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DTaP combination vaccine use and adherence: A retrospective cohort study

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ABSTRACT

Despite universal recommendation of the 4-dose diphtheria, tetanus, and pertussis (DTaP) vaccine series, coverage and timeliness in the US remain suboptimal. DTaP-containing combination vaccines (i.e. quadrivalent and pentavalent) are presumed to improve vaccine coverage rates and timeliness, but research supporting this claim is limited. We sought to investigate the associations between DTaP-containing vaccine use and adherence to the recommended DTaP immunization schedule among children in the US. Using a large claims database, we identified privately insured children born between 2009 and 2016 that received ≥1 DTaP-containing vaccine and had ≥24 months of enrollment from birth, excluding those with DTaP vaccinations not aligned with approved dose indications. Children were classified by DTaP-containing vaccine receipt: combination vaccines only, stand-alone vaccines only, or a mixture of both. Outcome measures included: 1) completion of the 4-dose series and 2) timely receipt of doses. Outcomes were adjusted for gender, birth year, race, and socioeconomic status. The study cohort contained 412,441 children. Of these, 40.5% (167,084) received combination vaccines only, 14.9% (61,342) received stand-alone vaccines only, and 44.6% (184,015) received a mixture of both. Combination vaccine recipients were nearly 3 times as likely to complete the 4-dose series (OR 2.93 (95% CI: 2.88, 2.99)) and for all doses received, more than 4 times as likely to receive doses on time (OR 4.12 (4.04, 4.21), relative to stand-alone vaccine recipients. Significance disparities in adherence were also observed, where minorities were up to 30% less likely (OR 0.70 (0.68, 0.71)) to complete the 4-dose series and up to 27% less likely (OR 0.73 (0.72, 0.75)) to receive doses on time, relative to white children. Our findings demonstrated that adherence to the recommended DTaP immunization schedule was significantly greater among combination vaccine recipients, relative to stand-alone recipients. Further research is needed to investigate underlying causes of disparities in adherence.

1. Background

Incidence of pertussis across the US has dramatically declined since the introduction of the tetanus, diphtheria toxoids, and whole-cell pertussis vaccines in the 1940s [1]. From the 1990s onward in the US, whole-cell pertussis vaccines were replaced with acellular pertussis (DTaP) vaccines [2]. The DTaP-containing vaccines currently used in the US are effective in preventing pertussis in the vast majority of children, with an estimated 97.7% effectiveness (95% CI: 94.7 to 99.0) among children who receive ≥4 doses. The incidence of reported pertussis in 2018 among children 1–6 years of age was 13.5 per 100,000 and among children 7–10 years of age, 11.6 per 100,000 [1].

The Advisory Committee on Immunization Practices (ACIP) currently recommends DTaP vaccines be administered at 2, 4, and 6 months (the primary series), with a 1st booster dose at 15–18 months and a 2nd booster dose at 4–6 years [3]. Based on the 2016–2018 National Immunization Survey (NIS), coverage of 3 or more doses in the US is approximately 93.8% (95% CI: 93.1, 94.5), whereas coverage for 4 or more doses is 80.3% (95% CI: 79.0, 81.5) [4]. While coverage of the first three doses is relatively high, the drop-off at the 4th dose observed nationally is concerning. Fur-

Abbreviations: ACIP, the Advisory Committee on Immunization Practices; DTaP, diphtheria, tetanus, acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio virus vaccine; NIS, the National Immunization Survey; OR, odds ratio; SES, socioeconomic status.

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thermore, even among the first 3 doses, timeliness of receipt remains suboptimal. Based upon data from the 2010 NIS, mean delays in receipt of the first 3 DTaP doses have been estimated to be 16, 27, and 44 days, respectively [5].

Between 2009 and 2018, there were six DTaP-containing vaccines available across the US for use by vaccine providers (Table 1). Of these, three are stand-alone trivalent formulations (DTaP: diphtheria, tetanus, and pertussis) and approved for all 5 doses of the ACIP's recommended schedule (e.g. *Daptacel*, *Infanrix*, and *Tripedia*). The remaining three are combination formulations (i.e. quadrivalent or pentavalent), with varied approved dosage schedules. *TriHIBit (Tripedia* reconstituted with the *Haemophilus influenzae* type b (Hib) Conjugate vaccine, *ActHIB*), introduced in 1996, was the first combination DTaP-containing vaccine licensed for use in the US, and recommended only for the 4th dose [6]. Both *Tripedia* and *TriHIBit* were discontinued in 2011. Following *TriHIBit* were the introductions of pentavalent combination vaccines *Pediarix* (GlaxoSmithKline, 2002) and *Pentacel* (Sanofi Pasteur, 2008). *Pediarix* is indicated for active immunization against diphtheria, tetanus, pertussis, Hepatitis B, and inactivated polio virus (IPV), whereas *Pentacel* is indicated for active immunization against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and inactivated polio virus [7,8]. *Pediarix* is approved for doses 1–3 with a trivalent DTaP vaccine recommended for the 4th dose, whereas *Pentacel* is approved for doses 1 through 4 [7,8].

