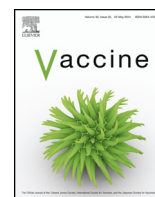


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Estimates of pertussis vaccine effectiveness in United States air force pediatric dependents



Greg Wolff^{a,b,*}, Michael Bell^a, James Escobar^a, Stefani Ruiz^{a,b}

^a United States Air Force School of Aerospace Medicine, 2510 5th Street, Bldg 840, Wright-Patterson AFB, OH 45433, United States

^b Solutions Through Innovative Technologies, 3152 Presidential Drive, Fairborn, OH 45324, United States

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ABSTRACT

Background: Pertussis vaccination compliance is critical for reduction in the prevalence of disease; however, the current acellular pertussis vaccine may not provide sufficient protection from infection. This study examined acellular pertussis vaccine effectiveness (VE) for Air Force dependents less than 12 years of age.

Methods: We conducted a case-control study among Air Force pediatric dependents from 2011 to 2013, comparing cases with positive pertussis test results to controls who received the same lab tests with a negative result. Our study population was categorized by age group and vaccination status based on the Centers for Disease Control and Prevention recommended pertussis vaccination schedule. VE was calculated with respect to vaccination status and pertussis lab results.

Results: We compared 27 pertussis laboratory positive cases with 974 pertussis laboratory negative controls, 2 months to <12 years old. Comparing completely vaccinated to non-vaccinated patients, the overall VE was 78.3% (95% confidence interval (CI): 48.6, 90.8; $p < 0.001$). VE was highest among those 15 months to <6 years old: 97.6% (95% CI: 78.5, 99.7; $p < 0.001$). Children 6 to <12 years old had the lowest VE: 48.5% (95% CI: -74.0, 84.7; $p = 0.28$). Comparing partially vaccinated patients to nonvaccinated patients yielded 64.2% (95% CI: -7.2, 88.1; $p = 0.06$) overall VE.

Conclusions: Acellular pertussis vaccination was effective at preventing laboratory confirmed pertussis among our Air Force pediatric dependent population, with highest protection among completely vaccinated, young children. Older children received the lowest amount of protection. Partial vaccination had near significant protection. Our overall calculated pertussis VE corroborates other pertussis VE studies looking at similar age groups.

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1. Introduction

Prior to the development of pertussis vaccination, the highest incidence of reported cases in the United States (U.S.) occurred in 1934, with 260,000 cases (205.7 cases per 100,000 people) [1–3]. In response, the whole-cell pertussis vaccine was developed and licensed in the U.S. for use in children beginning in the mid-1940s,

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CI, confidence interval; ClinChem, Clinical Chemistry Database; DFA, direct fluorescent antibody; DTaP, diphtheria, tetanus toxoids, and acellular pertussis; MTF, medical treatment facility; OR, odds ratio; PCR, polymerase chain reaction; Tdap, tetanus, diphtheria toxoids, and acellular pertussis; U.S., United States; USAF, United States Air Force; VE, vaccine effectiveness; VPD, vaccine preventable disease.

* Corresponding author at: Solutions Through Innovative Technologies, USAF-SAM/PHR, 3152 Presidential Drive, Fairborn, OH 45324, United States. Tel.: +1 937 938 3209.

E-mail address: greg.wolff.1@us.af.mil (G. Wolff).

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leading to a 99% rate decline by 1970 [2]. By 1976 the Centers for Disease Control and Prevention (CDC) reported the lowest number of pertussis cases in the U.S., 1010 cases (0.5 cases per 100,000 people [2,3]). However, since 1976, pertussis has been on a cyclical increase, a trend never before seen in the post-vaccine era [4]. The acellular formulation was developed in 1991, eventually replacing the whole cell formulation in the U.S. and subsequently reducing vaccine adverse events [2]. By 2012 48,277 cases (15.4 cases per 100,000 people) of pertussis were reported in the U.S [5,6]. Though diverse, heterogeneous trends of pertussis incidence have been observed globally over the past 20 years, increasing trends have been observed in several developed countries [7]. In 2012, Canada and the United Kingdom reported 14.1 cases per 100,000 people and 19.0 cases per 100,000 people [8,9], respectively. Additionally the same year, Australia witnessed one of the highest global incidence rates of pertussis (108.4 cases per 100,000 people) [8,9].

