Effect of Combination Vaccines on Hepatitis B Vaccine Compliance in Children in the United States

Samantha K. Kurosky, MSPH, Keith L. Davis, MA,* and Claudia M. Galindo, MD, MSc†*

Background: An increasingly crowded immunization schedule threatens the completion and compliance of hepatitis B vaccinations (HepB), the primary method of hepatitis B prevention. Combination vaccines have been proposed to alleviate this problem.

Methods: Data from the 2011 National Immunization Survey Public-Use Data File were utilized (GSK study identifier: HO-11–770) to compare HepB completion and compliance rates between 3 groups of children: those who received HepB combination vaccine, those who received non-HepB combination vaccine and those who received HepB single-antigen vaccine only. Completion was defined as the accumulation of 3 HepB doses by 18 months. Compliance was defined as the receipt of vaccine doses within the Advisory Committee on Immunization Practices' recommended age ranges.

Results: Of a sample of 4,040,116 children, 39.4% received a HepB combination vaccine, 43.0% received a non-HepB combination vaccine and 17.5% received a HepB single-antigen vaccine. Overall, 91.2% of children completed all 3 recommended doses, but only 61.8% completed them at age-appropriate times. Those receiving single-antigen only (odds ratio = 0.25, 95% confidence interval: 0.17–0.35) or non-HepB combination vaccines (odds ratio = 0.50, 95% confidence interval: 0.37–0.69) were substantially less likely to complete 3 doses of HepB than those who received the HepB combination vaccine.

Conclusions: Although completion rates were high, a large proportion of children did not receive HepB doses at age-appropriate times. Combination vaccine was associated with both higher completion and compliance outcomes compared with HepB single-antigen vaccine.

Key Words: hepatitis B vaccination, United States, combination vaccine, pediatrics, vaccine compliance

(*Pediatr Infect Dis J* 2017;36:e189–e196)

The Advisory Committee on Immunization Practices (ACIP) recommends 3 doses of hepatitis B vaccine (HepB): one at birth, one at 1–2 months and one at 6–18 months.[1] Receipt of all 3 doses produces adequate protection against hepatitis B virus for 98% to 100% of infants, whereas 80% to 95% are protected with 2 doses and 16% to 40% are protected after a single dose.[2] Between 2009 and 2013, the annual proportion of children who received all 3 doses by age 19–35 months (vaccine coverage) met or exceeded the national Healthy People 2020 goal of 90%.[3] However, this measure does not take into account whether each dose was administered in compliance with the age range for each dose recommended by ACIP. Assessing age-appropriate receipt of doses allows for evaluation of varying levels of protection between birth and 2 years. In 2013, 74.2% of children received a HepB dose within 3 days of birth, indicating approximately one-quarter of children lacked protection at the earliest recommended age.[3]

Evidence suggests a crowded and complicated childhood immunization schedule may be burdensome to parents and providers, in part leading to reduced vaccine completion and compliance.[4–7] To address these barriers, the ACIP recommends the use of combination vaccines, multiple antigens administered in the same syringe.[8] Several studies have found that the use of combination vaccines are associated with better HepB completion and compliance.[9–11] Notably, one study found that children receiving the DTaP-HepB-IPV combination vaccine (diphtheria, tetanus toxoid and acellular pertussis plus HepB plus inactivated poliovirus) had a higher completion rate for the overall childhood vaccination series compared with children who did not receive it.[10] Furthermore, 45.2% of the DTaP-HepB-IPV cohort received all recommended vaccinations at age-appropriate times, compared with 37.5% of those who did not receive the DTaP-HepB-IPV vaccine. However, these findings may not provide an accurate assessment of the effect of a HepB combination vaccine as both the combination and comparison cohorts could have received non-HepB combination vaccines that may have concurrently influenced completion and compliance rates.

Gaining an understanding of the association between combination vaccines and childhood vaccination completion and compliance rates may provide further insight into the potential effectiveness of future strategies involving vaccination modalities and formulations to increase vaccination coverage. Therefore, the aim of this study was to further isolate and quantify the effect of HepB combination vaccines on vaccine completion and compliance rates among young children in the United States.

MATERIALS AND METHODS

Using demographic and vaccination history data from a nationally representative sample of children 24 to 35 months of age in the United States, vaccine completion and compliance measures were compared between 3 groups of children: those who received HepB combination vaccine, those who received non-HepB combination vaccine and those who received HepB single-antigen vaccine only.

