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Mixing of diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in a population of children in managed care

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Abbreviations: ACIP, Advisory Committee on Immunization Practices; CI, confidence intervals; DTaP, diphtheria, tetanus and acellular pertussis vaccine; FDA, Food and Drug Administration; NCQA, National Committee for Quality Assurance; NDC, National Drug Code; NIS, National Immunization Survey; ORD, Optum Research Database; US, United States

The Advisory Committee on Immunization Practices recommends administering diphtheria, tetanus and acellular pertussis (DTaP) vaccines to children at 2, 4, 6, 15–18 months, and 4–6 y of age; preferably with the same-brand vaccine for the whole series. We estimated age-appropriate DTaP dose completion and the proportion of children receiving a "mixed" DTaP vaccination series (ie, including DTaP vaccines from ≥2 brands) across the 3 milestones. Commercially-insured children born between 01/01/2003 and 04/30/2011 were identified from United States health insurance claims data and assigned to ≥1 of 3 study cohorts based on the duration of continuous health plan enrollment: 1) birth to <8 months; 2) birth to <20 months; 3) birth to <7 years. Dose completion and brand mixing of the first 3, first 4 or all 5 doses were measured in the respective cohorts. Administered DTaP vaccinations were identified in claims data and classified by brand (based on vaccine components and manufacturer). The analysis included children who received ≥2 DTaP vaccinations and had known brand information for all doses. Age-appropriate dose completion was 77% with 3 doses (<8 months cohort), 71% with 4 doses (<20 months cohort), and 85% with 5 doses (<7 years cohort). Mixed DTaP series were received by 4.7% (95% confidence interval [CI]: 4.6%-4.7%) in the <8 months cohort, 29.0% (95% CI: 28.6%–29.4%) in the <20 months cohort, and 39.0% (95% CI: 34.5, 43.6) in the <7 years cohort. DTaP mixing was just 4.7% for the first 3 doses but subsequently increased with the number of administered doses.

Introduction

Pertussis outbreaks have decreased substantially in the United States (US) since the diphtheria and tetanus toxoids combined with whole cell pertussis vaccine was first introduced in the 1940s.[1,2] In 1991, the first diphtheria, tetanus and acellular pertussis vaccines (DTaP) were licensed for use in the US.[3] Currently, the US Advisory Committee on Immunization Practices (ACIP) recommends administering DTaP at ages 2, 4, 6 and 15–18 months (the fourth dose may be administered as early as age 12 months, but a minimum interval of 6 months from the third dose is recommended), followed by a fifth dose given between ages 4–6 y.[4,5]

In 2010, the DTaP vaccination completion rate among US children aged 19–35 months, as measured by the National Immunization Survey (NIS), was 95.0% for ≥3 doses and 84.4% for ≥4 doses.[6,7] Despite these high national estimated completion rates, pertussis outbreaks continue to occur.[8,9] Since the 1980s, pertussis epidemics have occurred on a regular cycle, peaking every 3–4 years,[10,11] with large epidemics in 2005, 2010 and 2012.[9,12]

Various DTaP vaccines are, or have been, available in the US, including trivalent vaccines (*Daptacel*®,[13] *Tripedia*®[14] and *Infanrix*™[15]), and quadrivalent/pentavalent vaccines (*TriHiBit*®,[14,16] *Pediarix*®,[17] *Pentacel*™[18] and *Kinrix*™[19]) (Supporting information Figure). Based on their components and their manufacturing process, these 7 vaccines can be grouped under 3 different brands (**Table 1**): Sanofi-Connaught, Sanofi-Pasteur, and GlaxoSmithKline. The manufacturer Sanofi-Aventis produced 4 vaccines grouped in 2 separate brands due to differences in the vaccines' production. The Sanofi-Connaught brand includes *Tripedia*®, which was licensed by Connaught in 1992

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Table 1. DTaP vaccines available during the study period (2003–2011) and vaccine brand definitions

Brand	Manufacturer	Vaccine Name	Formulation	Trivalent / Combination	Approved Dose Number	CPT® [a] Code
Sanofi-Connaught	SanofiAventis	*Tripedia*[b]	DTaP	Trivalent	1–5	90700[c]
		TriHiBit[b]	DTaP+Hib	Quadrivalent	4	90721
Sanofi-Pasteur	SanofiAventis	*Daptacel*	DTaP	Trivalent	1–5	90700[c]
		Pentacel	DTaP+IPV+Hib	Pentavalent	1–4	90698
GlaxoSmithKline	GlaxoSmithKline	*Infanrix*	DTaP	Trivalent	1–5	90700[c]
		Pediarix	DTaP+IPV+HepB	Pentavalent	1–3	90723
		Kinrix	DTaP+IPV	Quadrivalent	5	90696

