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Seroprevalence of Pertussis Infection in HIV-Infected Adults in the United States

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Abstract

Pertussis is a resurgent infection that can cause significant morbidity among adults. CD4+ T cells are necessary for its clearance, but pertussis studies in HIV-infected adults are limited to case reports. We analyzed stored serum samples from 299 HIV-infected adults to determine the seroprevalence of pertussis among this population. We found that 4.3% of subjects had serologic evidence of recent pertussis infection, and annual incidence of pertussis infection among subjects not vaccinated against pertussis in the last 5 years was 10.5–17.5%. Prospective studies are needed to define the clinical presentation of pertussis in HIV-infected adults and to optimize vaccination strategies.

Keywords

HIV; pertussis; seroprevalence; adults; United States

Introduction

Pertussis (or whooping cough) is a highly contagious respiratory infection caused by the gram-negative bacillus *Bordatella Pertussis*[1]. It can be fatal in infants, but can also cause significant morbidity in older children and adults, including multiple weeks of prolonged cough. Pertussis vaccines have been used in the United States (U.S.) since the 1940s, and were responsible for a 99% decrease in pertussis cases. However, pertussis has resurged over the last two decades in the U.S., from a nadir of 1,010 cases in 1976, to 48,277 cases reported in 2012[1,2]. Prospective population-based studies suggest that the reported cases underestimate the true burden of disease, particularly given the low sensitivity of available

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diagnostic methods, and that there are ~500,000 symptomatic cases among adults alone in the U.S. each year[3]. In addition, asymptomatic infections may outnumber symptomatic infections five-fold[4]. Globally, there are ~16 million symptomatic cases and 195,000 deaths from pertussis annually, with 95% of the disease burden in developing countries[1].

There is no data on the prevalence and clinical burden of pertussis infection among adults infected with the human immunodeficiency virus (HIV). Three case reports suggested that pertussis can cause severe, months-long respiratory infections in HIV-infected patients who have progressed to AIDS (the acquired immunodeficiency syndrome)[5–7]. As CD4+ T helper cells are critical for the clearance of pertussis[8], logic dictates that HIV-infected individuals could have more severe or prolonged pertussis infections than the general population. There are currently 37 million people living with HIV, including 1.2 million in the U.S., with most HIV-infected people living in developing countries where pertussis is prevalent[9,10].

To our knowledge, no prior studies have investigated the prevalence or clinical burden of pertussis among HIV-infected adults. To help fill this knowledge gap, we conducted a cross-sectional study using stored serum samples from 299 HIV-infected adults who attended our clinic in Norfolk, Virginia, to determine the seroprevalence of pertussis infections and associated factors.

Methods

This was an observational, cross-sectional study conducted at the primary HIV clinic at Eastern Virginia Medical School (EVMS) in Norfolk, Virginia. We used stored serum and data from 299 adults with well-controlled HIV infection who participated in one of two prior studies conducted from 2012–2014, had excess serum available, and consented that their excess serum and data could be used in future studies. Inclusion criteria for both prior studies included documented HIV infection, age ≥18 years, and HIV viral load <400 copies/ml on the most recent test[11]. As part of the original studies, dates of all vaccinations received at the clinic and/or reported by the patient, laboratory values, current medications, demographic data, and comorbidities were extracted from the medical record and from subject questionnaires. The EVMS Institutional Review Board approved the study.

On the day of collection, blood samples were centrifuged, and the serum aliquotted and stored at −80°C until laboratory analysis. Serum was tested by a commercial ELISA assay for the specific quantitative measurement of anti-pertussis toxin (PT) IgG (Abcam, Cambridge, MA). The test was optimized to international units per milliliter, and provided internal references for each plate.

The clinic used Adacel®, the combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) produced by Sanofi Pasteur, for pertussis vaccination during the period of the study. Of note, since 2006 the U.S. Advisory Committee on Immunization Practices has recommended a single dose of Tdap for all adults in place of the tetanus toxoid and reduced diphtheria toxoid vaccine (Td), if the last Td booster was received at least 10 years earlier[3].

