TAHOD population. These considerations highlight the need for the development of confirmatory diagnostic tests for IRS, as well as further research into the epidemiology of IRS in diverse populations.

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Jaime Robertson,1 Jun Ying,2 and Carl J. Fichtenbaum1
1Department of Internal Medicine, Division of Infectious Diseases and Institute for Health Statistics, University of Cincinnati College of Medicine, Cincinnati, Ohio

References


Reprints or correspondence: Dr. Jaime Robertson, University of Cincinnati College of Medicine, Dept. of Internal Medicine, Div. of Infectious Diseases, Infectious Disease Center, 200 Albert Salton Way, Cincinnati, OH 45267-0405 (roberja@ucmail.uc.edu).

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Incidence of Bordetella pertussis Infection in Adolescents and Adults

To the Editor—Ward et al. [1] analyzed serologic data from a large group of subjects who were followed-up prospectively, had known vaccination status, and were tested for all major pertussis antigens. The authors concluded that the Bordetella pertussis infection rate among 1228 subjects aged 15–65 years who had not been recently vaccinated was ∼1% over an 11-month period on the basis of significant increases in serum antibody titers to pertussis toxin (PT). The reported range in estimates (0.4%–2.7%) was based on increases in titers of antibodies to other pertussis antigens. The PT-based rate of ∼1% is at the low end of the range of PT-based incidence estimates reported in the 4 other serologic studies referenced in the article by Ward et al. [1]. These studies reported PT-based annual incidence estimates of ∼1% [2, 3], 2.2% [4], 3.3% [5], and 8% [6]. However, the studies used different sample populations, sample sizes, and laboratory methodology, all of which could influence the magnitude of the annual estimates.

We would like to point out the results of another serologic study, which was completed among a nationally representative sample of 5366 individuals aged 10–49 years [7]. This cross-sectional survey used a single-sample serological test for IgG antibodies to PT and a mixture model analysis to identify a subgroup of persons presumed to have been recently infected (including persons with asymptomatic infection). The annual incidence estimate was 2.9% (95% CI, 2.1%–3.6%).

We also have questions regarding the criteria used to define B. pertussis infection. Ward et al. [1] used several serologic criteria for B. pertussis infection, including a 2- or 4-fold increase in 12-month titer, compared with 1-month titer. In general, to evaluate a fold increase in a titer, one needs information about the precision of the assay (intra-assay and interassay variability), as measured by the coefficient of variation (SD divided by the mean × 100%). For example, the probability of observing a 2-fold difference (increase or decrease) between paired samples simply because of assay variability is .013, .095, and .203 for an assay with a coefficient of variation of 20%, 30%, and 40%, respectively [8]. We did not find information about the variability of the serologic assays [1, 9]. In addition, blood specimens for antibody assays were obtained before immunization and at 1 month and 1 year after vaccination [1, 9]. It is not clear why the 1-month titer, instead of the before-immunization titer, was used for comparison with the 12-month titer; the reported annual infection rate was based on following the subjects for 11 months (not 12 months) [1].

A final comment concerns the estimate of ∼5 asymptomatic or “clinically insignificant affected” subjects for every classic case of clinical pertussis [1]. We could replicate the ratio estimate of 5 but were not certain whether our calculation was correct. Assuming the maximum reported incidence rate of 2.7%, or 2700 new infections (including both asymptomatic and symptomatic infections) per 100,000 persons per year, and assuming the maximum reported incidence of symptomatic disease of 450 cases per 100,000 persons per year, then the ratio of asymptomatic to symptomatic infections would, in fact, be 5 (i.e., 2700 infections would include 2250 asymptomatic and 450 symptomatic infections). This estimate assumes that the true rate of B. pertussis infection among adolescents and adults is 2.7% per year.

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Andrew L. Baughman, Margaret M. Cortese, and Barbara A. Slade
National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

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serial blood specimens from each subject, and we assayed 9 pertussis antibodies as titer changes in sequential serum samples from the same individual (i.e., the assays were self-controlled).

A multitude of assay variables exist that result in chance inaccurate quantitations. Our assays were developed to exacting US Food and Drug Administration specifications and were based on standards they provided. The validation of the assays included standardization of reagents, plates, dilution accuracy, and use of quantitative positive controls. All titer increases were determined with paired serum samples from the same subjects (i.e., they were self-controlled). All paired serum samples from the same individual were run on the same day and on the same microtiter plates to minimize assay variation.

In an efficacy trial, one wants to maximize case detection but also avoid false-positive results. To accomplish this, besides using precise assays, we evaluated remaining assay variability to determine the cut-off points for positivity (i.e., 2- or 4-fold increase). With same-plate evaluations of each set of paired serum samples, the coefficient of variation for the various pertussis antibody assays (pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae) ranged from only 0% to 18% for IgG assays and from 0% to 22% for IgA assays. Therefore, the 2-fold and 4-fold cut-off points selected far exceeded the variation inherent in these assays. With these low coefficients of variation and our serologic criteria, one would expect <1 false-positive result per 10,000 assays.

Our estimate of a 1.1%–2.7% infection rate per year derives from examining the 36 permutations of results shown in table 1 of our article [1]. Independent of the criteria employed, we found the observed incidence values to be remarkably consistent. Undoubtedly, there are variations in different populations at different times and over longer intervals, but we believe few studies have been as rigorous as ours.

Lastly, among control subjects, there were no titer differences between the samples obtained before and at 1 month after hepatitis A immunization. Therefore, our incidence estimate does not differ whether we use the preimmunization (12-month interval) or the 1-month postimmunization sample (11-month interval). We used the 11-month interval so that our comparisons between samples from subjects who had received acellular pertussis vaccine and control samples from unvaccinated subjects were identical.

In conclusion, we find little meaningful difference between an estimate of 1.1%–2.7% and an estimate of 2.9%. An advantage of our study is that we could compare the infection rate to the active, prospectively ascertained disease incidence. We found a 5:1 ratio of asymptomatic to symptomatic cases, and this is, to our knowledge, the first estimate of this type to be assessed prospectively in a national cohort.

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Joel I. Ward, James D. Cherry, Martin Lee, and Swe-Ju Chang

University of California at Los Angeles (UCLA) Center for Vaccine Research, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, David Geffen School of Medicine UCLA, Torrance, California

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