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Unexpectedly Limited Durability of Immunity Following Acellular Pertussis Vaccination in Pre-Adolescents in a North American Outbreak

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Summary:
This first detailed analysis of a recent North American pertussis outbreak found widespread disease among fully vaccinated older children. Starting approximately three years after prior vaccine dose, attack rates markedly increased, suggesting inadequate protection or durability from the acellular vaccine.

Abstract:

Background: Despite widespread childhood vaccination against *Bordetella pertussis*, disease remains prevalent. It has been suggested that acellular vaccine may be less effective than previously believed. During a large outbreak, we examined the incidence of pertussis and effectiveness of vaccination in a well-vaccinated, well-defined community.

Methods: Our center provides care to 135,000 patients, 40% of the population of Marin County. One-hundred-seventy-one patients with a positive Polymerase Chain Reaction (PCR) test for *B. pertussis* from March 1 to October 31, 2010 were identified. Electronic medical records were reviewed for demographics and vaccination status.

Results: We identified 171 cases of clinical pertussis; 132 in pediatric patients. There was a notable increase in cases in patients aged 8-12. The rate of testing peaked in infants, but remained relatively constant until age 12. The rate of positive tests was low for ages zero to six, and increased in preadolescents, peaking at age 12. Vaccination rates of PCR positive preadolescents were approximately equal to that of controls. Vaccine Effectiveness was 41%, 24%, 79%, for ages 2-7, 8-12, 13-18, respectively.

Conclusions: Our data suggests that the current schedule of acellular pertussis vaccine doses is insufficient to prevent outbreaks of pertussis. We noted a markedly increased rate of disease from age 8 through 12, proportionate to the interval since the last scheduled vaccine. Stable rates of testing ruled out selection bias. The possibility of earlier or more numerous booster doses of acellular pertussis vaccine either as part of routine immunization or for outbreak control should be entertained.

Conflicts of Interest

Maxwell A. Witt: I have no conflict of interest.

Paul H. Katz, MD, MPH: I have no conflict of interest.

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Financial Disclosure

No Conflicts

Introduction

Whole-Cell pertussis vaccination has been shown to be highly effective at reducing rates of pertussis in young children. [1] The acellular pertussis vaccines were introduced in the US in 1991. Although comparably efficacious, adverse reactions from acellular pertussis vaccination are markedly reduced, when contrasted with whole-cell vaccine. [2] For this reason, the acellular vaccine is now the sole pertussis vaccine utilized in the United States, despite its higher cost. Efficacy for the acellular pertussis vaccine has been reported in the 84-85 percent range for children and 92 percent for adolescents and adults. [2,3] More recently, there have been suggestions that the efficacy of the acellular vaccine may not be as robust as reported in these initial studies. [4,5,6]. These vaccines have not been extensively studied for clinical efficacy in North America, and no studies exist for long-term immunogenicity. Additionally, it is well-known that immunity in response to natural infection is limited in duration, and persists for four to twenty years. [7] Despite this lack of data on durability of acellular pertussis vaccine, recommendations were made by the Centers for Disease Control (CDC) Advisory Committee on Immunization Practices (ACIP) to follow the existing schedule for the more effective, whole-cell vaccine (2, 4, 6, and 15-18 months, 4-6 years of age). [8,9]

In 2006, the ACIP broadened the recommendation to include vaccination of adolescents for pertussis. This was enabled by the 2005 licensure of acellular pertussis vaccines (Tdap) for adolescents and adults. The new guidelines recommend a Tdap booster at age 10-12 to address the limited durability of pertussis vaccine. A one-time booster for adults was recommended to address the persistent reservoir in adolescents and adults. [10,11]

During 2010, California experienced the largest epidemic of pertussis in 53 years. Statewide, the incidence was 20 cases per 100,000 people. [12] This is the highest rate in

California since 1958, when there was an incidence of 26 cases per 100,000. [12] Marin County had the second highest incidence in the state, with 136.48 cases per 100,000 people. [12] San Rafael Kaiser Permanente Medical Center was at the epicenter of this epidemic. In reviewing cases confirmed at our medical center during this outbreak, we noted effective protection of younger children. Our unvaccinated and under-vaccinated population did not appear to contribute significantly to the increased rate of clinical pertussis. Surprisingly, the highest incidence of disease was among previously vaccinated children in the eight to twelve year age group. We sought to examine the factors that resulted in this peak.