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We defined recent pertussis infection as anti-PT IgG levels ≥94 units/ml based on a study that validated this test and cutoff point for diagnosis of active pertussis infection[12]. We restricted the analysis of recent infection to the subjects who had not received Tdap in the prior six months, based on a second study that showed that although 8% of Tdap-vaccinated adults achieve peak anti-PT IgG levels ≥94 units/ml, the IgG levels uniformly drop below 94 units/ml by six months[13]. Of note, pertussis IgM assays are thought to lack adequate sensitivity and specificity[14].

For the analysis of annual incidence of pertussis infection, we used data from a Dutch study that described the average time periods since infection for different anti-PT IgG levels (100, 80, 50, and 40 units/ml)[15]. To ensure that elevated anti-PT IgG levels were not due to recent vaccination, we restricted this analysis to the 170 subjects who had not received Tdap in the prior 5 years. Several studies have shown that mean anti-PT IgG levels drop to 9–14 units/ml by 18–36 months after Tdap vaccination[13,16,17]. In addition, other studies have used anti-PT IgG levels ≥30 units/ml to diagnose recent pertussis infections in subjects not vaccinated against pertussis for ≥2.5 years[18,19].

Categorical variables were presented as percentages, and continuous variables were presented as means and standard deviations (SD). The primary outcomes were recent pertussis infection, as defined by anti-PT IgG levels ≥94 units/ml, restricted to subjects who did not receive Tdap in the prior six months, and anti-PT IgG levels as a continuous variable among all subjects. Variables of interest included time since Tdap receipt (1–6, 7–12, 13–24, 25–60, and >60 months since or no record of ever receiving Tdap), age, gender, race, years since HIV diagnosis, CD4 count, AIDS diagnosis, statin use, diabetes diagnosis, hepatitis C diagnosis, currently smoking, ever homeless, and season of sample collection (for recent pertussis infection analysis only). In the bivariate analysis, we used logistic regression to analyze the association between variables of interest and recent pertussis infection. To analyze the association between variables of interest and anti-PT IgG levels, we used correlation analysis for continuous variables, t-test for binary variables, and ANOVA for categorical variables with more than two options. In the multivariate analysis, multiple logistic regression models and ANCOVA were constructed to investigate the association between the variables with significant associations on bivariate analysis and the primary outcomes. Two-sided statistical tests were conducted at an α level of 0.05. Statistical analysis was performed using SAS version 9.4 (SAS institute, Cary, North Carolina).

Results

Samples were available from 299 subjects, of whom 22, 29, 39, 39, and 170 had last received Tdap 1–6, 7–12, 13–24, 25–60, or >60 months prior, respectively. Of the 170 subjects who had last received Tdap >60 months prior, 5 had received Tdap 61–87 months prior, and 165 had no record of ever receiving Tdap. 297 subjects were on antiretroviral therapy at the time of the study, and two subjects were elite controllers who had HIV viral loads <400 copies/ml despite never receiving antiretroviral therapy. Characteristics of the study subjects are shown in Table 1.

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Among the 277 subjects who had not received Tdap in the prior 6 months, 12 (4.3%) had anti-PT IgG levels indicating recent pertussis infection (≥94 units/ml). The two variables with significant associations with recent pertussis infection were time since Tdap receipt (OR of 10.1, 95% CI 2.4–42.5, for 13–24 months versus >60 months since Tdap receipt, p=0.007) and history of homelessness (OR of 8.2, 95% CI 2.2–31.1, ever homeless versus never homeless, p=0.002). Both of these variables remained significant on multivariate analysis.

