. Longer periods of hospitalization are seen in older individuals, with average lengths of stays of 6.3 days and 8.7 days for those 10–50 years of age and those over 50 years of age, respectively[28].

Overall, death from pertussis is rare in those over the age of 10 years, occurring in less than 0.1% of cases. Older adults appear to be at greater risk of pertussis-related mortality than younger adults. Of patients 55–94 years of age who died from pertussis, intracranial hemorrhage was often found to be the cause of death. In a study of hospitalized patients with pertussis in Spain 1995 to 1998, the CFR was higher in hospitalized individuals with pertussis over 50 years of age (29%) compared with those who were 1–5 years of age (1%)[28].

Diagnosis in Adolescents and Adults and Diagnostic Tools

Studies from Canada, Denmark, Germany, France, and the U.S. indicate that between 12% and 32% of adults and adolescents with a coughing illness lasting at least one week are infected with *B. pertussis*. In a comprehensive study in 1996–1997, pertussis diagnosed by culture, polymerase chain reaction (PCR),

or serologic criteria accounted for 33% of the prolonged cough illness in individuals 12–19 years of age, 19% in people 20–39 years of age, 19% in those 40–59 years of age, and 16% in people over 60 years of age[28].

Diagnosing pertussis is often difficult as many adolescent and adult cases do not present with the typical symptoms of the disease, and not all infants have enough strength to whoop. Diagnosis is further complicated by the lack of highly sensitive and specific laboratory diagnostic methods. Inter-person variability in the incubation and infectious periods may prevent the identification of source cases if their incubation or infectious periods lie in the extremes of the distributions not captured by standard definitions (e.g., CSTE clinical case definition; see section entitled Characteristics of Pertussis Disease). Whether individuals with asymptomatic infection can transmit pertussis is debated in the literature. In the absence of recognizable symptoms and diagnostic tests, the systematic exclusion of asymptomatically infected individuals as possible source cases limits what is known of the true burden[2].

Several studies have found the majority of adults cases observed to have presented with typical pertussis. One study found 81% of adults with pertussis had typical disease and 19% had atypical pertussis. Elsewhere, pertussis was diagnosed in adults with persistent cough. Baptista et al reported 69% of adult cases had classic[4] pertussis; the remaining 31% reported a cough illness lasting at

[4] In the study by Baptista et al, classic ("typical") pertussis in adults was characterized as an illness with cough lasting at least two weeks with at least one of the following pertussis-associated symptoms: paroxysm of coughing, inspiratory whooping, and post-tussive vomiting. This is distinct from reported "coughing illness lasting two weeks," in that the latter is closer to the symptoms of an upper respiratory infection [**23.** Baptista PN, Magalhães VS, Rodrigues LC. The

least 14 days. However, no adult cases, with or without typical pertussis symptoms, were diagnosed before their household child case was diagnosed with pertussis. Despite classic presentation of pertussis disease, pertussis is seldom considered a potential diagnosis in adults even when typical pertussis symptoms are present[23].

A prolonged, non-distinctive cough may be the only clinical feature of pertussis in adolescents and adults. Of those who do seek care, illness is often misdiagnosed, partly because clinicians continue to perceive pertussis as a childhood disease. When pertussis is considered, it is often not confirmed because routine laboratory tests are insensitive and those that may be more sensitive are not standardized and may not be routinely available. The timing, specimen transportation, and culture methods required for the diagnostic tests currently available all present problems that decrease sensitivity[28].

The observed association of classic pertussis symptoms with longer illness duration reflects the natural course of the disease. Among infants and children under 11 years of age, classic pertussis symptoms have also been correlated with additional clinic visits before the pertussis diagnosis was made. Younger patients receive medical care sooner than adolescents, likely seeing a healthcare provider before reaching the paroxysmal phase. Many children are sent home only to return later with classic symptoms, unless a known or suspected household exposure, a reported school or other exposure, and/or a physician's vigilance during an ongoing epidemic led to early testing. In contrast, adolescents were

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role of adults in household outbreaks of pertussis. *International Journal of Infectious Diseases*. 2010;14(2):e111-e114.].

brought into a healthcare provider later in the disease course than their younger counterparts. In adolescents, clinicians could rely on the duration of their disease and less on the presence of paroxysmal symptoms to think to test for pertussis. Given that adolescents had fewer visits during their illness than younger patients, this delay is likely less due to the physicians' clinical vigilance and more closely tied to a lack of urgency on the part of the caregiver or the adolescents themselves in seeking care[29].

Many factors contribute to the failure to diagnose pertussis, including the lack of clinical awareness, availability of sensitive culture and PCR assays, standardized serologic testing; the difficulty of obtaining appropriate specimens; and the absence of clear serologic diagnostic criteria. Pertussis in older adults is rarely suspected, detected, reported, or well-studied, and the disease burden is underappreciated. Because older adults are partially immune from previous immunizations and/or natural infections, it is difficult to distinguish infections by serologic analysis without carefully assessing changes in antibody levels between the acute and convalescent phases. Some antibody levels, including PT, wane quickly, and other antibodies, especially pertactin and FHA, lack specificity for pertussis[27].

Culture. Diagnosis is based on culture of *B. pertussis* from nasopharyngeal specimens obtained during the catarrhal and early paroxysmal stages (i.e., ideally collected within the first two weeks of illness)[5]. Nasopharyngeal aspirates for *B. pertussis* will yield similar or higher rates of recovery than nasopharyngeal swabs. Specimens should be obtained from the posterior nasopharynx, not the throat, with Dacron, polyester, rayon, nylon, or calcium alginate (not cotton)

swabs and should be plated directly onto selective culture medium or placed in transport medium[5,18].

Isolation of *B. pertussis* by bacterial culture is the gold standard diagnostic laboratory test for pertussis[5]; a positive culture confirms the diagnosis of pertussis. Organism culture is also necessary for antimicrobial susceptibility testing and molecular typing. Although bacterial culture is specific for diagnosis, it is relatively insensitive. Fastidious growth requirements make *B. pertussis* difficult to isolate. Isolation of the organism using direct plating is most successful during the catarrhal stage (i.e., the first one to two weeks of cough). Cultures are variably positive (30%–50%) and may take as long as two weeks, meaning results may be available too late for clinical usefulness[1]. Success in isolating the organism declines if the patient has received prior antibiotic therapy effective against *B. pertussis*, if specimen collection has been delayed beyond the first two weeks of illness (some report beyond the first three to four weeks[5], and/or if the patient has been vaccinated[18]. Negative cultures do not necessarily exclude pertussis as the cause of disease, especially in vaccinated children or when the cough has been present for greater than two to three weeks[5].

Polymerase chain reaction (PCR). Timing of PCR testing for pertussis can significantly affect its ability to accurately diagnose the disease. PCR has optimal sensitivity during the first three weeks of cough when bacterial DNA is still present in the nasopharynx. After the fourth week of cough, the amount of bacterial DNA diminishes quickly, increasing the risk of obtaining false-negative results. PCR may be able to detect *B. pertussis* at a later stage of the infection,

when the ability to culture declines[18]. Non-viable organisms can be detected by PCR, but cannot be distinguished from viable organisms[5].

The proportion of cases confirmed by PCR has increased substantially since its inclusion in the case definition in 1997. Many laboratories currently use PCR only to confirm pertussis, although there is no standardized PCR assay, reagent list, or procedure for identification of pertussis. As sensitivity and specificity can vary greatly between laboratories, interpretation criteria for diagnosis vary. Like culture, PCR is also affected by specimen collection. An inappropriately obtained nasopharyngeal swab will likely be negative by both culture and PCR. However, PCR is less affected by prior antibiotic therapy, since the organism does not need to be viable to be positive by PCR[1].

While PCR is increasingly used as the sole diagnostic test for pertussis, the CDC recommends PCR be used alongside culture. Collection methods for PCR are similar to those for culture, and often the same sample can be used for both tests. However, calcium alginate swabs cannot be used to collect nasopharyngeal specimens for PCR[18].

Serologic testing. Serological diagnosis is based on the detection of a significant change in the level of specific antibodies in paired sera of infected individuals[18]. Results of serological testing are difficult to interpret due to a lack of association of antibody levels and immunity to pertussis. There is no consensus on what constitutes protective antibody levels or on the role of different types of antibodies in protection against disease[18]. Like PCR, standardized tests are not available. A single-point serologic assay has been validated at the Massachusetts state public health laboratory for persons aged 11

years or older and is used for clinical diagnosis and reporting in that state only. In states other than Massachusetts, cases meeting the clinical case definition that are serologically positive only are reported as probable cases[18].

Serologic testing is not useful for diagnosing acute infection, but can be used to establish a diagnosis retrospectively. During the year following vaccination, serology based on single sera test cannot be used for diagnosis as it may not differentiate between antibodies following natural infection and antibodies resulting from vaccination. However, serology can be the most important diagnostic tool in adolescents and adults, as pertussis is often diagnosed when they are likely PCR- and culture-negative[5].

Direct fluorescent antibody (DFA) testing/staining. DFA testing of nasopharyngeal secretions is sometimes used for pertussis screening. While DFA testing can provide rapid results to healthcare providers treating ill infants, these results are not confirmatory as the tests are of variable sensitivity and specificity and should be used alongside culture or PCR. Cases that meet the clinical case definition and are DFA positive, but not culture- or PCR-positive, are reported as probable cases[5,18].

Pulsed-field gel electrophoresis (PFGE). Pulsed-field gel electrophoresis (PFGE) can be performed on isolates to help track transmission (e.g., strains from the same household or community), but is not done for routine surveillance[18].

In sum, if acute phase serum is not collected early enough in the illness, titers often have already risen, making detection of a four-fold rise between acute and convalescent sera unlikely. Some investigators have suggested that titer falls

may be diagnostic of acute pertussis. DFA may be positive when cultures are negative because of antibiotic use, but this test requires training to ensure proper use and is of considerable variable sensitivity and specificity. In contrast, PCR techniques are capable of amplifying the material available in the sample and can increase the sensitivity of the diagnosis, although viable and non-viable isolates cannot be differentiated. Although PCR has been increasingly accepted as a diagnostic assay, it is recommended that culture still be treated as the gold standard diagnostic method[28].

Treatment and Chemoprophylaxis

Although antimicrobial treatment reduces transmission, it does not generally lessen the severity of disease unless it is begun prior to paroxysmal coughing. The spread can be limited by decreasing the infectivity of the patient and by protecting close contacts. Because individuals with pertussis are infectious from the beginning of the catarrhal stage through the third week after the onset of paroxysms or until five days after the start of effective antimicrobial treatment, identifying and treating infected individuals and close contacts is essential for disease control. The recommended antimicrobial agents and doses are the same for treatment and chemoprophylaxis; all close contacts, regardless of vaccination status should receive chemoprophylaxis[1]. The CDC recommends three macrolides: Azithromycin, clarithromycin, and erythromycin[18]. Resistance of *B. pertussis* to macrolides is rare, and antimicrobial susceptibility testing is not routinely recommended, although it can be done via culture[1] and is recommended when treatment failure is suspected. If resistance to macrolides is

suspected or if their use is contraindicated, the CDC recommends treatment with trimethoprim–sulfamethoxazole (TMP-SMZ) in a regimen of two doses a day for 14 days. TMP-SMZ should not be used to treat infants younger than two months of age[18].

Close contacts younger than seven years of age who have not received four doses of a pertussis vaccine should complete the series using the minimum recommended intervals between doses (minimum age for first dose is six weeks; minimum intervals from dose one to dose two, and from dose two to dose three are four weeks; minimum interval from dose three to dose four is six months). Vaccination with a fifth dose of a pertussis vaccine is recommended for close contacts four to six years of age who have only received four doses. Close contacts can be vaccinated with the adolescent and adult formulation (Tdap) in accordance with the Advisory Committee on Immunization Practice (ACIP) recommendations. Vaccination, however, is not a substitute for chemoprophylaxis and might not prevent illness in a person who has already been infected with *B. pertussis*[18].

Pertussis-Containing Vaccines and the Vaccine Schedule

Although a pertussis-containing vaccine was licensed in 1915, manufacturers could not guarantee its potency or safety until 1949[30]. The first trivalent, pertussis-containing vaccine (tetanus-diphtheria-pertussis; DTP) became available in the U.S. in 1948. Although the official, harmonized, annual vaccination schedule endorsed by ACIP, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) was not

implemented until 1995[3], routine childhood immunization with trivalent DPT has been recommended and used since the 1940s[4][5]

Five doses of DTP are given as follows: three priming doses are administered at two, four, and six months of age; a reinforcing dose between 15 and 18 months of age; and a booster dose administered between four and six years of age. In 2006, the ACIP recommended all adolescents (11-18 years) and adults (19-64 years) should receive one dose of Tdap in place of a decennial tetanus-diphtheria (Td) booster. The preferential age for this booster dose is 11-12 year-olds (i.e., adolescents going into middle school)[31]. In 2012, the ACIP recommended pregnant women receive a dose of Tdap with every pregnancy, as should all age-appropriate contacts of newborn infants who have not received Tdap previously[32].

Whole-Cell Pertussis Vaccines (DTwP). DTwP is composed of a suspension of formalin-inactivated *B. pertussis* cells. The vaccine, in combination with diphtheria and tetanus toxoids, was developed in the 1930s and used widely by the late 1940s. Routine vaccination with DTwP has been highly effective in reducing the burden of disease and deaths[31]. Controlled efficacy studies conducted in the 1940s and subsequent observational studies found DTP vaccines to be 70-90% effective in preventing serious pertussis disease[33]. Although safe and immunogenic, DTwP is associated with a variety of adverse events, including local erythema, swelling and tenderness at the injection site, fever, and other mild systemic events, such as drowsiness, fretfulness, and

[5] In 1943, the AAP suggested routine use of whole-cell pertussis vaccine [**4.** Clark TA. Changing Pertussis Epidemiology: Everything Old is New Again. *Journal of Infectious Diseases.* 2014;209(7):978-981.].

anorexia. More serious, rare events of febrile convulsions, hypotonic-hyporesponsive episodes, and acute encephalopathy have been documented after DTwP vaccination. General concerns about safety prompted the development of more purified (acellular) pertussis vaccines that are associated with fewer adverse events, but retain high immunogenicity[31,33]. Between 1991 and 1997, published reports indicated that when given to infants aged two to six months of age, acellular pertussis vaccines were effective in preventing disease and associated with fewer local, systemic, and certain more serious adverse events than DTwP[33].

Acellular Pertussis Vaccines (DTaP). In 1991, the Food and Drug Administration (FDA) licensed DTaP, a less reactogenic, acellular DTP[34]. In February 1992, the ACIP recommended the fourth and fifth doses of pertussis-containing vaccine be switched to DTaP, although whole-cell vaccine could still be used for these doses in children over 15 months of age, if acellular vaccine was not otherwise available[35]. Between 1991 and 1997, published reports indicated that when given to infants aged two to six months of age, acellular pertussis vaccines were effective in preventing disease and associated with fewer local, systemic, and certain more serious adverse events than DTwP[33]. The ACIP recommended DTaP be used for all five doses of DTP-containing vaccine in March 1997. Dr. Thomas Clark of the ACIP Pertussis Working Group described a washout period regarding the introduction of the new acellular series. Although the recommendation was made in 1997, Clark estimates whole-cell vaccine was no longer in use by about 2000[6]; DTwP has not been available in the U.S. since 2002[31].

