

ONLINE FIRST

Early Impact of the US Tdap Vaccination Program on Pertussis Trends

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Objective: To evaluate the impact of the adolescent Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine) vaccination program on pertussis trends in the United States.

Design: Retrospective analysis of nationally reported pertussis cases, January 1, 1990, through December 31, 2009.

Setting: United States.

Participants: Confirmed and probable pertussis cases.

Intervention: The US Tdap vaccination program.

Main Outcome Measure: Rate ratios of reported pertussis incidence (defined as incidence among 11- to 18-year-olds divided by the combined incidence in all other age groups) modeled through segmented regression analysis and age-specific trends in reported pertussis incidence over time.

Results: A total of 200 401 pertussis cases were reported in the United States from 1990 to 2009. Overall

incidence ranged from 1.0 to 8.8 per 100 000 persons (1991 and 2004, respectively). Slope coefficients (estimated annual rate of change in rate ratios) from segmented regression showed a steady increase in pertussis incidence among adolescents 11 to 18 years old compared with all other age groups before Tdap introduction (slope=0.22; $P < .001$), and a steep decreasing trend post introduction (slope=-0.48; $P < .001$), suggesting a direct impact of vaccination among adolescents. Indirect effects of adolescent vaccination were not observed among infants younger than 1 year.

Conclusions: Changes in pertussis incidence in the United States from 2005 to 2009 revealed a divergence between 11- to 18-year-olds and other age groups, suggesting that targeted use of Tdap among adolescents reduced disease preferentially in this age group. Increased Tdap coverage in adolescents and adults is needed to realize the full direct and indirect benefits of vaccination.

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PERTUSSIS, MORE COMMONLY known as whooping cough, is a highly contagious illness caused by the bacterium *Bordetella pertussis*. This vaccine-preventable disease is most often characterized by symptoms that include prolonged cough with paroxysms, posttussive vomiting, and/or inspiratory whoop. Infants younger than 1 year have the highest morbidity and mortality from

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pertussis and are more likely to be hospitalized or experience severe complications from their infection.¹⁻⁴ The absence of classic symptoms in adolescents and adults compared with children makes pertussis difficult to recognize and diagnose in older age groups.⁵ Furthermore, adolescents and adults are important reser-

voirs of infection, spreading disease to unvaccinated or undervaccinated infants.⁶⁻⁹ Childhood vaccines that protect against pertussis have been used in the United States since the late 1940s, and vaccination coverage remains high (83.9% coverage in 2009 for ≥ 4 DTaP [diphtheria and tetanus toxoids and acellular pertussis vaccine] doses).¹⁰ However, pertussis remains endemic in the United States, with cyclic increases occurring every 3 to 5 years. Incidence is highest among infants younger than 1 year, but reported rates of disease have increased among adolescents and adults from 1980 to 2005. Multiple factors have likely contributed to the increase in the disease, including waning immunity, cyclicality in disease, and changes in diagnostic testing and reporting.^{11,12}

To target waning immunity, reduced-dose acellular pertussis vaccines combined with tetanus and diphtheria toxoids (Tdap) developed by 2 manufacturers were licensed in 2005 as a booster dose among adolescents and adults in the

United States.^{11,13} In 2006, the Advisory Committee on Immunization Practices (ACIP) recommended routine use of Tdap as a single dose among adolescents 11 to 18 years old, with preferred administration at 11 to 12 years of age. The ACIP also recommended that among adults 19 to 64 years old, a single dose of Tdap be administered to replace a single dose of Td (tetanus and diphtheria toxoids vaccine). From 2006 to 2009, Tdap coverage among adolescents 13 to 17 years of age increased from 10.8% to 55.6%.^{14,15} Coverage among adults continues to be low; the 2009 National Health Interview Survey reported that 6.6% of adults 19 to 64 years of age had received Tdap.¹⁶

We reviewed 20 years of national passive surveillance data to evaluate the impact of the adolescent Tdap vaccination program on pertussis trends in the United States, including the direct impact on adolescent disease and the indirect impact on infant disease trends.