[a]CPT copyright 2012 American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association.
[b]Production of *Tripedia* was discontinued by Sanofi Pasteur in February 2011.[30]
[c]*Tripedia*, *Pediarix* and *Daptacel* are all billed using the same CPT® code, therefore National Drug Codes were used to distinguish vaccine brands when they were available on the claim.

and eventually produced by Sanofi-Pasteur. When *Tripedia*® is reconstituted with *ActHIB*®, it is known as *TriHiBit*®. As of February 2011, *Tripedia*® was no longer marketed. The Sanofi-Pasteur brand includes *Daptacel*® (2002) and *Pentacel*™ (DTaP+IPV+Hib, 2008), which were licensed by the Canadian subsidiary Aventis-Pasteur, Ltd. The third brand includes *Infanrix*™ (1997), *Pediarix*® (DTaP+IPV+HepB, 2002), and *Kinrix*™ (DTaP+IPV, 2008), all produced by the GlaxoSmithKline group of companies. The DTaP vaccines produced by GSK contain 3 pertussis antigens: inactivated pertussis toxoid (PT; 25mcg), filamentous hemagglutinin (FHA; 25mcg) and pertactin (PRN; 8 mcg). The DTaP vaccines produced by Sanofi-Pasteur contain 5 pertussis antigens: detoxified PT (10 mcg), FHA (5 mcg), PRN (3 mcg), and fimbrial proteins 2 and 3 (5 mcg). *Tripedia*® contains 2 pertussis antigens: PT (approximately 23.4mcg) and FHA (approximately 23.4 mcg). For pertussis vaccines, protective antibodies levels have not been established because there is no proven correlate of protection.[20]

Due to the lack of data regarding the efficacy, safety, and immunogenicity of using vaccines from multiple brands in a DTaP vaccination series (i.e., "mixing"), the Food and Drug Administration (FDA) and ACIP recommend immunizing with the same DTaP vaccine brand throughout the entire series.[4] However, if the prior vaccination source cannot be determined or the same brand is not available, then the ACIP recommends proceeding with any of the licensed DTaP vaccines.[21] Recent research into the safety and immunogenicity of 2 different mixed brand schedules for pentavalent DTaP/Hib/IPV vaccine found significant differences in antibody response and adverse events between the 2 groups, but this study lacked a comparison group of children receiving all 3 doses of the same brand.[22] Although these results suggest that safety and immunogenicity of mixed and unmixed series may differ, data from 2 studies examining the immunogenicity of mixed versus an unmixed primary DTaP series found similar tolerability and immunogenicity, as did a study examining interchangeability for the fourth dose in the series. Greenberg et. al. (2002) found that 1–2 doses of *Tripedia*® followed by *Infanrix*™ for the remaining dose(s) had comparable safety and immunogenicity to a 3-dose series of *Tripedia*®.[23] A similar study by von König et. al. (2000) found DTaP series with 1–2 doses of the now discontinued *Acel-Immune*® (Wyeth) followed by *Tripedia*® for the remaining doses, had comparable safety and immunogenicity to a 3-dose series of *Tripedia*®.[24] While these studies evaluated the immunogenicity of mixed series, clinical efficacy was not tested. Further, some of the vaccines evaluated in these studies are no longer on the market, and it's unknown whether results would be similar when comparing mixed vs. unmixed primary DTaP series of the currently licensed vaccines.

Estimates for the receipt of different DTaP vaccine brands in a series (i.e., mixing) in the real-world setting are not currently available. Given the limited and conflicting information about the safety and efficacy of mixed series, in particular for the currently licensed vaccines, additional research may be warranted, and understanding how frequently infants receive mixed vaccination series will inform this need. The primary purpose of this study was to estimate the proportion of infants and children who receive a mixed DTaP vaccination series within the first 3 doses of the series, within the first 4 doses, or over all 5 doses. Age-appropriate dose completion rates were also determined.

Results

Study cohorts and characteristics

Figure 1 presents the study sample selection. Among children with ≥2 DTaP vaccinations, complete brand information was available for approximately 45% (N = 254,119) of children who were continuously enrolled from birth to <8 months, 17% (N = 59,513) of children in the <20 months cohort, and 3% (N = 462) of children in the <7 years cohort.