Among the 170 subjects who had not received Tdap in the prior 5 years, 3, 5, 17, and 20 subjects had anti-PT IgG levels >100, 80, 50, and 40 units/ml, respectively. A Dutch study showed that anti-PT IgG levels drop to 100, 80, 50 and 40 units/ml after an average of 58.6, 102.6, 208.9, and 297.6 days from infection, respectively[15]. Based on this, the annual pertussis infection rate among our HIV-infected subjects was 10.5–17.5% (3/170 × 365.25/58.6, 5/170 × 365.25/102.6, etc.). Anti-PT IgG levels in relation to time since Tdap receipt are shown in Table 1 and Figure 1.

Among all 299 subjects, anti-PT IgG levels were associated with time since Tdap receipt, with lower IgG levels further from vaccination ($F=5.14$, $df_{num}=4$, $df_{den}=294$, $p=0.0005$, Table 1). However, as both vaccination and infection increase anti-PT IgG levels, it is difficult to delineate the independent effect of vaccination on antibody levels. Anti-PT IgG levels were also associated with CD4 count (r coefficient 0.16, p=0.007), ever being homeless (t=(−2.49), df=117.42, p=0.01), and statin use (t=(−2.18), df= 75.24, p=0.03). All associations remained significant on multivariate analysis.

Discussion

We conducted a cross-sectional study to determine the seroprevalence of pertussis infection among 299 adults with well-controlled HIV infection in Virginia. We found that 4.3% of subjects not vaccinated with Tdap in the last 6 months had serologic evidence of recent pertussis infection, and that the annual pertussis infection rate among subjects not vaccinated in the last 5 years was 10.5–17.5%. This rate is 1000-fold higher than the annual incidence of reported cases for the general U.S. population in 2014[20], consistent with other seroprevalence studies that have found pertussis to be vastly underreported[15,18,19]. It is also 10-fold higher than the seroprevalence rate reported from a study among healthy American adolescents and adults in 1997–1999[4]. Our higher rates compared to the American seroprevalence study could be because our study was done 15 years later, after pertussis rates increased, and/or because rates may be higher in HIV-infected adults. Regardless of the etiology, our data among HIV-infected adults in Virginia, a state with a lower incidence of reported pertussis cases than the nation as a whole[20], suggests that pertussis is a prevalent and underdiagnosed infection among HIV-infected adults throughout the U.S..

Pertussis is classically considered a childhood illness, and consequently medical providers caring for adults often fail to consider pertussis in the differential diagnosis of cough illnesses. This is reflected in the fact that 82% of reported U.S. pertussis cases are from people less than 20 years of age[20]. However, a Dutch seroprevalence study demonstrated that although the vast majority of reported cases were in children, incidence of pertussis

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actually increased with age, peaking in the 20–24 year old age group but remaining higher than the incidence in children through age 59[15]. Similarly, an Israeli seroprevalence study of subjects at least three years of age demonstrated peak incidence rates in subjects >60 years old, despite this age group having the lowest incidence of reported pertussis cases[21]. Further, a Chinese seroprevalence study in subjects 4–86 years old revealed peak incidence of pertussis in the 31–40 followed by the 41–60 year old age groups[18]. Studies among U.S. adult and adolescent subjects with cough illness suggest 13–15% of these illnesses can be attributed to pertussis[22,23]. Taken together, these data indicate that pertussis should be considered and tested for in adult patients with cough illness, including HIV-infected adults.

Tdap is 92% effective against symptomatic pertussis infection in the 2.5 years following vaccination in healthy adults and adolescents[24]. However, protection after infection or vaccination is not lifelong[25], and studies of the acellular vaccine in children suggest that protection significantly decreases 5–10 years after vaccination[26]. There are no studies of either the efficacy or immunogenicity of Tdap in HIV-infected adults. However, studies of pertussis vaccines in HIV-infected children indicate that HIV infection lowers antibody response, and that higher CD4 counts at vaccination improve antibody response[27–29]. Given the high pertussis prevalence we demonstrate in HIV-infected adults, studies are needed to determine the efficacy and duration of protection conferred by Tdap in this population, so that vaccination strategies can be optimized.