The Advisory Committee on Immunization Practices (ACIP) recommends vaccination with diphtheria, tetanus toxoids, and

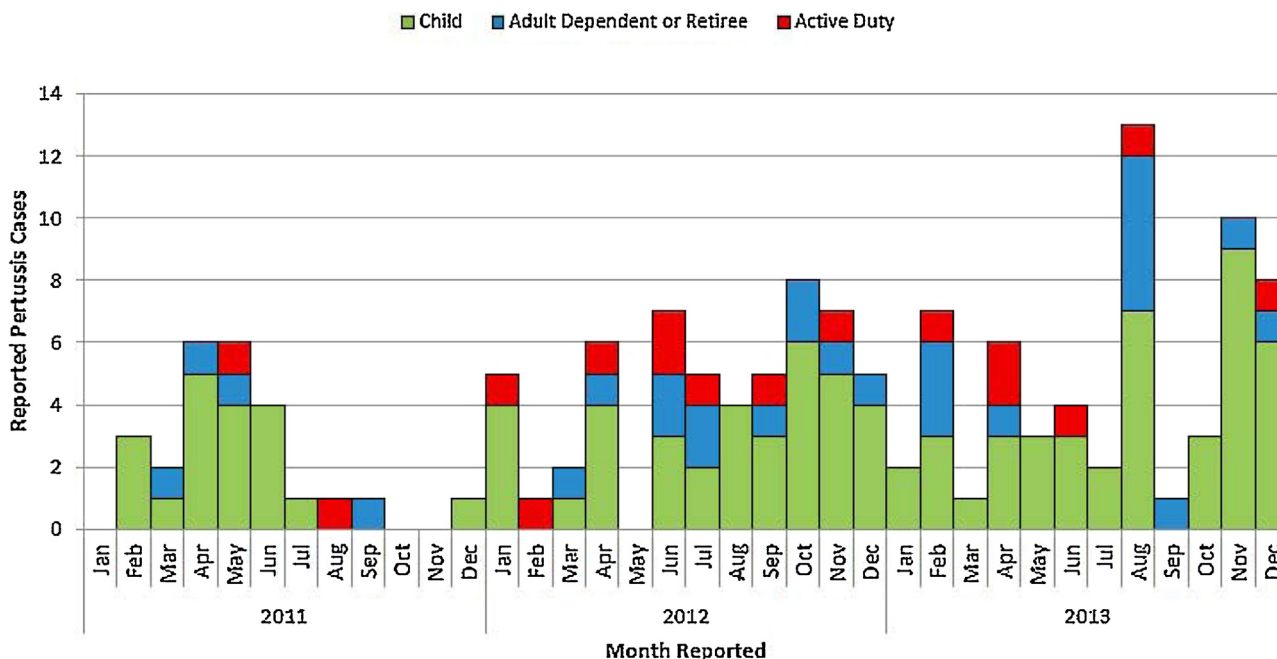


Fig. 1. Reported pertussis cases at USAF medical treatment facilities, 2011–2013.

acellular pertussis (DTaP) sequentially for children at 2 months, 4 months, 6 months, 15 to 18 months, and 4 to 6 years of age [10]. Globally, the World Health Organization recommends three doses of pertussis vaccine during the first year of life, followed by one booster dose between the ages of 1–6 years old, with a preference at 2 years of age [11]. Current members serving in the U.S. Air Force (USAF) (active duty, Guard, and Reserve) are required to receive one dose of Tdap during basic training (if lacking documentation of previous vaccine) or a one-time dose of Tdap in place of a tetanus booster during adulthood [12]. Spouses and children of USAF service members are requested to follow the ACIP pertussis vaccination guidelines.

