Effects of a Minimum Interval Immunization Schedule for Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccination During a Pertussis Outbreak

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Objective: To examine the impact of a minimum interval schedule for administering diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP) in infants during a statewide pertussis outbreak on receipt of inactivated polio vaccine (IPV) and pneumococcal conjugate vaccine (PCV).

Design: Retrospective cohort study using the state immunization registry.

Setting: Arizona.

Participants: Arizona children born between February 1 and September 30, 2005, who received their initial DTaP dose during a statewide pertussis outbreak (N=45 129).

Main Exposures: Children who received at least 1 dose of DTaP on the minimum interval schedule (minimum interval group) compared with children who received all doses of DTaP on the standard childhood and adolescent immunization schedule (standard group).

Outcome Measures: Timing and receipt of 3 doses of the DTaP, IPV, and PCV.

Results: Compared with children in the standard group, children in the minimum interval group were more likely to receive 3 doses of DTaP (relative risk, 1.34; 95% confidence interval, 1.32-1.35), 3 doses of IPV (1.27; 1.25-1.29), and 3 doses of PCV (1.37; 1.35-1.39).

Conclusion: Recommending a minimum interval DTaP schedule during a statewide pertussis outbreak had a positive association with the receipt of IPV and PCV, 2 vaccines normally administered at the same time as DTaP.


The introduction of the pertussis vaccination program in the 1950s in the United States has significantly reduced the incidence of pertussis; since the 1980s, however, the annual number of reported pertussis cases has increased. Although much of this rise appears to be due to increased case reports among adolescents and adults, infants remain particularly susceptible to severe disease. Pertussis infection and mortality is highest in the first few months of life. To protect these infants, receipt of 3 doses of an acellular pertussis vaccine is required for optimal protection during the first year of life.

According to the standard schedule for the diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), the first dose of the vaccine is administered starting at 2 months of age. Infants are recommended to receive the next 2 doses at 4 and 6 months of age, with 8-week intervals between each dose. If needed, a minimum interval schedule for DTaP immunization can be used to administer this vaccine earlier than the standard infant DTaP immunization schedule. The main purpose of this schedule is to provide a mechanism for children who have not completed the recommended immunizations to do so as quickly as possible. As an alternative, this schedule can be used in an outbreak setting to accelerate vaccination coverage of susceptible children. The minimum interval DTaP schedule starts with an initial dose administered as early as 6 weeks of age; the second and third doses can be given at intervals of 4 to 8 weeks after the previous doses.

One advantage of the standard immunization schedule is that other vaccines are generally administered to infants at the same clinic visit when DTaP is administered. However, the use of the minimum interval schedule for DTaP results in a lack of syn-
We performed a retrospective analysis of immunization data from 2 separate cohorts extracted from the ASIS in February 2008. All children were followed up through 12 months of age. Data reported in the registry were compared with death certificates recorded in the ADHS Office of Vital Records to exclude the study individuals who died before age 1 year. Children who were known to have moved out of the state were also excluded from the analyses. This study was granted an exemption by the ADHS Human Subjects Review Board.

To capture children who were eligible to receive their first dose of DTaP during the outbreak, from May to October 2005, we extracted ASIS vaccination data from children born between February 1 and September 30, 2005, who received their initial DTaP dose during the outbreak period (outbreak cohort).

To evaluate the effect of the minimum interval schedule during a nonoutbreak period, we analyzed vaccination data from a second cohort of children. These children were born between February 1 and September 30, 2004, and received their first DTaP dose during the same 6-month period 1 year before the statewide outbreak, from May through October 2004 (nonoutbreak cohort).

Vaccination schedules for individuals in both cohorts were categorized as the standard vaccination schedule or the minimum interval vaccination schedule, depending on when each dose of DTaP was administered. The minimum interval schedule was defined as receipt of the first dose of DTaP vaccine during the sixth week of life (42-48 days after birth) and receipt of subsequent doses 4 to 6 weeks (28-48 days) after the prior dose. Children who received at least 1 dose of DTaP on the minimum interval schedule were assigned to the minimum interval group. Those who received all doses of DTaP on the recommended schedule or later were assigned to the standard group (Figure).