Characteristics of children in the 3 cohorts, and comparisons between those with complete brand information and those with incomplete brand information, are provided in **Table 2**. Gender and geographic distributions were similar across the 3 cohorts. The cohorts comprised slightly more males (51–53%) than females, and children were primarily from the South and Midwest regions, consistent with the geographic distribution in the source database population. Most subjects received a pentavalent vaccine for their first dose in the series. Differences by year of birth were due to the length of enrollment required for inclusion in each of the cohorts: the <8 months and <20 months cohorts therefore include patients born more recently than the <7 years

cohort. Significant differences were observed between children with complete and incomplete brand information in the number of DTaP vaccinations, type of vaccine administered upon series initiation (trivalent, or quadrivalent/pentavalent), provider type, and birth year for all 3 cohorts; and by geographic region for the <8 months and <20 months cohorts.

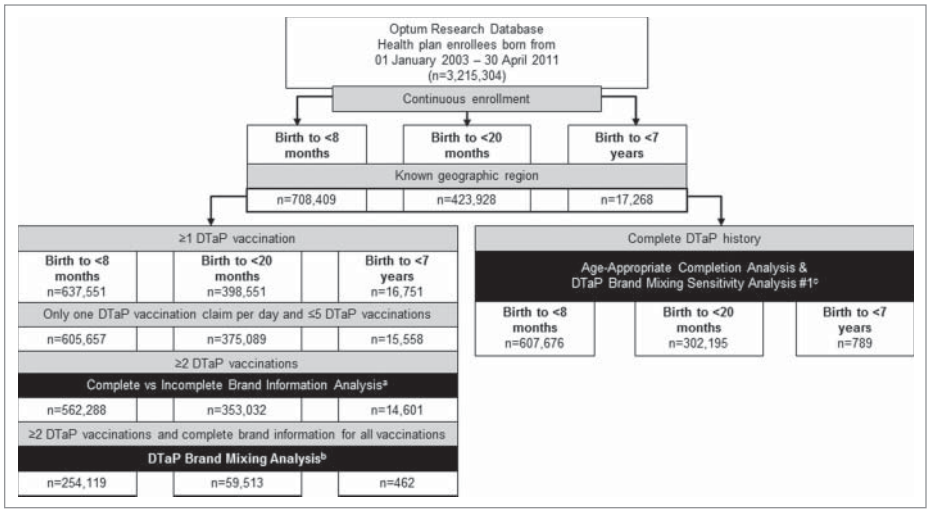

Figure 1. Study cohort selection [a]Brand could not be determined for >95% of trivalent DTaP vaccinations recorded with CPT code 90700. Comparisons between children with complete vs incomplete brand information were made among those with ≥2 DTaP vaccinations. [b]The main analysis of DTaP brand mixing was conducted among children with ≥2 DTaP vaccinations and complete brand information. [c]Between 2003–2005, trivalent DTaP vaccinations submitted for reimbursement with the code 90700 were changed to a general vaccination code by one of the claims processing systems, therefore some children vaccinated during this period may have incomplete vaccination history. Children with vaccinations processed by the affected system during this time period were excluded to identify a subset with complete DTaP vaccination history for analysis of age-appropriate dose completion and the DTaP brand mixing sensitivity analysis #1.

Age-appropriate DTaP Series Completion

Age-appropriate dose completion rates in the subsets of patients with complete DTaP history were 77% with 3 doses in the <8 months cohort, 71% with 4 doses in the <20 months cohort, and 85% with 5 doses in the <7 years cohort. Vaccination completion increased by birth year. Among infants in the <8 months cohort, 3-dose completion increased from 71% for the 2003 birth cohort to 79% for the 2010 birth cohort. Among children in the <20 months cohort, 4-dose completion increased from 66% in the 2003 birth cohort to 73% in the 2009 birth cohort. Five-dose completion remained stable at 85% for children born in 2003 or 2004 (Supporting Information **Table 2**).

DTaP brand mixing

The DTaP mixing results are presented in **Table 3**. Among infants in the <8 months cohort with ≥2 DTaP vaccinations and complete brand information, 4.7% had DTaP mixing within the first 3 doses. In the <20 months cohort, 29.0% of children had mixing within the first 4 series doses, and in the <7 years cohort, 39.0% of children had mixing within the 5-dose vaccination series.