METHODS

SURVEILLANCE AND DESCRIPTIVE EPIDEMIOLOGY

Pertussis is reported electronically to the Centers for Disease Control and Prevention (CDC) through the Nationally Notifiable Diseases Surveillance System, a passive surveillance system that relies on case reports from health care providers, laboratories, and other public health personnel.^{1,2,17,18} For this analysis, we included pertussis cases reported from 1990 to 2009; cases reported from Puerto Rico and other US territories were excluded.

Cases were classified by state and local public health personnel according to the Council of State and Territorial Epidemiologists case definition.¹⁹ The clinical case definition requires cough of greater than 2 weeks duration with at least 1 of the following clinical symptoms: paroxysms, inspiratory whoop, or posttussive vomiting. A confirmed case is defined as a person with acute cough illness of any duration and with isolation from culture, or a clinical case with either a positive result from polymerase chain reaction (PCR) or epidemiologic linkage to a laboratory-confirmed case; PCR was added to the case definition as a confirmatory test in 1997. Cases in persons 11 years or older from Massachusetts with a single acute serum IgG antipertussis toxin antibody level of at least 20 µg/mL are also classified as confirmed.²⁰ Clinical cases with no laboratory confirmation and no epidemiologic link to a laboratory-confirmed case are classified as probable. We used the state and local health department-determined classification for this analysis and included all cases classified as confirmed, probable, or with an unknown status.

STATISTICAL ANALYSIS

For age-specific trend over time analyses, cases were divided into the following age groups: younger than 1 year, 1 to 10 years, 11 to 18 years, and 19 years or older. Incidence rates were calculated using observed case counts as numerators and population estimates from the National Center for Health Statistics as denominators (bridged-race, intercensal population estimates were used for 1990-1999, and 2009 postcensal vintage estimates for 2000-2009). Case fatality was calculated using the proportion of cases with known outcome as the denominator. Pearson χ^2 , percentage change, and risk ratios were used for the comparison of proportions; $P < .05$ and 95% CIs that excluded 1.0 were considered statistically significant.

To assess for direct effects of Tdap vaccination, rate ratios were modeled using segmented regression analysis.²¹ Because Tdap coverage is significantly higher among adolescents compared with adults, we focused our analysis on adolescents and calculated rate ratios by dividing the incidence of disease among 11- to 18-year-olds by the incidence of disease in all other age groups combined (ie, <11 years or ≥ 19 years). Calculated incidence rate ratios were then modeled to allow for the evaluation of Tdap vaccination over time while accounting for temporal variability in disease trends.²¹ For the model, we defined 1990 to 2004 as the pre-Tdap period, and 2005 to 2009 as the post-Tdap period. To evaluate if increasing incidence in children from 2007 to 2009 was driving our rate ratio trends in adolescents, we conducted a secondary analysis that excluded the contribution of 1- to 10-year-olds from our denominator.

Because pertussis rates were significantly elevated in all age groups from 2004 to 2005, with much of the increase among older age groups, there was concern that accelerated increases and subsequent decreases in disease among adolescents during these years were influencing the observed trends. Therefore, 2 sensitivity analyses were conducted, including the exclusion of states that reported an overall annual incidence of more than 20.0 per 100 000 persons in either 2004 or 2005 and omitting data in its entirety from 2004 to 2005 from the segmented regression analysis. All models were assessed for autocorrelation.

To assess for indirect effects of the Tdap vaccination program, we examined rates of disease among infants younger than 1 year. The average incidence from 1990 to 2003 (pre-Tdap) was compared with the average incidence from 2006 to 2009 (post-Tdap). Since incidence was notably elevated in all age groups during 2004 to 2005, these years were excluded from this analysis to remove any influence of outlying data points on the calculated means. The means were compared using a pooled t test; $P < .05$ was considered statistically significant.

RESULTS

A total of 200 401 pertussis cases were reported in the United States from 1990 to 2009 (66.5% confirmed, 26.7% probable, and 6.8% with unknown case classification status). Patients were predominantly white (66.6%), and 53.8% were female (1.5% with unknown sex). The proportion of reported pertussis cases was similar across age groups (1-10 years [26.3%], ≥ 19 years [25.2%], 11-18 years [24.6%], and <1 year [22.7%]); 2474 (1.2%) cases had a missing age. The overall case fatality ratio was 0.18% (253 of 142 840 with known outcome), with the highest age-specific case fatality ratio observed among those younger than 1 year (0.77% [230 of 29 749 with known outcome]).

