
Predictors of Age-Appropriate Receipt of DTaP Dose 4

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Background: In the United States, the national childhood immunization schedule calls for children to receive four doses of DTaP (diphtheria and tetanus toxoids and acellular pertussis) vaccine administered at 2, 4, 6, and 15 to 18 months. Dose 4 of DTaP is among the most frequently missed vaccines for children who are not adequately immunized.

Methods: Using the 2001 National Immunization Survey, the effect of the timeliness of the first three DTaP doses was assessed on completion of the four-dose series by age 24 months and on time by age 12 to 18 months.

Results: Missing Dose 4 was more prevalent among children who received Dose 3 late (but <16 months) than among children who received Dose 3 on time (24% vs 10%). Similarly, receiving Dose 4 late (or not at all) was more prevalent among children who received Dose 3 late (but <9 months) (39% vs 22%). An invalid Dose 4 was administered to 4.6% of those with Dose 3 late but before 9 months and to 10.6% of those with no Dose 3 before 9 months, compared to 1.2% of those with Dose 3 on time.

Conclusion: Physicians and staff can identify children at risk for missing the fourth DTaP dose or receiving it late by assessing timeliness of receipt of DTaP Dose 3 and implementing steps to ensure that at-risk children receive Dose 4 as recommended.
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Background

In the United States, the national childhood immunization schedule calls for children to receive four doses of DTaP (diphtheria and tetanus toxoids and acellular pertussis) vaccine administered at 2, 4, 6, and 15 to 18 months (with administration of Dose 4 as early as 12 months acceptable if the child is unlikely to return at 15 to 18 months).¹ Children who receive a dose late may be able to catch up at their next dose by following the guidelines that specify minimum intervals between doses²; for DTaP Doses 3 and 4, the minimum interval is 6 months. Several studies have indicated that Dose 4 of DTaP is among the most frequently missed vaccine for children who are not adequately immunized.^{3–7} This is of concern because Dose 4 of DTaP helps to maintain adequate immunity during the preschool years, especially for the prevention of pertussis, which is highly communicable.^{7,8}

Risk factors for failing to receive DTaP Dose 4 have not been well described. A previous study of the association between timely early doses of hepatitis B vaccine

and completion of the three-dose hepatitis B series suggested that timeliness of early doses may play an important role in completion of a series.⁹ This study examined the effect of the timeliness of Doses 1 through 3 of DTaP on receipt of Dose 4 before 24 months and by 12 to 18 months. In addition, for children who received DTaP Dose 3 late, the percentage that received Dose 4 before the minimum 6-month interval was determined; such doses are considered invalid and must be repeated.

Methods

In the United States, the National Immunization Survey (NIS) is the primary tool for assessing immunization coverage in preschool children. The NIS is a stratified random-digit-dial survey of households with age-eligible children conducted in all 50 states and 28 urban areas. Demographic data and permission to contact the child's immunization provider(s) are obtained in the household survey, followed by a mailed survey of health providers to obtain vaccination histories. Only provider-verified vaccinations are included in the final estimates. Sampling weights are used in the analysis to ensure that the results are representative of the U.S. population of children aged 19 to 35 months. Details of the NIS methods appear elsewhere.^{10,11}

To allow all children equal time to receive vaccinations, vaccinations administered before 24 months among children

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at least 24 months of age ($N=16,441$) were examined. As per national guidelines, the child was on time for each of Doses 1 through 3 if he/she received the dose by 2, 4, and 6 months, respectively (i.e., before turning 3, 5, and 7 months, respectively). Dose 4 was considered on time if it was administered at 12 to 18 months of age (i.e., <19 months) and was given at least 6 months after Dose 3. Dose 4 was considered late if it was not received before 19 months.