To compare the socioeconomic status of the groups among the cohorts, we used participation in the Vaccines for Children (VFC) program as a proxy variable. The VFC program is a federally funded program that provides recommended pediatric vaccines to children who are at risk of not being vaccinated because of an inability to pay.

STATISTICAL ANALYSES

In each cohort, we calculated the mean age at each dose of DTaP, IPV, and PCV and the percentage of children who received 3 doses of each vaccine. These values were compared between the standard and minimum interval groups for each cohort. We used $\chi^2$ tests for comparison of categorical variables and risk ratios to determine differences in the vaccine completion percentages for 3 doses of DTaP, PCV, and IPV. Because the populations in both groups were not normally distributed, we calculated interquartile ranges to examine the variability in the ages when each dose of vaccine was given.

OUTBREAK COHORT

During May through October 2005, 45,129 children had vaccination records reported in the ASIS. Of these, 19,228 (42.6%) were included in the minimum interval group and 25,901 (57.4%) were included in the standard group. Girls constituted 49.0% of children in the standard group and 49.7% of children in the minimum interval group. In the 2 groups, 19.4% and 16.2% of children, respectively, qualified for the VFC program.

METHODS

DATA SOURCE

Since 1998, all immunizations administered to children in Arizona have been required to be reported to the Arizona State Immunization Information System (ASIIS). Providers can report vaccine administration via several mechanisms, including electronic transactions from their billing systems or electronic medical records, direct entry into a secure Internet-based application, or mailing of paper forms to the ASIIS for entry. The ASIIS also includes population-based data on children born in Arizona from birth certificate data that are downloaded on a daily basis from the ADHS Office of Vital Records. These data are used to track the percentage of the population eligible to receive vaccinations.

STUDY DESIGN

Figure. Definitions of minimum interval and standard schedule groups by week of vaccine administration.

chronization with other recommended routine vaccinations. Concern that the minimum interval schedule for DTaP would adversely affect the administration of other childhood vaccines has deterred health departments from recommending the minimum interval DTaP schedule as an outbreak control measure. Although studies have shown that hepatitis B vaccine completion rates have been improved when a minimum interval schedule was used, few data evaluating the impact of the DTaP minimum interval schedule on vaccine completion rates are available.

In 2005, Arizona experienced a community-wide pertussis outbreak involving more than 830 reported cases. In May 2005, the Arizona Department of Health Services (ADHS) recommended the use of the DTaP minimum interval schedule for all infants who had not yet received the first 3 DTaP vaccinations. The ADHS recommendation remained in effect until the outbreak ended in October 2005. To determine whether the minimum interval schedule had an adverse effect on receipt of the inactivated polio vaccine (IPV) and the pneumococcal conjugate vaccine (PCV), we performed a retrospective cohort analysis of immunization records for Arizona children during the outbreak period. In addition, we performed a similar analysis of a second cohort to determine how frequently the minimum interval schedule is used and whether it adversely affects the receipt of other vaccines in a nonoutbreak setting.
Children in the minimum interval group were 34% more likely to have received 3 DTaP doses by 1 year of age (relative risk [RR], 1.34; 95% confidence interval [CI], 1.32-1.35), 27% more likely to have received 3 doses of IPV by 1 year of age (1.27; 1.25-1.29), and 37% more likely to have received 3 doses of PCV by 1 year of age (1.37; 1.35-1.39) than those in the standard group. Compared with the children in the standard group, children in the minimum interval group were significantly more likely to have received all 3 doses of DTaP, PCV, and IPV by 1 year of age (P < .001) and to have completed these 3 doses at an earlier age (Table 1 and Table 2).