As a retrospective study using stored serum samples, we are unfortunately unable to determine whether the pertussis infections in our cohort were symptomatic, as we did not have data on cough illnesses among subjects in the year preceding sample collection. Among healthy adults and adolescents, asymptomatic infections are five-fold more common than symptomatic infections[4]. Whether this is also true in HIV-infected adults is unknown, as prior studies on pertussis in HIV-infected adults are limited to case reports[5–7]. In addition, as pertussis is seasonal with peaks every few years, comparisons between our results and other studies from different time periods should be undertaken with caution.

In conclusion, we demonstrate that pertussis is a prevalent infection among HIV-infected adults in the U.S., with an annual incidence of 10.5–17.5%. HIV providers should consider pertussis in evaluating patients with cough illness. Prospective studies are needed both to define the clinical presentation of pertussis in HIV-infected adults, and to determine the best vaccination and infection control strategies.

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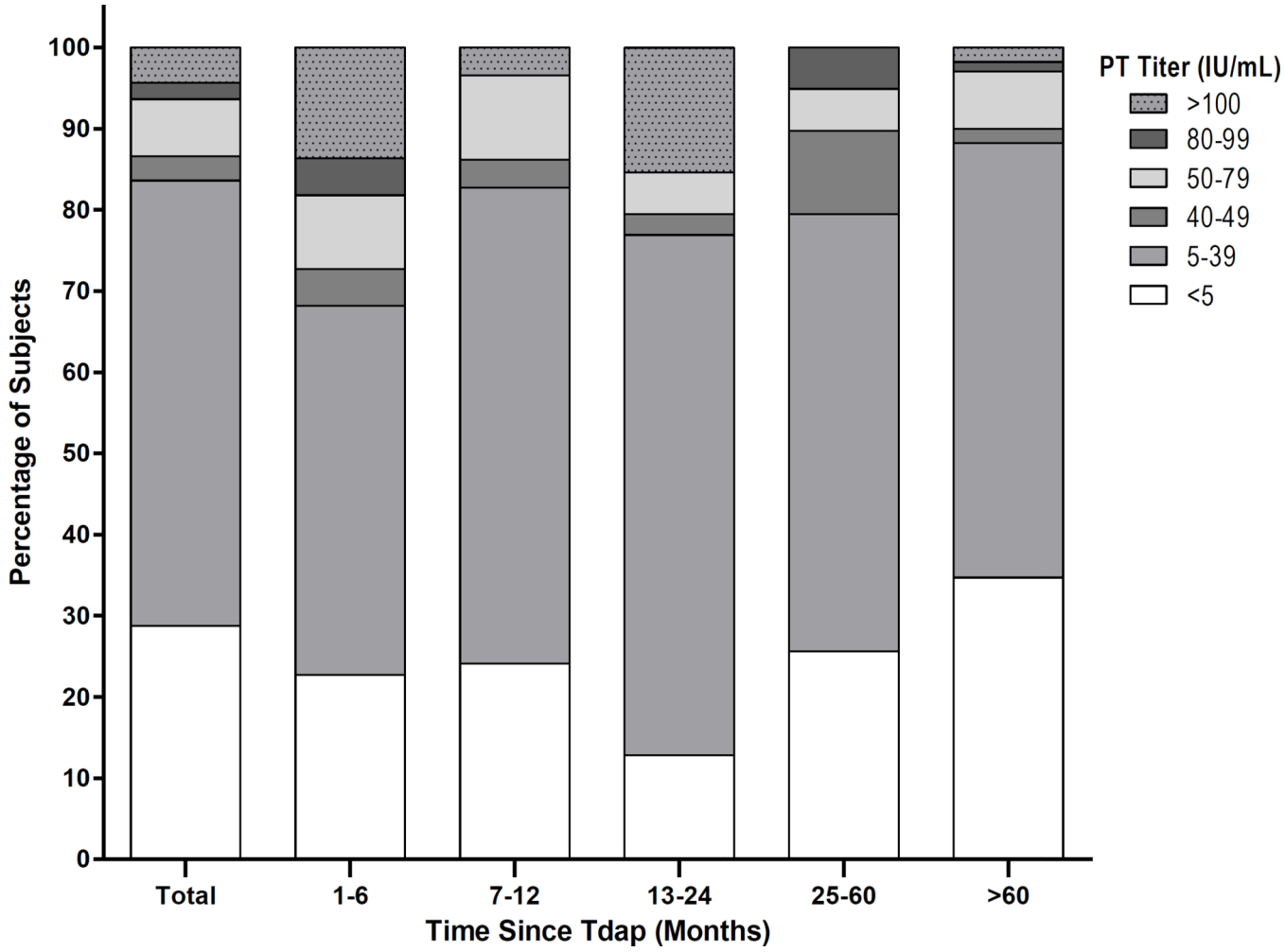