This analysis accounted for the possibility that a late Dose 3 could preclude receipt of Dose 4 before 24 months of age. Because of the 6-month interval required between Doses 3 and 4, Dose 3 administered on or after 18 months would prevent receipt of Dose 4 before 24 months, and Dose 3 administered on or after 13 months would prevent receipt of Dose 4 on time. To examine receipt of Dose 4 before 24 months among those who could have received it by that time, the analysis was limited to children who received Dose 3 before 16 months (i.e., by 15 months) ($n=15,108$), thus allowing at least 2 months to receive Dose 4 before 24 months after the required 6-month interval. Similarly, timeliness of Dose 4 among children who received Dose 3 on time ($n=11,224$) was compared to that among children who received Dose 3 late but before 9 months (i.e., by 8 months) ($n=2441$) allowing them to receive Dose 4 at 15 to 18 months as recommended. The interval between Doses 3 and 4 was also examined to determine validity of Dose 4.

From late in 2000 until mid 2002, a shortage of DTaP led the Advisory Committee on Immunization Practices (ACIP) to recommend deferral of Dose 4 if providers did not have sufficient vaccine quantities.^{12,13} The 2001 NIS includes children who were eligible for the fourth DTaP dose during February 1999 through December 2001; the DTaP shortage may therefore have impacted this analysis. To evaluate the sensitivity of the analysis to the vaccine shortage, 1999 NIS data, prior to the shortage, were also examined.

Estimates of coverage rates, odds ratios (ORs), and 95% confidence intervals (CIs) were calculated using SUDAAN (Research Triangle Institute, Research Triangle Park NC, 1997), which accommodates complex sample designs. Multivariate logistic regression was used to assess the effect of timeliness of Doses 1 through 3 of DTaP as well as demographic/provider factors (maternal education and age, child's race/ethnicity and birth order, whether family moved since child's birth, and number and types of vaccination providers) on receipt of Dose 4 of DTaP before 24 months.

Results

Overall, 98% of children received at least one dose of DTaP before 24 months, 96% received at least two doses, and 94% received at least three doses, while only 80% received all four doses before age 24 months (not shown). In bivariate and multivariate analyses, it was found that timeliness of Doses 2 and 3 of DTaP were the strongest predictors of receipt of the fourth dose before 24 months (Table 1). Among children with Dose 3 before 16 months, receipt of Dose 3 on time was a strong predictor of receiving Dose 4 before 24 months (adjusted $OR=1.8$). Other significant characteristics included mother aged >30 years, mother with higher

education level, firstborn child, and having only one vaccination provider. However, none of these factors was a stronger predictor of receipt of the fourth DTaP dose than the timeliness of Dose 3.

Timeliness of vaccination receipt also decreased progressively by dose, with 87% receiving Dose 1 by 2 months, 77% receiving Dose 2 by 4 months, and 67% receiving Dose 3 by 6 months. Sixty-four percent received Dose 4 at 12 to 18 months with a 6-month interval after Dose 3 (not shown).

Given that Dose 3 was the strongest predictor of missing Dose 4, the impact of timeliness of Dose 3 on timely receipt of Dose 4 was more closely examined (Table 2). Of the children who received Dose 3 late but before 9 months ($n=2441$), only 61% received Dose 4 on time, compared with 78% among children who received Dose 3 on time. In addition, receipt of a late Dose 3 was associated with more children receiving an invalid Dose 4; an invalid Dose 4 was administered to 4.6% of those with Dose 3 late but before 9 months and to 10.6% of those with no Dose 3 before 9 months, compared to 1.2% of those with Dose 3 on time. Results of timeliness of Doses 3 and 4 were similar in 1999, suggesting that the DTaP shortage did not substantially impact this analysis.

Discussion

DTaP vaccination has dramatically decreased morbidity and mortality among children,¹⁴ but optimal protection relies on adherence to the ACIP guidelines. Overall, one third of children did not receive Dose 4 by age 18 months. Timeliness of Dose 4 was found to be more strongly associated with timeliness of earlier doses, especially Dose 3, than with other factors previously identified.⁵

Children who received Dose 3 late but early enough to have sufficient time to catch up were more likely not to receive Dose 4 before 24 months, compared to those who received Dose 3 on time. Among the 25% of children who received Dose 3 late but before 16 months, 24% did not receive Dose 4 before 24 months. In addition, 8% of children did not receive Dose 3 before 16 months (i.e., they had little or no opportunity to receive Dose 4 before 24 months due to the 6-month interval requirement), of which nearly all (95%) failed to receive Dose 4 before 24 months. Combining these two groups, 14% of children were missing their Dose 4 of DTaP at 24 months of age in association with a late Dose 3 (i.e., two thirds of the 20% of children who did not receive their Dose 4 before 24 months).