Methods

Approval for the study was obtained from the Institutional Review Board of the Kaiser Foundation Research Institute (Oakland, California). Kaiser Permanente Medical Center in San Rafael, California is the primary source of care for 135,000 people, the majority of whom reside in Marin County, California. This medical center consists of a core hospital with 120 inpatient beds and six associated clinics. Approximately forty percent of the total population of 252,409 in Marin County receives their care solely at this medical center. [13,14] Kaiser Permanente is an integrated healthcare system with its own laboratories, hospitals and clinics, with an electronic medical record. This structure permits review of all laboratory results, hospitalizations and outpatient visits in Northern California.

Nasopharyngeal specimens for pertussis testing were obtained utilizing a BD BBL Cultureswab™ with liquid Stuart media (BD Catalog#: 220133, Becton, Dickinson and Company, Franklin Lakes, New Jersey). Laboratory testing is centralized with Real-Time Polymerase Chain Reaction (PCR) (Cepheid Corporation, Sunnyvale, California) as the basis of

all pertussis testing, with required concomitant testing for both *Bordetella pertussis* and *Bordetella parapertussis,* performed utilizing the Cepheid GeneXpert® platform, which amplifies IS481 or IS1001 for detection of *B. pertussis* or *B. parapertussis*, respectively.

All patient data was retrieved from the electronic medical record, including those of case patients and the population as a whole.

At the start of the epidemic, the Department of Pediatrics made a practice agreement that any patient between 0 and 18 years of age with one or more week of unexplained cough illness would receive a PCR test for pertussis. Any intimate contact of a known case of pertussis with cough symptoms would also be tested for pertussis. The Department is a part of an integrated health system, and clinical guidelines and practice advisories are generally followed in a rigorous manner. No additional epidemiologic information was recorded.

All positive PCR results for *B. pertussis* from this Medical Center between March 1 and October 31, 2010 were identified and patient records were reviewed for age, vaccination status, vaccination refusal, and date of last vaccination at the time of clinical pertussis presentation. Vaccination status was categorized using the CDC vaccination guidelines. [8,9,10] Patients who had completed the full number of CDC recommended vaccine doses for their age at the time of clinical presentation were identified as current. If there were prior records of vaccinations, but fewer than the recommended number, the patient was identified as under-vaccinated. If there were no records of vaccination, their charts were reviewed further to determine if vaccination was received elsewhere, or if a Personal Belief Exemption or Permanent Medical Exclusion was identified.

The manufacturers of vaccines administered prior to 2002 could not be retrieved. Vaccines utilized since 2002 included: Infanrix®, Pediarix™, Boostrix™ (GlaxoSmithKline, Research Triangle Park, NC) and Daptacel™ , Pentacel™ , and Adacel™ (Sanofi Pasteur, Bridgewater, NJ).

Data was entered into a Microsoft® Excel® 2007 datasheet for processing (Microsoft Corporation, Redmond, Washington). Information was then anonymised.

Statistical analysis was completed utilizing R: A Language and Environment for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria, 2011) with accessory packages Deducer (Ian Fellows, 2011) and JGR - Java Gui for R (Markus Helbig, Simon Urbanek, Ian Fellows, 2011).

Effectiveness was calculated using the "Screening Method." [15] For the purposes of this calculation, cases were divided into ages 2-7, 8-12, 13-18, and a total of 2-18. Cases less than two years of age were excluded, as they would not be able to be fully immunized. We defined the age groups to permit contrasting high and low pertussis incidence age groups. We also selected the 13-18 year age group to reflect the recommended vaccine dose at ages 10-12.

$$VE = 1 - \frac{PCV}{1-PCV} * \frac{1-PPV}{PPV}$$, where:

PCV= Proportion of Cases Vaccinated

PPV= Proportion of Population Vaccinated

VE= Vaccine Effectiveness

Selection and Description of Participants

All persons with a positive PCR test for *Bordetella pertussis* between March 1 and October 31, 2010 were entered into the study.

Results

We identified 171 individuals with positive PCR tests for *Bordetella pertussis*; 48% male, 52% female. There were no fatalities. Ages ranged from infancy to 90 years. Vaccine histories were generally unavailable on those over 18, and these patients were therefore excluded. Of the 132 (77.2%) patients 18 years of age or under at time of illness, 81% were fully vaccinated, 11% under-vaccinated, and 8% never vaccinated. Of the 103 (60.2%) individuals 12 years of age or younger, 85% were fully vaccinated, 7% under-vaccinated, and 8% never vaccinated.