According to the General Best Practice Guidelines for Immunization, the use of combination vaccines is generally preferred over separate injections of equivalent component vaccines [9]. Presumed advantages of combination vaccines include improved vaccine coverage rates and timely receipt of vaccines, which may be attributed to the reduced number of injections per visit [9–13]. However, many healthcare providers in the US currently do not adhere to this recommendation, often only administering DTaP-containing combination vaccines for part of the primary series, then switching to a stand-alone DTaP vaccine [14]. As a result, the presumed advantages of combination vaccines may be reduced in the presence of such vaccine mixing. While prior studies have investigated DTaP-containing combination vaccine use and adherence, these studies have been limited in terms of scope (i.e. state-level retrospective cohort studies) [15,16] and susceptibility to several forms of bias due to study design (e.g. telephone or mail-in surveys), including recall, response, or sampling bias [17,18].

In this study, we sought to investigate the associations between DTaP-containing vaccine use and adherence to the ACIP's recommended DTaP immunization schedule among a cohort of privately insured children in the US, using data from a large national claims database.

2. Methods

This was a retrospective cohort study with objectives to:

I. Assess adherence to the recommended DTaP immunization schedule (i.e. completion of the 4-dose series and timely receipt of doses received), stratified by DTaP-containing vaccine use (i.e. combination, stand-alone, or a mixture of both).
II. Among children who completed the 4-dose series, assess the association of combination vaccine use with timely receipt of all 4 doses, relative to stand-alone vaccine use
III. Describe the associations of potential confounding factors with completion and timely receipt

2.1. Data Source & Study Cohort

Data were extracted from Optum's de-identified Clinformatics® Data Mart (CDM), a database of administrative health claims for members of large commercial and Medicare Advantage health plans (detailed description provided in Supplement) [19]. An overview of the cohort selection is provided in Fig. 1. All privately-insured children born between Jan. 1, 2009 – Dec. 31, 2016 with a complete data entry for gender were initially eligible for inclusion in the study cohort (n = 1,182,873). To maximize the likelihood of capturing vaccine doses received, all children must have had continuous enrollment for at least 24 months from birth. In order to assess adherence, all children must have had record of $\geq$ 1 DTaP-containing vaccine received during the study period (Jan. 1, 2009 to Dec. 31, 2018).

Children with records of receiving >1 DTaP-containing vaccine per day, >5 total DTaP-containing vaccines, or any DTaP-containing vaccinations prior to their start of enrollment date were excluded, as these scenarios were indicative of inaccurate data entry and as well as vaccine use not aligned with approved dose indications. Further, children with records of DTaP-containing vaccinations outside of the indicated age range were excluded. The general age indication for DTaP vaccines is $\geq$6 weeks or <7th birthday, except for *Pentacel*, where the upper-bound of the indication <5th birthday.

As patient birthdates were not available in the Optum CDM database, patient enrollment start date was used as a proxy for birthdate. To validate this proxy, we compared the time from enrollment start to each of the 4 respective DTaP doses in the 4-dose series, relative to the ACIP's recommended DTaP immunization schedule, for the overall cohort as well as stratified by exposure groups (as defined in the following *Exposure Groups* section). Median time to the respective doses aligned well with the ACIP's recommended schedule across all strata, suggesting that enrollment start date worked sufficiently well as a proxy for birthdate. Full results from this validation are available in the Supplement.