This study also found that more children who were late for the third DTaP dose received an invalidly early Dose 4, compared to children who were on time. Physicians not aware of the interval requirement or without complete vaccination histories could inadvertently administer an invalid dose during the otherwise

Table 1. Factors predicting completion of fourth dose of DTaP^a before 24 months

Factors	Bivariate analysis			Multivariate analysis			<i>p</i> value
	Unweighted <i>n</i>	% Dose 4 <24 mo. ^b	95% CI	Unweighted <i>n</i>	Adjusted OR ^c	95% CI	
Dose 1							0.32
On time ^d	14,430	85.2	84.3–86.2	14,012	1.2	0.9–1.5	
Late ^e	2,011	42.8	39.4–46.3	1,096	referent		
Dose 2							<.01
On time ^f	12,897	88.3	87.3–89.2	12,760	1.6	1.3–2.1	
Late	3,544	50.9	48.3–53.5	2,348	referent		
Dose 3							<.01
On time ^g	11,224	90.2	89.3–91.1	11,224	1.8	1.5–2.3	
Late but before 16 mo. ^h	3,884	76.3	74.1–78.5	3,884	referent		
Not before 16 mo.	1,333	5.1	3.3–6.9	—	—	—	
Maternal education							0.02
<High school	2,110	75.0	72.2–77.8	1,865	referent		
High school	4,983	76.7	74.8–78.5	4,503	1.0	0.8–1.3	
>High school	2,884	81.5	79.2–83.8	2,668	1.3	1.0–1.7	
College graduate	6,464	85.1	83.6–86.5	6,072	1.4	1.0–1.8	
Race/ethnicity							0.14
Hispanic	3,222	80.3	78.0–82.6	2,941	1.4	1.0–1.8	
White	9,874	81.2	80.0–82.5	9,210	1.1	0.9–1.4	
Black	2,486	73.5	70.7–76.4	2,167	referent		
Other	859	80.3	75.5–85.0	790	1.0	0.6–1.6	
Provider type							0.33
All public	2,445	74.9	72.0–77.7	2,173	referent		
All private	8,907	81.8	80.5–83.1	8,309	0.9	0.7–1.1	
Other	5,089	78.7	76.8–80.6	4,626	1.0	0.8–1.2	
Number of providers							<0.01
1	11,499	81.6	80.4–82.7	10,621	1.5	1.2–1.8	
≥2	4,941	75.9	73.9–77.9	4,487	referent		
Moved since birth							0.05
Yes	1,499	74.9	71.3–78.6	1,333	referent		
No	14,942	80.4	79.4–81.5	13,775	1.3	1.0–1.7	
Age of mother (years)							<0.01
<20	445	81.8	76.2–87.4	403	1.7	1.0–2.9	
20–29	7,068	76.1	74.5–77.8	6,416	referent		
30+	8,928	82.8	81.6–84.1	8,289	1.3	1.1–1.6	
Firstborn status							<0.01
No	9,831	76.6	75.3–78.0	8,882	referent		
Yes	6,610	84.7	83.2–86.2	6,226	1.5	1.3–1.8	

^aMultivariate analysis limited to 15,108 children who received the third dose <16 months.^bWeighted analysis.^cWeighted OR adjusted for other factors in table.^dReceived first dose by 2 months (i.e., <3 months).^eReceived fourth DTaP dose >18 months or no fourth dose recorded.^fReceived second dose by 4 months (i.e., <5 months).^gReceived third dose by 6 months (i.e., <7 months).^hReceived third dose at 7 to 15 months.