DTaP formulations contain inactivated PT and may contain one or more other bacterial components (e.g., FHA, pertactin, and/or fimbriae) and have substantially less endotoxin than DTwP. As such, DTaP is considerably less reactogenic than DTwP and thus far more acceptable to parents. However, as the correlates of protection for pertussis are still poorly understood, using acellular vaccines that contain various types and amounts of antigens confounds any attempt to better understand whether the selected components impart decisive immunity or whether a vital component inherently included in the whole-cell vaccine is absent. All vaccines have PT, and a national study in Sweden found monocomponent PT vaccine drastically reduced pertussis burden[17]. Although immunity against pertussis, whether natural or vaccine-derived, may not life-long, an understanding of the immunogenicity, imparted protection, and reactogenicity of pertussis antigens is crucial for the development of new vaccines or new, acceptable vaccine schedules.

Acellular Pertussis Vaccine-Adolescent and Adult Formulation (Tdap). Two formulations of Tdap, pertussis-containing acellular vaccines for adolescents and adults, were licensed in 2005. In 2006, ACIP recommended Tdap be used to replace one decennial Td dose for those between the ages of 11-64 and to be used routinely in adolescents aged 11-12 years old thereafter[31]. The ACIP expanded the Tdap recommendations in 2010 to include both under-vaccinated children seven to 10 years of age and senior adults 65 years of age and older. In 2011, ACIP recommended that all healthcare personnel who have not yet received a dose of Tdap, regardless of age, should be vaccinated[18]. Tdap was recommended for every

pregnancy vaccine-eligible contacts (a strategy known as "cocooning") by the ACIP in 2012[32].

Although the two Tdap vaccines differ slightly in formulation, they are thought to have equivalent safety, immunogenicity, and protective efficacy. Both vaccines have one-third the concentration of PT found in DTaP. Ward et al noted that with one dose, both Tdap vaccines induce a significantly greater antibody response to *B. pertussis* antigens in adults than that observed in infants of seven months of age after receiving three DTaP doses. In this trial, the 92% efficacy of a single dose of Tdap among adolescents and adults supports this conclusion, as pertussis antigen components of the monovalent vaccine that was used in this trial are identical to the acellular pertussis components in one recently licensed Tdap vaccine (Boostrix, Glaxo-SmithKline, 8ug PT) and are similar to those in the other acellular pertussis vaccine (Adacel, Sanofi Pasteur, 2.5ug PT). The question remains whether a nearly four-fold difference in PT is correlated with a difference in length of immunity. Neither the duration of protection nor the prevention of secondary disease were assessed in the study by Ward et al[27,31].

Pertussis Vaccination Coverage and Vaccine Efficacy

In 1998, coverage in the U.S. with at least three doses of DTP (DTP3+) was estimated to be 65.4% among infants seven months of age and 90.0% among children 13 months of age[36]. By 2002, coverage for DTP3+ had risen to 66.5% among infants seven months of age and 90.0% among children 13 months of age[37]. In 2012, DTP3+ coverage reached 68.1% among infants seven months of age and 89.3% among children 13 months of age[6,10,38,39].

From 2006-2009, Tdap coverage among adolescents 13-17 years of age increased from 10.8% to 55.6%[40]. Tdap coverage among adolescents reached 78% by 2011[41]. Coverage among adults continues to be low; NHIS reported that 6.6% of adults 19-64 years of age had received Tdap[40]. Tdap coverage among adults aged 19-64 years scarcely rose: 5.7% in 2008 crept up to 12.5% in 2011. The data on children and teens are provider-verified; data for adults are largely self-reported, making it hard to know, of those who did report, how many doses of Td were really Tdap and vice versa[16].

Waning Immunity and Transmission Related to Vaccines

Naturally acquired immunity to pertussis wanes within seven to 20 years, although secondary infections occurring within three and a half years have been documented[4]. Even with vaccination, reinfection and onset of milder disease occurs; and pertussis periodicity has not changed since the initiation of vaccination with either whole-cell or acellular vaccines, suggesting that disease transmission has continued[4]. Immunity provided by whole-cell and acellular vaccines wane within five to 10 years post-vaccination[31].

Whole-cell DTP (DTwP) conferred 83% protection after three priming doses and 94% efficacy after four doses, although efficacy trials reported a range of 70%-90% protection against severe pertussis disease following receipt of four doses. Point estimates of efficacy for DTaP vaccines range from 59% to 89%[33] and is 80%-85% for DTP3+[42]. Using data from the 2010 California epidemic, the CDC found that the estimated vaccine effectiveness (VE) fell every year after the fifth dose, estimating a 27.4% relative decline in VE between 12 months and 60

months or longer post-vaccination[43]. Overall VE for five doses of DTaP was 88.7%. Within the first year of receipt, VE was 98%; three or more years, VE was less than 90%; and by five or more years, VE fell to 71%[6]. It should be noted that vaccine trials have been criticized for not including milder, atypical cases (however hard to identify by clinical or laboratory diagnosis) and thus inflating the apparent efficacy of the vaccine, as the clinical case definition that depicts the paroxysmal phase of disease appears inadequate to identify many cases of mild disease, particularly because vaccination has been shown to limit the duration and clinical severity of disease[29].

Pediatric vaccination against pertussis has not decreased the incidence of disease in older populations or the occurrence of outbreaks, nor has it eliminated the transmission of infections to unimmunized children. Infections among adolescents and adults result from waning immunity, since immunization or infection may not induce long-lived immunity. During a study conducted by Ward et al, 63% of subjects had a prolonged illness with cough each year, with an average duration of 24.4 days. The group found that *B. pertussis* accounted for 0.7% to 5.7% of the episodes, depending on the duration of cough. Immunization with DTaP prevented pertussis, but did not decrease the overall burden of prolonged illnesses with cough, as pertussis constituted only a small proportion of the illnesses. The overall annual incidence was 370 cases of pertussis per 100,000 persons between the ages of 15 and 65 years. If these rates are extrapolated to the total U.S. population, almost a million pertussis cases per year occur in the U.S. in persons 15 years of age and older, not including asymptomatic or mildly symptomatic infections or infections that are identified

with less specific diagnostic criteria. Ward et al concluded a high proportion of the disease burden is potentially preventable by vaccination, which might reduce community transmission[27].

Warfel et al hypothesized that current aP vaccines fail to prevent colonization and transmission. To study the transmission dynamics, Warfel et al vaccinated infant baboons at two, four, and six months of age with DTaP or DTwP and subsequently challenged the animals with *B. pertussis* at seven months. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring symptoms. Nonhuman primates vaccinated with DTaP were protected from severe symptoms, but not infection and readily transmitted *B. pertussis* to contacts. aP vaccines did not prevent colonization following direct challenge or infection by transmission. Vaccination with DTwP and previous infection, however, induced a more rapid clearance compared with naïve and DTaP-vaccinated animals. While all groups possessed robust antibody responses, key differences in T-cell memory suggest that DTaP vaccination induces a suboptimal immune response that is unable to prevent infection. The inability of aP to prevent colonization and transmission provide a plausible explanation for pertussis resurgence and suggest that attaining herd immunity will require the development of improved vaccination strategies that prevent *B. pertussis* colonization and transmission[22,44].

Several recent observational studies concluded that children primed with DTaP vaccine had a twofold to fivefold greater risk of pertussis diagnosis compared with DTwP-primed children, and recent case-control and cohort studies concluded that five years following the fifth DTaP dose, children are

fourfold to 15-fold more likely to acquire pertussis compared with within the first year. Above all, Warfel et al found that DTaP vaccines do not prevent infection or transmission of *B. pertussis* even one month after completing the primary vaccination series. The data presented by Warfel et al suggest that antibodies induced by DTaP vaccination are sufficient for preventing severe pertussis symptoms, but do not mitigate colonization. Although these data suggest DTaP is less effective than DTwP in preventing colonization, neither vaccine was able to prevent colonization as well as immunity from a previous infection, and the rate of undiagnosed *B. pertussis* carriage in vaccinated individuals is unknown[44].

Lavine et al analyzed age-specific whooping cough vaccine histories in Massachusetts from 1990 to 2008. The discrepancy between the estimates of disease-free duration after DTwP vaccination (10.5 vs. 6.6 years) is consistent with the observation that the time between vaccination and infection has decreased over time (average rate of 4.4 months' duration per year), assuming the reporting rate for each age group was constant over time. However, the biologically and statistically significant trend in disease-free duration, together with the increase of disease in adolescents, suggests that the disease-free duration did truly decrease over time. This trend may be a result of a rising force of infection in recent years, which increases the rate at which people will be exposed after their vaccine-induced immunity had waned. Furthermore, the age distribution during epidemics significantly differed from the overall age distribution. In particular teenagers (ages 10–19 years) were overrepresented in the epidemics, with the proportion of teenage cases during epidemics approximately twice as high as that of infants and a third again as much as that of

adults. The durations of immunity provided by DTwP and DTaP are very similar, implying that the change from wP to aP is not likely the cause of the decrease in the disease-free duration. Lavine et al instead hypothesize that an elevated force of or more frequent exposure to infection in recent years has led to the reduction in time to infection after vaccination[45].

Lavine et al also showed that reinfection of older individuals is important in contemporary pertussis epidemiology. Epidemic peaks had a unique age distribution with a disproportionate number of cases in teenagers (aged 11–19 years), identifying teens as the primary cause of large, symptomatic outbreaks. Despite the evidence that they can transmit to infants and their role in outbreaks, the clinical cases observed in teenagers did not appear to be the main source for the large numbers of cases in pre-vaccination-age infants. Infants and teenagers may belong to somewhat separate chains of transmission, given that each had different seasonal peaks that were out of phase with each other. A recent study of age-specific *B. pertussis* seasonality in the Netherlands reported similar results, suggesting that the separation of infant and teenage peaks may be a geographically widespread phenomenon and lending credence to the theory that infant cases are more likely due to contact with sub-clinically infected adults than symptomatically infected teenagers[45].

Despite the overwhelming evidence of a strong resurgence of pertussis in adolescents and adults, why were very few cases seen in teenagers and adults during the pre-vaccination era and for the first 40 years post-vaccination? Lavine offers the potential explanation that in the pre-vaccine era, when pertussis circulation was high and symptomatic infections more common, most people

received a natural boost in immunity by being exposed to pertussis before immunity had completely waned. By the 1970s, however, most people obtained immunity through vaccination rather than transmissible, natural infection. With circulating pathogen diminished, immunity was rarely boosted, thereby creating a large pool of people susceptible to pertussis. This phenomenon likely allowed epidemic outbreaks to occur in the current era despite high vaccine coverage. Alternatively or in tandem with the changing dynamics of pertussis transmission, the vaccine-driven pathogen may have evolutionarily selected for a strain that can infect more quickly or symptomatically after vaccination[45]. Following a subsequent transmission study, Lavine et al suggests that by vaccinating teenagers we would further erode the immunity extant in adults of child-bearing age, thus increasing circulation in this age group[46].

Seemingly in stark contrast, Taranger et al found that a mass vaccination campaign of infants in a city in Sweden with PT alone dramatically reduced pertussis disease, hospitalization, and mortality across all ages. Vaccination with monocomponent PT vaccine interrupted transmission of *B. pertussis* in the population. According to Taranger et al, if the incidence of pertussis had been affected only by individual vaccine efficacy (point estimate 71% after three doses), vaccination rate (56% had received three doses), and disease-induced immunity (~10%), it should have decreased by less than 50%, and the decrease would have only been evident towards the end of the campaign. Instead, pertussis, as confirmed by culture, had decreased by more than 90% after the first two years, with a substantial reduction in incidence among infants under six months of age and adults alike. The protection achieved, Taranger et al assert, can be attributed

to a decrease in the circulation of *B. pertussis* achieved by vaccination of infants[17].

These amazing results should be interpreted in light of two limitations. First, no information on asymptomatic or mild cases were provided for either the vaccines or other members of the population, including household members. Although the overall vaccination rate was low, pertussis disease in previously vaccinated or infected individuals is often milder or asymptomatic. Without data on these other presentations, we cannot accurately assess the true reduction in incidence. Second, the mass vaccination campaign began in 1995 and data was collected through the beginning of 1999. Just as most studies were limited in the duration of follow-up possible, long-term VE could not be assessed. This study documented a substantial decrease in pertussis within the first few years post-vaccination, which follows the known immunogenicity and protection afforded by DTP. However, long-term follow-up of monocomponent PT vaccine is needed to accurately gauge VE. Although VE was beyond the scope of the study, it would be of particular interest to the public health and scientific communities, as the correlates of protection for pertussis remain unknown; waning immunity following DTP vaccination, whether induced by wP or aP, continue to be hotly debated; and voluminous resurgences of pertussis continue, the periodicity and thus, transmission, unchanged.

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The Changing Epidemiology of Pertussis in the Acellular Vaccine Era

Abstract:

Background. Pertussis (commonly called whooping cough) remains endemic in the U.S., despite routine childhood pertussis-containing vaccine (DTP) in children since the 1940s. Although infants contribute have the highest reported incidence rates compared to other age groups, incidence in adolescents and adults has been steadily increasing since the 1980s. In 1992, the Advisory Committee on Immunization Practices (ACIP) recommended that trivalent diphtheria-tetanus-acellular pertussis vaccines (DTaP) be substituted for the whole-cell formulation (DTwP) for doses four and five of the five-dose pertussis vaccine schedule, and in 1997, DTaP was recommended for all five doses. To combat the increasing incidence of pertussis in adolescents, the Advisory Committee on Immunization Practices (ACIP) recommended adolescents and adults receive a tetanus-diphtheria-acellular pertussis booster (Tdap) in 2006. To date, however, no study has been done in the U.S. on the rates of hospitalization among all age groups following the switch to acellular vaccines for routine infant immunization. We sought to characterize the changing epidemiology of pertussis by examining the rates and rate differences of hospitalization across all age groups and infant subgroups in the acellular vaccine era.

Methods. Hospitalization records were obtained from the Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP) managed by the Agency for Healthcare Research and Quality (AHRQ). NIS and U.S. Census data were used to analyze national trends of hospitalizations due to pertussis disease. We calculated rates of pertussis hospitalizations for all ages during the years 1997-2011 and rate differences

between the early acellular pertussis (aP) vaccine period (1997-2001) and the late aP period (2007-2011).

Results. Hospitalization rates decreased significantly in infants between the early aP period (1997-2001) and the late aP period (2007-2011), but increased in all other age groups over the same period (-20.43 infant hospitalizations per 1,000,000 population (95% Confidence Interval (CI): -20.59, -20.27) versus +0.48 hospitalizations per 1,000,000 population in those 50 years and older (95% CI: 0.48, 0.48)). Among infant subgroups, rates decreased significantly among infants 0-1 month of age and infants 2-6 months of age (-114.66 hospitalizations per 1,000,000 population (95% CI: -151.88, -77.45) and -22.03 hospitalizations per 1,000,000 population (95% CI: -43.00, -1.07), respectively). Rates in infants 7-11 months of age decreased marginally (-9.17 hospitalizations per 1,000,000 population (95% CI: -16.46, 1.87)).

Conclusions. Although the decreasing rates of infant hospitalizations are significant, rates of pertussis in infants are still high. Increasing rates of hospitalizations in non-infant age groups suggests ongoing transmission and susceptibility. This warrants research into new mitigation strategies across the lifespan.