Data Source

Data for this study (GSK study identifier: HO-11–770) were taken from the 2011 National Immunization Survey (NIS), an annual survey conducted by the Centers for Disease Control and Prevention to assess vaccination coverage of children 19 to 35 months of age in the United States.[12] The NIS uses list-assisted random digit dialing to contact a sample of households with children in the targeted age range

Accepted for publication May 8, 2016.

From the *RTI Health Solutions, Research Triangle Park, NC; and †Janssen, Pharmaceutical Companies of Johnson and Johnson, Raritan, NJ.

Claudia M. Galindo, MD, MSc, affiliated with GSK, Philadelphia, PA, at the time of this research.

At the time of study development and first manuscript drafts, CMG was an employee of the GSK group of companies and held shares in the GSK group of companies as part of her employee remuneration. Currently, CMG is an employee of Janssen and hold stock options from this company. SKK and KLD are employees of RTI Health Solutions, a contract research organization that received funding from GlaxoSmithKline Biologicals SA to conduct the analysis described in this manuscript. Although RTI Health Solutions was contracted to complete the research study described herein, neither SKK nor KLD were compensated for their contributions as authors on this manuscript.

GlaxoSmithKline Biologicals SA funded all costs associated with research (GSK study identifier: HO-11–770) and the development and publishing of the present manuscript. RTI Health Solutions was funded by GlaxoSmithKline Biologicals SA to perform the data analysis.

Address for correspondence: Samantha K. Kurosky, MSPH, RTI Health Solutions, 200 Park Offices Drive, Research Triangle Park, NC 27709-2194. E-mail: skurosky@rti.org.

ISSN: 0891-3668/17/3607-e189

DOI: 10.1097/INF.0000000000001548

to capture information on the child's demographic characteristics and vaccination history.[13] This study analyzed data from the NIS Public-Use Data File that includes sampling weights designed to adjust for sampling bias and reflect the general US population. Detailed NIS methods and institutional review board approval for data analysis are reported elsewhere.[13,14] This study was approved by RTI International's institutional review board (Federal-Wide Assurance #3331).

Eligibility Criteria

Children included in the sample were required to live in the United States (excluding the US Virgin Islands), have an adequate provider-reported vaccination history and received at least 1 dose of HepB by 24 months. The NIS Public-Use Data File includes a variable indicating whether a child for whom a household interview was completed has inadequate provider-reported data. Inadequate provider-reported data are determined by meeting one of the following definitions: (1) failure to obtain parental or guardian consent to contact the child's vaccination provider; (2) inadequate information to contact the provider; (3) provider nonresponse and (4) among those who had multiple vaccination providers reported, less than 100% of providers responded.[15] To ensure full capture of HepB given during the first 24 months of life, children less than 24 months of age were excluded. Only vaccines received between birth and 24 months were included in the analysis. This capture period was used to align with methods in other published studies of vaccine completion and compliance.[9–11,16,17]

Study Cohorts

Children were assigned to 1 of 3 cohorts, (1) received at least 1 HepB combination vaccine (BC); (2) received at least one non-HepB combination vaccine and no HepB combination vaccine (NBC) or (3) received single-antigen HepB vaccine only (SAO), based on the type of vaccines received among their first 3 HepB doses. Those who received fewer than 3 doses were assessed on all HepB doses received.

Those who received at least 1 HepB combination vaccine [either the *Haemophilus influenzae* type b (Hib) and HepB vaccine (*Comvax*; Merck and Co., Inc., Whitehouse Station, NJ) or DTaP-HepB-IPV (*Pediarix*™; GSK, Rixensart, Belgium)] were assigned to the BC cohort. These children may or may not have received single-antigen or non-HepB combination vaccines. Among the remaining children, all had received at least one single-antigen HepB vaccine and some had received a non-HepB combination vaccine (DTaP-IPV/Hib). On closer examination, we found those who had received the non-HepB combination vaccine not only differed demographically but also had substantially different patterns of completion and compliance compared with children who received only single-antigen HepB vaccine. Therefore, among the remaining children, we assigned those who received at least one dose of the non-HepB combination vaccine (DTaP-IPV/Hib) to the NBC cohort and those who received only single-antigen HepB vaccine to the SAO cohort. Figure 1 displays sample selection and cohort classification methods.

Completion

Vaccine completion was defined as the total count of doses received by 18 months, irrespective of the timing of the vaccinations received. Completion was stratified by receipt of at least 3 doses (complete), 1 or 2 doses (partial) or none (never). Due to sample inclusion criteria, the "none" category included children who received at least one dose between 18 and 24 months.