There were 22,798 patients eighteen years of age or younger in our patient population. In this group, vaccination rates were excellent, ranging from 88-94 percent for a given age. Among confirmed cases of pertussis, vaccination rates were comparable in the 2-7 and 8-12 age groups, when contrasted with age-matched controls. Among the 58 cases of pertussis in children aged 10-12, 55 (95%) had received five or more doses of pertussis vaccination. Eight of these 58 (14%) children had received their sixth booster-dose prior to onset of disease. In the 13-18 year age group and in the entire cohort of those 2-18 years of age, there was a highly significant increase in cases in unvaccinated children ($p = 0.009$ and 0.01 respectively). See table 1.

Rates of laboratory confirmed clinical pertussis among fully vaccinated children showed a broad increase from ages 8 through 13 years. Calculated annualized attack rates for specific age groups ranged from zero to 3666 cases per 100,000 person-years, for the two and ten year age

groups respectively, among vaccinated children. This disparity was highly significant (p=0.002, one sample t-test). See figure 1. Non-annualized, age-specific attack rates among vaccinated children were from 0- 1,981 per 100,000 population for the two and ten year age groups, respectively.

During the study period, 1,358 persons eighteen years of age or younger were tested for pertussis. The rate of laboratory testing for pertussis and the attack rate of clinical pertussis, by age, are shown in Figure 1. Testing rates were highest in infants but decreased after age twelve.

PCR positivity rates for pertussis are shown by age in figure 2. The percent positive was two percent for those under six, and maximal at age thirteen, with 36 percent of tests being positive (95% Confidence Interval: 24%-38%).

Vaccine Effectiveness, utilizing the Screening Method, was determined to be 41%, 24%, 79%, 51% for ages 2-7, 8-12, 13-18, and 2-18, respectively. [15] See table 1.

Discussion

Pertussis is one of the most prevalent vaccine-preventable diseases in the developed world. [16] Despite widespread childhood vaccination and a greatly reduced incidence, there are still many cases, with outbreaks peaking every 2-5 years. [17] The incidence in the United States has been estimated to be between 800,000 and 3.3 million cases per year. [17] The primary reason for these large numbers is believed to be a persistent reservoir of disease in adolescents and adults, which the revised CDC vaccine schedule sought to address. [10,11] We found a lower than expected protection from disease by the primary five-dose series of acellular pertussis

vaccine, suggesting that pertussis vaccine, administered according to the current guidelines, may not adequately protect the pre- and early- adolescent population.

Surprisingly, in the 2-7 and 8-12 age groups, there was no significant difference in attack rates between fully vaccinated and under- and un-vaccinated children; however the attack rate in the 2-7 age group, vaccinated or not, was significantly lower than the 8-12 age group (P =0.002). The 13-18 age group and the aggregate of all age groups did demonstrate a significantly increased risk for pertussis in the under- and un-vaccinated group, possibly demonstrating the enhanced protection of the booster vaccination dose at age twelve. There were two overnight admissions for observation, but no other hospitalizations among our cohort, suggesting a mitigating effect of the current vaccine.

We noted a marked disparity between the lower attack rates of children less than 8 and children over 12 and the high attack rates for those children 8-12 years old. This was highly significant (P =0.002). The sharp increase in the number of cases at age 8 appears to correlate to the interval from the end of the pre-school vaccine series. There is a decrease in the number of cases occurring at age 13 onward, corresponding to the booster dose given from ages 10-12. See figure 1. This is confirmed by examination of the mean interval from last vaccination, grouped by age, among our laboratory confirmed clinical cases. See figure 3. These findings may be explained by the patterns of pertussis vaccination, which reflect ACIP recommendations as well as statutory requirements in California. [8, 9,18]

Our data suggests that there is an increasingly susceptible population as the interval from last scheduled vaccination increases. This would lead to a reduced level of herd immunity within an age group, resulting in greater risk of acquisition of disease by vaccinated, yet unprotected

individuals. [19] It also brings into question the durability of the immunity provided by the acellular pertussis vaccine.