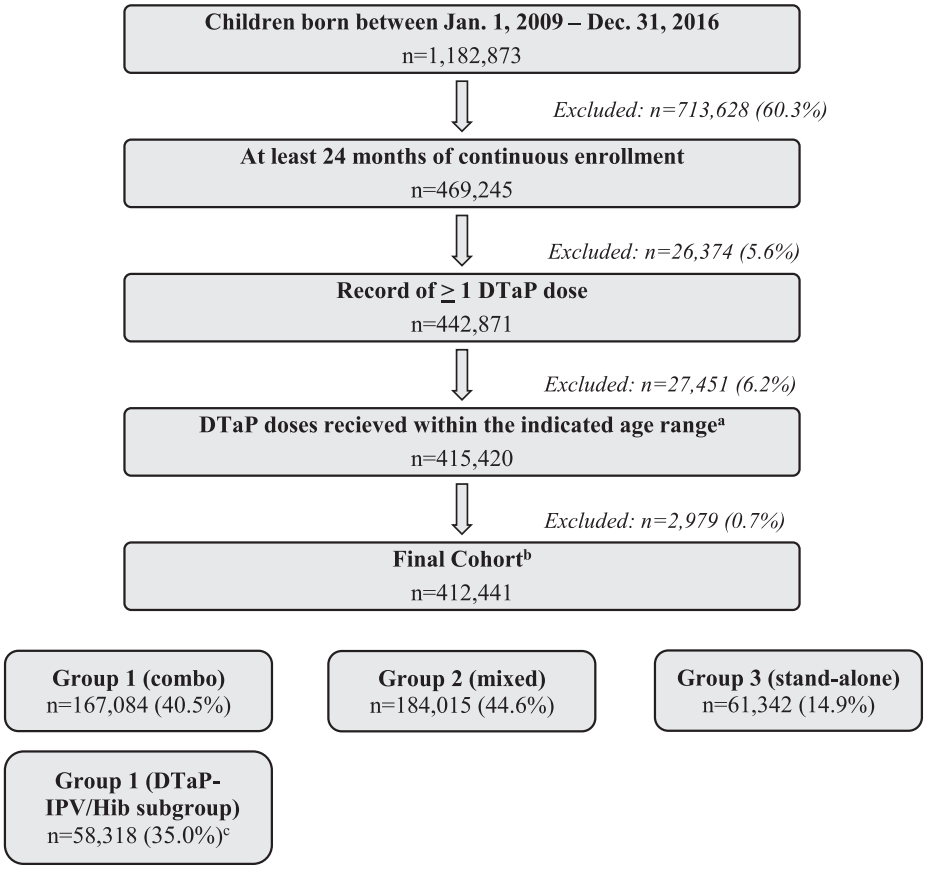
2.2. Ethics Approval

This study did not require Institutional Review Board approval or waiver of authorization, as the data used was de-identified and free from any identifiable protected health information.

Table 1
DTaP-containing vaccines available from 2009 to 2018 (study period).

Manufacturer	Brand Name	Formulation	Stand-Alone/Combination	Approved Doses	CPT® Code[a]
Sanofi Pasteur	*Daptacel*	DTaP	Stand-Alone	1–5	90700[b]
GlaxoSmithKline	*Infanrix*	DTaP	Stand-Alone	1–5	90700[b]
Sanofi Pasteur	*Tripedia*[c]	DTaP	Stand-Alone	1–5	90700[b]
Sanofi Pasteur	*Pentacel*	DTaP-IPV/Hib	Pentavalent	1–4	90698
Sanofi Pasteur	*TriHiBit*[c]	DTaP/Hib	Quadrivalent	4	90721
GlaxoSmithKline	*Pediarix*	DTaP-IPV-HepB	Pentavalent	1–3	90723

[a] CPT Copyright 2017 American Medical Association. All rights reserved. CPT® is a registered trademark of the American Medical Association.
[b] Stand-alone DTaP vaccines share the same CPT code.
[c] *Tripedia* and *TriHIBit* were discontinued in 2011.



[a] Indicated age range for DTaP vaccines is between 6 weeks to 7 years of age (i.e. up to the 7th birthday) for all DTaP-vaccines in this study, with the exception of DTaP-IPV/Hib (Pentacel), where the upper-bound of the indication is 5 years of age (i.e. up to the 5th birthday).

[b] Patients with missing gender data, records of DTaP doses administered prior to their birthdate, and/or ≥ 6 recorded DTaP doses were excluded.

[c] Percentage calculated using sample size of Group 1 as denominator.

Fig. 1. Flowchart of cohort selection and exposure group designation.

2.3. Exposure Groups

DTaP-containing vaccines administered during the study period (Jan. 1, 2009 to Dec. 31, 2018) were identified using CPT codes (Table 1). Vaccine administration dates were captured via the date of service associated with the respective claims. Children were classified into one of three primary exposure groups, based upon DTaP-containing vaccines received. Children in Group 1 were those who received DTaP-containing combination vaccines only (i.e. quadrivalent or pentavalent). Group 2 children were those who received a mixture of DTaP-containing combination vaccines and stand-alone DTaP-containing vaccines (i.e. trivalent). Group 3 children were those who received stand-alone DTaP vaccines only.

Given that DTaP-IPV-HepB (*Pediarix*) is only approved for doses 1–3, with *Infanrix* recommended for the 4th dose, children who received 3 doses of DTaP-IPV-HepB and 1 dose of a stand-alone DTaP vaccine were assigned to Group 1. Since we could not differentiate between *Infanrix* and other stand-alone DTaP doses (as they share the same CPT codes), we considered any stand-alone DTaP dose administered at the 4th dose among children who received 3 doses of *Pediarix*. A detailed breakdown of types of vaccines received for each of the four doses is provided in the Supplement.

To investigate timeliness specifically among children who completed the 4-dose series exclusively with combination vaccines, we defined a subgroup of Group 1 consisting of children who received 4 DTaP-IPV/Hib (*Pentacel*) doses, as it is the only DTaP-containing combination vaccine approved as a 4-dose series. We denoted these children as Group 1: DTaP-IPV/Hib subgroup.