TRENDS IN PERTUSSIS INCIDENCE, 1990-2009

From 1990 to 2003, the overall incidence of reported pertussis increased gradually in the United States from 1.7 per 100 000 to 4.0 per 100 000 persons, before reaching a peak in 2004 and 2005 (average rate in 2004-2005: 8.7 per 100 000 persons). Following the peak, incidence declined to a rate of 3.5 per 100 000 persons in 2007 before increasing to 5.5 per 100 000 persons in 2009 (**Figure 1**).

Gradual increases were observed among all age groups prior to a peak in 2004 and 2005, followed by sharp de-

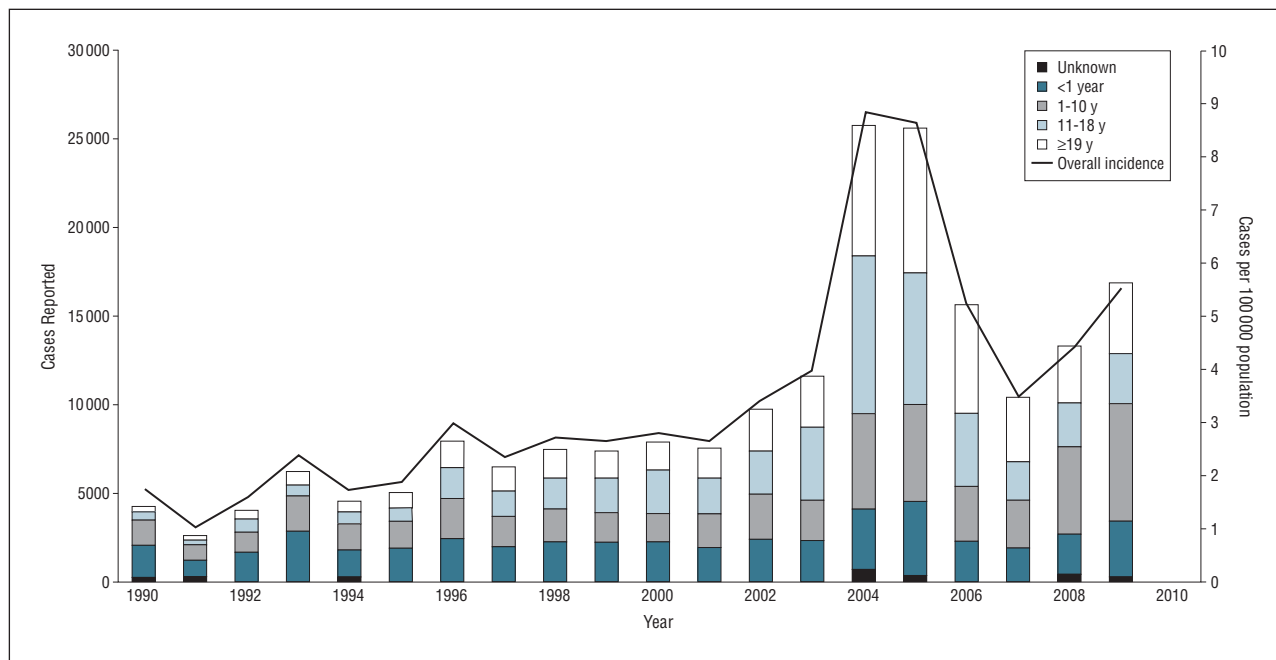


Figure 1. Reported pertussis cases, by age group, and overall incidence, 1990 to 2009.