As shown in **Table 3**, DTaP mixing estimates from the sensitivity analysis which evaluated mixing among children with complete DTaP history (Sensitivity #1) confirmed the mixing rates observed in the primary analysis of the first 3 and 4 doses in the series. The sample size of patients enrolled from birth to <7 years with complete DTaP history was too small to provide reliable estimates for the 5-dose series.

Additional sensitivity analyses which examined the impact of unknown brand information resulted in widely ranging mixing estimates (**Table 3**), but both showed lower mixing rates within the first 3 doses of the series and higher rates for the first 4 doses and the complete 5 dose series.

Estimates of DTaP mixing by gender, geographic region and birth year are shown in **Table 4**. The percentages of males and females who received mixed series were similar within each cohort, but DTaP mixing varied by geographic region: in the <8 months cohort, DTaP mixing was more prevalent in the South and West regions of the US versus the Midwest and Northeast regions; in the <20 months cohort, DTaP mixing was lowest in the Northeast region vs. the other regions; and in the <7 years cohort, DTaP mixing was lowest in the Northeast region and highest in the West region (**Table 4**).

Figure 2 illustrates the results of our DTaP mixing analysis by birth year. For those in the <8 months cohort, the highest mixing rate (10%) was observed among infants born in 2008. For those in the <20 months cohort, the highest mixing rate (44%) occurred among children born in 2005, and for those in the <7 years cohort, the mixing rate was higher for children born in 2004 (44%).

Discussion

In this analysis of immunized children in a managed care plan, we estimated that DTaP mixing rates for the first 3 doses in the vaccination series were approximately 4–5% (ranging up to 19% in sensitivity analyses), while mixing for doses 1–4 and 1–5 was much higher. This was not surprising given that the first 3 DTaP doses are typically administered by age 6 months, while doses 4 and 5 are administered approximately 1 and 3.5 y later, respectively. Over the course of several years, multiple factors, including vaccine supply, change in providers, or patient relocation, may result in DTaP product mixing in a vaccination series.

When we examined the proportion of children with mixed series by birth year, increased mixing was observed among infants

Table 2. Patient and vaccine characteristics of children with complete and incomplete brand information with corresponding P values

	Birth to <8 Months Continuous Enrollment			Birth to <20 Months Continuous Enrollment			Birth to <7 Years Continuous Enrollment		
	Complete Data[a] N=254 ,119	Incomplete Data[b] N=308 ,169	Complete/ Incomplete	Complete Data[a] N=59 ,513	Incomplete Data[b] N=293 ,519	Complete / Incomplete	Complete Data[a] N=462	Incomplete Data[b] N=14 ,139	Complete/ Incomplete
	%	%	P value[a]	%	%	P value[a]	%	%	P value[a]
Gender									
Male	51.2	51.4	0.151	51.4	51.4	0.990	52.8	51.6	0.614
Female	48.8	48.6		48.6	48.6		47.2	48.4	
Geographic region									
Northeast	11.3	11.2	<0.001	10.9	11.3	<0.001	10.8	11.7	0.480
Midwest	30.2	27.0		27.2	28.2		26.2	28.1	
South	43.5	43.4		46.5	42.8		40.9	40.8	
West	15.0	18.5		15.4	17.6		22.1	19.4	
Year of birth									
2003	4.5	18.9	<0.001	8.3	14.7	<0.001	58.2	74.5	<0.001
2004	7.5	10.9		9.4	12.4		41.8	25.5	
2005	9.4	14.5		9.1	16.0		—	—	—
2006	10.4	18.2		10.8	17.1		—	—	—
2007	11.9	17.2		12.2	17.6		—	—	—
2008	17.9	11.8		25.2	14.6		—	—	—
2009	23.4	5.6		24.9	7.5		—	—	—
2010	15.1	3.0		—	—	—	—	—	—
Number of DTaP vaccinations									
2	14.0	18.0	<0.001	8.5	7.7	<0.001	9.3	4.0	<0.001
3	85.9	81.6		41.5	22.8		26.6	7.5	
4	0.1	0.4		49.0	68.7		48.3	39.0	
5	0.0	0.1		1.1	0.8		15.8	49.5	
First vaccination provider type									
Pediatrics	86.9	90.0	<0.001	86.2	89.1	<0.001	77.3	88.9	<0.001
Family practice	9.3	7.3		9.2	8.0		10.2	7.5	
Other specialty	3.7	2.6		4.5	2.8		12.6	3.6	
Unknown	0.1	0.1		0.2	0.1		0.0	0.0	
First administered DTaP vaccine type									
Trivalent	3.0	86.0	<0.001	7.1	56.7	<0.001	0.2	65.4	<0.001
Quadrivalent/Pentavalent	97.0	14.0		92.9	43.3		99.8	34.6	