2.4. Outcome definitions

The outcomes assessed were defined based on adherence to the ACIP's recommended immunization schedule [20], where adherence was measured via completion and timeliness. In the US, DTaP-containing vaccine doses during the first 24 months of life are recommended to be administered at 2, 4, and 6 months (the primary series), and between 15 and 18 months (the 1st booster dose). Based on the recommended schedule, the following outcomes were assessed:

Outcome 1: Complete

Children were classified as complete if they received 4 doses of DTaP-containing vaccines within 20 months of life.

Outcome 2: Timely Receipt

Children were classified as timely if all received DTaP-containing vaccine doses were administered ≤2 months after the respective recommended age. For doses 1 through 4, the recom-

mended ages were 2, 4, 6, and 18 months, respectively. For Objective I, timely receipt of all doses received was assessed, regardless of completion. For Objective II, timely receipt was assessed among those children who completed the 4-dose series.

2.5. Statistical analysis

Descriptive statistics were calculated to describe the study cohort characteristics, stratified by exposure group, including exposure group size, gender, birth year, race, poverty status (400% Federal Poverty Line threshold), and coverage of DTaP-containing doses received across the 4-dose series. In the Optum CDM database, patient race and poverty level are collected through self-reported means, and when unavailable, can additionally be imputed based upon other available data.

For Objective I, the proportion of children classified as adherent with regard to each outcome was tabulated by exposure group, and the adjusted odds of being adherent were calculated, with the stand-alone vaccines group (Group 3) serving as the reference. For Objective II, the proportion of children classified as timely versus delayed receipt were tabulated by exposure group (Group 1 (subgroup) and Group 3), and the adjusted odds of timely receipt were calculated, with Group 3 serving as the reference. All odds ratios (ORs) were estimated using a multivariable logistic regression model and adjusted for potential confounding factors, including patient gender, race, socioeconomic status (SES; based on federal poverty level), and birth year. 95% Confidence Intervals were estimated using robust standard errors. For Objective III, we reported the estimated ORs for the potential confounding factors across the overall cohort, based upon the regression model for Objective I. All analyses were conducted using R 3.4.3 [21].

2.6. Sensitivity & Subgroup Analyses

Additional sensitivity analyses were conducted, varying the specifications of the Outcome definitions. For Outcome 1, we considered completion by 18, 19, and 24 months of life. For Outcome 2, we considered a maximum of 1 month after the recommended age as the allowance to determine timely receipt. Further, given that the 4th DTaP dose has a recommended age range, as opposed to the fixed recommended age for doses 1–3, we conducted additional sensitivity analyses where we considered 18 months of age to be the upper bound for timely receipt of the 4th dose (i.e. a 4th dose administered after 18 months of age was considered delayed). Extending from the Timely Receipt analysis in Objective I, as an additional subgroup analysis, we assessed Timely Receipt of the first 3 doses among children who received $\geq$ 3 doses, and as well as Timely Receipt of all 4 doses among those children that completed the 4-dose series. All sensitivity and subgroup analyses are available in the Supplement.

3. Results

3.1. Study cohort

A summary of the cohort characteristics is provided in Table 2. A total of 412,441 children were included in the final cohort, with 167,084 (40.5%) classified as Group 1 (combo), 184,015 (44.6%) classified as Group 2 (mixed), and 61,342 (14.9%) classified as Group 3 (stand-alone). Of the Group 1 children, 58,318 (14.1%) were additionally classified as Group 1: DTaP-IPV/Hib subgroup. Gender was relatively balanced across the cohort, with the overall cohort consisting of 200,5640 females (48.6%) and 211,877 males (51.4%).

The number of children born from 2009 to 2016 decreased mostly monotonically across the cohort, with the greatest proportion of children born in 2009 (14.0%, n = 58,565) and the least born in 2016 (11.8%, n = 48,760). Among Group 1 children, there were proportionally less children born in 2012 (8.7%, n = 14,578) relative to the overall cohort (11.9%, n = 48,898), and proportionally more children born in 2016 (15.0%, n = 25,130). Among Group 2 children, most notably, there were proportionally more children born in 2012 (14.5%, n = 26,592). Among Group 3 children, there were proportionally more children born from 2009 to 2013, but proportionally less in 2014–2016, relative to the overall cohort.

In terms of race, 66.1% (n = 272,668) of the children in the cohort were white, followed by 11.0% Hispanic (n = 45,309), 7.7% Asian (n = 31,622), 6.3% black (n = 25,920), and 9.0% (n = 36,922) unknown. This pattern was similar across the exposure groups, except for Group 1, where there were proportionally more white children (69.4%, n = 115,915) and Group 3, where there proportionally less (63.3%, n = 38,799). The majority of the cohort was classified as being above the 400% federal poverty level (FPL) (79.4%, n = 327,528), with 0.5% (n = 2,170) classified as below the 400% FPL; this trend remained relatively constant across the exposure groups.