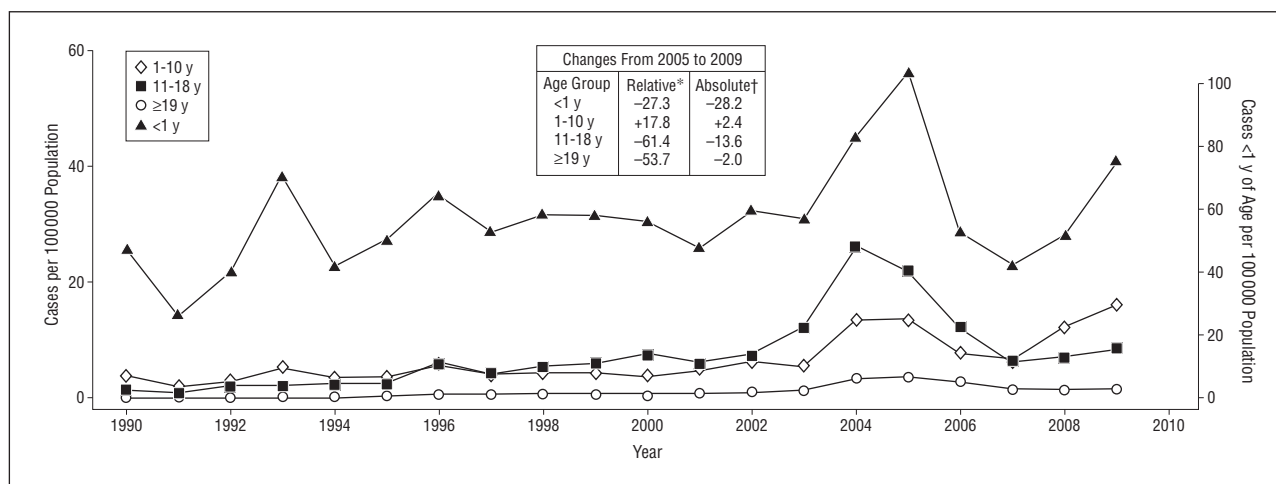


Figure 2. Incidence of reported pertussis, by age group, 1990 to 2009. *Percentage change; †cases per 100 000 population.

clines from 2005 to 2007. In line with the cyclic nature of pertussis, incidence increased from 2007 to 2009 with the largest increases in those younger than 1 year and in those 1 to 10 years old and the smallest increases among adolescents and adults (Figure 2). Throughout the study period, rates of disease among infants younger than 1 year were consistently highest (range: 26.4 per 100 000 persons in 1991 to 103.5 per 100 000 persons in 2005), whereas the incidence of pertussis among adults 19 years or older was lowest (range: 0.14 per 100 000 persons in 1991 to 3.8 per 100 000 persons in 2005).

IMPACT OF Tdap

From 1990 to 2003, the incidence of pertussis among 11- to 18-year-olds increased gradually from 1.4 per 100 000 to 12.3 per 100 000 population, before escalating to 26.5 per 100 000 persons in 2004. Following the peak, the rate

of pertussis among 11- to 18-year-olds had a relative decrease of 70.7% from 2005 to 2007 ($P < .001$). Following the low in 2007, rates of pertussis among adolescents increased 31.7% by 2009 ($P < .001$) (Figure 3A). There was a steady increasing annual trend in the ratio of incidence among adolescents to incidence among all other age groups during the pre-Tdap period (slope=0.22; $P < .001$) (Figure 3B). In the post-Tdap period the direction reversed to a significant and sustained decreasing annual trend in rate ratios which continued until 2009 (slope=-0.48; $P < .001$). When the 1- to 10-year-old age group was removed from the denominator, trends in rate ratios held. Sensitivity analyses from which we excluded high incidence states and all data points from 2004 to 2005 did not alter results.

Incidence in infants younger than 1 year fluctuated from 1990 to 2003 before peaking in 2005. Since 2005, incidence among infants has declined 28.2% (103.5 per