[a]Children with ≥2 DTaP vaccinations and complete brand information on all administered DTaP vaccinations.
[b]Children with ≥2 DTaP vaccinations who are excluded from the DTaP brand mixing analysis due to incomplete brand information for at least one vaccination.
[c]Chi-square p-values testing the difference in the distribution of proportions comparing patients with complete and incomplete brand information.

Table 3. Proportion of children with mixing in their DTaP vaccination series

Cohort	Age-appropriate Doses	Analysis (N)	%	95% CI
Birth to <8 Months Continuous Enrollment	Doses 1–3	Estimate (N=254, 119)	4.7	(4.6, 4.7)
		Sensitivity #1 (N=231, 242)	5.1	(5.0, 5.2)
		Sensitivity #2 (N=300, 020)	4.2	(4.2, 4.3)
		Sensitivity #3 (N=300, 020)	19.2	(19.1, 19.4)
Birth to <20 Months Continuous Enrollment	Doses 1–4	Estimate (N=59, 513)	29.0	(28.6, 29.4)
		Sensitivity #1 (N=48, 003)	29.1	(28.7, 29.5)
		Sensitivity #2 (N=191, 859)	12.0	(11.9, 12.2)
		Sensitivity #3 (N=191, 859)	78.0	(77.8, 78.2)
Birth to <7 Years Continuous Enrollment	Doses 1–5	Estimate (N=462)	39.0	(34.5, 43.6)
		Sensitivity #1 (N=15)	80.0	(51.9, 95.7)
		Sensitivity #2 (N=5, 999)	13.0	(12.1, 13.8)
		Sensitivity #3 (N=5, 999)	95.3	(94.7, 95.8)

Estimate: Includes children with ≥2 DTaP vaccinations and complete brand information on all administered DTaP vaccinations.
Sensitivity #1: Conducted among children with complete DTaP vaccination history by excluding those with vaccinations processed between 2003 and 2005 by the claims processing system that changed DTaP vaccinations submitted for reimbursement with CPT® code 90700 to a general vaccination code.
Sensitivity #2: DTaP vaccinations with unknown brand were assumed to be the same brand as the first administered DTaP vaccine with known brand information.
Sensitivity #3: Children with a DTaP vaccination with unknown brand were assumed to have a mixed series.

born in 2008 and later for the <8 months cohort; mixing rates were highest among children born in 2005 and 2008 in the <20 months and <7 years cohorts, respectively. Potential reasons for changes in the proportion of DTaP mixing over time include contract changes, the FDA approval of *Kinrix™* in 2008, and a shortage of Hib vaccine produced by Merck (*PedvaxHIB®*, *Comvax®*) from 2007–2009,[25] which may have resulted in a switch to Sanofi-Pasteur's Pentacel® vaccine which contains Hib, in order to complete the Hib series (See Supporting information Figure). Although mixing of quadrivalent/pentavalent-containing DTaP series may be due to the other (non-DTaP) vaccine components, we did not evaluate whether the mixing of DTaP (across brands and among trivalent/quadrivalent/pentavalent) vaccines is associated with compliance/completion of Hib, IPV and HepB vaccination series. In addition, while there is precedent to indicate that DTaP vaccination shortages resulted in delayed vaccination,[26] it was not in the objective of this study to evaluate delayed vaccination.

Age-appropriate DTaP dose completion rates were consistent with completion as measured by the National Committee for Quality Assurance (NCQA)[27] and the NIS,[6] (Supporting information **Table 2**). The slightly higher rates observed in our study may be explained by the additional month of observation, which would capture some delayed vaccinations. In addition, our study measured vaccination status by birth year, whereas the NCQA and the NIS report results by measurement year, although for the <8 months and <20 months cohorts, these time periods are similar. Observed differences may also be due to the methods used to capture vaccinations. Similar to the NCQA, our study captured vaccinations billed to the health plan by providers, whereas the NIS measures vaccinations by surveying a random parent sample and reviewing provider vaccination records.[28] Although completion rates estimated in our study are comparable to NCQA and NIS rates, mixing rates may differ across the various databases.