Studies in the general U.S. population exploring the benefits of acellular vaccines have observed an overall pertussis vaccine effectiveness (VE) ranging from 51% to 89% [13–15]. Data collected through routine passive surveillance from the Air Force Reportable Event Surveillance System, an electronic repository of reportable diseases, detected an increased number of pertussis cases during 2012–2013 (55 and 60 cases, respectively) when compared to cases reported in 2011 (25 cases, Fig. 1). These cases of pertussis were most frequently observed in children (dependents) of USAF service members, although adult members (both service members and spouses) contributed to the case reporting. This study examines and further characterizes pertussis VE from 2011 to 2013 for USAF dependents younger than 12 years of age. The protocol for this study was reviewed and approved as exempt by the Air Force Research Laboratory Institutional Review Board.

2. Materials and methods

A test-negative study was conducted to examine the effectiveness of acellular pertussis vaccination against laboratory-confirmed pertussis cases within the population. This method has been described elsewhere [16,17]. Briefly those who seek care for respiratory illnesses are different than those who do not with regard to both their exposure (vaccination vs. no vaccination) and disease status (positive disease known vs. unknown). The test negative study design minimizes these classification biases by only utilizing controls who seek medical care if they develop a

pertussis-like illness since the incidence of non-pertussis disease is assumed similar between vaccinated and unvaccinated subjects.

USAF dependent children 2 months to less than 12 years old who were seen at any USAF medical treatment facility (MTF) from January 1, 2011, to December 31, 2013, were eligible to be included in the study. Laboratory data were derived from the Clinical Chemistry database (ClinChem), a Department of Defense database composed of laboratory results. ClinChem variables included individual demographics (gender, age, and beneficiary type) and pertussis laboratory data. ClinChem data were linked to the TriCare® enrollment database to obtain service member's (sponsor's) rank, service branch, and pay grade. TriCare® is health insurance coverage for military and their family members (dependents). The Military Personnel Database is a Department of Defense database containing demographic personnel data. Sponsor's race and ethnicity were identified through Military Personnel and used as proxies for dependent's race and ethnicity. Finally, the Air Force Complete Immunization Tracking Application database, a USAF database containing vaccination-related data, was queried to identify vaccination (DTaP and Tdap) histories. This was matched to individuals who received any pertussis laboratory testing during the study timeframe. Data were de-identified prior to study commencement by replacing Social Security numbers with unique study identification numbers.

Per the 2012 *Armed Forces Reportable Medical Events: Guidelines & Case Definitions* [18], a case was defined as any study patient with confirmed *Bordetella pertussis* infection identified through polymerase chain reaction (PCR), direct fluorescent antibody (DFA), or culture from a clinical specimen tested between January 1, 2011, and December 31, 2013. Controls included all negative *B. pertussis* test results submitted for testing during the same timeframe as cases. Patients born before 2002 were excluded from the study because of unavailability of complete vaccination histories. Infants less than 2 months of age at the time of their pertussis lab test were too young to receive vaccination and therefore were excluded from the study.

The final study population was categorized by vaccination status and age based on the CDC-recommended pertussis vaccine schedule [10]. DTaP (Tripedia®, Infanrix®, Trihibit®, Daptacel®,

Table 1
Number of pertussis vaccines received by age group.

Age group	Number of vaccines received (% of age group)					
	0	1	2	3	4	5
2 Months to <4 months	28 (45.2)	34* (54.8)	–	–	–	–
4 Months to <6 months	7 (12.1)	14 (24.1)	37* (63.8)	–	–	–
6 Months to <15 months	18 (9.5)	5 (2.7)	24 (12.7)	142* (75.1)	–	–
15 Months to <6 years	42 (9.5)	8 (1.8)	21 (4.7)	69 (15.6)	303* (68.4)	–
6 Years to <12 years	38 (15.3)	6 (2.4)	6 (2.4)	11 (4.4)	13 (5.2)	175* (70.3)

* Completely vaccinated for age group.