Introduction

Pertussis remains endemic in the U.S., with cyclic increases every three to five years, despite routine use of childhood pertussis-containing vaccine (DTP) for more than 50 years and high coverage levels in children since the mid-1990s[31,47]. Pertussis incidence has been steadily increasing since the 1980s, with

~50% of cases in adolescents (over 10 years of age). Reported mean annual pertussis incidence among U.S. infants increased by 49% in the 1990s compared with the 1980s (51.1 cases versus 34.2 cases per 100,000 infant population)[20]. Infant mortality associated with pertussis during the same period rose 44% (1.67 deaths per million infants versus 2.40 deaths per million infants) and hospitalizations among children less than two years of age increased 23% from 1994-1998 to 1999-2003 (35.0 hospitalizations per 100,000 children less than two years of age versus 42.9 hospitalizations per 100,000 children less than two years of age)[48]. These reported increases may be partly related to a greater awareness that pertussis causes prolonged cough in adolescents and adults, as well as the use of less efficacious vaccines that have led to waning vaccine-induced immunity[48]. Because immunity to pertussis, whether imparted naturally or vaccine-induced, can wane within a relatively short time, and because vaccine effectiveness is imperfect, pertussis occurs in both vaccinated and unvaccinated individuals[31].

In 1992, the ACIP recommended acellular pertussis vaccines (DTaP), which were less reactogenic than whole-cell DTP (DTwP), be used for the fourth (reinforcing) and fifth (booster) doses of the five-dose DTP series at ages 15-18 months and four to six years, respectively. In 1997, the ACIP recommended all doses of the DTP series be switched to DTaP. DTwP has not been available in the U.S. since 2002[6,31]. To combat apparent waning immunity and increasing rates of pertussis in adolescents, the ACIP recommended all adolescents (11-18 years; preferred age 11-12 years) receive a reduced-dose of acellular pertussis vaccine combined with tetanus and diphtheria toxoids (Tdap)[31,49]. Adults (19-64 years)

were encouraged to receive a dose of Tdap in place of one decennial tetanus-diphtheria (Td) booster[31].

Infants are known to be at disproportionate risk of severe pertussis disease and comprise the largest burden, making case ascertainment and reporting likely more reliable for this age group. As such, studies on pertussis disease tend to focus on those under one year of age. However, an understanding of the burden in adolescents and adults, in addition to infants, is needed to better inform vaccination policies and push for continued vaccine research. To date, no study has been done in the U.S. on the rates of hospitalization among all age groups during and following the switch to acellular vaccines. Therefore, we sought to characterize the changing epidemiology of pertussis during the switch to acellular vaccines by examining the rates and rate differences of hospitalization across all age groups and including infant subgroups.

Methods

Data Sources. The Nationwide Inpatient Sample (NIS), developed by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (AHRQ-HCUP), is the largest all-payer inpatient health care database in the United States[50]. NIS collects all charge data from more than 1,000 short-term and non-Federal hospitals each year, including individuals covered by Medicare, Medicaid, or private insurance, as well as those who are uninsured. This sampling design approximates a 20% stratified sample of U.S. community hospitals. Up to 15 International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coded discharge diagnoses and 15 procedures

are recorded, with first-listed diagnoses (principal) regarded as the primary reason for hospitalization. Participating hospitals are sampled by stratified probability sampling. Sampling probabilities are proportional to the number of community hospitals across five strata: ownership/control, bed size, teaching status, urban/rural, and U.S. region. In 2011, 1,049 hospitals in 46 states participated in HCUP[51].

We used NIS to examine annual and period trends for several age groups. National estimates derived from NIS were weighted to make national inferences and were calculated following the HCUP-recommended weighting procedures using the SAS Surveymeans and Surveyfreq procedures. As a study of de-identified data, our study was considered exempt research by the Emory University Institutional Review Board.

Study Population. We calculated annual and period rates of pertussis hospitalization as hospital discharges per 1,000,000 persons in the U.S. population from 1997 through 2011. Annual, age -specific denominator data were obtained from the U.S. Census Bureau Population Estimates Program[52]. All patients diagnosed with pertussis in NIS were identified as having ICD-9-CM code 033.0 (*Bordetella pertussis*) as the first or second of 15 recorded diagnoses (i.e., a principal diagnosis and as many as 14 secondary diagnoses).

NIS data from 1997 through 2011 were used to examine trends in hospitalizations for pertussis within the following age groups: infants (less than one year of age), one to four years of age, five to 10 years of age, 11 to 17 years of age, 18 to 22 years of age, 23 to 49 years of age, and 50 years of age and older. In addition, we examined trends in infants aged less than two months of age (0-59

days; vaccine-ineligible), infants two to six months of age (60-210 days; eligible for one to three doses of DTP), and infants seven to 11 months of age (211-364 days; eligible), as these infant age groups have the highest risk of pertussis disease and complications that would require hospitalization[26].

We examined rates of pertussis hospitalizations from 1997 through 2011, excluding 2002 and 2006. Because acellular pertussis vaccines were not uniformly used until about 2000-01[6] for all doses, we treated 1997-2001 as baseline or early acellular pertussis (aP) vaccine years (herein referred to as the early aP period). We included 2001 to account for any lag in acellular vaccine uptake. Because we could not definitively group 2002 into the purely aP period or the period when both whole-cell and acellular vaccines were used (i.e., whole-cell vaccine were used as priming doses, acellular vaccine for the fourth reinforcing dose and fifth booster dose[53]), we treated the study year as a transition year and excluded it from analysis. The period 2003-2005 was regarded as the middle aP period, as 2003, by our estimation, was the first true year acellular vaccine was used for all DTP doses. The period 2007-2011 was treated as the late aP period, following the implementation of Tdap in 2006. To account for the 2006 ACIP Tdap recommendation, we treated 2006 as a transition year and excluded it from analysis. The selection of the period 2007-2011 allowed us to compare the most

[6]Dr. Thomas Clark of the ACIP Pertussis Working Group described a washout period regarding the introduction of the new acellular series. Although the recommendation to change all doses in the DTP series to acellular vaccine was made in 1997, Clark estimated use of the whole-cell vaccine was not completely phased out until about 2000 [**6.** Clark TA. ACIP Feb 2013 Meeting Minutes. February 21, 2013 2013:55-73.]. Pediatric DTwP has not been available in the U.S. since 2002 [**31.** Broder KR. Preventing Tetanus, Diphtheria, and Pertussis Among Adolescents: Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccines. *MMWR Recomm Rep*. March 24, 2006 2006;55:1-34, **31.** Ibid.].

recent five-year period with the baseline five-year period.

Statistical Analyses. We compared hospitalization rates in the late aP period (2007-2011) with rates in the early aP period (1997-2001) and estimated age-specific differences in rates of pertussis hospitalization. We estimated the average annual rate of hospitalization for each period, with the standard error computed as prescribed by HCUP (Surveymeans procedure, subset analysis: http://www.hcup-us.ahrq.gov/tech_assist/standarderrors/508/508course.html) and consistent with previous methodologies[54]. Differences in rates are the difference in average annual rates. The variance for the difference in rates is the sum of the variances in the average rate. 95% confidence intervals (CI) were calculated using the normal approximation.

National weighted frequencies of pertussis hospitalizations and their respective standard errors (SEs) were calculated using NIS weight (DISCWT and DISCWT_U) and stratum (NIS_STRATUM and STRATUM) variables. Annual hospitalization rates were computed using NIS-weighted frequencies as numerators and annual, mid-year population estimates from the U.S. Census Bureau (person-year estimates) as denominators[52]. To use the appropriate denominator for the infant subgroups, we calculated the respective denominators by dividing the number of months included in the subgroup by twelve and multiplying this ratio with the annual, mid-year U.S. Census Bureau estimates for the "0" age group (e.g., for the two to six month age group in a given study year, the Census data for the "0" age group was multiplied by (5 months included/12 months in the calendar year)). We evaluated trends in annual pertussis hospitalization rates from 1997-2011 by age group and infant age group.

Because pertussis disease is a protracted illness with the risk of severe complications and hospitalization, particularly in infants, we examined the length of stay (LOS) by age group. To place our findings in the context of seasonal trends, we examined the periodicity of hospitalizations by secular month of discharge for all age groups from 1997-2011. Additionally, we compared NIS hospitalization data to surveillance data obtained from CDC in the NNDSS over the study period for all age groups and for two sets of infant age groups, wherein the second set of age groups splits the range of infants two to six months of age into infants two to three months of age (60-120 days) and infants four to six months of age (121-210 days). To place our findings in the context of secular trends in pertussis disease (demonstrated by Auger et al[41]), we examined the percentage of infants hospitalizations recorded in NIS against the absolute number of pertussis cases reported to NNDSS and total hospitalization captured in NIS. All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and Microsoft Excel 2013 (Microsoft, Redmond, WA).

Results

Demographics. From 1997 through 2011, 212,156 cases of pertussis were reported to NNDSS. Using the national weighting procedures as prescribed by HCUP, NIS recorded 9,698 pertussis hospitalizations nationally during the same period, with 7,859 reporting pertussis as the primary or secondary diagnosis (Table 1). Annually, infants (less than one year of age) accounted for 86.7% of hospitalizations on average (range: 51.1%-94.1%); adolescents contributed 1.5%, on average (range: 0%-3.9%); and older adults (50 years and older) contributed

5.5%, on average (range: 1.3%-20.0%). About half (52.9% (range: 43.4%-67.0%)) of those hospitalized were female, with a consistent pattern observed annually[7]. Of hospitalizations in all ages, 46.0% of patients were white (range: 29.7%-62.0%), 33.8% were Hispanic (range: 16.6%-56.4%), and 11.9% were black (range: 7.1%-16.6%), on average. Overall, both ethnicities varied little in the number of hospitalizations each contributed annually. During the upsurge of pertussis cases in 1999 and epidemic year 2005, white patients contributed the largest proportion of all hospitalizations (44.4% and 51.0%, respectively); in comparison, Hispanic patients contributed the largest proportion of hospitalizations (45.7%) to the 2010 epidemic. Those who reported an income of $24,999 or less or up to the 25th percentile of income in the U.S. comprised 26.7% of all pertussis hospitalizations, on average (range: 9.7%-44.2%).

Hospitalizations in Infants. 6,587 infants[8] were hospitalized for pertussis over the study period. Of these, 44.25% of hospitalizations occurred in infants one month of age or younger, on average (range: 42.2%-61.9%); this age group is ineligible for DTP vaccination (Figure 1). In stark contrast, infants seven to 11 months of age, who are eligible for all three priming doses of DTP, contributed 3.4% of all hospitalizations in infants, on average (range: 1.8%-8.7%). No pertussis hospitalizations were recorded in NIS among seven to 11 month-old infants during study year 2000. During the upsurge in 1999 and the epidemic year 2005, infants one month of age or younger accounted for 56.2% and 51.6%,

[7] In 2001, more male hospitalizations for pertussis were captured by NIS (56.6% males compared with 43.4% females).
[8] Not all healthcare providers reported age in months for infants (i.e., age was marked "0"). Only infants whose ages were also reported to NIS in months were used for analyses in this study so as to perform infant subgroup and all-age analyses with the same population.

respectively, of all infant hospitalizations. In 2010, infants two to six months of age contributed 50.6% of all infant hospitalizations.

Rates of Hospitalization. Of the infant age groups, infants one month or younger had the highest rates of hospitalization, two- to three-fold higher than infants two to six months of age. Infants seven to 11 months of age consistently had the lowest rates of hospitalization, at least eight-fold lower than infants two to six months of age and at least 16-fold lower than infants one months of age or younger. These proportions remained stable over the entire study period (Table 2.1). Among all age groups, infants had the highest rates of hospitalization for pertussis (Table 2.2), with peaks in this age group observed in 1997, 1999, 2004, 2005, and 2010. Children one to four years of age had increased rates of hospitalization in epidemic years 2005, and 2010, as well as 1998 and 1999.

Rates across all ages peaked during the upsurge in pertussis cases in 1999 and in the epidemic years 2005 and 2010, driven by rates of hospitalizations in infants (Figure 2a). Rates of pertussis hospitalizations in infants increased between the early aP and middle aP periods and decreased from the middle aP period to the late aP period (Figure 2b). Infants had a higher rate of hospitalization during the 2005 epidemic than the 2010 epidemic.

Among the infant age groups, infants less than two months of age, who are ineligible to begin DTP vaccination, had the highest rates of hospitalization. Rates in infants two to six months of age, who are eligible to receive at least two doses of DTP, followed the overall rate of infant hospitalizations. Infants seven to 11 months of age, who are eligible for all three priming doses of DTP, consistently had the lowest rates of hospitalization for pertussis in infancy. All groups had

higher rates during 1999, 2005, and 2010. Between the early and middle aP period, rates in infants one month of age and younger and in infants two to six months of age increased. In these age groups, rates decreased between the middle and late aP periods. Rates in seven to 11 months decreased across all aP periods.

Infants less than two months of age had the largest decrease in hospitalizations, five-fold greater than that in infants two to six months of age (-114.66 hospitalizations per 1,000,000 population (95% CI: -151.88, -77.45) and -22.03 (95% CI: -43.00, -1.07), respectively). In comparison, rates in infants seven to 11 months of age (-9.17 hospitalizations per 1,000,000 population (95% CI: -16.46, 1.87)) were ~13-fold less than rates in infants less than two months of age.

Rates in all age groups excluding infants increased from the early aP period to the late aP period (Figure 3a). Hospitalization rates in the age groups ranging in age from one year to 22 years, increased between the early and middle aP period, but decreased between the middle and late aP periods. Among those 23-49 years of age and those 50 years and older, rates increased steadily across all three study periods. The rate of pertussis hospitalizations in adults 50 years and older increased 10-fold between the early aP period and the late aP period.

Rate Differences. The largest increases of hospitalization rates were in patients between the ages of 18 and 22 years and older adults above 50 years of age (0.2959 hospitalizations per 1,000,000 population (95% confidence interval (CI): 0.2196 to 0.3723) and 0.4769 hospitalizations per 1,000,000 population (95% CI: 0.4681 to 0.4857), respectively) (Table 3). Adolescents 11 to 17 years of age had the smallest increase (0.0171 hospitalizations per 1,000,000 population

(95% CI: 0.0169 to 0.0174), followed by adults 23-49 years of age (0.1083 hospitalizations per 1,000,000 population (95% CI: 0.1083, 0.1085).

Length of Stay. The majority of hospitalizations lasted less than 10 days (range: 0-9 days) across all age groups (data not shown). LOS was substantially greater in infants than among all other age groups. On average, 497 infants (range: 206-1575 hospitalizations) were hospitalized for pertussis annually between less than a day and more than 30 days. 413 infants (range: 163-1240 hospitalizations) were hospitalized for less than 10 days annually; 106 infants (range: 24-244 hospitalizations) were hospitalized between 10 and 19 days annually; 21 infants (range: 5-40 hospitalizations) were hospitalized between 20-29 days annually; and 11 infants (range: 0-51 hospitalizations) were hospitalized for 30 or more days annually. Hospitalizations peaked across all age groups during the 2005 epidemic. During 2005, 51 infants were hospitalized for 30 or more days. 71 children one to four years of age were hospitalized during the 2005 epidemic for up to nine days.

Between 1997 and 2011, a total of 360 adults 50 years of age or older were hospitalized with pertussis (annual range: 0-80) for up to nine days. During the 2010 epidemic, those 50 years and older had the greatest number of hospitalizations lasting up to nine days after infants. Whereas the absolute number of hospitalizations up to nine days remained stable in infants and children one to four years of age, with the exception of the aforementioned upsurge and epidemic years (i.e., 1999, 2005, and 2010), the number of hospitalizations steadily increased in adults 50 years and older, particularly between 2008-2011 (39, 69, 50, and 58 hospitalizations, respectively) compared

to eight hospitalizations in 1997, five hospitalizations in 2000, and no hospitalizations in this age group in 1998 or 1999.