Limitations

A major limitation of this analysis was that brand information was missing for a large proportion of patients who received trivalent DTaP vaccinations recorded with CPT® code 90700. While approximately 6–8% of all DTaP vaccination claims in the Optum Research Database (ORD) include a National Drug Code (NDC) indicating the specific DTaP vaccine product

Table 4. DTaP vaccine mixing stratified by patient characteristics within each continuous enrollment cohort among patients with at least 2 administered vaccinations and known brand for all administered doses

	Birth to <8 Months Continuous Enrollment		Birth to <20 Months Continuous Enrollment		Birth to <7 Years Continuous Enrollment	
	Total N	Mixing n (%)	Total N	Mixing n (%)	Total N	Mixing n (%)
Overall	254,119	11,817 (4.7)	59,513	17,251 (29.0)	462	180 (39.0)
			Gender			
Male	130,194	6,012 (4.6)	30,603	8,781 (28.7)	244	96 (39.3)
Female	123,925	5,805 (4.7)	28,910	8,470 (29.3)	218	84 (38.5)
			Geographic region			
Northeast	28,617	1,038 (3.6)	6,470	1,369 (21.2)	50	11 (22.0)
Midwest	76,756	2,563 (3.3)	16,205	4,826 (29.8)	121	35 (28.9)
South	110,505	6,218 (5.6)	27,679	8,282 (29.9)	189	79 (41.8)
West	38,241	1,998 (5.2)	9,159	2,774 (30.3)	102	55 (53.9)

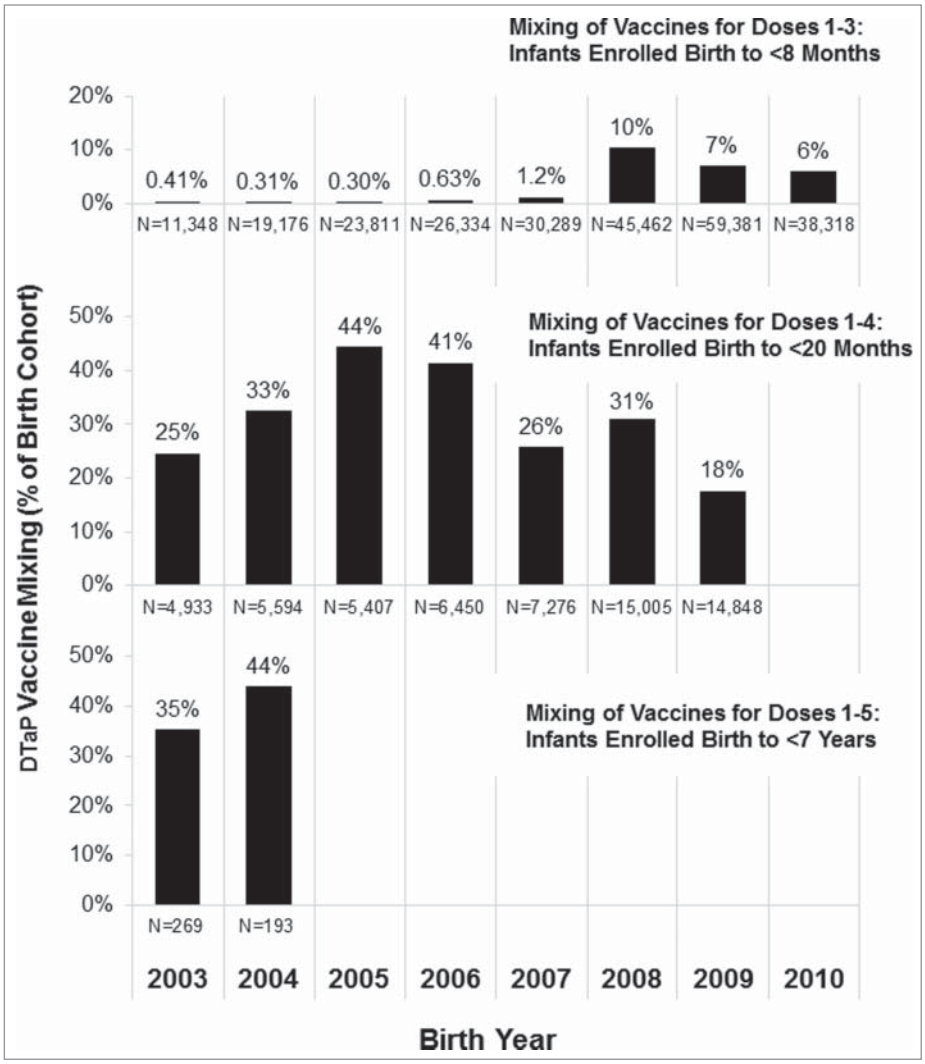

Figure 2. DTaP vaccination mixing by year of birth.