Pediarix[®], Pentacel[®], and Kinrix[®]) and Tdap (Adacel[®] and Boostrix[®]) vaccinations were included in a child's vaccination count if the child received vaccination greater than or equal to 14 days [19] before the date of pertussis lab test. Children who received the recommended number of vaccine doses for their age group were classified as completely vaccinated. Children who received at least one vaccine but less than the recommended number of doses for their age group were classified as partially vaccinated. Children having no record of pertussis vaccination were classified as unvaccinated.

Data management and statistical analyses were conducted using Microsoft Access 2010 (Microsoft, Redmond, WA), Stata 13.0 (StataCorp LP, College Station, TX), and SAS 9.3 (SAS Institute Inc., Cary, NC). Chi-square and Fisher's exact tests were used to examine demographic and vaccination status differences between cases and controls. Odds ratios (ORs) were computed using logistic regression to demonstrate the magnitude of these associations using a two-tailed significance level (alpha) of 0.05 for determining statistical significance. VE was calculated by subtracting the odds ratio from one and multiplying by 100 for the percent effectiveness.

3. Results

In total, 27 cases and 974 controls were identified from the USAF pediatric population during the study period. Pertussis PCR detected 26 cases and pertussis DFA detected an additional case. The control group consisted of 947 negative pertussis PCRs, 10 negative pertussis DFAs, and 17 negative pertussis cultures. Counts of acellular vaccinations by age group are displayed in Table 1. Counts of children fully vaccinated for their age group are indicated with an asterisk. A majority of the study population (69.0%) was completely vaccinated.

Demographic characteristics of cases and controls are depicted in Table 2. A larger proportion of controls were completely vaccinated ($n=679$, 69.7%) compared to cases ($n=12$, 44.4%). Unvaccinated children had significantly greater odds of disease compared to those who were fully vaccinated for their age (OR=4.60, 95% confidence interval (CI): 1.95, 10.88; $p<0.001$). Partially vaccinated children also had a higher odds of disease compared to those fully vaccinated; however, this difference was not significant (OR=1.65, 95% CI: 0.57, 4.73; $p=0.36$, data not shown). Non-significant age group differences were observed between cases and controls. The oldest age group (6 years to less than 12 years) had 4.19 times the odds (95% CI: 0.55, 32.21; $p=0.17$) of developing pertussis compared to the youngest children (2 months to less than 4 months). The highest proportion of cases were identified in 2013 ($n=15$, 55.6%) compared to other years. Children of officers had significantly higher odds (OR=2.50) of pertussis compared to those of enlisted personnel (95% CI: 1.15, 5.41; $p=0.02$). When compared to Guard, Reserve, and retirees aggregate, dependents of active duty service members were significantly (95% CI: 1.70, 9.37; $p<0.001$) protected from pertussis, having 74.9% reduced odds of disease (OR=0.25). Latino children

had higher odds of pertussis than non-Latinos (OR=1.98, 95% CI: 0.66, 5.94; $p=0.22$), a non-significant finding. No significant trends were noticed when examining the association of race and pertussis. Gender differences were non-significant; however, males had a 19% increased odds of pertussis (95% CI: 0.54, 2.58; $p=0.67$) compared to females.

Pertussis VE in completely vaccinated versus unvaccinated children is examined in Table 3. The overall VE was statistically significant at 78.3% (95% CI: 48.6, 90.8; $p<0.001$). Examining all children less than 6 years of age, the VE for fully vaccinated children compared to those unvaccinated was also statistically significant at 94.2% (95% CI: 71.0, 98.9; $p<0.001$). Children 15 months to less than 6 years old had the highest VE, 97.6% (95% CI: 78.5, 99.7; $p<0.001$). VE was determined to be the lowest and least precise in the oldest age group, 6 years to less than 12 years old; however, this result was not statistically significant (48.5%, 95% CI: –74.0, 84.7; $p=0.28$). Insufficient cases among those aged 2 months to less than 15 months precluded the calculation of age-specific VE in those age groups.