Vaccine Effectiveness (VE) calculations were performed using the Screening Method, which utilizes an odds ratio of full vaccination between cases and the general population to determine VE. [15] In this study, we were able to accurately determine the population vaccination rate, and identify all cases within the patient population and their vaccination status. Our Vaccine Effectiveness data confirms markedly lower than expected protection afforded by the pre-school series of acellular pertussis vaccinations in the 8-12 year age group.

It is important to note that our calculations of vaccine effectiveness were limited by the number of cases. Vaccine Effectiveness, a useful metric for estimating vaccine performance, is not a substitute for traditional, placebo-controlled trials to determine true Vaccine Efficacy, and the values are not interchangeable. [6,15] However, Vaccine Effectiveness can also be more useful than Vaccine Efficacy, when it comes to evaluating the success of a vaccine. Vaccine Effectiveness quantifies, easily and on a large scale, the performance of the vaccine in a real world environment.

It has been suggested that acellular pertussis vaccine may have reduced efficacy when contrasted with whole-cell pertussis vaccine. [4,9] It has been suggested that the acellular pertussis vaccine may have a reduced durability of immunity, and no vaccine trial has examined immunity from these vaccines beyond 22 months. [2] The recommendation for booster vaccination between ages ten and twelve may be too late to provide protection to this group.

Fortunately, the aggressive vaccination schedule for younger children appears to effectively protect those less than five years of age, except infants less than six months of age,

who remain vulnerable. High efficacy in the first year or two after primary vaccination is well documented. [2, 20, 21, 22] Transmission from parents has been recognized to be a high risk to infants, but older siblings may introduce the disease into a household, and present a direct risk to the infants as well. [23,24] This natural demography underscores the importance of our findings. We confirmed vaccine failures and probable decreased herd immunity among this group of pre-teens.

A final consideration involves the difference in vaccine performance between endemic pertussis and an outbreak situation. At-risk exposures are logarithmically increased during an outbreak, markedly enhancing the risk of acquisition of disease. [19]

Most studies of clinical pertussis have been based on passive reporting to health departments, lack defined population denominators, and have potential selection bias in testing rates or methods. Our study examines a stable, defined population having well-recorded vaccination histories, a well-defined rate of disease and uniformly documented laboratory testing. The Practice Agreement to test all prolonged cough illness helps eliminate bias towards enhanced reporting of cases with complications or over-reporting when all cough illness is sampled. The high percentage of persons in our community who obtain their care solely from our Medical Center provides an ideal opportunity to examine a population. Reporting bias in our data is virtually eliminated by the structurally complete capture of patient data. If there were ascertainment bias, the rate of testing would suggest dampening, not accentuation, of the age-based differences in rates of disease in our population. However, since the rate of testing is relatively flat by age, ascertainment bias is likely minimal. The documentation of prior vaccinations permitted accurate ascertainment of vaccination status.

There were limitations to our study. It was retrospective. Many clinicians believe that pertussis vaccination is highly effective, and may not suspect or test for pertussis in vaccinated children. [25] Pertussis testing in our study was not part of a protocol, although the Practice Agreement sought to reduce effects of variance in clinician practices. Previous investigations have shown that that vaccination results in a shorter, less severe illness, which may have contributed to minor cases being missed, and the incidence of pertussis underestimated. [26]

PCR testing was not confirmed by concommitant bacterial culture in our study; however PCR testing has generally been demonstrated to be highly specific. [27] Difficulty discriminating certain strains of *B. holmesii* or *B. bronchiseptica* from *B. pertussis* and *B. parapertussis* has been recognized. [28] *B. holmesii* was unlikely to have been present in our population as there were no specimens positive for both *B. pertussis* and *B. parapertussis*; a finding which should have been expected with *B. holmesii* infection due to amplification of both IS481 and IS 1001 in *B. holmesii*. [28, 29] Among cases reported to the California Department of Public Health, there were no isolates of either *B. holmesii* or *B. bronchiseptica,* and *B. bronchiseptica* rarely causes disease in immune competent individuals. [29, 30]

It is of note that despite the high level of vaccine coverage in our population, relative to the United States, 11% of our children are not fully vaccinated, and do not reach levels of protection required for herd immunity. [31] When contrasted to with rates of vaccination in European countries, our relatively high rate falls short. [32]

This is the first review of clinical pertussis in a large North American outbreak since the acellular vaccine was introduced. It examined the frequency of disease in a closed, well-

monitored population. We confirmed an increasing rate of vaccine failure with an increasing interval from the primary vaccine series.