Seasonality. Pertussis hospitalizations from 1997 through 2011 peaked during July and August (Figure 4). On average, 78 cases (range: 6-215) were hospitalized with pertussis in the month of July and 72 cases (range: 11-186) were hospitalized in August. Pertussis hospitalizations also increased modestly in January across all study years, with an average of 52 hospitalizations (range: 27-113) recorded in NIS annually. Of all age groups, infants contributed the greatest number of hospitalizations in all seasons, particularly in July and August during the upsurge in 1999, as well as the epidemic years 2005 and 2010. In 1999, infants accounted for 93% of all hospitalizations in July and 90% of all hospitalizations in August. In 2005, 215 infants were hospitalized in July and 186 in August, compared with 10 and 16 hospitalizations in children one to four years of age, respectively, and compared with 5 hospitalizations in adults 50 years of age and older in both July and August. 136 infants were hospitalized in July 2010 and 116 infants were hospitalized the following month. During the same months, no hospitalizations in children ages one to four years of age were recorded in NIS, and no adults 50 years of age and older were hospitalized within NIS during July; in August 2010, five adults 50 years of age and older were hospitalized with pertussis. Infants accounted for 89% and 85% of all hospitalizations across all months in 2005 and 2010, respectively. After infants, adults 50 years of age and older contributed the second greatest proportion of all hospitalizations per month over the study period, contributing ~2% (range: 0-29 hospitalizations)

and 7% (range: 0-76 hospitalizations) across all months in 2005 and 2010, respectively.

NIS and NNDSS. We examined rates of hospitalization among all pertussis discharges through the NIS database by age group (Table 4). The frequency and rates of hospitalization by age group followed the known epidemiology of pertussis: infants had the highest number of cases and rates of hospitalizations. With the exception of 1999, 2005, and 2010, rates of hospitalization for pertussis decreased. The national incidence, however, fluctuated across upsurge, epidemic, and non-epidemic years. NNDSS reports a greater absolute number of cases, as well as a higher rate, in 2004 than in 2005 (25,927 cases, IR 8.88 cases per 100,000 population; and 25,616 cases, IR 8.72 per 100,000 population, respectively). Of all study years, 2010 had the greatest number of cases and highest IR (27,550 cases, IR 8.97 per 100,000 population). In stark contrast, NIS recorded the greatest number of hospitalizations and highest hospitalization rate in 2005 (1,281 hospitalizations, IR 6.02 per 1,000,000 population). From 2002 onwards, over 1,000 cases of pertussis in adults 40 years and older were reported to NNDSS, peaking in 2005 and 2010 (4,449 and 3,806 cases, respectively). In 2005, more adult cases were reported to NNDSS than infants; the reverse was true in 2010 (3,967 and 4,120 infant cases, respectively). The ratio of hospitalizations in all ages in the NIS to reported cases in all ages remained fairly steady across the study period (average: 0.05; range: 0.02-0.10). The ratio of infant hospitalizations to reported cases in infants, however, fell from 1997-2005 (average: 0.21; range: 0.16-0.29) compared with 2006-2011 (average: 0.12; range: 0.11-0.16).

According to the CDC, approximately half of all infants who contract pertussis are hospitalized [26]. Infants younger than six months of age are at particular risk; infants younger than six months of age are at greatest risk[26]. After further stratifying infants by age group (zero to one month, two to three months, four to six months, and seven to 11 months of age), the number of infants hospitalized for pertussis declined as age in month increased (Table 5). Of all pertussis hospitalizations recorded in NIS, the percentage of infants hospitalized for pertussis during the same time period ranged from 18.91% (range: 9.32%-36.23%) in infants younger than two months of age, 17.56% (range: 2.48%-26.77%) in infants two to three months of age, 8.81% (range: 2.51%-10.86%) in infants four to six months of age, and 6.72% (range: 22.01%-0.00[9]%) in infants seven to 11 months of age, on average. The years in which the most infants with pertussis were reported to NNDSS differed from the years with the greatest numbers of infants hospitalized for pertussis in NIS. Infants under one month of age through six months of age had the highest absolute number of cases reported to NNDSS and the highest absolute number of hospitalizations in NIS in 2010. Infants two months of age and older had the greatest number of cases reported to NNDSS in 2004. With the exception of 2010, more infants were hospitalized during the earlier years (1997-2003) within the study period, whereas more infants were reported to NNDSS more often in the later years of this study period (2004-2011).

[9] In 2000, no infants seven to 11 months of age were hospitalized, as recorded by NIS.

From 1997-2011, the percentage of infants hospitalized with pertussis declined steadily (Figure 5). The number of hospitalizations peaked modestly, following the secular trends displayed prominently in the absolute number of cases reported to NNDSS. The number of cases reported to NNDSS remained relatively stable from 1997 until 2001-02. After 2003, the number of pertussis cases reported annually to NNDSSS did not fall below 10,000 cases.

Discussion

Primary Findings. From 1997-2011, hospitalizations for pertussis decreased significantly among infants (<1 year). During the same period, significant increases in hospitalizations occurred in all other age groups (>1 year to >50 years).

Infants seven to 11 months were the only age group that experienced declines in hospitalizations across all three periods. Not all of these declines were statistically significant, likely due to the relatively small sample size. However, as this group is the only infant group likely to have been vaccinated with all or most of the priming doses, a non-significant decrease in hospitalizations across all aP periods could bolster the evidence that acellular vaccines provide robust short-term immunity. The significant decreases in rates of hospitalizations of infants two to six months of age, who likely have at most two priming doses of DTP, may also reflect excellent short-term protection elicited by the acellular vaccine.

Hospitalization Rates in Early aP Versus Late aP. Hospitalization rates of pertussis declined significantly in infants six months of age and younger between the early and late aP periods. In contrast to infants six months of age or younger,

the decrease in rates of hospitalization among infants seven to 11 months of age between the early and late aP periods was not significant. Infants in this age group are eligible for receipt of all three priming doses of DTP.

In all other age groups, rates of hospitalization for pertussis increased significantly between the early and late aP periods. No hospitalizations were recorded in NIS for adults 18-22 years of age during the early aP period. These findings could suggest an increase in healthcare provider awareness, but corroborate past findings that pertussis is increasing in adolescents and adults. The largest increase across these periods occurred in individuals 50 years of age or older, further bolstering evidence that immunity to pertussis wanes over time and contributing evidence to the hypothesis that pertussis exposure and transmission has increased over time. This population has either acquired immunity via receipt of wP or through natural infection; or may not have previously been exposed to pertussis, although this possibility seems unlikely.

Hospitalization Rates in Early aP Versus Middle aP. Between the early and middle aP periods, increases in hospitalizations across all age groups were observed, particularly in infants. Hospitalizations in this age group declined thereafter, but were consistently greatest among infants one month of age and younger, followed by infants two to six months of age. Hospitalization rates between the early and middle aP periods did not increase in infants seven to 11 months of age, who are eligible for all three priming doses of DTP. Comparing infants eligible for the priming doses of DTP with infants who have received two DTP doses or fewer may have less to do with uptake and vaccine effectiveness

than potential skewing, given that the 2005 epidemic year, which hit infants hardest than any other study year, is considered here.

Hospitalization Rates in Middle aP Versus Late aP. Hospitalization rates among all infant subgroups decreased between the middle and late aP periods, including among infants seven to 11 months of age, again suggesting excellent short-term pertussis vaccine effectiveness. Hospital rates decreased among children one to 10 years of age, adolescents 11-17 years of age, and adults 18-22 years of age, but increased among adults 23 years of age or older.

Hospitalizations in Infants and Older Age Groups. Although adolescents accounted for a great proportion of reported pertussis cases in 2005, the greatest number of hospitalizations occurred in infants. Adults and adolescents are known reservoirs of pertussis disease for young infants; immunity imparted by pertussis vaccines and pertussis disease can wane within five to 10 years; and carriage of *B. pertussis* reportedly differs between whole-cell and acellular vaccination, wherein acellular vaccines do not diminish carriage or transmission as well as whole-cell vaccines[10]. Increased disease, transmission, and carriage in older age groups will likely lead to continued hospitalization of infants. As adolescents and adults may not present with severe disease, medical care in these age groups is likely not sought and hospitalization likely not required, increasing the risk of transmission to susceptible populations. However, the observed increases in rates of non-

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[10] Warfel et al found that although whole-cell vaccines diminished carriage and transmission compared to acellular vaccines, neither vaccine fully prevented carriage of *B. pertussis [**44.** Warfel JM, Zimmerman LI, Merkel TJ. 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. 2013;111(2):787-792.]*. Warfel et al found that although whole-cell vaccines diminished carriage and transmission compared to acellular vaccines, neither vaccine fully prevented carriage of *B. pertussis [**44.** Ibid.]*.

infant hospitalizations and apparent decrease in rates hospitalizations in infants may reflect greater awareness of the signs and potential severity of pertussis disease.

During the early aP period, more infant cases were reported to NNDSS than adult cases, compared to the middle and late aP periods. With media attention surrounding the upsurge in 2004, epidemic year 2005, and corresponding outbreaks leading to the recommendation of an additional a booster dose (Tdap), the observed increases in adult cases and hospitalizations could be a reporting artifact (i.e., more mild and/or moderate disease is being captured than ever before). By the same token, during this period, physicians were also more aware of what to look for in adolescents and adults presenting with nonspecific, prolonged respiratory disease. This would indicate that the increases in hospitalizations in these older age groups are reflective of true, increased pertussis transmission and disease. However, complications requiring hospitalization occur in roughly half of all infant cases, but at most 2% in adolescents and adults[26]. Because disease is harder to diagnose in older age groups (that is, not infants or young children), laboratory-confirmed diagnoses are needed to increase the specificity of incidence studies in these populations. For this reason, we limited our study to patients whose primary or secondary diagnoses[11] recorded in NIS were pertussis.

Demographics and Seasonality. The demographics of hospitalizations for pertussis recorded in NIS followed the known epidemiology of pertussis disease:

[11] Primary or secondary diagnosis of up to 15 recorded diagnoses during 1997-2007 and up to 25 diagnoses during 2008-2011.

Infants comprised the largest burden throughout all study years; white and Hispanic subpopulations experienced the most hospitalizations; for most study years, females comprised slightly more than half of all hospitalized cases; and for most study years, hospitalized cases were more frequently in lower income brackets. Hospitalizations, driven by cases in infants, peaked in July and August on average throughout the study period. The upsurge and epidemic years follow the expected pertussis secular trends, with inter-epidemic years ranging from three to five years; however, the seasonality observed during epidemic years (i.e., 2005, 2010) is likely tied to increased transmission and circulation of pertussis.

Length of Stay. Increased LOS is largely inversely proportional to age. Across all study years, infants contributed the largest proportion of hospitalizations and were the only age group consistently hospitalized beyond 10 days across all study years. Previously reported average LOS for adolescents (10-19 years of age) and adults 20 years of age or older were 6.3 and 8.7 days, respectively, which falls within our findings[28]. However, for all LOS, a surprising number of adults 50 years of age and older and adults 23 years of age and older (including those over 50 years of age) were the only other age groups consistently hospitalized up to nine days across all study years. Although we did not investigate the presence of comorbidities or other clinical findings present at the time of hospitalization that would predispose older adults to severe pertussis disease, the economic burden associated with this finding bears further investigation to inform more effective prevention measures.

NIS and NNDSS. Although we observed some differences in NIS compared to NNDSS, our findings demonstrate that pertussis hospitalizations in

NIS followed trends of pertussis disease reported to NNDSS during 1997-2011. The ratio of infant hospitalizations in NIS to reported infant cases in NNDSS varied surprisingly from the accepted rate of hospitalization in this age group (~50%[26]). The ratio of hospitalizations to reported cases ranged from 0.11-0.29, with an average of 17% of hospitalizations in NIS being reported to NNDSS. Although our data suggest infant hospitalizations may be less frequent than previously thought, several factors likely contributed to this underestimation. While pertussis may have been underdiagnosed in NIS, we limited our study to hospitalizations with either a primary or a secondary diagnosis of pertussis, of 15-25 possible diagnoses; and further limited our analyses to only include infants whose age was recorded in months.

In 2010, more cases of pertussis were reported to NNDSS than 2005. Yet, NIS captured more hospitalizations in 2005 than in 2010. Although a higher absolute number of adults were hospitalized for pertussis in 2010 than in 2005 (81 and 34, respectively), adults comprised a higher proportion of all hospitalizations for pertussis in NIS in 2005 than 2010. Infants in both epidemic years contributed at least 80% of hospitalizations. The MMWR summary data for 2005 has the highest reported rate of pertussis (160.81 per 100,000 population) among infants six months of age or younger, but notes that adolescents 10-19 years of age and adults 20 years of age or older years contributed the greatest number of reported cases (60%)[55]. Despite underreporting, of all reported pertussis cases, hospitalization for pertussis occurs in roughly 1.4%-7.5% of adolescents 10-19 years of age and 3.5%-5.7% of adults 20 years of age or older[28].

The combination of waning immunity afforded by pertussis vaccination, lessened severity of disease in vaccinated individuals, reported increased carriage of *B. pertussis* in nonhuman primates[12] vaccinated with DTaP compared to DTwP, and the subsequent increase in transmission form a perfect storm for the occurrence of epidemic years with greater numbers of cases and hospitalizations. Because disease is milder or non-apparent, treatment and isolation are not sought, leading infectious individuals to come into contact with susceptible members of the population. Waning immunity across all ages and increased carriage in adolescents vaccinated with DTaP dramatically increase the risk and duration of transmission to susceptible populations. Seasonal and secular trends in pertussis may indicate that epidemic years require a critical mass of susceptible people in the population to flourish. This is particularly apparent in the seasonality observed in NIS, wherein hospitalizations in July and August dramatically peak only during epidemic years. During upsurge years 1999 and 2004, the absolute number of hospitalizations did not differ from non-epidemic years. Infants contributed the greatest number of hospitalizations for each month, greatly increasing the peaks of the 2005 and 2010 epidemics. During July and August, summer camp season winds down and families often travel abroad. In August and September, children and adolescents return to school and a greater mixing of these age groups naturally occurs, potentially leading to the

[12] Warfel et al conducted a study on the difference in *B. pertussis* carriage between nonhuman primates vaccinated with whole-cell or acellular pertussis vaccine. [**44.** Warfel JM, Zimmerman LI, Merkel TJ. 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*. 2013;111(2):787-792.] Warfel et al conducted a study on the difference in *B. pertussis* carriage between nonhuman primates vaccinated with whole-cell or acellular pertussis vaccine. [**44.** Ibid.]

introduction and transmission of pertussis within a larger pool of susceptible people.