Compliance

Vaccine compliance was defined as the receipt of each dose within the ACIP-recommended age range (Table 1). Age ranges for each dose were converted to days, ending at the greatest number of days that could compose the given number of months in the schedule. Doses received within a 4-day grace period before the minimum acceptable age requirement were included in the analysis, and those received before the grace period were excluded from the analysis.

As first described by Luman et al,[16–18] several variations of compliance were assessed. The first measure consisted of categorizing children into mutually exclusive groups: full compliance (received all 3 doses on time), 2 doses on time, one dose on time or no doses on time. The second measure was the sum of the total number of days the child was undervaccinated (missing an expected dose according to the age and spacing requirements of the ACIP schedule). Days during which the child was undervaccinated (regardless of the number of doses missing on that day) were counted toward the total number of days undervaccinated until the child was vaccinated or reached 24 months of age. Severe delay was defined as 7 months or more of undervaccination.[17] A measure of late vaccination was defined as receipt of at least one HepB vaccine dose after the recommended age range and before 24 months.

Statistical Analysis

All analysis was conducted in SAS version 9.3 (SAS Institute, Inc., Cary, NC, 2011). Weighted percentages, means, standard errors and confidence intervals (CIs) were estimated using survey procedures to account for the complex survey design. Differences in completion and compliance between the study cohorts were tested using t tests for continuous variables and χ^2 tests for categorical variables.

Multivariable logistic regression models were estimated for 3 binary outcome measures: vaccine completion (complete versus incomplete), severe delay (7 or more months of undervaccination) and late vaccination (at least one late dose). Demographic, household and provider characteristics as well as the assigned vaccine cohort (BC, NBC, SAO) were included as covariates in each regression model.

RESULTS

An unweighted total of 27,305 households completed the 2011 NIS. Of these, 28.5% were excluded due to inadequate provider-reported vaccination history data. Among those who were excluded due to inadequate provider-reported vaccination history data, reasons for inadequate provider data included lack of parental consent to contact the child's provider (73%) and provider nonresponse or incomplete response (27%).[15] An additional 23.8% were excluded on the basis of age, location, or lack of combination or single-antigen HepB vaccine by 24 months of age. The final unweighted size was 13,028 children, reflecting a weighted population of 4,040,116 children in the United States. Among them, 708,663 (17.5%) were in the single cohort, 1,738,950 (43.0%) were in the mixed cohort and 1,592,503 (39.4%) were in the combination cohort.

Household and Provider Characteristics

More than half of mothers were 30 years of age or older (54.1%), married (62.8%) and educated beyond high school (51.8%; Table 2). Approximately 58.5% of children were living above the poverty level, 47.9% were non-Hispanic white and 49.8% were covered by public health insurance (ie, Medicaid or the State Children's Health Insurance Program). Almost two-thirds of children had a single vaccine provider, and more than half of providers were in private practices.

The SAO cohort had a greater proportion of mothers who were married, college graduates and above the poverty line compared with both the NBC and BC cohorts (all $P < .01$). Furthermore, 71.9% of the SAO cohort received vaccinations from a private provider