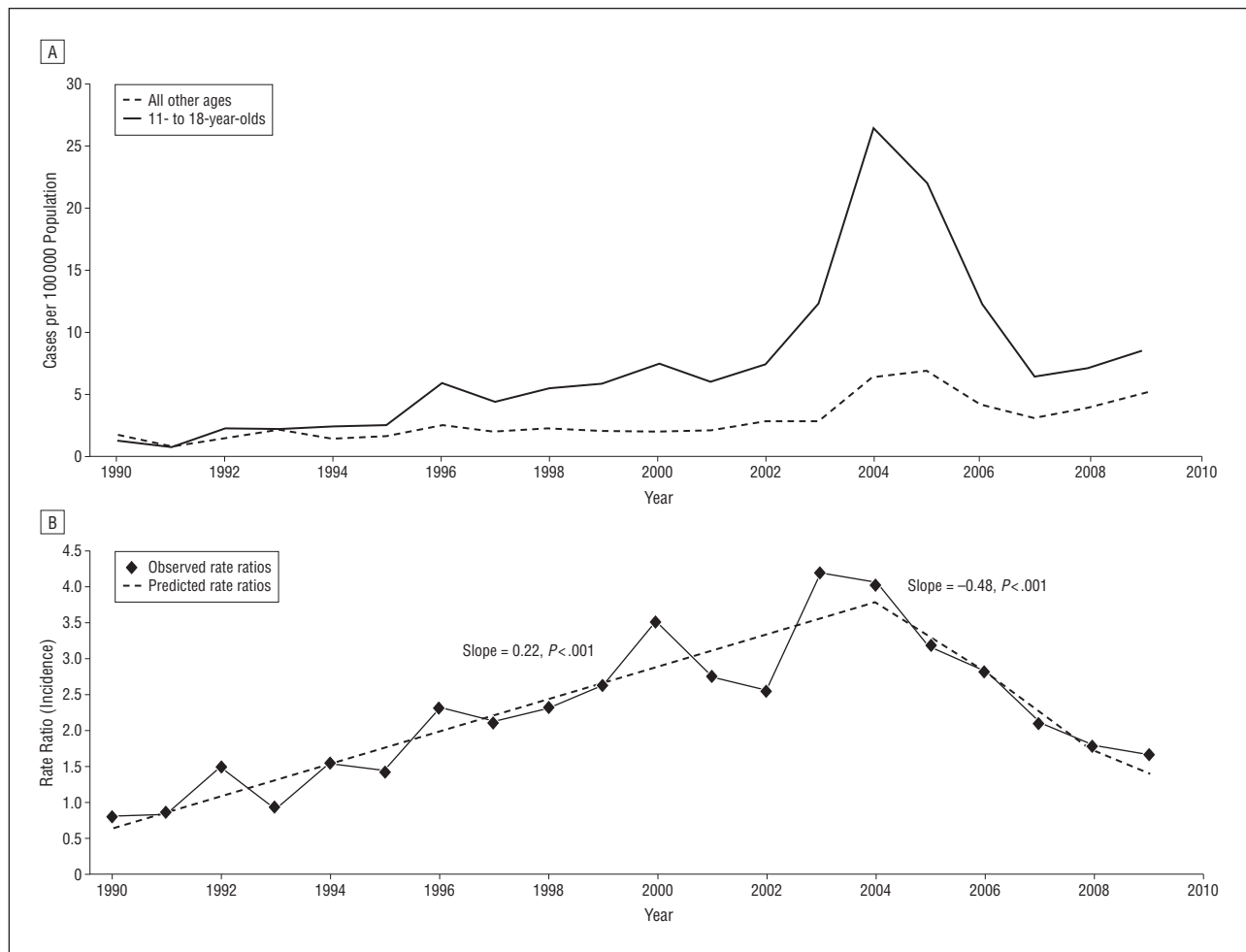


Figure 3. Pertussis incidence and rate ratios. A, Pertussis incidence, 1990 to 2009. The solid line, incidence among 11- to 18-year-olds; the dashed line, incidence among all other age groups combined. B, Rate ratios of pertussis incidence, 1990 to 2009. The solid line, observed rate ratios of incidence among 11- to 18-year-olds compared with the combined incidence among all other age groups; the dashed line, predicted rate ratios of incidence among 11- to 18-year-olds compared with the combined incidence among all other age groups.

100 000 vs 75.2 per 100 000 in 2009; $P < .001$). From 1990 to 2003, the mean incidence of pertussis among infants was 52.1 per 100 000 persons and from 2006 to 2009, the mean incidence was 55.4 per 100 000 persons ($P = .64$).