In the case of the recent California epidemic, it appears that the effectiveness of the current vaccine schedule, when paired with the imperfect vaccination rate, may be insufficient to prevent an epidemic. Earlier vaccine booster doses may be required to provide adequate herd immunity, absent an increase in vaccination rate, efficacy, or durability. Earlier booster doses could prevent immunity from waning, and address disease in the 8-12 age group. Recent recommendations from the ACIP have supported the safety of administration of Tdap to individuals as young as seven, regardless of prior vaccination histories. [33] Research into natural pertussis immunity and more durable and effective vaccines should be expanded. An earlier booster dose and targeted vaccine programs are strategies that should be entertained and could be vital to controlling widespread outbreaks of disease. Targeted vaccine programs in adolescence, rather than additional boosters defined by age, might be an alternative vaccination strategy that would address parental concerns regarding additional scheduled vaccine doses and increased cost. Further research is needed to evaluate the long-term efficacy of the acellular pertussis vaccine, as well as the potential benefits or adverse effects of introducing an earlier booster dose.

Notes:

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Potential conflicts of interest: All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Figure Legends

Figure 1. Pertussis attack rate and PCR Testing rate per 100,000 person-years

Figure 2. *B. pertussis* testing rate and test positivity by age.

Figure 3. Mean interval between clinical presentation and last acellular pertussis vaccination in fully vaccinated persons

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Table 1. Vaccine Effectiveness by age.

PPV= Proportion of the Population fully Vaccinated, PCV= Proportion of Cases fully Vaccinated

Age Group (Years)	PPV* (%)	PCV* (%)	Effectiveness (%)	Effectiveness: 95% Confidence Intervals (%)
2-7	91	86	41	21-54
8-12	89	86	24	0-40
13-18	89	62	79	73-84
2-18	90	81	51	44-58

* PPV= Proportion of the Population fully Vaccinated, PCV= Proportion of Cases fully Vaccinated

Table 2. Attack Rate in Vaccinated and Under and Unvaccinated Patients

Age Group (Years)	Attack Rate in Vaccinated Persons (Per 100,000 person-years)	Attack Rate in Under & Unvaccinated Persons (Per 100,000 person-years)	P-Value (T-Test)
2-7	359	606	0.57
8-12	2453	3211	0.43
13-18	452	2189	0.009
2-18	1011	2073	0.01