In terms of DTaP-containing doses received, coverage of the 2nd and 3rd doses was highest among children in Group 1 and Group 2, with more than 90% of these children having received $\geq$ 3 doses. Comparably, coverage was lower among children in Group 3, where only 72.0% had received $\geq$3 doses. Across the overall cohort and the respective exposure groups, there was consistently a notable drop-off in coverage from the 3rd to 4th dose, ranging in magnitude from approximately 9–12%.

3.2. Adherence outcomes

The results from Objective I are presented in Table 3. Completion of the 4-dose series was highest among combination vaccine recipients (Group 1) (75.6%), followed by mixed (Group 2) (72.7%) and stand-alone vaccine recipients (Group 3) (51.4%). Relative to stand-alone vaccine recipients, children who received combination vaccines only were nearly 3 times as likely to complete the 4-dose series (OR 2.93 (95% CI: 2.88, 2.99)), whereas children who received a mixture of vaccines were approximately 2.5 times as likely (OR 2.54 (95% CI: 2.49, 2.59)). Timely receipt of the age appropriate doses was highest among combination vaccine recipients (81.1%), followed by mixed (70.3%) and stand-alone vaccine recipients (51.0%). Relative to stand-alone vaccine recipients, children who received combination vaccines only were more than 4 times as likely to have received their respective doses on time (OR 4.12 (95% CI: 4.04, 4.21), whereas children who received a mixture of vaccines were approximately 2.3 times as likely (OR 2.28 (95% CI: 2.24, 2.32)).

The results from Objective II are presented in Table 4. Assessing timely receipt among those who completed the 4-dose series, 96.8% of children who received combination vaccines exclusively (Group 1: DTaP-IPV/Hib subgroup) received their doses on time, compared to 92.1% of stand-alone recipients. Those children who received exclusively combination vaccines were nearly 2.5 times as likely to receive all 4 doses on time, relative to children who received stand-alone vaccines only (OR 2.49 (95% CI: 2.34, 2.66)).

3.3. Associations of Potential Confounding Factors

The associations of the potential confounding factors with adherence outcomes (Objective III) are reported in Table 5. In terms of gender, males were approximately 2% less likely to receive their respective doses on time (OR 0.98 (95% CI: (0.96, 0.99)); no

Table 2
Characteristics of study cohort, overall and stratified by exposure groups.

Variable	Overall Cohort	Group 1 (combo)	Group 1(DTaP-IPV/Hib subgroup)[a]	Group 2 (mixed)	Group 3 (stand-alone)
N (%)	412,441	167,084 (40.5%)	58,318 (14.1%)	184,015 (44.6%)	61,342 (14.9%)
Gender, % (no.)					
Female	48.6 (200564)	48.5 (81105)	48.7 (28410)	48.8 (89823)	48.3 (29636)
Male	51.4 (211877)	51.5 (85979)	51.3 (29908)	51.2 (94192)	51.7 (31706)
Birth year, % (no.)					
2009	14.2 (58565)	13.6 (22730)	16.8 (9816)	13.4 (24668)	18.2 (11167)
2010	13.3 (54834)	13.9 (23304)	19.4 (11312)	12.1 (22302)	15.0 (9228)
2011	13.2 (54342)	11.3 (18864)	12.3 (7190)	14.9 (27440)	13.1 (8038)
2012	11.9 (48898)	8.7 (14578)	5.6 (3284)	14.5 (26592)	12.6 (7728)
2013	11.8 (48524)	11.3 (18927)	7.6 (4455)	12.0 (22005)	12.4 (7592)
2014	11.9 (49167)	13.8 (23019)	12.7 (7394)	10.9 (20131)	9.8 (6017)
2015	12.0 (49351)	12.3 (20532)	10.4 (6051)	12.4 (22883)	9.7 (5936)
2016	11.8 (48760)	15.0 (25130)	15.1 (8816)	9.8 (17994)	9.2 (5636)
Race, % (no.)					
Asian	7.7 (31622)	6.6 (10949)	7.5 (4387)	8.4 (15512)	8.4 (5161)
Black	6.3 (25920)	5.8 (9678)	5.4 (3150)	6.6 (12227)	6.5 (4015)
Hispanic	11.0 (45309)	9.5 (15879)	8.0 (4646)	11.9 (21905)	12.3 (7525)
White	66.1 (272668)	69.4 (115915)	69.9 (40742)	64.1 (117954)	63.3 (38799)
Unknown	9.0 (36922)	8.8 (14663)	9.2 (5393)	8.9 (16417)	9.5 (5842)
Poverty status, % (no.)					
Below 400% FPL	0.5 (2170)	0.5 (901)	0.3 (190)	0.5 (948)	0.5 (321)
Above 400% FPL	79.4 (327528)	79.8 (133320)	80.6 (46985)	79.3 (145982)	78.6 (48226)
Unknown	20.1 (82743)	19.7 (32863)	19.1 (11143)	20.2 (37085)	20.9 (12795)
Doses Received, % (no.)[b]					
2 Doses	95.4 (393669)	96.5 (161189)	100.0 (58,318)[c]	100.0 (184015)	79.0 (48465)
3 Doses	91.2 (376276)	93.2 (155679)	100.0 (58,318)[c]	95.9 (176404)	72.0 (44193)
4 Doses	80.3 (331205)	82.8 (138323)	100.0 (58,318)[c]	83.8 (154264)	63.0 (38618)