administered, <5% of the over 2.5 million claims with CPT® code 90700 in this analysis had brand information indicated by an NDC code. In addition, the continuous enrollment period for some patients included a period when modified DTaP vaccination coding limits our ability to confidently measure vaccination completion. This may have resulted in inaccurate estimation of the mixing rate, although results were similar in the first sensitivity analysis which limited the analysis to the patient subset with complete DTaP history.

Inclusion and exclusion criteria may have limited the generalizability of this research. In particular, infants and children were required to be continuously enrolled from birth until 8 months, 2 y or 7 y of age to assure capture of all vaccinations administered in the series. However, longer enrollment may be a sign of more stable employment, residence and therefore healthcare provision which may lead to lower rates of mixing.

Vaccination rates were validated against national measures in order to support the generalizability of the study sample to the US population however it is important to note that mixing rates may still differ among enrollees in the ORD relative to the general population. The data used for this study come from a national managed care population; therefore, results are primarily applicable to patients in managed care settings and may not be applicable to patients who were uninsured or receiving Medicaid.

Other study limitations are typical of claims-based analyses. The degree to which claims data accurately capture an individual's medical history is limited because claims data are collected for payment and not for research; therefore vaccinations administered but not submitted for payment to the health plan would not be observed. In addition, the presence of a procedure code on a medical claim is not a perfect predictor of the service provided, as there may be coding errors. Finally, this study did not evaluate the safety or efficacy of mixing DTaP products in a vaccination series. Although evidence suggests that safety and efficacy may be impacted when different vaccine products are used in a vaccination series,[22] more research is needed.

Conclusion

In this analysis of infants and children less than 7 y of age in a commercial health plan, we found that mixing vaccines from various sources within a DTaP series was lower for the first 3 doses, and substantially higher over the first 4 doses and for the full 5-dose DTaP vaccination series. Although sensitivity analyses demonstrated that rates of vaccine mixing may be underestimated due to missing information, the measured rates of mixing in this analysis are by themselves significant and underscore the need for additional research on safety and efficacy associated with mixed DTaP series. Future research to understand the clinical outcomes among individuals immunized with a heterogeneous vaccination series compared to a homogeneous vaccine series is needed. In addition, research to examine the association between DTaP mixing and the incidence of pertussis, or the extent to which mixing vaccination sources contributes to waning immunity, would be useful.

Methods

Data source

Data for this retrospective cohort study were obtained from the ORD, a large US health insurance claims database. The

health plans represented in the database consist primarily of discounted fee-for-service independent practice association model plans. Membership in the plans is geographically diverse, with a concentration in the South and Midwest. The database contains electronic pharmacy and medical claims for more than 3 million infants and children during the study period. Medical claims include International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, Current Procedural Terminology codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, and NDC.

No identifiable protected health information was extracted or accessed during the course of the study. Pursuant to the Health Insurance Portability and Accountability Act,[29] the use of de-identified data does not require Institutional Review Board approval or waiver of authorization.

Study cohorts

Commercially-insured children born between 01 January 2003 and 30 April 2011 who had data available regarding sex, geographic region, and birth date were eligible for inclusion. Children must have been continuously enrolled in the health plan within 1 month of birth, with medical and pharmacy benefits. Three study cohorts were generated based on the continuous enrollment duration: (1) the "<8 months cohort" included infants who were continuously enrolled from birth up to 8 months; (2) the "<20 months cohort" included children enrolled from birth up to 20 months; and (3) the "<7 years cohort" included children enrolled from birth up to 7 years. Children could be included in more than 1 cohort. Children with claims for >1 DTaP vaccination per day (5% of patients) or with claims for >5 DTaP vaccinations recorded (<1% of patients) were excluded. Completion and mixing of doses 1 through 3, doses 1 through 4, and doses 1 through 5 were assessed in the <8 months cohort, the <20 months cohort, and the <7 years cohort, respectively.