Since the 1980s, rates of pertussis have been increasing, with a greater proportion of adolescents and adults contributing to the burden than previous decades. Pertussis hospitalization rates within the NIS database from 1997-2011 reflect these trends, as do the rates of hospitalization by age group, season, and ratio to reported cases. Using NIS, Cortese et al described rates of infants hospitalizations for pertussis during 1993-2004 and found an inverse relationship between infant age (months), a proxy for vaccine receipt, and hospitalization for pertussis[47]. Because infants under one year of age are at greatest risk of disease and hospitalization, our dataset reflects the same finding: infants three months of age and younger (i.e., infants vaccine ineligible and infants eligible for at most one dose of DTP) had greater hospitalization rates than infants four to six months of age and infants seven to 11 months of age (i.e., infants eligible for at least two doses of DTP and infants eligible for at least three doses DTP, respectively). Auger et al compared observed rates of pertussis hospitalizations in infants preceding the implementation of Tdap with expected rates following the Tdap recommendation using NIS data from 2000-2011[41]. Rates initially increased during the pre-Tdap years. Expected rates for the post-implementation period were lower for three of the four study years (2008-2009 and 2011, lower and significantly different; 2010 was lower, but not significantly different), suggesting that Tdap vaccination is shifting the epidemiology of pertussis in infants[41]. Neither study provided information on vaccination history or laboratory confirmation available for patients hospitalized with pertussis, and

no other study aimed to quantify the changing burden of pertussis hospitalization in children, adolescents, or adults.

Conclusions. We found rates of pertussis hospitalization to increase from the early aP period to the middle aP period, but decrease significantly thereafter in infants, particularly those who are too young to have been vaccinated with a pertussis-containing vaccine; rates in older age groups, however, increased from the early to the late aP period. Although no previous herd effect has been demonstrated[16], the substantial decrease observed from the early aP period to the late aP period suggests some level of protection is occurring, despite increased carriage and transmission in older age groups who have received acellular vaccine.

The switch from whole-cell to acellular vaccines was undertaken without establishment of the correlates of protection for pertussis. Because acellular pertussis vaccines vary by antigenic components and concentrations, attempts to attribute adequate vaccine failure or protection immunologically to any one component has been difficult, although PT) alone was demonstrated to be effective. Similarly, there are limited published data of long-term follow-up with any specific pertussis vaccine so virtually all data on long term effectiveness generally cannot determine whether waning immunity is seen with all vaccines or specific vaccines[13]. A national study of mass vaccination with monocomponent

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[13] Taranger et al demonstrated excellent short-term monocomponent PT vaccine effectiveness when used in Sweden following a lapse of more than 10 years in DTP administration. However, follow-up did not last beyond four years after the implementation of the mass vaccination campaign described in their paper [**17.** Taranger J. Mass Vaccination of Children with Pertussis Toxoid--Decreased Incidence in Both Vaccinated and Nonvaccinated Persons. *Clinical Infectious Diseases*. October 1, 2001 2001;33:1004-1009, **17.** Ibid.].

PT vaccine in Sweden resulted in a substantial drop in pertussis morbidity, hospitalization, and mortality across all ages[17]. Whether carriage is eliminated and transmission stymied, DTaP exhibits excellent short-term immunity and, potentially, important herd effects. Absolute hospitalization rates in infants, however, remain substantially higher than any other age group, and the increase in rates of hospitalization among non-infant age groups are small, but significant.

Immunity to pertussis wanes and adolescents and adults are often the reservoir of pertussis disease for infants, as adolescents and adults often present with asymptomatic or mildly symptomatic symptoms, frequently with a prolonged cough [2,31,56]. A recent study in a nonhuman primate model demonstrated that baboons vaccinated with acellular pertussis vaccine did not eliminate colonization and carriage of *B. pertussis*; did not clear infection faster than naïve animals; and readily transmitted pertussis to unvaccinated[44]. Baboons immunized with whole-cell vaccine cleared infection within three weeks; subjects vaccinated with acellular vaccine were colonized for up to six weeks post-infection[57]. How predictive the baboon model is of human pertussis is unclear. Despite the implications that acellular pertussis vaccines would not impact transmission, data from Sweden, with use of a monovalent PT vaccine documented initial induction of herd immunity. Whether the increasing burden in adolescents and adults in the most recent epidemics can be attributed to better awareness of disease among these age groups, improved reporting and surveillance, poor vaccine performance, and/or a real increase in disease remains unclear.

Our findings should be interpreted in light of several limitations. First, NIS records do not include vaccination status or history. To ascribe good or diminishing protection afforded by the introduction and increased usage of the acellular vaccine, we would need the vaccination history of those hospitalized with pertussis. Despite vaccination rates exceeding 90% for children 19-35 months of age from 1994 onward[47], we cannot definitively attribute rates of hospitalization to a vaccine failure or a failure to vaccinate. While our dataset is unique in that it includes all ages, including those only vaccinated with acellular vaccines, the significantly increasing rates observed in adolescents and children cannot be causally linked to vaccination with acellular vaccines. Because adolescents and adults do not typically present with the classic symptoms of the disease and because rates of vaccination are not consistently available for these age groups, any effort to assess the impact of the switch to acellular vaccine would require vaccination status.

Second, no laboratory confirmation data for pertussis diagnoses are available in NIS records. ICD9 codes have been used in other studies[41,47], but the validity of using ICD9 as a proxy for accurate disease diagnosis has not been established. Symptomology is not uniform in adults, adolescents, or vaccinated individuals, and varies greatly by age. Clinical diagnosis, in conjunction with culture or PCR, is most accurate when a case presents with classic symptoms. ICD-9 codes have low sensitivity, likely resulting in substantial underestimates. By using primary and secondary diagnoses conferred by NIS, we hoped to both minimize the number of mistakenly diagnosed adults and adolescents and capture the greatest number of true pertussis hospitalizations, but our dataset

likely missed cases or included other respiratory diseases, diminishing the true meaning of the observed differences in rates of hospitalizations across the early and late aP periods.

Although surveillance systems did not change over the study period, national attention to the resurgence of pertussis and increasing rates of VPDs may have prompted an increase in reporting, as well as an increase in doctor's visits, emergency department (ED) visits, and hospitalizations. As a result, the significant changes in our rates and rate differences could be artifactual, likely artificially biasing our findings away from the null.

To study the incidence of pertussis in age groups beyond infants, hospitalizations are an imperfect measurement as infants are arguably the easiest age group to diagnose, are at highest risk of severest disease, and comprise at least half of all pertussis hospitalizations. However, our data show an increasing number of older adults are being hospitalized for pertussis. If this is not artifactual, it calls attention to the need for greater emphasis on adult education and vaccination, education of primary care providers, and research into new vaccines and vaccination schedules to combat the extant waning immunity seen with all previous vaccines (in addition to immunity following natural infection) and increased carriage seen with acellular pertussis vaccines.

We present the first national study on the secular trends of pertussis in the acellular vaccine era among all ages in the U.S. Auger (2013) and Cortese (2008) used NIS data only to describe the burden of pertussis in infants; to our knowledge, no other national study has been undertaken for the years 1997-2011, the acellular era. We found increasing rates of hospitalization in every age group

except infants, although infants were most often hospitalized beyond nine days. Although adults do not typically have hospital stays as long as infants, the frequency of hospitalizations in older age groups has significant implications: (1) the natural history of pertussis disease results in a lengthy illness, leading to missed work; and (2) frequently missed diagnoses in older age groups leads to extended transmission. Previous studies have demonstrated that ~75% of pertussis cases in young infants resulted from exposure to asymptomatic or mildly symptomatic household members[56]. Although the mother was identified as the source of infection in 33% of the cases[56], it is evident that cocooning and adolescent vaccination are not enough to stem the tide. Reducing pertussis in young infants will likely require vaccination strategies targeting infants, adolescents, and adults in tandem[58]. It is equally important to evaluate the risk factors for pertussis hospitalizations among adults and other at-risk age groups, enabling earlier suspicion and detection of disease, as well as earlier initiation of effective treatment in these populations. Furthermore, special preventive measures can be taken implemented sooner, thereby minimizing the transmission of pertussis.

To accurately evaluate the impact of vaccination on disease, baseline rates of disease in those vaccinated with DTwP, DTaP, or a combination of DTwP/DTaP during the transition (1992-2001) must be established. Therefore, this study sought to describe the new epidemiology of pertussis hospitalization in infants, children, adolescents, and adults to better inform future studies on the impact of acellular vaccines and the changes to the vaccination schedule implemented in 1992, 1997, and 2006. Although we cannot attribute our findings explicitly to a

vaccine failure, we hope our findings will be used to contextualize any future studies aiming to assess the impact of the switch from whole-cell vaccine to acellular vaccine. Future research should also be directed towards determining the immunologic correlates of protection, improving diagnostic tests, evaluating and enhancing coverage and delivery methods for Tdap in adolescents and adults, and an investigation into the safety, effectiveness, and cost-benefit of repeated, decennial Tdap doses[31].

Tables and Figures

Table 1.1. Characteristics of Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS), 1997-2011: Age.

Year	Total ages (n%)	Infants (<1 year)[1]	1-4 years	5-10 years	11-17 years	18-22 years	23-49 years	older
1997	563.79 (100%)	524.84 (93.09%)	6.39 (1.13%)	0	18.14 (3.22%)	0	6.31 (1.12%)	8.11 (1.44%)
1998	409.07 (100%)	348.82 (85.27%)	19.65 (4.80%)	0	10.63 (2.60%)	0	29.97 (7.33%)	0
1999	676.71 (100%)	635.81 (93.96%)	26.58 (2.94%)	9.83 (1.45%)	4.49 (0.66%)	0	0	0
2000	346.71 (100%)	326.12 (94.06%)	10.21 (2.94%)	0	0	0	5.27 (1.52%)	5.11 (1.47%)
2001	384.62 (100%)	345.12 (89.73%)	10.24 (2.66%)	0	4.58 (1.19%)	0	19.82 (5.15%)	4.86 (1.26%)
2002	457.82 (100%)	380.23 (83.05%)	19.84 (4.33%)	13.65 (2.98%)	0	9.85 (2.15%)	24.23 (5.29%)	10.02 (2.19%)
2003	470.76 (100%)	405.44 (86.12%)	14.45 (3.07%)	8.67 (1.84%)	13.04 (2.77%)	0	19.80 (4.21%)	9.36 (1.99%)
2004	647.88 (100%)	594.24 (91.72%)	28.02 (4.32%)	5.21 (0.80%)	0	0	10.20 (1.57%)	10.21 (1.58%)
2005	1,281.41 (100%)	1,081.08 (84.37%)	81.12 (6.33%)	9.48 (0.74%)	15.06 (1.18%)	26.63 (2.08%)	33.64 (2.63%)	34.40 (2.68%)
2006	446.23 (100%)	326.80 (73.24%)	10.00 (2.24%)	10.08 (2.26%)	0	4.92 (1.10%)	43.33 (9.71%)	51.10 (11.45%)
2007	251.54 (100%)	217.40 (86.43%)	5.55 (2.21%)	0	9.86 (3.92%)	0	9.77 (3.88%)	8.96 (3.56%)
2008	375.78 (100%)	283.67 (75.49%)	19.42 (5.17%)	5.32 (1.42%)	9.44 (2.51%)	0	18.56 (4.94%)	39.37 (10.48%)
2009	472.82 (100%)	341.82 (72.29%)	25.52 (5.40%)	0	10.08 (2.13%)	0	25.78 (5.45%)	69.62 (14.72%)
2010	783.36 (100%)	625.24 (79.82%)	18.07 (2.31%)	6.08 (0.78%)	13.72 (1.75%)	9.90 (1.26%)	29.84 (3.81%)	80.51 (10.28%)
2011	290.23 (100%)	150.01 (51.69%)	13.69 (4.72%)	5.63 (1.94%)	0	23.26 (8.01%)	39.69 (13.68%)	57.95 (19.97%)
Total	7858.73	6586.64 (100.00%)	308.75 (100.00%)	73.95 (100.00%)	109.04 (100.00%)	74.56 (100.00%)	316.21 (100.00%)	389.58 (100.00%)

1. Hospitals in NIS did not uniformly report infant age in months. To produce uniform analyses in infant age groups and all age groups, we only included infants whose ages were reported in months. N denotes variables that used ages in months or years for infants (i.e., sex, race, income).

Table 1.2. Characteristics of Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS), 1997-2011: Sex.

Year	Sex[2]	Female
1997	N=563.79	310.74 (55.12%)
1998	N=465.68	268.06 (57.56%)
1999	N=710.92	410.54 (57.75%)
2000	N=432.61	246.30 (56.93%)
2001	N=429.58	186.58 (43.43%)
2002	N=620.97	330.62 (53.24%)
2003	N=565.85	236.98 (41.88%)
2004	N=780.63	427.83 (54.81%)
2005	N=1,769.84	892.38 (50.42%)
2006	N=517.78	301.31 (58.19%)
2007	N=347.09	178.37 (51.39%)
2008	N=422.79	188.88 (44.67%)
2009	N=553.82	272.80 (49.26%)
2010	N=1,003.16	524.76 (52.31%)
2011	N=345.97	231.95 (67.04%)
Total	N=9530.48	5008.1 (100.00%)

2. 9 patients were of unknown sex.

Table 1.3. Characteristics of Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS), 1997-2011: Race.

Year	Race[3]	White	Black	Hispanic	Asian or Pacific Islander	Native American	Other
1997	N=428.01	265.27 (61.98%)	63.69 (14.88%)	70.92 (16.57%)	0	0	28.13 (6.57%)
1998	N=293.99	142.50 (48.47%)	45.16 (15.36%)	78.86 (26.82%)	16.03 (5.45%)	0	11.44 (3.89%)
1999	N=611.61	271.68 (44.42%)	61.57 (10.07%)	204.32 (33.41%)	38.87 (6.36%)	0	35.17 (5.75%)
2000	N=353.6	173.87 (49.17%)	58.55 (16.56%)	80.54 (22.78%)	14.89 (4.21%)	0	25.75 (7.28%)
2001	N=346.58	130.13 (37.55%)	36.41 (10.51%)	156.57 (45.18%)	14.28 (4.12%)	0	9.19 (2.65%)
2002	N=482.51	178.09 (36.91%)	46.88 (9.72%)	213.33 (44.21%)	9.72 (2.01%)	0	34.49 (7.15%)
2003	N=468.22	222.00 (47.41%)	74.82 (15.98%)	152.45 (32.56%)	0	0	18.95 (4.05%)
2004	N=70.11	235.85 (41.37%)	81.23 (14.25)	229.46 (40.25%)	13.86 (2.43%)	0	9.71 (1.70%)
2005	N=1,312.59	390.18 (29.73%)	109.06 (8.31%)	730.17 (55.63%)	14.88 (1.13%)	4.44 (0.34%)	63.86 (4.87%)
2006	N=398.06	202.90 (50.97%)	39.08 (9.82%)	130.90 (32.88%)	8.60 (2.16%)	5.93 (1.49%)	10.65 (2.68%)
2007	N=221.21	100.53 (45.45%)	15.61 (7.06%)	84.18 (38.05%)	5.55 (2.51%)	5.08 (2.30%)	10.26 (4.64%)
2008	N=318.74	151.32 (47.47%)	52.87 (16.59%)	70.62 (22.16%)	0	0	43.93 (13.78%)
2009	N=443.25	239.75 (54.09%)	39.15 (8.83%)	118.81 (26.80%)	10.68 (2.41%)	19.25 (4.34%)	15.61 (3.52%)
2010	N=889.14	348.47 (39.19%)	88.82 (9.99%)	405.97 (45.66%)	24.63 (2.77%)	10.13 (1.14%)	11.12 (1.25%)
2011	N=288.44	162.55 (56.35%)	28.46 (9.87%)	68.70 (23.82%)	13.71 (4.75%)	10.39 (3.60%)	4.63 (1.61%)
Total	N=6926.06	3215.09 (100.00%)	841.36 (100.00%)	2795.80 (100.00%)	185.70 (100.00%)	55.22 (100.00%)	332.89 (100.00%)

3. 429 patients for pertussis were of unknown race.