Pertussis VE was also calculated and compared between partially vaccinated and unvaccinated children (data not shown). The overall pertussis VE for partially vaccinated children was nearly significant at 64.2% (95% CI: –7.2, 88.1; $p=0.06$). In partially vaccinated children aged 15 months to less than 6 years, the VE was significant at 84.6% (95% CI: 17.0, 97.1; $p=0.03$) and lowest but not significant among children 6 years to less than 12 years at 50.0% (95% CI: –191.4, 91.4; $p=0.67$). However, lack of precision of these estimates yields an uncertain population effect. Data were not sufficient to calculate VE in partially vaccinated children aged 2 months to less than 15 months old.

4. Discussion

Unvaccinated children in our USAF pediatric population had more than 4.5 times the odds of pertussis compared to those who were fully vaccinated for their age. The oldest age group had 4.2 times the odds of pertussis compared to the youngest age group, which could be due to a longer period of risk in this age group (6 years compared to 2 months).

The overall pertussis VE was relatively high at 78.3% and corroborates findings from civilian children in other studies [2,15]. There was an inverse relationship between VE and age. Our highest VE among completely vaccinated children was identified in the age group 15 months to less than 6 year olds and had a VE of 97.6%. Our lowest VE in completely vaccinated children was among those 6 years of age or older and found to be 48.4%. This inverse relationship could stem from waning immunity. Previous studies have documented the challenge of waning pertussis immunity in school-aged and adolescent populations, with lower immunity levels occurring 1–10 years after vaccination [20–26]. The CDC recommendation for a booster dose of Tdap once between 11 and 18 years of age, preferably between 11 and 12 years of age [27], is supported by our relatively low VE in the oldest age group of our study.

Table 2
Characteristics of laboratory tested pertussis cases and controls.

	Pertussis cases (n=27)		Non-pertussis controls (n=974)		Odds ratio ^a	p-Value ^b
	N	% of total cases	N	% of total controls		
Vaccination status						
Completely vaccinated	12	44.44	679	69.71	Reference	
Partially vaccinated	5	18.52	172	17.66	1.65	0.3559
Unvaccinated	10	37.04	123	12.63	4.60	0.0005
Age group						
2 Months to <4 months	1	3.70	61	6.26	Reference	
4 Months to <6 months	1	3.70	57	5.85	1.07	0.9621
6 Months to <15 months	1	3.70	188	19.30	0.33	0.4287
15 Months to <6 years	8	29.63	435	44.66	1.12	0.9144
6 Years to <12 years	16	59.26	233	23.92	4.19	0.1687
Study year						
2011	2	7.41	82	8.42	Reference	
2012	10	37.04	115	11.81	3.57	0.1066
2013	15	55.56	777	79.77	0.79	0.7589
Rank						
Enlisted	15	55.56	738	75.77	Reference	
Officer	12	44.44	236	24.23	2.50	0.0164
Status						
Active duty	19	70.37	862	90.45	Reference	
Other ^c	8	29.63	91	9.55	3.99	0.0006
Ethnicity						
Non-Latino	20	74.07	843	86.55	Reference	
Latino	4	14.81	85	8.73	1.98	0.2209
Missing	3	11.11	46	4.72	2.75	0.1126
Race						
White	20	74.07	637	65.40	Reference	
Black	0	0.00	142	14.58	–	0.9553
Non-White, non-Black	4	14.81	152	15.61	0.84	0.7505
Missing	3	11.11	43	4.41	2.22	0.2114
Gender						
Female	11	40.74	437	44.87	Reference	
Male	16	59.26	537	55.13	1.19	0.6706

^a Odds ratios calculated using logistic regression.

^b p-Value calculated by chi-square for all variables except race (calculated by Fisher's exact test).

^c Other includes children of guard, reserve, and retired members.

In our study, VE in partially vaccinated children mirrored that of completely vaccinated children for all age groups, but with lower magnitudes of effectiveness. Notably, partially vaccinated children in our study had an overall VE of 64.2% ($p=0.06$) compared to unvaccinated children. This protection approached statistical significance and may represent a clinically significant finding. The high level of protection offered by partial vaccination may have stemmed from characteristics unique to our study population. All dependents in our study have at least one parent in the USAF who is a military member and required to be vaccinated against pertussis. It is unlikely that this produced bias since controls were required to have the same exposure, however, identifying if a child had one or two Active Duty parents, and thus one or two parents mandatorily vaccinated against pertussis, could not be ascertained.