Figure 1.

Anti-Pertussis Toxin (PT) IgG Levels by Time since Pertussis Vaccination with Tdap

The cumulative percentage of subjects with anti-PT IgG at certain levels or below among all 299 subjects included in the study.

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Table 1

Subject Demographics and anti-Pertussis Toxin IgG Levels

Variable		Total	Time Since Subject Received Pertussis Vaccine				
			1–6months	7–12months	13–24months	25–60months	>60months
n		**299**	**22**	**29**	**39**	**39**	**170**
Demographics							
Age (years)							
	mean ± SD	45.1 ± 11.0	44.4 ± 12.4	48.2 ± 8.3	46.3 ± 10.8	44.9 ± 9.1	44.4 ± 11.7
	range	20–71	21–66	30–63	26–62	24–60	20–71
Gender							
	n (%) male	208 (70)	17 (77)	22 (76)	28 (72)	27 (69)	114 (67)
Race							
	n (%) black	203 (68)	10 (45)	17 (59)	27 (69)	28 (72)	121 (71)
	n (%) white	94 (31)	12 (55)	12 (41)	12 (31)	11 (28)	47 (28)
	n (%) other	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Comorbidities							
Homeless	**n (%) yes**	84 (28)	4 (18)	11 (38)	11 (28)	7 (18)	51 (30)
Smoker	**n (%) yes**	127 (42)	9 (41)	9 (31)	15 (38)	18 (46)	76 (45)
Diabetic	**n (%) yes**	31 (10)	3 (14)	4 (14)	2 (5)	9 (23)	13 (8)
Hepatitis C	**n (%) yes**	40 (13)	4 (18)	4 (14)	4 (10)	4 (10)	24 (14)
Statin Use	**n (%) yes**	66 (22)	4 (18)	11 (38)	10 (26)	9 (23)	32 (19)
HIV Factors							
AIDS Dx	**n (%) yes**	186 (62)	15 (68)	17 (59)	21 (54)	23 (59)	110 (65)

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Variable	Total	Time Since Subject Received Pertussis Vaccine				
		1–6months	7–12months	13–24months	25–60months	>60months
n	**299**	**22**	**29**	**39**	**39**	**170**
Years Since HIV Dx *						
mean ± SD	11.2 ± 8.0	8.8 ± 9.7	11.1 ± 7.8	13.2 ± 9.1	11.7 ± 7.2	11.0 ± 7.8
range	0–33	0–28	0–31	2–31	1–27	0–33
CD4 Count (cells/mm^3)						
mean ± SD	633 ± 332	561 ± 388	665 ± 322	673 ± 271	662 ± 278	621 ± 351
range	36–1853	77–1451	129–1442	183–1406	152–1325	36–1853
Results						
Anti-Pertussis Toxin IgG						
GMC (IU/mL)	10.6	16.8	14.1	18.1	11.7	8.2
n (%) ≥94 IU/mL	15 (5)	3 (14)	2 (7)	6 (15)	1 (3)	3 (2)

SD= standard deviation, n = number in each category, dx=diagnosis, GMC= geometric mean concentration.

Homeless indicates ever homeless.

* n=297 for this variable.