Table 1.4. Characteristics of Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS), 1997-2011: Income.

Year	Income (1997)[4]	$1-$25,000	$25,001-$35,000	$35,001-$45,000	$45,000 and above
1997	N=480.41	170.25 (35.43%)	191.53 (39.87%)	61.40 (12.79%)	57.23 (11.91%)
	Income (1998-2002)	**$1-$24,999**	**$25,000-$34,999**	**$35,000-$44,999**	**$45,000 and above**
1998	N=501.86	60.07 (11.97%)	167.64 (33.40%)	156.98 (31.28%)	117.17 (23.35%)
1999	N=696.45	67.53 (9.70%)	166.84 (23.96%)	253.61 (36.41%)	208.47 (29.33%)
2000	N=426.52	51.25 (12.02%)	124.82 (29.26%)	115.53 (27.09%)	134.92 (31.63%)
2001	N=429.69	44.44 (10.34%)	125.86 (26.29%)	90.15 (20.98%)	169.24 (39.39%)
2002	N=440.69	62.20 (10.35%)	128.49 (21.39%)	177.33 (29.52%)	232.67 (38.73%)
	Income (2003-2011)[5]	**0-25th Percentile**	**26th -50th Percentile**	**51st-75th Percentile**	**76th-100th Percentile**
2003	N=556.20	167.89 (30.19%)	156.14 (28.07%)	124.05 (22.30%)	108.12 (19.44%)
2004	N=790.14	324.52 (41.07%)	179.37 (22.70%)	161.42 (20.43%)	124.83 (15.80%)
2005	N=1,739.82	664.12 (38.17%)	528.99 (30.4%)	293.57 (16.87%)	253.14 (14.55%)
2006	N=517.79	172.23 (33.26%)	111.94 (21.62%)	119.09 (23.00%)	114.53 (22.12%)
2007	N=324.91	143.51 (44.17%)	92.27 (28.40%)	54.04 (16.63%)	35.08 (10.8%)
2008	N=418.09	160.4 (38.36%)	115.61 (27.65%)	70.79 (16.93%)	71.29 (17.05%)
2009	N=548.15	221.48 (40.40%)	172.51 (31.47%)	97.61 (17.81%)	56.55 (10.32%)
2010	N=1,011.37	280.03 (27.69%)	237.29 (23.46%)	301.08 (29.77%)	192.97 (19.08%)
2011	N=341.05	61.42 (18.01%)	107.15 (31.42%)	90.70 (26.59%)	81.78 (23.98%)
Total	N=9222.91	2651.34 (100.00%)	2606.46 (100.00%)	2167.35 (100.00%)	1957.99 (100.00%)

4. 46 patients were of unknown income status.
5. For income quartiles reported in NIS for 2003-2011, see HCUP QRTL Ranges at http://www.hcup-us.ahrq.gov/db/vars/zipinc_qrtl/nisnote.jsp.

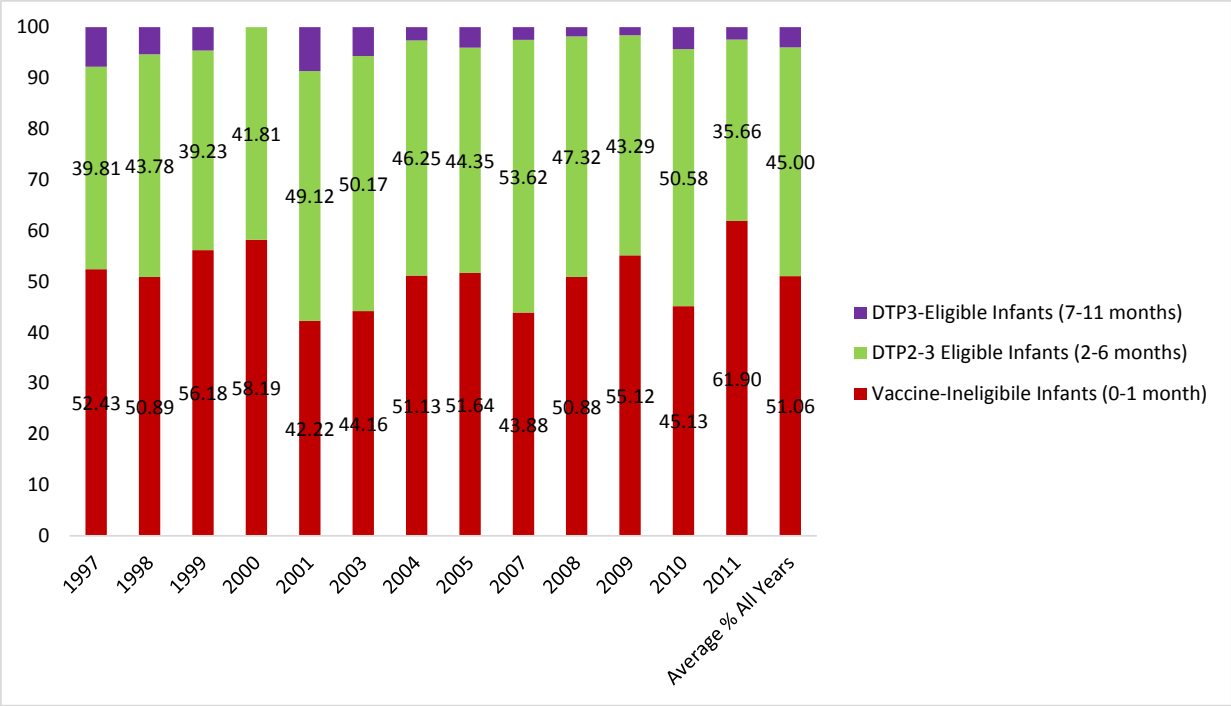

Figure 1. Average Annual Percentage of Hospitalizations for Pertussis by Infant Age Group (Months), 1997-2011. DTP refers to receipt of a pertussis-containing vaccine (whole-cell or acellular), DTP2-3 indicates eligibility for the receipt of at least two priming doses of pertussis containing vaccine, and DTP3 refers to eligibility for the receipt of three priming doses of pertussis vaccine. No hospitalizations were recorded in NIS for infants seven to 11 months of age.

Table 2.1. Rates of Pertussis Hospitalization per 1,000,000 Population in Infant Age Groups (Months), 1997-2011.

Year		Infant Age Groups		
		Vaccine-Ineligible Infants (0-1 months)	DTP2-3-Eligible Infants (2-6 months)	DTP3-Eligible Infants (7-11 months)
1997	Rate (95% CI)	441.01 (425.99, 456.03)	133.94 (128.11, 139.77)	26.10 (20.04, 32.17)
1998	Rate (95% CI)	283.8 (456.03, 275.33)	97.66 (94.60, 100.72)	11.87 (8.59, 15.15)
1999	Rate (95% CI)	565.00 (551.74, 578.27)	157.84 (151.21, 164.48)	18.45 (15.77, 21.14)
2000	Rate (95% CI)	299.13 (289.69, 308.56)	86.01 (82.73, 89.30)	0.00
2001	Rate (95% CI)	217.89 (203.77, 232.01)	101.40 (96.83, 105.98)	17.86 (15.28, 20.44)
2003	Rate (95% CI)	270.21 (261.77, 278.64)	122.78 (118.32, 127.24)	13.88 (10.23, 17.53)
2004	Rate (95% CI)	454.11 (443.47, 464.76)	164.32 (159.79, 168.85)	9.32 (6.71, 11.92)
2005	Rate (95% CI)	836.53 (815.17, 857.89)	287.39 (276.57, 298.21)	25.94 (22.46, 29.42)
2007	Rate (95% CI)	137.98 (130.19, 145.77)	67.44 (64.10, 70.78)	3.15 (0.50, 5.79)
2008	Rate (95% CI)	209.56 (199.00, 220.25)	77.95 (74.44, 81.45)	2.97 (0.39, 5.54)
2009	Rate (95% CI)	282.35 (272.93, 292.87)	88.71 (85.56, 91.85)	3.26 (0.52, 6.00)
2010	Rate (95% CI)	429.28 (412.35, 446.21)	192.43 (185.67, 199.18)	16.32 (13.02, 16.32)
2011	Rate (95% CI)	174.35 (165.86, 182.84)	40.18 (37.67, 42.68)	2.75 (-0.34, 5.85)

1. Pertussis cases reported in NIS did not exceed age 87 years during 1997-2011.

Table 2.2. Rates of Pertussis Hospitalization per 1,000,000 Population in All Age Groups, 1997-2011

Year		All Age Groups							
		Infants (<1 year)	1-4 years	5-10 years	11-17 years	18-22 years	23-49 years	50-87[1] years	
1997	Rate (95% CI)	140.19 (135.70, 144.68)	0.41 (-0.23, 1.05)	0.00	0.66 (-0.48, 1.81)	0.00	0.06 (-0.15, 0.26)	0.12 (0.04, 0.20)	
1998	Rate (95% CI)	108.02 (106.67, 109.37)	1.28 (0.99, 1.56)	0.00	0.38 (0.22, 0.55)	0.00	0.27 (0.23, 0.31)	0.00	
1999	Rate (95% CI)	176.64 (173.29, 179.99)	1.73 (1.44, 2.03)	0.40 (0.23, 0.57)	0.16 (0.01, 0.31)	0.00	0.00	0.00	
2000	Rate (95% CI)	108.27 (106.54, 109.98)	0.66 (0.37, 0.95)	0.00	0.00	0.00	0.05 (0.01, 0.09)	0.06 (0.01, 0.12)	
2001	Rate (95% CI)	97.21 (94.47, 99.95)	0.70 (0.38, 0.96)	0.00	0.16 (0.01, 0.30)	0.00	0.18 (0.14, 0.21)	0.06 (0.01, 0.12)	
2003	Rate (95% CI)	125.89 (123.95, 126.98)	0.93 (0.65, 1.20)	0.36 (0.12, 0.61)	0.44 (0.30, 0.58)	0.00	0.17 (0.17, 0.21)	0.11 (0.06, 0.16)	
2004	Rate (95% CI)	183.43 (181.12, 185.74)	1.78 (1.51, 2.05)	0.22 (0.03, 0.41)	0.00	0.00	0.09 (0.05, 0.13)	0.12 (0.07, 0.17)	
2005	Rate (95% CI)	393.32 (387.44, 399.19)	5.10 (4.64, 5.56)	0.47 (0.26, 0.69)	0.50 (0.35, 0.65)	1.27 (1.01, 1.52)	0.30 (0.26, 0.33)	0.39 (0.34, 0.44)	
2007	Rate (95% CI)	75.45 (73.96, 76.94)	0.35 (-0.11, 0.81)	0.00	0.33 (-1.12, 0.47)	0.00	0.09 (0.05, 0.12)	0.10 (0.05, 0.14)	
2008	Rate (95% CI)	80.01 (78.23, 81.80)	1.20 (0.94, 1.47)	0.22 (0.03, 0.41)	0.32 (0.17, 0.46)	0.00	0.16 (0.12, 0.21)	0.42 (0.37, 0.37)	
2009	Rate (95% CI)	104.46 (102.71, 106.22)	1.57 (1.26, 1.89)	0.00	0.34 (0.19, 0.49)	0.00	0.23 (0.19, 0.27)	0.72 (0.67, 0.76)	
2010	Rate (95% CI)	216.80 (212.65, 220.95)	1.11 (0.85, 1.37)	0.25 (0.08, 0.41)	0.47 (0.32, 0.61)	0.44 (0.25, 0.64)	0.26 (0.22, 0.30)	0.81 (0.76, 0.85)	
2011	Rate (95% CI)	51.45 (50.00, 52.90)	0.85 (0.59, 1.20)	0.23 (0.04, 0.42)	0.00	1.03 (0.85, 1.22)	0.35 (0.31, 0.39)	0.59 (0.53, 0.65)	

1. Pertussis cases reported in NIS did not exceed age 87 years during 1997-2011.

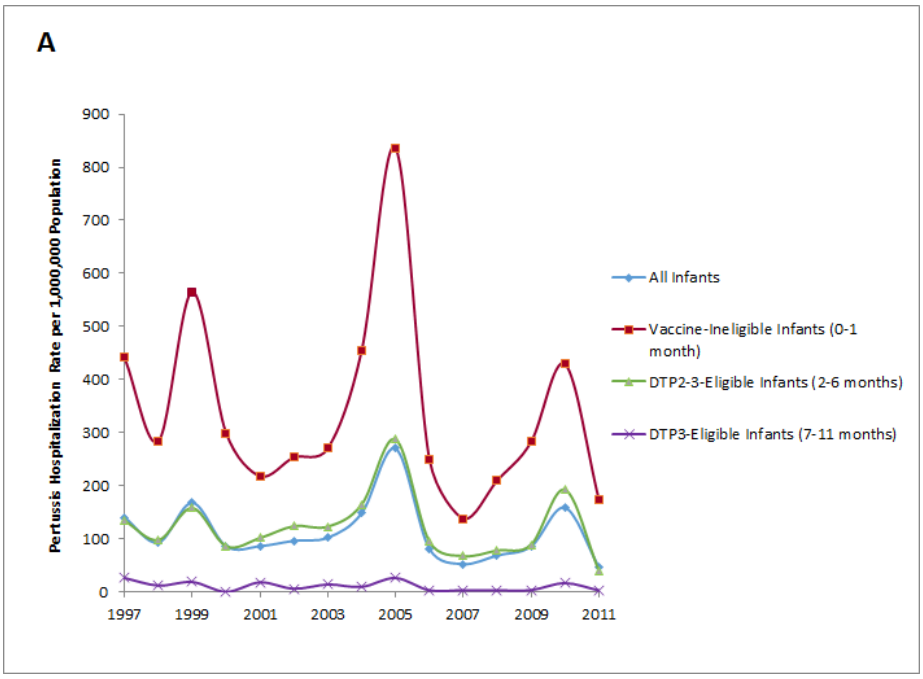

Figure 2a. Hospitalizations for Pertussis among Infant Age Groups (Months) During the Implementation of Acellular Vaccines, 1997-2011. Panel A shows the annual rates for pertussis hospitalizations in infants (age reported in months) from 1997 through 2011. DTP refers to receipt of a pertussis-containing vaccine (whole-cell or acellular), DTP2-3 indicates eligibility for the receipt of at least two priming doses of pertussis containing vaccine, and DTP3 refers to eligibility for the receipt of three priming doses of pertussis vaccine.