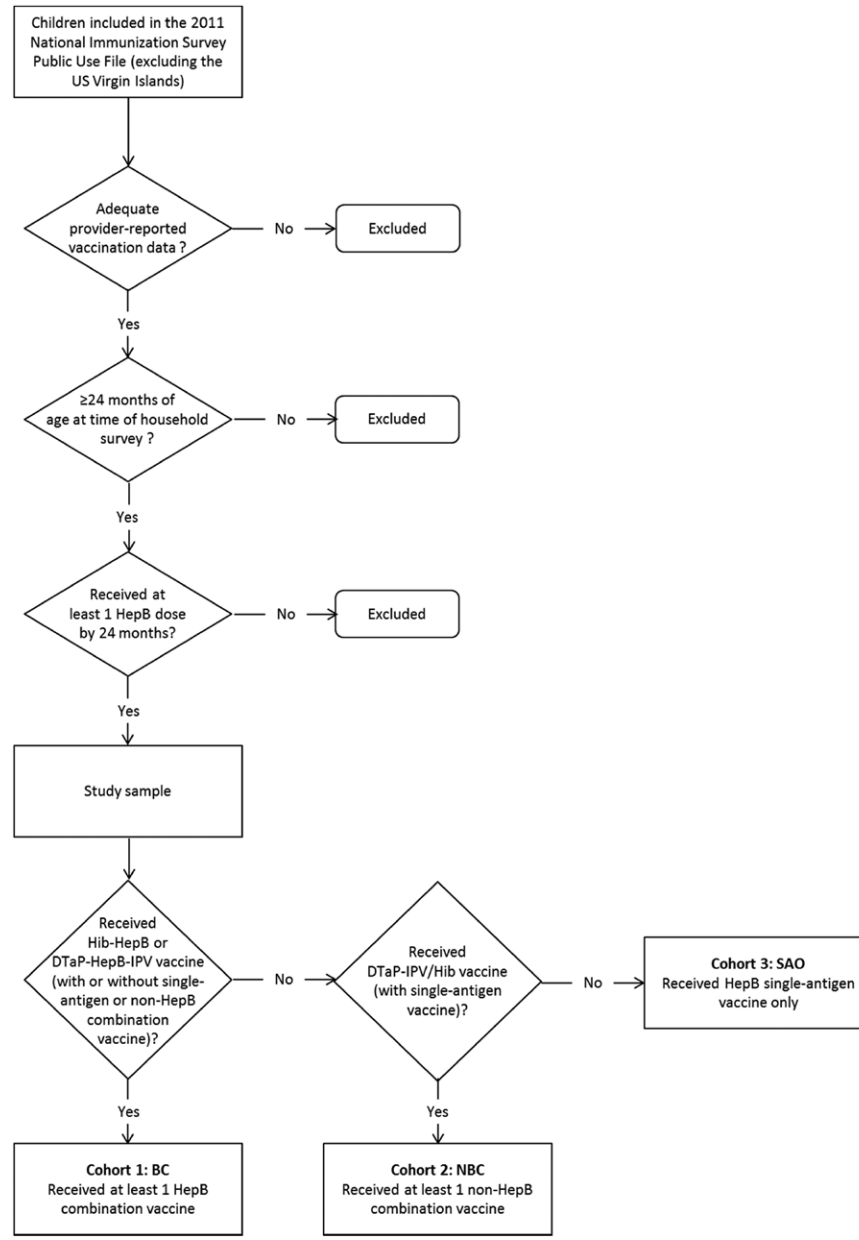

FIGURE 1. Sample selection and cohort classification. BC indicates hepatitis B combination vaccine cohort; DTaP-HepB-IPV, diphtheria, tetanus toxoid and acellular pertussis plus hepatitis B plus inactivated poliovirus vaccine; DTaP-IPV/Hib, diphtheria, tetanus toxoid and acellular pertussis plus inactivated poliovirus plus *Haemophilus influenzae* type b vaccine; HepB, hepatitis B vaccine; Hib-HepB, *Haemophilus influenzae* type b plus hepatitis B vaccine; NBC, non-hepatitis B combination vaccine cohort; SAO, single-antigen hepatitis B vaccine only cohort.

TABLE 1. ACIP-Recommended Age Ranges for the First 3 Doses of Hepatitis B Vaccine

Dose Number	Recommended Age of Administration[a]	Minimum Acceptable Age[b]	Minimum Acceptable Interval to Next Dose	Age in Days When Delay Count Initiated[c]
1	Birth	Birth	4 weeks	32
2	1–2 months	1 month	8 weeks	93
3	6–18 months	6 months	—	580

[a]Doses given within 4 days before the minimum age are considered acceptable.
[b]Only monovalent vaccine can be used before 6 weeks of age; dose must be given at birth before hospital discharge.
[c]Calculated from ACIP-recommended age ranges for each dose.[17,26]
ACIP, Advisory Committee on Immunization Practices.

compared with 56.1% of the NBC cohort ($P < .001$) and 49.1% of the BC cohort ($P < .001$). In the SAO cohort, 39.3% were covered by public health insurance compared with 53.8% of the NBC cohort ($P < .001$) and 50.0% of the BC cohort ($P < .001$). Fewer children in the BC cohort received vaccinations from a private provider (49.1%) and fewer had public health insurance (50.0%) compared with children in the NBC cohort (56.1% and 53.8%, respectively; both $P < .05$).

Completion

Overall, 91.2% of children completed 3 HepB doses, 8.6% completed 1 or 2 doses and 0.3% received no doses by 18 months of age (Table 3). The BC cohort had a higher completion rate of 3 doses (94.9%) compared with the NBC (90.8%) and SAO (83.6%) cohorts (both $P < .001$).

