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# Choice of measures of vaccination and estimates of risk of pediatric pertussis

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ABSTRACT

*Background:* Vaccination uptake at the individual level can be assessed in a variety of ways, including traditional measures of being up-to-date (UTD), measures of UTD that consider dose timing, like age-appropriate vaccination, and risk reduction from individual doses. This analysis compared methods of operationalizing vaccination uptake and corresponding risk of pertussis infection.
*Methods:* City-wide case-control study of children in Philadelphia aged 3 months through 6 years, between 2001 and 2013. Multiple logistic regression was used to isolate the independent effects of each measure of vaccination uptake and the corresponding relative odds of pertussis.
*Results:* Being UTD on vaccinations was associated with a 52% reduction in risk of pertussis (OR 0.48, 95% CI: 0.34, 0.69). Evaluation of delayed receipt of vaccine versus on-time UTD yielded similar results. There was a decrease in risk of pertussis for each additional dose received with the greatest reduction in pertussis infection observed from the first (OR 0.48, 95% CI: 0.28, 0.83) and second dose (OR 0.17, 95% CI: 0.08, 0.34). Additional doses conferred minimal additional protection in this age group.
*Conclusion:* Examining vaccination status by individual doses may offer improved predictive capacity for identifying children at risk for pertussis infection compared to the traditional UTD measure.


## 1. Introduction

Vaccination coverage is a common measure of individuals vaccinated in a community and can represent vaccine program effectiveness. It is assessed by examining individual immunization records and summarizing to the population, such as reporting percent vaccinated. In assessing the individual immunization records, the researcher needs to choose the proper metric. One frequently used measure is being up-to-date (UTD) on vaccinations, which implies all recommended doses of a vaccine have been administered by a specific age [1–4]. UTD may include the nuanced timing of a dose, or whether the dose fell within the vaccine schedule recommendations, and therefore studies employing this measure may be examining different phenomenon from studies that examine UTD without considering dose timing [5–8]. When the timing of a dose is considered, the metric is often referred to as delayed or age-appropriate vaccination.

Despite overall high vaccination coverage levels (US national coverage estimates of four DTaP doses by 24 months of age are close to 80% [9]), this may not reflect the delays in receiving vaccination. Luman et al. found that 23% of children traditionally classified as UTD at 24 months may have been undervaccinated during a portion of this time, and 42% had delays in more than one vaccine [10]. This leaves the child potentially vulnerable during the undervaccinated period. Compared to age-appropriate vaccination status, Glanz et al. reported children were up to 28.4 times as likely to be diagnosed with pertussis (95% CI, 3.2–252.6) when they were undervaccinated by four doses, and 18.6 times as likely (95% CI, 4.9–70.0) when they were undervaccinated by three doses [11]. Although even undervaccinated children receive a base level of protection against severe diseases compared to non-vaccinated individuals [12].

Given multiple methods of assessing vaccination status, comparison across studies may be hindered by the specific type of vaccination coverage definition. Using national immunization data, Dombkowski et al. revealed important characteristics like education and insurance status might be ignored when examining vaccination coverage as a dichotomous UTD variable versus a

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multi-categorical age-appropriate vaccination variable [13]. In addition to identifying differences in vaccination characteristics, it is also important to identify if there are differences in disease risk, the focus of the present study.

Therefore, it is necessary to compare the measures directly in the same population. We focused on reported incident cases of pertussis in the Philadelphia population of children between 2001 and 2013, and sought to compare the different vaccination coverage metrics as predictors of disease. This disease is of particular interest as there has been a sharp increase in cases over recent years within the U.S., as well as internationally, and in fact, in 2012 Philadelphia experienced twice as many cases as in the previous year.

## 2. Materials and methods

### 2.1. Study population

We undertook a city-wide nested case-control study of children in Philadelphia aged three months through six years, between 2001 and 2013. Potential pertussis cases were reported to the Philadelphia Department of Public Health (PDPH) [14] and four controls per case were randomly selected from the city's immunization information system (KIDS Plus IIS), frequency matched by date of birth to within two weeks. Controls were excluded if they had been reported to the PDPH with pertussis-like symptoms. The study population included children aged three months through six years to capture the full ACIP recommended five-dose series of childhood pertussis vaccination [15]. Given the very high pediatric vaccination rates in Philadelphia, children with two or fewer vaccines (any type) were excluded as these children were considered born in Philadelphia but moved or resided elsewhere. This study was approved by the Institutional Review Boards for the City of Philadelphia and Drexel University (Philadelphia, PA).