For infants born during the outbreak, individuals in the minimum interval group received all 3 doses of DTaP at a considerably younger age than children in the standard group, at mean ages of 24.1 (95% CI, 24.0-24.2) vs 30.0 (29.9-30.0) weeks, respectively (Table 2). On average, children in the minimum interval group received their first dose of DTaP 2 weeks earlier and their second dose of DTaP 5 weeks earlier compared with children in the standard group (Table 2). In addition, the mean age at which all 3 doses of IPV and PCV were administered was considerably younger for the minimum interval group than for the standard group (Table 2).

During the outbreak, the length of the interquartile ranges for the minimum interval group varied from 2.7 to 9.4 weeks, with the least variability observed at DTaP dose 1 and the greatest variability at DTaP dose 3. The interquartile ranges in the standard group were highest for IPV dose 3 (6.5 weeks) and lowest for DTaP dose 1 (1.6 weeks). Greater variation was observed with each additional dose administered, and children in the minimum interval group showed greater age variability compared with the children in the standard group. This finding was expected because some children in the minimum interval group received every dose on the minimum interval schedule (11.7%), whereas others reverted to a standard schedule or had longer intervals between each dose.

**NONOUTBREAK COHORT**

There were 44,853 children with vaccination records reported in the ASIIs who received their first DTaP dose during the 6-month period 1 year before the statewide outbreak. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort. Of these, 5355 (11.9%) were included in the nonoutbreak cohort.
SOCIOECONOMIC IMPACT

To determine whether socioeconomic status affected receipt of vaccinations on the minimum interval schedule, we evaluated the percentage of children qualifying for the VFC program by comparing the minimum interval group with the standard group for each of the cohorts. The percentage of children eligible for the VFC program was similar for both groups in a nonoutbreak setting. However, during the outbreak, a higher percentage of VFC program-eligible children were included in the standard group. These data suggest that, during an outbreak, children of lower socioeconomic status are less likely to participate in the minimum interval schedule ($\chi^2 = 77; P < .001$).

COMMENT

The use of a minimum interval schedule has been shown to have a positive effect on completion rates for the hepatitis B vaccine. Our study is, to our knowledge, the first to examine whether use of the minimum interval immunization schedule for DTaP has an adverse effect on the administration and timing of other vaccines in outbreak and nonoutbreak settings. Instead of a negative impact, receipt of at least 1 dose of DTaP on the minimum interval schedule during an outbreak had a positive association with completion rates for other vaccines. During their first year of life, children who received any DTaP vaccinations on the minimum interval schedule were more likely to receive 3 doses of DTaP, IPV, and PCV compared with children who received DTaP doses on the standard interval schedule. This was true regardless of the presence of an outbreak. During the outbreak, children in the minimum interval group were also more likely to receive all 3 vaccines at an earlier age than those in the standard group. This finding is critical because previous studies indicate that receipt of just 1 DTaP dose in infants (age, <1 year) is protective against pertussis-associated hospitalization. In addition, another study estimates that using the minimum interval schedule for the first dose of DTaP would prevent 1236 cases of pertussis and 7 deaths attributable to pertussis each year in the United States.

The percentage of children receiving vaccinations on the minimum interval schedule increased from 11.9% in the nonoutbreak cohort to 42.6% during the outbreak, indicating that many providers and clinics were following the public health recommendation to use the minimum interval schedule. Outside of an outbreak setting, the main purpose of the minimum interval schedule is to provide a mechanism for children who have not completed the recommended immunizations to do so as quickly as possible. Before the outbreak, there were no known initiatives or recommendations to promote the minimum interval schedule in Arizona children. Therefore, it was surprising that more than 10% of the children in the nonoutbreak cohort received at least 1 dose of DTaP on the minimum interval schedule. Examination of the nonoutbreak cohort revealed 763 instances of children who had not received a DTaP vaccination according to the standard schedule but who then received a minimum interval dose, which might have indicated attempts to bring children onto the standard schedule.