FPL: Federal Poverty Level.
[a] DTaP-Hib/IPV combination vaccines only; these children are a subgroup of Group 1.
[b] DTaP-containing doses received within the study period (Jan. 1, 2009 to Dec. 31, 2018). By definition, all children included in the Overall Cohort had record of receiving ≥1 DTaP-containing vaccine dose.
[c] By definition, children in the Group 1 subgroup had received 4-doses of DTaP-containing combination vaccines.

Table 3
Percentage of children classified as complete versus incomplete and timely vs delayed receipt (Objective I), stratified by exposure group.

Exposure Group	Total (N =)	Outcome 1: Complete[a]			Outcome 2: Timely Receipt[b]		
		Incomplete % (n =)	Complete % (n =)	OR[c] (95% CI)	Delayed Receipt % (n =)	Timely Receipt[d] % (n =)	OR[e] (95% CI)
Group 1 (combo)	167,084	24.4 (40830)	75.6 (126254)	2.93 (2.88, 2.99)	18.9 (31626)	81.1 (135458)	4.12 (4.04, 4.21)
Group 2 (mixed)	184,015	27.3 (50212)	72.7 (133803)	2.54 (2.49, 2.59)	29.7 (54733)	70.3 (129282)	2.28 (2.24, 2.32)
Group 3 (stand-alone)	61,342	48.6 (29784)	51.4 (31558)	Ref.	49.0 (30045)	51.0 (31297)	Ref.

Percentages were calculated as row percentages for each respective outcome (e.g. Percentage = (# of group 1 children incomplete)/(group 1 total)).
[a] Children were classified as complete if they received 4 doses of DTaP-containing vaccines within 20 months of life.
[b] Children were classified as timely if all received DTaP-containing vaccine doses were administered ≤2 months after the respective recommended age.
[c] OR values reported are the odds of being complete, relative to Group 3. ORs were adjusted for patient gender, birth year, race, and federal poverty status.
[d] Timely receipt was assessed regardless of completion (i.e. timeliness assessed among children who received ≥1 doses).
[e] OR values reported are the odds of timely receipt of the age-appropriate doses, relative to Group 3. ORs were adjusted for patient gender, birth year, race, and federal poverty status.

Table 4
Percentage of children, among those who completed the 4-dose series, classified as timely[a] versus delayed receipt (Objective II), stratified by exposure group.

Exposure Group	Total (N =)	Delayed Receipt % (n =)	Timely Receipt % (n =)	OR[b] (95% CI)
Group 1 (DTaP-IPV/Hib subgroup)	54,282	3.2 (1743)	96.8 (52539)	2.49 (2.34, 2.66)
Group 3 (stand-alone)	31,558	7.9 (2499)	92.1 (29059)	Ref.

Percentages were calculated as row percentages for each respective outcome (e.g. Percentage = (# of group 1 children incomplete)/(group 1 total)).
[a] Children were classified as timely if all received DTaP-containing vaccine doses were administered ≤2 months after the respective recommended age.
[b] OR values reported are the odds of timely receipt of the age-appropriate doses, relative to Group 3. ORs were adjusted for patient gender, birth year, race, and federal poverty status.

significant association between gender and completion was observed. In terms of race, black children were approximately 24% less likely (OR 0.76 (95% CI: (0.74, 0.78)) to complete the 4-dose series, and Hispanic children were approximately 30% less likely (OR 0.70 (95% CI: 0.68, 0.71)), relative to white children. Further, black children were approximately 22% less likely (OR 0.78 (95% CI: 0.76, 0.80)) to receive their respective doses on time, and Hispanic children were approximately 27% less likely (OR 0.73 (95% CI: 0.72, 0.75)), relative to white children. In terms of SES, children above the 400% FPL were approximately 8% more

Table 5
Odds ratios (ORs) from multivariable logistic regression models (Objective I).

Variable	OR[a] (95% CI) Outcome 1: Complete[b]	OR[c] (95% CI) Outcome 2: Timely Receipt[d]
Exposure group		
Group 1 (combo)	2.93 (2.88, 2.99)*	4.12 (4.04, 4.21)
Group 2 (mixed)	2.54 (2.49, 2.59)*	2.28 (2.24, 2.32)
Group 3 (stand-alone)	Ref.	Ref.
Gender		
Female	Ref.	Ref.
Male	0.98 (0.97, 1.00)	0.98 (0.96, 0.99)*
Race		
Asian	1.00 (0.98, 1.03)	1.07 (1.04, 1.10)*
Black	0.76 (0.74, 0.78)*	0.78 (0.76, 0.80)*
Hispanic	0.70 (0.68, 0.71)*	0.73 (0.72, 0.75)*
White	Ref.	Ref.
Unknown	2.14 (1.96, 2.33)*	2.34 (2.14, 2.56)*
Poverty status		
Below 400% FPL	Ref.	Ref.
Above 400% FPL	1.01 (0.98, 1.04)	1.08 (1.05, 1.11)*
Unknown	2.74 (2.52, 2.99)*	2.91 (2.67, 3.18)*