Study limitations included the low number of pertussis cases ($n=27$, 2.7% of the population). Wide subgroup confidence intervals made the true population effect difficult to interpret. While the majority of service members are expected to be treated for illness and injury at an MTF, it is possible that military dependents (children) were treated outside the military facilities and consequently were not included in the final data capture of potential pertussis cases. Our calculated VE was consistent with other published studies; however, larger case sizes would be required to examine meaningful results for vaccination effectiveness by age

level. Moreover we relied on data previously collected for clinical and surveillance purposes rather than research purposes. Consequently, vaccination data could not be validated on their accuracy. Notation indicating whether a child was truly unvaccinated or missing vaccination records was unavailable in our dataset. Therefore, all children without vaccination records were categorized as unvaccinated, and all vaccination data were assumed to be complete. This study also assumes that our study population received all vaccinations at an MTF when, in fact, they could have obtained their vaccinations through an off-base clinic without documentation in the Air Force Complete Immunization Tracking Application vaccination database. These limitations could have led to vaccinated children being misclassified as unvaccinated, thus biasing the results toward the null and diluting the association. If exposure were misclassified, our results erred on the conservative side; however, significant differences were still identified. Had there been certainty of no misclassification, greater magnitudes of associations would have been observed, thus potentially yielding significant differences among age categories that didn't initially produce significant results. Finally, multiple laboratory confirmatory tests utilized in our study included PCR, DFA, and culture from over 50 laboratories. These tests may have introduced differential verification bias due to varying degrees of sensitivity and specificity. However, this limitation is negligible.

Table 3
Vaccine effectiveness for completely vaccinated vs. unvaccinated children.

Age group	Pertussis cases	Non-pertussis controls	Vaccine effectiveness (%) (95% CI)	p-Value ^a
Overall (all age groups)				
Completely vaccinated	12	679	78.26 (48.58, 90.81)	0.0002
Unvaccinated	10	123		
<6 years				
Completely vaccinated	2	514	94.23 (70.95, 98.85)	<0.0001
Unvaccinated	6	89		
2 months to <4 months				
Completely vaccinated	1	33	–	–
Unvaccinated	0	28		
4 months to <6 months				
Completely vaccinated	0	37	–	–
Unvaccinated	0	7		
6 months to <15 months				
Completely vaccinated	0	142	–	–
Unvaccinated	1	17		
15 months to <6 years				
Completely vaccinated	1	302	97.55 (78.45, 99.72)	<0.0001
Unvaccinated	5	37		
6 years to <12 years				
Completely vaccinated	10	165	48.48 (–73.95, 84.74)	0.2826
Unvaccinated	4	34		

^a Overall comparison p-value calculated by chi-square test. All other group p-values calculated by Fisher's exact test.

5. Conclusion

Trends in reported cases of pertussis and pertussis vaccination in U.S. military members and beneficiaries have been previously investigated [28–30]. However, this study examined the pertussis burden on a Department of Defense pediatric dependent population not previously described as well as assessed VE for both completely and partially vaccinated children stratified by ACIP age groups. Acellular pertussis vaccination was effective at preventing laboratory-confirmed pertussis in our pediatric USAF dependent population. Overall VE was calculated as 78.3% for completely vaccinated children. VE varied among age groups, with higher levels of effectiveness in younger children and lower levels in older children. Our study results support previously reported findings of overall VE [2,13–15], increased pertussis incidence in older children [7,20–26], and the increase of pertussis cases in the U.S. over the last 30 years [2,5–7]. Novel findings from this study include some evidence suggesting partial vaccination as a protector against laboratory-confirmed pertussis, 64.2% VE.

Our findings have demonstrated beneficence against pertussis in completely vaccinated children.

While overall significance among those partially vaccinated was not established, there is a possibility for clinical significance with development of some protective immunity.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the official policy or position of the U.S. Air Force, the Department of Defense, or the U.S. Government.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2015.04.084>

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