### 2.2. Exposure, outcome, and covariates

The primary exposure of vaccination status was operationalized in four ways: UTD (the commonly used metric), delayed UTD, and a cumulative number of doses handled both categorically and continuously for trend estimation (Fig. 1). Children were considered UTD if they received all vaccinations recommended for their age group by their current age; otherwise they were not UTD. Delayed UTD was assessed by establishing a valid timeframe for each individual dose (Table 1), and then comparing timing of dose delivery per an algorithm adapted from expert clinical opinion and these references [11,12]. If all doses where administered, but one or more were not delivered within the valid timeframe, the child was deemed "delayed UTD". If all doses were administered within the timeframe, they were deemed "on time UTD", while one or more doses missing would classify the child as not UTD. For all measures, any pertussis-containing vaccination (i.e., diphtheria, tetanus, acellular pertussis) through the child's present age was included, and doses administered within two weeks of each other were considered duplicates with the later dose discarded.

Reported cases of confirmed or probable pertussis were defined by the Council of State and Territorial Epidemiologists (CSTE) as a cough illness, without other apparent causes, lasting at least two weeks, with one or more paroxysms of coughing, inspiratory "whoop," or posttussive vomiting. Confirmed cases required positive laboratory diagnostics, either isolation of the *Bordatella pertussis* bacterial organism or polymerase chain reaction (PCR) detection of its genetic code, or epidemiological linkage (contact) to a lab-confirmed case. Specimens were obtained using nasopharyngeal swabs; serology was available for a subset of the sample and was incorporated into the laboratory diagnostics if available. Probable cases fit the clinical criteria, but were either not laboratory confirmed by a positive PCR or culture, or epidemiologically linked to another case.

Covariates examined for potential confounding included maternal age, maternal marital status (married, not married), race (white, black, other), ethnicity (Hispanic, non-Hispanic), maternal nativity (U.S. born, foreign born), child age (<1 yr, ≥1 yr), child sex, maternal education (no high school diploma, high school diploma or equivalent, college and higher), maternal insurance status as time of birth (private insurance, no private insurance), and maternal parity (primiparous, multiparous). A priori, we considered effect modification by age, race, and maternal parity, with vaccination status. All data were imported from KIDS Plus IIS and Pennsylvania Department of Health Vital Statistics records and linked via unique identifiers, when available. All records that were unable to be automatically linked were manually matched using a combination of name, sex, date of birth, and place of residence.

### 2.3. Statistical analysis

Descriptive statistics were used to assess crude relationships between the covariates and the primary exposure and outcome. For continuous variables, student's *t*-test for normally distributed data and Wilcoxon Rank Sum test for non-normally distributed data were used to test for differences between groups. For categorical data Chi-squared testing was used to examine relationship between groups. Statistical significance was set as a $p$-value <0.05.

To isolate the independent effects of each factor we used multivariable logistic regression. Covariates were included as potential confounders if they were associated with both the exposure and outcome ($p < 0.20$), or if they changed this relationship by >10% [16]. These models represented the adjusted odds of exposure (and disease) between vaccination uptake and pertussis. Vaccine effectiveness (VE) was defined as 1—odds ratio (OR) and corresponds to the average reduction in reported pertussis incidence from vaccination, controlling for potential confounding [17]. Interaction was assessed by stratifying the population to examine change in association estimates and statistically confirmed through comparing models with and without the interaction terms via a likelihood ratio test ($p < 0.05$).

Analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC) and R 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

## 3. Results

From 2001 through 2013, there were 235 pertussis cases that met the inclusion criteria, and 940 controls, for a total sample size of 1175 children aged three months through six years. Vaccination characteristics of cases and controls are provided in Table 2. In general, cases had fewer total vaccinations of any type (mean of 14.9 versus 16.0, $p = 0.03$) as well as fewer total pertussis vaccinations (mean of 2.1 versus 2.6, $p < 0.01$). When broken down by individual doses, 21% of cases had no DTaP vaccinations, compared to only 6% of controls ($p < 0.01$). A crude dose–response on reduction of disease incidence was not observed—additional doses were inconsistent in their effects, with only receipt of two doses being statistically significant (7% of cases versus 14% of controls, $p = 0.01$). Cases were UTD on their pertussis vaccinations 64% of the time compared to 80% of the time for controls ($p < 0.01$). We did not observe any waning immunity effect, as both cases and controls had approximately equivalent time since last DTaP dose (mean of 45 and 43 weeks, respectively; $p = 0.65$).

Table 3 presents the sociodemographic characteristics of this sample. Compared to controls, cases were more likely to be of white



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