* Statistically significant at an alpha level of 0.05 ($p < 0.05$).
[a] OR values reported are with regard to the odds of being complete. ORs were adjusted for patient gender, birth year (not listed here), race, and federal poverty status.
[b] Children were classified as complete if they received 4 doses of DTaP-containing vaccines within 20 months of life.
[c] OR values reported are with regard to the odds of timely receipt of the age-appropriate doses. ORs were adjusted for patient gender, birth year (not listed here), race, and federal poverty status.
[d] Children were classified as timely if all received DTaP-containing vaccine doses were administered ≤2 months after the respective recommended age. Timely receipt was assessed regardless of completion (i.e. timeliness assessed among children who received ≥1 doses).

likely (OR 1.08 (95% CI: 1.05, 1.11)) to receive their respective doses on time, relative to children below the 400% FPL; no significant association between SES and completion was observed.

3.4. Sensitivity Analyses

Overall, the results from the sensitivity analyses demonstrated that the primary findings from Objective I and Objective II remain relatively constant, even when varying the specific definitions of the outcomes. Although the magnitude of some estimated ORs varied by +/- approximately 10% to 15%, the statistically significant trends as described in Objective I and II remained. Similarly, the trends changed in a predictable fashion, relative to the modified outcome definitions (e.g. reducing Outcome 2 to a 1-month threshold results in decreased timely receipt). Full results of the sensitivity analyses are available in the Supplement.

4. Discussion

In this study we investigated the associations between DTaP-containing vaccine use and adherence to the ACIP's recommended DTaP immunization schedule among a cohort of privately insured children in the US during the first two years of life. We observed significant associations between receipt of DTaP-containing combination vaccines and adherence, where combination vaccine recipients were nearly 3 times as likely to complete the 4-dose series and more than 4 times as likely to receive doses on time, relative to stand-alone recipients. While the presence of these associations may not be entirely surprising, the magnitude of the associations themselves were indeed remarkable.

Several prior studies have similarly investigated the relationship between receipt of combination pediatric vaccines and adherence to the recommended immunization schedule via retrospective studies using electronic patient records as well as survey data [15,16,18]. Using administrative Medicaid claims data in the state of Georgia, Marshall et al. demonstrated that combination vaccine recipient (HepB/Hib or DTaP-IPV-HepB) was associated with overall higher vaccine coverage rates across several pediatric vaccine series [15]. In a follow-up study using the same claims database, Happe et al. demonstrated that recipient of combination vaccines (DTaP-IPV-HepB) was associated with significantly improved timeliness for 3 doses of DTaP [16]. In a study using data from the 2012 NIS survey, Kurosky et al. showed that children who received at least one combination vaccine had higher completion rates and compliance with the full vaccine series at 24 months (4:3:1:3:3:1:4 series) [18].

In addition to our findings of increased adherence among combination vaccine recipients, we also observed significant disparities in adherence to the recommended schedule. After adjusting for the type of DTaP vaccines received, gender, birth year, and SES, black and Hispanic children were significantly less likely to complete the 4-dose series and to receive respective doses on time, relative to white children. Further, children who were more socioeconomically deprived were significantly less likely to receive doses on time. These findings are reflective of other disparities that have been previously reported for receipt of HPV, MMR, and seasonal influenza vaccines [22–24].

As for the underlying causes of these disparities, we can effectively rule out the cost of the vaccine, as all children included in this analysis were actively enrolled in a private insurance plan. That said, our analysis was not designed to explicitly investigate these disparities, and therefore, was not all-encompassing with regard to other potential patient and parent barriers to immunization, such as education, area of residence, or access to vaccinations [25]. Further, it is possible that race and SES to some degree may have been inaccurately captured, due to limitations of the data (i.e. self-reporting and imputation) or in the case of SES, perhaps even the definition of the variable itself (i.e. 400% federal poverty line not adequately characterizing the patient's true SES). Given the known association between race and SES, the effect of race and SES may have remained intertwined to some degree in our analysis, potentially resulting in an overestimated estimated effect of race on adherence or underestimated effect of SES. Nevertheless, these findings point toward concerning inequities in adherence, and further research is needed to better understand the underlying causes of these disparities.

Expanding upon prior DTaP vaccine adherence research, a fundamental strength of our study was the source of data used. By using electronic claims data from a large national claims database, we were able to accurately measure vaccine use across a cohort of more than 400,000 children over the course of nearly a decade. An inherent advantage of using claims data is the relative accuracy and completeness of the vaccination records. CPT codes allow for identification and differentiation of vaccines received and referencing the date of service associated with the claim enables an accurate assessment of the vaccine administration date (as opposed to using a date of payment instead). Additionally, with the Optum CDM database integrating both medical claims and pharmacy fills, we were able to capture vaccines administered in both doctors' offices as well as pharmacies.