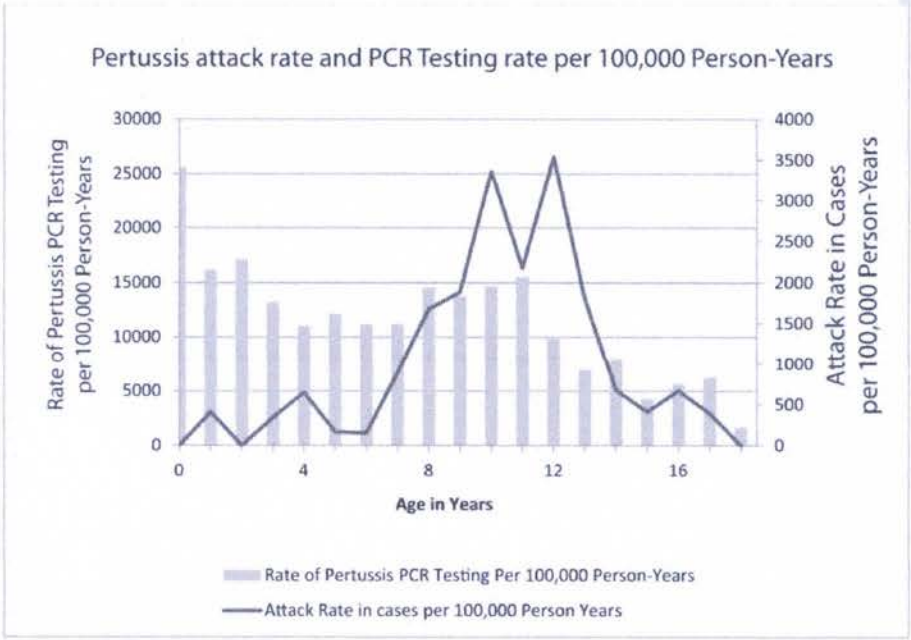

Figure 1: Pertussis attack rate and PCR Testing rate per 100,000 Person-Years

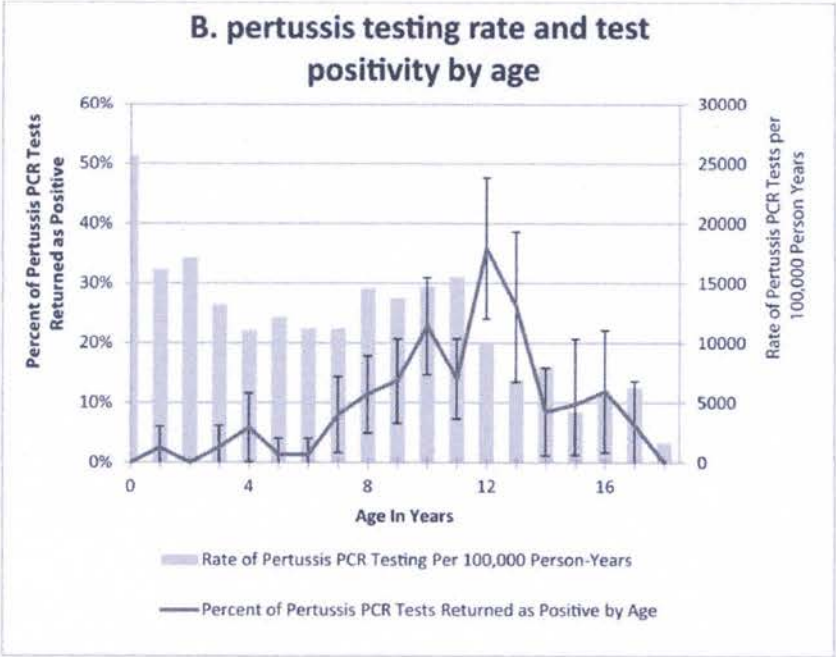

Figure 2. *B. pertussis* testing rate and test positivity by age.

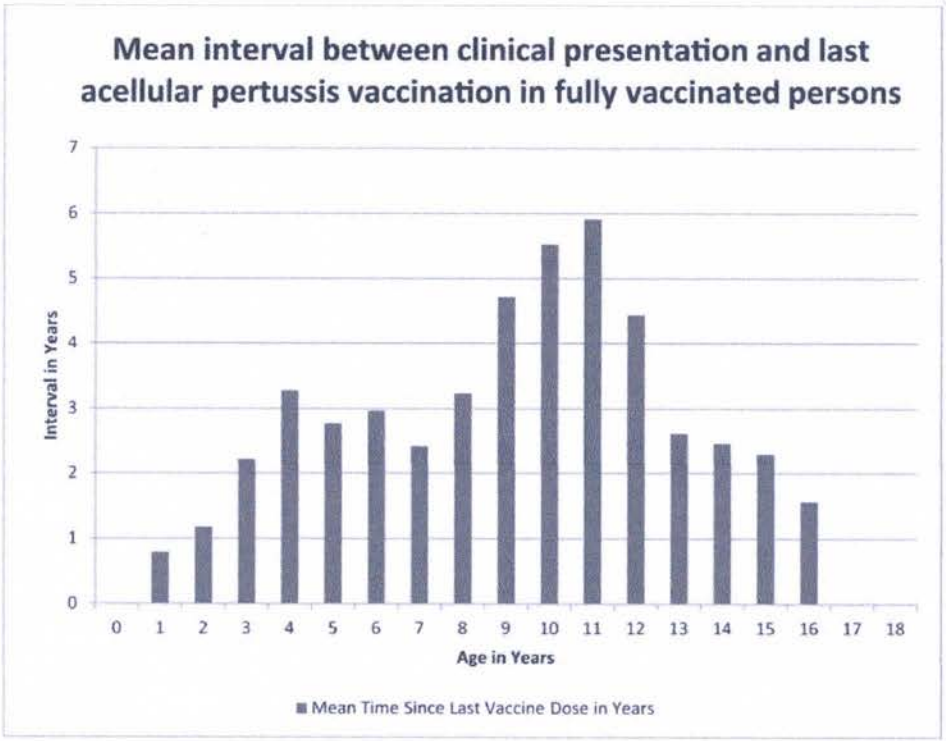

Figure 3. Mean interval between clinical presentation and last acellular pertussis vaccination among fully vaccinated persons