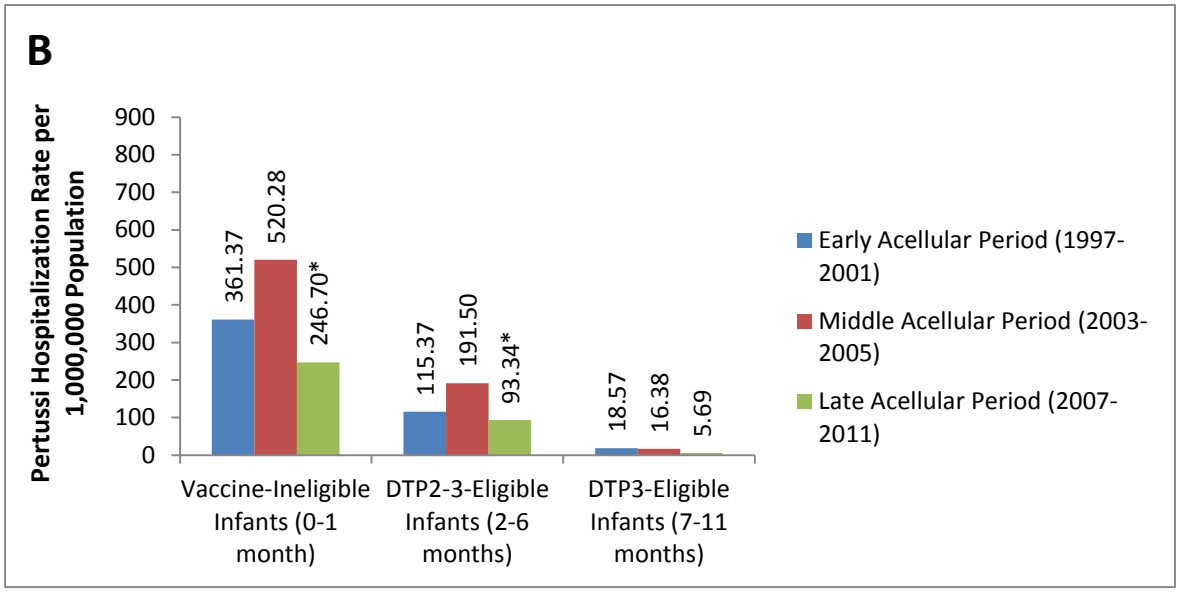

Figure 2b. Hospitalizations for Pertussis among Infant Age Groups (Months) During the Implementation of Acellular Vaccines, 1997-2011. Panel B shows the average annual rates of hospitalization for infant pertussis from the early pertussis vaccine (aP) period (1997-2001), the middle aP period (2003-2005), and the late aP period (2007-2011). Rates for 2002 and 2006 were excluded from analysis. Asterisks indicate $p<0.05$ for the decline in the hospitalization rate as compared with rates in the early aP period.

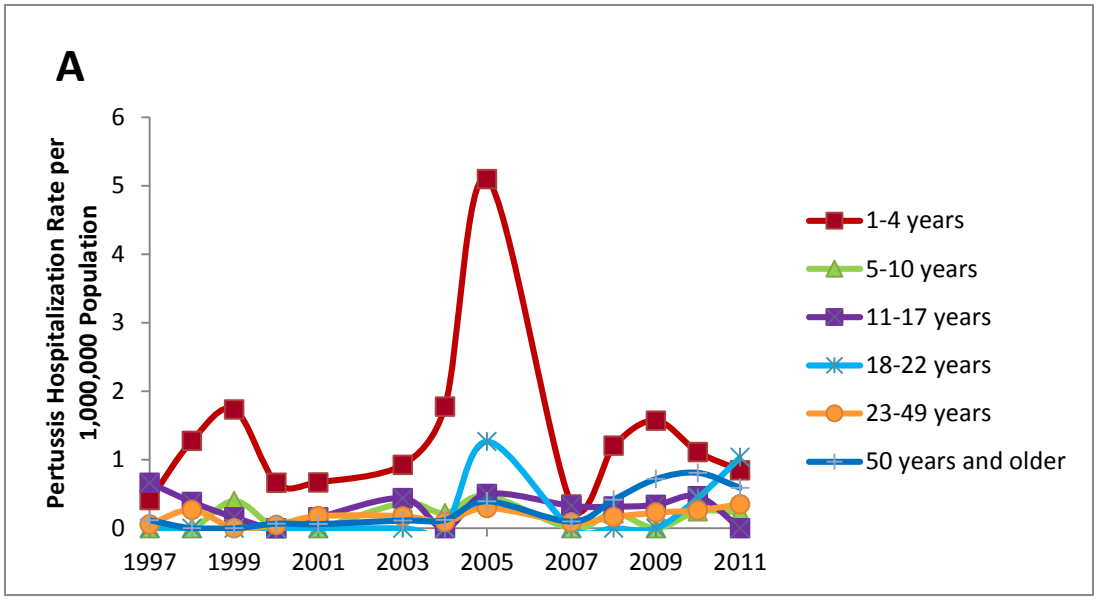

Figure 3a. Hospitalizations for Pertussis among All Non-Infant Age Groups (>1 Year) During the Implementation of Acellular Vaccines, 1997-2011. Panel A shows the annual rates for pertussis in all age groups (>1 year) from 1997 through 2011. No hospitalizations were recorded for patients 18-22 years of age during 1997-2001. Rates for 2002 and 2006 excluded from analysis.

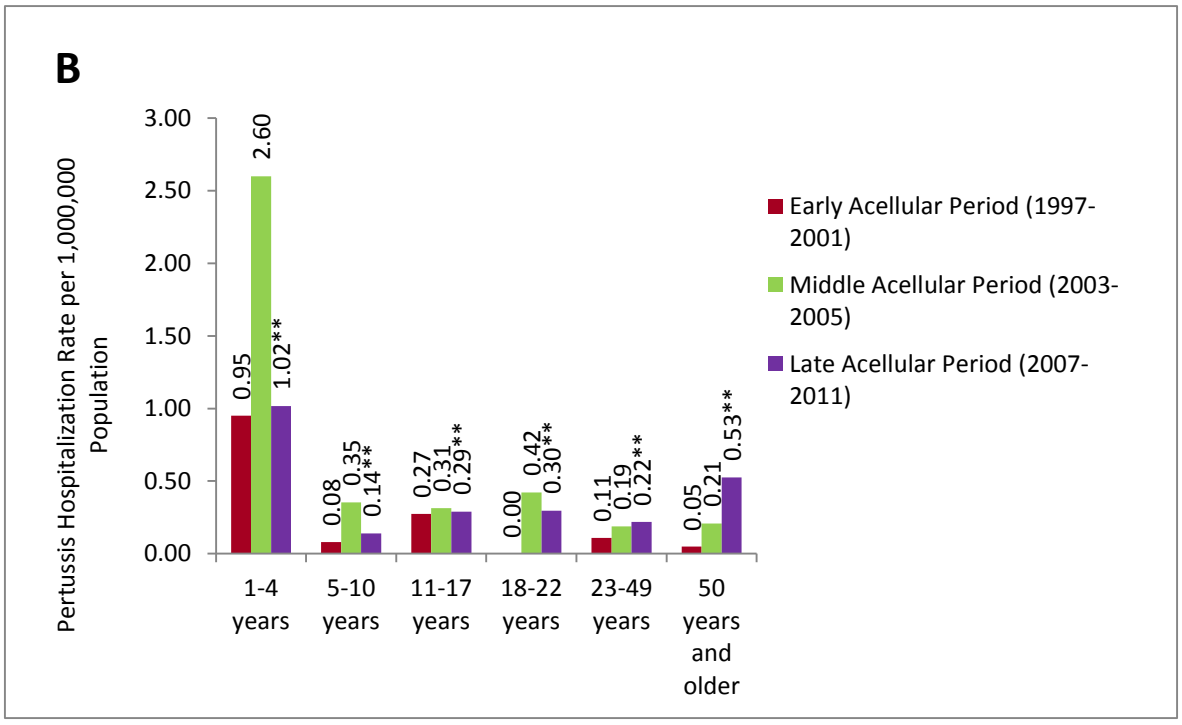

Figure 3b. Hospitalizations for Pertussis among All Non-Infant Age Groups (>1 Year) During the Implementation of Acellular Vaccines, 1997-2011. Panel B shows the average annual rates of hospitalization for pertussis from the early pertussis vaccine (aP) period (1997-2001), the middle aP period (2003-2005), and the late aP period (2007-2011). No hospitalizations were recorded for patients 18-22 years of age during 1997-2001. Rates for 2002 and 2006 excluded from analysis. Double asterisks indicate $p<0.05$ for the increase in the hospitalization rate as compared with rates in the early aP period.

Table 3. Differences in Rates of Hospitalizations for Pertussis in Infant Age Groups (Months) and All Age Groups During the Implementation of Acellular Pertussis Vaccines, 1997-2011.

	Early aP[4] (1997-2001)	Middle aP (2003-2005)	Late aP (2007-2011)	Difference in Hospitalization Rates per 1,000,000, Early aP to Late aP (95% CI)
Infant Age Groups				
Vaccine-Ineligible[1] Infants (0-1 month)	361.37	520.28	246.70	-114.66 (-151.88, -77.45)
DTP2-3-Eligible[2] Infants (2-6 months)	115.37	191.50	93.34	-22.03 (-43.00, -1.07)
DTP3-Eligible[3] Infants (7-11 months)	14.86	16.38	5.69	-9.17 (-16.46, 1.87)
All Age Groups				
Infants (<1 year)	126.07	234.21	105.64	-20.43 (-20.59, -20.27)
1-4 years	0.95	2.60	1.02	0.06 (0.06, 0.07)
5-10 years	0.08	0.35	0.14	0.06 (0.06, 0.06)
11-17 years	0.27	0.31	0.29	0.02 (0.02, 0.02)
18-22 years	0.00	0.42	0.30	0.30 (0.30, 0.30)
23-49 years	0.11	0.19	0.22	0.11 (0.11, 0.11)
50 years and older	0.05	0.21	0.53	0.48 (0.48, 0.48)

1. Vaccine-eligible infants refers to receipt of a pertussis-containing vaccine (DTP, whole-cell or acellular).
2. DTP2-3 indicates eligibility for the receipt of at least two priming doses of pertussis containing vaccine.
3. DTP3 refers to eligibility for the receipt of three priming doses of pertussis vaccine.
4. Acellular pertussis (vaccines period abbreviated aP.

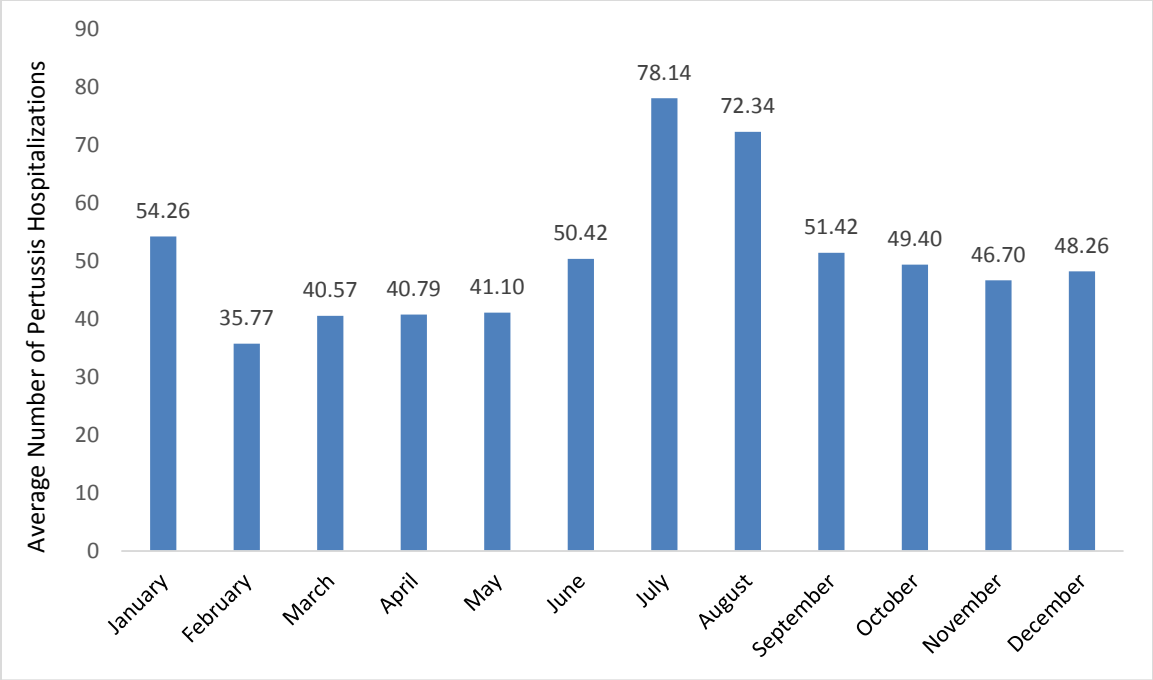

Figure 4. Average Frequency of Hospitalization for Pertussis by Calendar Month. Figure 4 shows the average number of hospitalizations by calendar month for all study years and all ages.

Table 4. Rates of Pertussis Cases Reported to the National Notifiable Disease Surveillance System (NNDSS) and Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS) for Infants (<1 Year) and Adults (>40 Years), 1997-2011.

	Hospitalizations in Infants (<1 Year) (NIS)	Hospitalizations in Older Adults (>50 Years) (NIS)	All Hospitalizations (NIS)	Overall Hospitalization Rate (per 1,000,000 population)	Infant Cases Reported (NNDSS)	Adult (>40 Years) Cases Reported (NNDSS)	Total Reported Cases (NNDSS)	National Incidence Overall (per 100,000 population)	Ratio of Reported Cases to Hospitalized Infant Cases	Ratio of All Reported Cases to All Hospitalized Cases
1997	525	8	564	2.08	1,978	587	6564	2.46	0.27	0.09
1998	349	0*	409	1.70	2,134	731	7405	2.74	0.16	0.06
1999	636	0*	677	2.57	2,168	754	7288	2.63	0.29	0.10
2000	326	5	347	1.54	2,091	758	7867	2.88	0.16	0.05
2001	345	5	385	1.51	1,886	811	7580	2.69	0.18	0.06
2002	380	10	458	2.12	2,352	1,131	9771	3.4	0.16	0.06
2003	405	9	471	1.95	2,217	1,463	11647	4.04	0.18	0.05
2004	594	10	648	2.73	3,233	3,664	25927	8.88	0.18	0.03
2005	1,081	34	1,281	6.02	3,967	4,449	25616	8.72	0.27	0.07
2006	327	51	446	2.27	2,029	3,331	15632	5.35	0.16	0.04
2007	217	9	252	1.15	1,720	1,969	10454	3.49	0.13	0.03
2008	284	39	376	1.55	2,180	1,691	13278	4.4	0.13	0.04
2009	342	70	473	1.57	3,089	2,093	16858	5.54	0.11	0.03
2010	625	81	783	3.29	4,120	3,806	27550	8.97	0.15	0.04
2011	188	58	290	1.11	2,772	2,851	18719	6.1	0.07	0.02

*No hospitalizations were recorded in NIS among adults 50 years of age or older.

Table 5.1. Reported Cases and Hospitalizations in Infants 0-1 Month and 2-3 Months, 1997-2011.

	Vaccine-Ineligible[1] Infants (0-1 Month) Hospitalized (NIS)	Vaccine-Ineligible Infants (0-1 Month) (NNDSS)	Percentage Reported Vaccine-Ineligible Infants 0-1 Month Hospitalized	DTP-Eligible[2] Infants 2-3 Months Hospitalized	DTP-Eligible Infants 2-3 Months (NNDSS)	Percentage Reported DTP-Eligible Infants (2-3 Months) Hospitalized
1997	275	803	34.27	172	643	26.77
1998	178	919	19.32	105	657	15.97
1999	357	986	36.23	213	682	31.26
2000	190	976	19.44	116	691	16.85
2001	146	837	17.41	126	647	19.47
2002	167	1,020	16.36	155	801	19.40
2003	179	989	18.10	165	795	20.78
2004	304	1,412	21.52	233	1,072	21.69
2005	165	1,773	9.32	127	1,388	9.13
2006	165	900	18.36	127	720	17.60
2007	95	779	12.25	96	575	16.72
2008	144	920	15.69	114	732	15.55
2009	188	1,278	14.74	107	1,022	10.50
2010	282	1,334	21.15	243	1,262	19.25
2011	116	1,215	9.56	16	644	2.48

1. Vaccine-eligible infants refers to receipt of a pertussis-containing vaccine (DTP, whole-cell or acellular).
2. DTP2-3 indicates eligibility for the receipt of at least two priming doses of pertussis containing vaccine.