DTaP vaccination identification and brand classification

Medical claims data were used to identify the brand (defined in **Table 1**), number, and timing of DTaP vaccine doses. DTaP vaccinations are typically administered to infants and children during routine well child visits. Administered vaccinations are submitted for reimbursement to health plans using CPT® codes indicating whether the DTaP vaccine administered was a trivalent vaccine or not (**Table 1**). Approximately 6–8% of all DTaP vaccination claims in the ORD also include NDCs indicating the specific DTaP vaccine product administered (see Supporting information **Table 1**). As defined in **Table 1**, DTaP vaccinations were classified into 3 brands based on claims with a CPT® code or an NDC. The "trivalent" DTaP vaccines share the same CPT® code (CPT® code 90700); and unless a corresponding brand-specific NDC code was reported, these were classified as having missing/unknown brand information. Vaccinations administered within 2 weeks of a previous dose were considered duplicate doses.

Dose completion

For each child, age-appropriate dose completion was estimated for the 3 different cohorts. To have dose completion, patients in the <8 months cohort were required to have 3 DTaP vaccine doses, those in the <20 months cohort were required to have 4 doses, and those in the <7 years cohort were required to have 5 doses.

Some DTaP vaccine claims submitted for reimbursement between 2003 and 2005 had the DTaP-specific CPT® code 90700 changed to a generic immunization code by one of the claims processing systems. Therefore, to accurately estimate age-appropriate DTaP dose completion rates, patient subsets with complete DTaP history were identified within each of the study cohorts by excluding patients with claims processed by the affected system between 2003 and 2005.

Among children in the complete DTaP history subset, the percentage in each continuous enrollment cohort (i.e. <8 months, <20 months, and <7 years) with age-appropriate dose completion are reported.

DTaP brand mixing

For the mixing assessment, patients were required to have at least 2 DTaP vaccinations and complete DTaP brand information (i.e., known vaccine brand for all vaccinations administered during each of the continuous enrollment periods). The criteria used to determine vaccination brand are shown in **Table 1**. Children with different DTaP vaccine brands administered during the continuous enrollment period were said to have a mixed series.

Statistical methods

Among patients with at least 2 administered DTaP vaccinations, vaccination characteristics of those with complete and incomplete DTaP brand information (i.e., at least 1 dose classified as having missing/unknown brand), were compared within each continuous enrollment cohort using t-tests for differences in means or chi-square tests for differences in proportions.

Among all patients meeting the selection criteria for the DTaP mixing analysis, the proportions and 95% confidence intervals (CI) of patients with DTaP mixing in each of the <8 months, <20 months, and <7 years cohorts are reported. CIs were estimated using the exact binomial distribution.

Three sensitivity analyses were conducted to determine the impact of missing or incomplete information on the estimated DTaP mixing rate. In the first sensitivity analysis, the impact of incomplete DTaP history was examined by estimating the proportions and 95% CI of patients with DTaP mixing for the subset of patients with complete DTaP history (i.e., only those children whose enrollment period did not intersect with the period in 2003–2005 when data were missing on DTaP vaccinations billed with CPT® code 90700).

The remaining 2 sensitivity analyses were designed to evaluate the impact of missing brand information on the estimated DTaP mixing rates. First, all DTaP vaccinations with indeterminate brand (CPT® code 90700 without a brand-specific NDC) were assumed to be the same brand as the first observed vaccination

with known brand information. Second, it was assumed that all patients with a DTaP vaccination with indeterminate brand were in the mixing subgroup. For inclusion in these sensitivity analyses, patients must have received at least 2 DTaP vaccinations with known brand information for at least one administered dose.

Data extraction and statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

Disclosure of Potential Conflicts of Interest

Ami Buikema and Fang Liu are employees of Optum, which was contracted by GlaxoSmithKline to conduct the study. Shanthy Krishnarajah is an employee of and owner of stock in GlaxoSmithKline. Cristina Masseria was an employee of GlaxoSmithKline at the time of the study and is currently a Pfizer employee.

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Authors' Contributions

Cristina Masseria conceived the study and its general design, assisted with interpretation of results and critically reviewed the manuscript. Ami Buikema developed the study design, assisted with the statistical analyses with respect to hypothesis testing, interpreted the results, and helped to draft the manuscript. Fang Liu performed the statistical analyses with respect to hypothesis testing, assisted with interpretation of results, and critically reviewed the manuscript. Shanthy Krishnarajah participated in critical decisions regarding the study's design, assisted with interpretation of results and critically reviewed the manuscript. All authors have read and approved the final manuscript.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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