CI, confidence interval; DTaP, diphtheria and tetanus toxoids and acellular pertussis; OR, odds ratio.

recommended 15- to 18-month period. A child who receives an invalid dose must receive an additional dose in order to be considered adequately immunized. Furthermore, for an invalid Dose 4 of DTaP, the repeat dose must be administered a minimum of 6 months after the invalid dose,² rather than from the original Dose 3, thus pushing completion of the recommended series even further forward. DTaP has also been shown to produce increased rates of adverse reactions when administered too frequently.^{15,16} Thus, an invalid Dose 4 of DTaP represents not only wasted vaccine, time, and

money,¹⁷ but also unnecessary increased risk of adverse reactions and difficulty in completing the series by 18 months.

This study had several limitations. First, information regarding vaccinations administered after the time of the interview was not available in the NIS; furthermore, the analysis was limited to vaccinations received before 24 months. Although some doses may have never been administered, doses not received before 24 months were considered to be late. Also, the number of children who are either late for or are missing one or more

Table 2. Timeliness of Dose 4 of DTaP by timeliness of Dose 3

Time of dose		Unweighted <i>n</i>	% Dose 4 on time ^a	95% CI	% Dose 4 late ^b	95% CI	% Dose 4 invalid ^c	95% CI
2001	On time ^d	11,224	78.2	77.0–79.4	20.6	19.4–21.7	1.2	0.9–1.5
	Late but <9 mo. ^e	2,441	60.7	57.6–63.8	34.7	31.6–37.7	4.6	3.3–5.9
	Not <9 mo.	2,776	14.3	12.3–16.2	75.2	72.8–77.6	10.6	9.0–12.2
1999	On time	10,762	78.8	77.6–80.0	19.7	18.5–20.8	1.5	1.1–1.9
	Late but <9 mo.	2,561	62.2	59.2–65.2	32.4	29.5–35.2	5.4	4.1–6.8
	Not <9 mo.	2,447	15.1	12.9–17.3	71.9	69.1–74.7	13.0	10.9–15.1

^aReceived fourth DTaP dose between 12 and 18 months of age and ≥ 6 months between the third and fourth doses.

^bReceived fourth DTaP dose >18 months of age or no fourth dose recorded.

^cReceived fourth DTaP dose <12 months of age or dose administered <6 months after the third dose.

^dReceived third dose by 6 months (i.e., <7 months).

^eReceived third dose at 7 to 9 months.

CI, confidence interval; DTaP, diphtheria and tetanus toxoids and acellular pertussis.

of their DTaP doses could be underestimated due to possible response bias, as households with lower immunization coverage might be less willing to complete the interview. Conversely, we relied on complete identification of vaccination providers by the household respondent and complete reporting of vaccination histories by those providers. If some providers were omitted, or if some providers did not provide complete information, timeliness and completion of doses may have been underestimated.

Strengths of this study should also be noted. First, the NIS is a large nationally representative sample of preschool children, with relatively high CASRO (Council of American Survey Research Organizations) response rates (approximately 67%) and complex weighting methodology to adjust for potential biases. Second, to improve accuracy of information and validity of findings, healthcare provider records were used to verify vaccination histories.

Some additional analyses are warranted. Although the vaccine shortage of 2000–2001 did not substantially affect results in the 2001 NIS data, most children in this analysis received their Dose 4 before the shortage. This analysis should be re-evaluated with future NIS data, which will more completely reflect the effect of the shortage. Additional research should also evaluate the impact of changes to the recommended schedule. For example, during 2002, the 6-month interval requirement between DTaP Doses 3 and 4 for determining validity of Dose 4 was relaxed to 4 months,² and a heptavalent vaccination was licensed that combines DTaP, hepatitis B, and *Haemophilus influenzae* type b (Hib).¹⁸

The findings in this study can provide key information for clinical prevention efforts. Late receipt of Dose 3 could be used as a “red flag” to alert the physician that the child is at risk for missing Dose 4 or for receiving it too soon after Dose 3.

Physicians can help to ensure that children appropriately complete the DTaP series by reinforcing the

importance of the DTaP Dose 4 with parents of children who are late for Dose 3, keeping the child’s immunization history up to date, and employing reminder/recall systems. In addition, physicians should ensure that they do not miss an opportunity to immunize the child on future visits after the 6-month minimum interval requirement between Doses 3 and 4 is satisfied.

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