One particularly interesting finding in our study was that, in a nonoutbreak setting, the mean age at receipt of dose 3 for all vaccines was similar in both the minimum interval and standard groups. This was remarkably different from the outbreak cohort, in which children received their third dose of all vaccines at a younger age in the minimum interval group compared with the standard group. These findings suggest that, during an outbreak, children are more likely to receive multiple doses of vaccine on a minimum interval schedule and, therefore, at a younger age compared with children on a standard schedule.

Our study had several limitations. Despite a legal requirement for health care providers to report all vaccinations administered to children, all vaccinations are submitted to the registry. This study could not evaluate whether there were significant differences between children whose records were reported to the ASIIS compared with children whose records were not. However, because of the large sample sizes used in our study, it is unlikely that underreporting had a major effect on the outcomes.

To evaluate the timeliness and completeness of registry data, the ASIIS staff monitors the number of health care providers using the system and the frequency with which they use it. In December 2005, 82.4% of public providers and 87.3% of private providers had reported vaccinations to the system within the past 6 months. In addition, 72.9% of these providers reported immunization data on a monthly basis. Data from the population-based National Immunization Survey in 2006 indicated that 89.4% of Arizona children who were 13 months of age had received 3 DTaP doses. Our study showed that 73.2% of children who were 12 months of age and were born between February 1 and September 30, 2005, received 3 DTaP doses. These data suggest that the ASIIS may underestimate the true vaccination coverage rates in Arizona. This finding is consistent with those of previous studies of immunization registries, which have indicated that registry-based data results in lower vaccination coverage estimates than data from health care provider reports and population surveys. In these studies, the primary reason for the lower estimates was incomplete or missing records, which can result from children moving in and out of the state or from health care providers not reporting vaccine administrations.

As with any passive surveillance system, there are significant delays in the reporting of vaccination data to the immunization registry. In 2005, only 48.1% of the administered vaccinations were entered into the registry within 30 days. However, the data used in this study were accessed in 2008, minimizing the impact of reporting delays on our analyses.

The minimum interval schedule used in this study differs from the recommendations of the Advisory Committee on Immunization Practices for minimum ages and intervals between doses of vaccines. The criteria used for inclusion in the minimum interval group were more stringent than the Advisory Committee on Immunization Prac-
tices recommendations and required children to receive their DTaP doses at least 7 days before the recommended age according to the standard immunization schedule. This definition was used to avoid misclassification of doses that were administered early out of convenience rather than representing these early administrations as attempts to follow the health department’s recommendation.

We intend to examine the effect of the recommendation on the same children at 2 years of age, looking at not only the DTaP/IPV/PCV set of vaccines but also the vaccine series consisting of 4 doses of DTaP, 3 doses of poliovirus vaccine, 1 dose of measles vaccine, 3 doses of *Haemophilus influenzae* type b vaccine, and 3 doses of hepatitis B vaccine. In addition, our analyses were not able to consider the effects of health care costs and health insurance reimbursement issues. Further analyses are needed to determine the influence of these economic factors.

Our findings suggest that, in both outbreak and non-outbreak settings, recommending the use of the minimum interval schedule for DTaP does not have an adverse effect on the receipt of other childhood vaccines normally given at the same time as DTaP. Furthermore, recommending a 4-week minimum interval DTaP schedule during an outbreak, starting with DTaP dose 1 at 6 weeks of age, was associated with an increased probability of receiving 3 doses of IPV and PCV. Based on our findings, implementation of the minimum interval DTaP schedule should be considered to increase vaccination rates among susceptible individuals during a pertussis outbreak.

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**Author Contributions:** Dr Bronson-Lowe 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:** Bronson-Lowe and Anderson. **Analysis and interpretation of data:** Bronson-Lowe and Anderson. **Drafting of the manuscript:** Bronson-Lowe and Anderson. **Critical revision of the manuscript for important intellectual content:** Anderson. **Statistical analysis:** Bronson-Lowe. **Administrative, technical, and material support:** Anderson. **Study supervision:** Anderson.

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**REFERENCES**