COMMENT

The primary goal of establishing the US Tdap vaccination program in 2005 was to directly reduce the burden of pertussis among adolescents 11 to 18 years of age. Four years after vaccine introduction, the early benefits of the US vaccination program were seen. Our analysis of national reported pertussis data reveals a significant decrease in the relative contribution of adolescent disease to the total overall burden of pertussis following the introduction of vaccine in 2005. While overall incidence appears to be increasing since 2007, our analysis revealed a divergence between 11- to 18-year-olds and other age groups, suggesting that the targeted use of Tdap among adolescents reduced disease preferentially in this age group. Secondary analyses that removed the influence of 1- to 10-year-olds provided reassurance that observed trends were not being driven by the recent increasing bur-

den of disease in this age group. Our findings offer strong support of direct vaccine impact and show promising progress of the Tdap program at reaching its primary goal. Tdap vaccines have been shown to be effective among the adolescent age group, with recent postlicensure studies of Tdap reporting vaccine effectiveness estimates ranging from 65.6% to 78.0% among adolescent populations.^{22,23} Continued improvements in vaccine coverage among persons 11 years or older should amplify this early impact of Tdap.

In addition to directly protecting immunized persons, vaccination programs may have the added benefit of producing indirect effects among subgroups of individuals or the population as a whole.²⁴⁻³⁰ While aspirational, a secondary goal of the adult and adolescent US Tdap vaccination program is to decrease the burden of pertussis among infants too young to be protected by vaccine. In our study, the average incidence of pertussis among infants younger than 1 year did not change significantly following Tdap introduction. Although declines in infant disease were not observed, this is not entirely unexpected. Tdap coverage among adolescents and especially among adults is still modest at best.^{15,16} In-

creased vaccination coverage of those at highest risk to transmit disease is needed before the indirect effects of Tdap are fully realized. Although the primary target of Tdap vaccination, adolescents also may not play a sizeable role in transmitting disease to infants. Studies of social mixing suggest that adolescents tend to interact primarily with other adolescents and have less contact with very young infants.^{31,32} Adults, especially parents and other caregivers of infants, have been identified in numerous studies as an important source of disease transmission to this youngest age group.^{6-9,27,33} While these data underscore the importance of a widespread approach to increasing Tdap coverage among adults, historically it has been challenging to obtain high immunization coverage in adult vaccination programs.³⁴⁻³⁶ In the next 5 years, it is therefore unlikely that Tdap coverage among the general adult population will reach proportions sufficient to provide the necessary level of protection among infants. Instead, efforts should focus on interrupting the transmission of disease to infants through targeted vaccination of adults in close contact with infants, such as household contacts and infant caregivers, a strategy known as "cocooning."³⁷⁻³⁹ In addition, in light of the June 2011 ACIP recommendations for maternal vaccination during pregnancy, health care providers should work to implement vaccination programs and provide education to women on the potential benefits of vaccination during pregnancy for the newborn infant.⁴⁰

Vaccination is the primary way to prevent morbidity and mortality from pertussis. Our analysis of national pertussis surveillance data suggests that the adolescent Tdap vaccination program is having an early impact on disease in adolescents. We used passive data from a national surveillance system that underestimates the burden of pertussis in the United States because of difficulties around diagnosis and reliance on reports from health care providers to local and state health departments.^{1,2,17,18} Our data suggest that the vaccine is likely playing an important role; however, other factors, such as the natural waxing and waning of pertussis and temporal changes in diagnostic testing and reporting, may also be contributing to our findings. Continued monitoring of pertussis trends, especially in the setting of increasing overall disease incidence in 2010 as well as improving coverage with an effective vaccine, is necessary to further evaluate the impact of Tdap. Furthermore, longitudinal surveillance data will be critical for informing the US vaccination program as to whether additional booster doses of Tdap will be necessary to maintain immunity among adults. Efforts must also be undertaken to evaluate the effectiveness of strategies such as cocooning and maternal vaccination during pregnancy, especially as barriers to implementation are overcome. Our analysis provides encouraging results that can support clinician and public health practitioner efforts to increase Tdap vaccination.

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Author Contributions: Ms Skoff had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Skoff, Cohn, Clark, Messonnier, and Martin. *Acquisition of data:* Skoff, Clark, and Martin. *Analysis and interpretation of data:* Skoff, Cohn, Clark, Messonnier, and Martin. *Drafting of the manuscript:* Skoff and Martin. *Critical revision of the manuscript for important intellectual content:* Cohn, Clark, Messonnier, and Martin. *Statistical analysis:* Skoff and Martin. *Administrative, technical, and material support:* Skoff and Clark. *Study supervision:* Clark, Messonnier, and Martin.

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