It is important to note that our findings do not necessarily establish a causal relationship between the receipt of combination vaccines and improved adherence. Nevertheless, the associations that we observed provide evidence to support the preferential recommendation of DTaP-containing combination vaccines for infants and toddlers. With growing concern surrounding the drop-off in

coverage at the 4th DTaP dose, DTaP-containing combination vaccines can potentially play a key role in improving coverage at the 4th dose. Two commonly cited challenges faced by providers regarding suboptimal 4th dose coverage include delay in receipt of the first 3 doses, leading to ineligibility for the 4th dose at the 12 month visit (an established visit in many child health practices, at which time the 4th dose is often administered), and failure to administer all recommended doses at a given visit [26]. In these cases, administering combination DTaP-containing vaccines may prove beneficial, aiding in timely receipt of the first 3 doses, as well as increasing the likelihood that a child would receive all recommended doses at a given visit.

However, failure to receive all recommended doses or to receive respective doses on time is also influenced by factors beyond just the type of vaccine received, such as parental attitudes and beliefs, or more generally, vaccine hesitancy [27]. Within the context of our study, by including only children with records of receiving at least one DTaP-containing vaccine, we can assume that these respective parents were to some degree accepting of vaccination for their children. Though, even amongst vaccine-accepting parents, prior studies have shown that there may be additional hesitancy specific to combination vaccines and the possibility of "overloading" the child's immune system [28,29]. Therefore, it is possible that the adherence-related benefits of DTaP-containing combination vaccines may not be immediately realized in these instances, as such parents may simply refuse them even if offered. Under these circumstances, it would be critical for providers to first address the combination vaccine-specific concerns, which may be accomplished through dispelling of relevant misconceptions and reiterating the benefits of combination vaccines [29,30].

While the data source used in this study allowed us to accurately assess adherence across a large cohort of children, there were some inherent limitations to the data that must also be acknowledged. Firstly, generalizability of our findings may be limited due to the types of children captured in our study as well as our inclusion/exclusion criteria. As our cohort consisted of only privately insured children, our findings may not be generalizable to the overall US population, including those that are publicly insured (i.e. Medicaid) or the uninsured. Further, we required that children have ≥24 months of continuous enrollment, resulting in more than 60% of the ~1.1 million originally identified children being excluded from our cohort. This minimum enrollment time maximized the probability that we could accurately assess receipt of the full 4-dose series, thereby minimizing the potential for information bias (i.e. misclassification). However, doing so may have also inadvertently introduced a degree of selection bias, as longer continuous enrollment time may a proxy of higher SES (i.e. employment stability, residence stability) and potentially quality of healthcare utilized, thus leading to higher overall completion and timely receipt across our identified cohort.

An additional limitation inherent to the database was the lack of true birthdates, where the start of a child's enrollment was used as a proxy for birthdate. As noted in the Methods, our validation of this proxy suggested that it was sufficiently accurate, where median time to each of the 4 respective DTaP doses aligned well with the ACIP's recommended schedule. While it is possible that there still may be some degree of measurement error induced by the use of this proxy, we found no evidence to suggest that the magnitude or direction of error varied across the exposure groups. Therefore, in combination with our sensitivity analyses which demonstrated that the relative trends remain consistent even when considerably altering the time specifications of the outcome definitions, it is unlikely that the use of enrollment start date as a proxy for birthdate had any substantial implications on our findings.

Lastly, the way in which we have defined our exposure groups may render the combination vs. stand-alone comparison different from mixed vs. stand-alone. In order to be classified into either the combination or stand-alone group, the child must have received at least one DTaP-containing doses of the respective type. However, children classified as mixed recipients, by definition, had to have received at least two different DTaP-containing doses (i.e. one stand-alone and one combination dose). Although a subtle detail, it is important to note, as it may have biased the findings specific to the mixed recipient group, since there were no children who received only one dose within this group.

5. Conclusions

Among privately insured children of a large national health plan, recipients of DTaP-containing combination vaccines (i.e. quadrivalent and pentavalent) were significantly more likely to adhere to the ACIP's recommended DTaP immunization schedule compared to recipients of standalone DTaP vaccines (i.e. trivalent). Additionally, we observed significant racial and socioeconomic disparities in adherence that warrant further investigation as to identify possible underlying causes. Future research building upon the analytical framework implemented here may seek to further explore the associations between DTaP-containing combination vaccine receipt and adherence to other pediatrics vaccines, such as IPV, Hib, and Hep B.

6. ICMJE Statement

All authors attest they meet the ICMJE criteria for authorship.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All listed authors are full-time employees of Sanofi Pasteur (US).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.009.

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