Table 5.2. Reported Cases and Hospitalizations in Infants 4-6 Months and 7-11 Months, 1997-2011.

Table 5.2. Reported Cases and Hospitalizations in Infants 4-6 Months and 7-11 Months, 1997-2011.

	DTP-Eligible[3] Infants 4-6 Months Hospitalized (NIS)	DTP-Eligible Infants 4-6 Months (NNDSS)	Percentage DTP-Eligible Reported Infants (4-6 Months) Hospitalized	DTP3-Eligible[4] Infants (7-11 Months) Hospitalized (NIS)	DTP3-Eligible Infants (7-11 months) (NNDSS)	Percentage Reported DTP3-Eligible Infants Hospitalized
1997	37	355	10.36	41	185	22.01
1998	48	389	12.29	19	231	8.03
1999	36	331	10.95	29	206	14.16
2000	20	308	6.47	0	184	0.00
2001	44	273	15.95	30	152	19.64
2002	48	357	13.55	10	215	4.46
2003	38	352	10.86	23	170	13.52
2004	42	542	7.80	16	383	4.07
2005	30	674	4.45	5	421	1.14
2006	30	348	8.63	5	217	2.21
2007	20	260	7.86	5	189	2.88
2008	20	349	5.84	5	229	2.23
2009	41	562	7.24	5	344	1.58
2010	73	990	7.41	27	712	3.77
2011	13	530	2.51	5	407	1.13

3. DTP3 refers to eligibility for the receipt of three priming doses of pertussis vaccine.
4. Acellular pertussis (aP) vaccines period abbreviated aP.

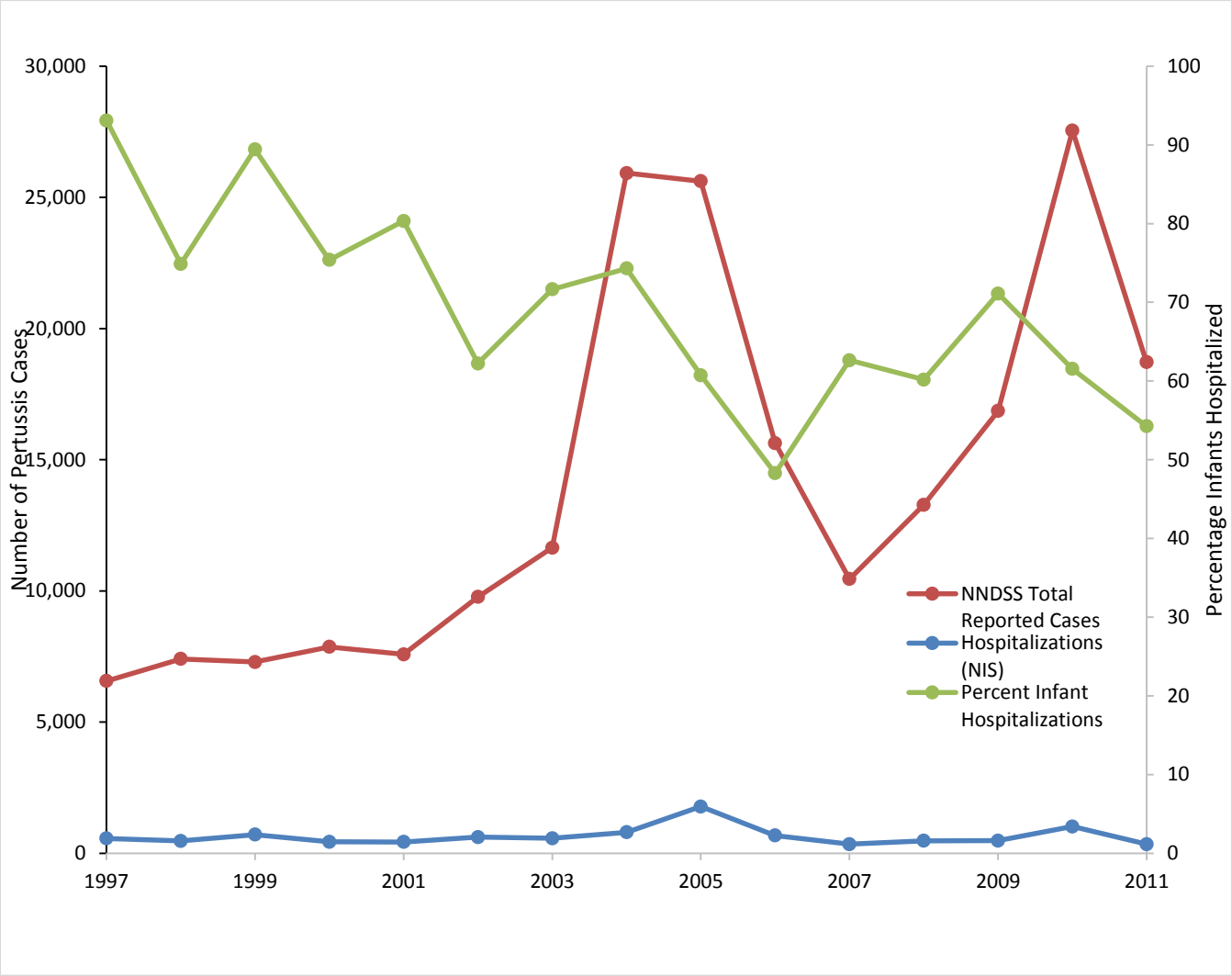

Figure 5. Pertussis Hospitalizations in the Nationwide Inpatient Sample (NIS) Compared with Pertussis Cases Reported to the National Notifiable Disease Surveillance System (NNDSS), with Percentage Infants Hospitalized in NIS, 1997-2011. Numbers and percentages for 2002 and 2006 are excluded.

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Public Health Implications

and

Future Directions

Public Health Implications and Future Directions: Strategies to Mitigate the Burden of Pertussis

Secondary ARs for pertussis approach 80%-90% for unimmunized household contacts[31]. Wendelboe et al determined that of the 47-60% of source cases identified in infant cases, parents accounted for 55% of source cases for pertussis[25]. Other studies have demonstrated that ~75% of pertussis cases in young infants resulted from exposure to asymptomatic or mildly symptomatic household members; the mother was identified as the source of infection in 33% of the cases[56]. In a separate study, Wendelboe et al estimated that casual community contacts are responsible for 20%-47% of pertussis transmission to infants[2]. Castagnini et al found that immunizing mothers postpartum alone is not an effective prevention strategy; all household and key contacts should also be immunized[59]. In 2011, the ACIP recommended all pregnant women who had not previously received Tdap and all anticipated close contacts of the infant should receive a dose of Tdap, if age-eligible for Tdap and never previously vaccinated[32], and in 2012, the ACIP recommended women receive Tdap with every pregnancy. Between 2011 and 2012, Tdap coverage among adolescents 13-17 years of age rose to 85% from 60.1% Td/Tdap coverage in 2006 and 72.3% coverage in 2007 (10.8% to 30.4% Tdap, respectively)[60]. Routine, increased Tdap vaccination is needed to prevent pertussis. Waning immunity, whether naturally or vaccine-induced, and the prevalence of asymptomatic or mild disease in which medical care is not felt to be needed should provide the impetus to consider new vaccination schedules.

The observed increase of *B. pertussis* circulation in adolescents and adults may be attributable to various factors, including increased awareness, suboptimal vaccines, waning immunity, and pathogen adaptation. Mothers and siblings play an important role in the transmission of pertussis to young infants, and effective selective vaccination of household members may help prevent the transmission of pertussis to newborns. Additionally, Edwards et al found active transplacental transport of pertussis antibody following Tdap vaccination during pregnancy[15,14]. To explore whether vaccination of mothers could be effective, de Greeff et al calculated infant infection probabilities for various cocooning vaccination strategies. de Greeff et al predicted vaccination of mothers would not only have a substantial, direct effect on reducing transmission from mother-to-infant, but also have an indirect effect by preventing the infection of the infant by the father-to-mother-to-infant and the others-to-mother-to-infant routes. de Greef et al found that the estimated risk of infection of the infant is approximately 40% if the mother is an infected primary case, and 10%–20% if it is the father or sibling. Based on these estimated transmission probabilities, vaccination of mothers appears to be a particularly promising means of preventing infection of the infant, potentially preventing half of the household infections in infants. The analyses in this study also suggest that in households with an infant, a mother and father, and a single sibling, the protective effect of vaccination of the sibling

[14] Edwards et al noted antibodies to PT and FHA readily crossed the placenta and were observed in infant sera in concentrations comparable to or higher than those in maternal sera, with a half-life of about six weeks. However, the caveat remains that low maternal pertussis antibody levels in the absence of adolescent-adult pertussis booster vaccination, and the rapid decay of maternally derived antibodies in infant sera, leave infants with little humoral antibody protection against pertussis [**15.** Edwards K. Immune Responses to Pertussis Vaccines and Disease. *JID*. April 2014 2014;209:S10-S15.].

is comparable to that of the mother. This is attributable to the fact that siblings are more likely than the mother to introduce the infection into the household (26% vs. 53%). Casual contacts beyond the household may also play a role in the transmission to young infants, and the effect of vaccinating household members may vary depending on the intensity and frequency of contact. In an earlier study, de Greeff et al could not determine the source of infection within the household for one-third of the infants, leaving a sizeable fraction of infant infections possibly caused by other contacts[24]. While de Greef implies that vaccination of potential contacts of infants would prevent transmission, the baboon model challenges that assumption, as neither carriage nor transmission were fully prevented after vaccination[44].

Lavine et al asserts that by vaccinating teenagers, we are further eroding the immunity extant in adults of child-bearing age, thus increasing circulation in this age group. To fully assess the likelihood of these possible outcomes, a better understanding of the causes of the changes in pertussis epidemiology over the past 15 years is necessary. Regarding the utility of a teenage booster vaccine, Lavine et al predicted that (1) it will reduce incidence in teenagers, but (2) it is unlikely to have a large effect on infant pertussis[46].

The mechanism of immunity to pertussis after natural infection or immunization is complex and not fully understood. Immunity has been shown to wane seven to 20 years after natural infection and five to 10 years after immunization with wP. Current aP elicit antibodies to the key antigens of pertussis, but the minimum serum antibody concentrations that protect against infection and disease have not yet been determined. Cell-mediated immunity

against pertussis is also elicited by immunization, but its role in protecting against infection and disease is unclear. Developing strategies to extend protection among adults will be essential for maximal disease control. Implementing Tdap boosters every 10 years in adults is unlikely to be sufficient given the poor compliance with 10-yearly tetanus-diphtheria boosters and the evidence of rapidly waning immunity within the first five years post-vaccination and a steady decline to pre-vaccination levels within 10 years post-vaccination[6,43]. Innovative approaches are needed, such as targeting adults about to start a family or possibly boosting women during pregnancy (a subject of ongoing studies). The cocooning strategy should be aimed at new families to create a protective environment for the most vulnerable infants where it is economically feasible[61].

To mitigate pertussis infections and outbreaks, emphasis should be placed on keeping coverage rates in infants, children, and adolescents high and increasing uptake in adults. Tdap should be administered during every pregnancy, with effort placed on immunizing all eligible close contacts (cocooning), as well. Health care providers should be encouraged to speak with every adult patient who has not yet received a dose of Tdap. Pediatricians should ensure all patients are up-to-date on all vaccines in accordance with ACIP recommendations. With the exception of contraindications delineated by the ACIP, alternate schedules should never be considered so as to minimize missed opportunities. All healthcare providers should be knowledgeable about the various presentations of pertussis disease in infants, children, adolescents, and adults. If pertussis is suspected, culture with PCR testing should not be delayed,

as both tests take time and the chemoprophylaxis needs to be started as early as possible to minimize the risk of transmission.

Likewise, public health departments, alongside healthcare providers, should communicate the evidence for vaccine efficacy and current recommendations to public. Although the seasonality of pertussis appears to follow the secular trends (i.e., increased number of cases during the summer months of an upsurge or resurgence year), public health departments and healthcare providers may be interested in ensuring they talk with patients about pertussis disease and vaccination prior to the periodic uptick during the months of July and August. Lastly, vigilant parents should bring children to healthcare providers, and healthcare providers should report any suspected cases to the local health department and utilize the SPSS to report pertussis cases to CDC.

Future research into the differences in carriage and transmission between wP and aP should be considered. The correlates of protection should also continue to be investigated, particularly through research into new vaccines. Typing, sensitivities, and other attributes of current circulating *B. pertussis* strains would contribute to our understanding of the changing epidemiology of this disease. If possible, studies on mild and asymptomatic cases would also shed light on transmission dynamics, potential differences across the different aP vaccines (or even including wP vaccines, if research could be conducted in countries still using wP with other comparable population factors, such as coverage). Future research should also evaluate the risk factors for pertussis hospitalizations among adults and other at-risk age groups, enabling earlier suspicion and detection of disease, as well as earlier initiation of effective

treatment in these populations. Furthermore, special preventive measures can be implemented sooner, thereby minimizing the transmission of pertussis, as well as the risk of hospitalization.

The Pertussis Work Group of the ACIP advised against a second Tdap booster dose. The Work Group had also decided against performing a cost-benefit analysis of replacing all decennial Td with Tdap because limited data suggested antibody titers returned to baseline shortly after vaccination[6]; therefore, vaccination could not be relied upon to maintain immunity for 10 years. Because immunity wanes, it is apparent that disease will continue to circulate in all strata of population, regardless of cocooning strategies.

Of all the future directions, research into and development of a long-lasting immunogenic, protective vaccine is needed to curb pertussis. The new vaccines must provide higher rates and a longer duration of protection. To do so, vaccine development must consider transmission and colonization, in addition to reactogenicity and the duration of protection. That immunity induced naturally or by vaccine wanes makes it difficult to determine whether long-term correlates of protection exist or whether repeated boosters are biologically viable solutions. If pertussis vaccines continually fail to confer life-long immunity, vaccine research should also support repeated boosters. Such a vaccine schedule change would be the closest action to repeated exposure that minimized disease in other age groups years ago[45].

Although pertussis is most devastating for young infants, it circulates in all ages. The amount of time and productivity lost to the morbidity--whether due to severe disease in infants or mild disease presenting as incessant coughing for weeks on

end in adolescents and adults--cannot and should not be overlooked. If a new vaccine that confers longer-lasting immunogenicity were developed or there were a way to institute vaccination policies in the work place, just as there are markedly successful policies in place for primary and secondary schools, quinquennial Tdap--and pertussis control--maybe attainable.

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Appendix 1: Review Board Letter of Exemption

EMORY UNIVERSITY

Institutional Review Board

February 19, 2014

Jerusha Barton
Rollins School of Public Health
Claudia Nance Rollins Building
2nd Floor
1518 Clifton Road, NE
Atlanta, GA 30322

RE: Determination: No IRB Review Required
eIRB#: IRB00072725
Title: *U.S. Hospitalizations for Pertussis During the Transition to Acellular Pertussis Vaccine, 1997-2011*
PI: Jerusha Barton

Dear Jerusha Barton:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of research with "human subjects" or "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will be using publicly available de-identified data to examine rates in U.S. pertussis hospitalizations.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Scott S. Katz, MS
Analyst Assistant

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu
An equal opportunity, affirmative action university

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