TABLE 2. Background Child, Family and Provider Characteristics by Hepatitis B Vaccine Type

	Total			SAO[a]			NBC[b]			BC[c]			SAO vs. NBC	SAO vs. BC	NBC vs. BC
Characteristics	%	LCL	UCL	%	LCL	UCL	%	LCL	UCL	%	LCL	UCL	*P* Value	*P* Value	*P* Value
Maternal age													.07	.004	.03
19 years or less	2.3	1.7	2.9	1.5	0.4	2.6	2.9	1.9	3.9	2.0	1.3	2.8			
20 to 29 years	43.6	42.0	45.3	39.0	35.0	43.1	42.4	40.0	44.8	47.0	44.3	49.8			
30 years or more	54.1	52.4	55.7	59.5	55.4	63.5	54.8	52.4	57.2	50.9	48.2	53.6			
Maternal marital status													.003	.002	.76
Not married[d]	37.2	35.5	38.9	30.9	27.0	34.8	38.2	35.7	40.7	38.8	36.1	41.6			
Married	62.8	61.1	64.5	69.1	65.2	73.0	61.8	59.3	64.3	61.2	58.4	63.9			
Maternal education													<.001	<.001	.16
<12 years	19.4	18.0	20.9	16.4	13.0	19.7	19.6	17.3	21.8	20.7	18.3	23.1			
12 years	28.8	27.1	30.5	21.9	18.4	25.4	30.0	27.3	32.6	30.6	27.9	33.3			
>12 years, noncollege graduated	21.7	20.4	22.9	18.2	15.1	21.3	21.5	19.7	23.4	23.4	21.3	25.5			
College graduate	30.1	28.7	31.4	43.5	39.7	47.3	29.0	27.1	30.8	25.3	23.3	27.4			
Census region													.11	.07	.002
Northeast	15.8	15.0	16.7	18.5	16.2	20.8	16.4	14.8	17.9	14.0	12.6	15.4			
Midwest	20.0	20.0	22.0	19.7	17.2	22.3	21.3	19.5	23.0	21.3	19.5	23.1			
South	38.5	37.2	39.9	36.5	33.0	40.0	40.6	38.3	42.9	37.2	34.7	39.6			
West	24.7	23.1	26.2	25.3	21.1	29.5	21.8	19.3	24.3	27.5	24.8	30.3			
Poverty status													<.001	<.001	.58
Below poverty line	35.9	34.3	37.6	26.0	22.5	29.4	38.9	36.4	41.4	37.1	34.4	39.8			
Above poverty line	58.5	56.8	60.2	66.8	62.8	70.7	55.8	53.2	58.3	57.9	55.2	60.6			
Unknown[e]	5.6	4.6	6.5	7.3	4.4	10.1	5.3	4.0	6.6	5.0	3.7	6.4			
Number of children in household													.02	.04	.37
1	25.0	23.6	26.5	29.1	25.3	32.8	24.3	22.3	26.4	24.0	21.6	26.4			
2 or 3	59.0	57.3	60.7	57.9	53.9	61.8	58.2	55.6	60.7	60.4	57.8	63.1			
4 or more	16.0	14.6	17.3	13.1	10.3	15.9	17.5	15.1	19.8	15.6	13.8	17.4			
Child's race/ethnicity													.02	.03	.06
Non-Hispanic white only	47.9	46.3	49.6	48.7	44.8	52.6	48.4	45.9	50.8	47.2	44.5	49.8			
Non-Hispanic black only	13.7	12.6	14.9	11.9	9.4	14.3	15.5	13.7	17.3	12.6	10.8	14.4			
Non-Hispanic other and multiple race	10.7	9.6	11.9	14.2	11.0	17.3	9.9	8.5	11.3	10.1	8.2	12.0			
Hispanic	27.6	25.9	29.3	25.3	21.3	29.2	26.2	23.7	28.8	30.1	27.5	32.8			
Child's sex													.47	.55	.88
Female	47.9	46.3	49.6	46.6	42.7	50.6	48.4	45.9	50.8	48.1	45.4	50.7			
Male	52.0	50.4	53.7	53.4	49.4	57.3	51.6	49.2	54.1	51.9	49.3	54.6			
Number of vaccination providers for child													.81	.11	.09
1	64.1	62.5	65.8	65.9	62.1	69.6	65.3	62.7	67.9	62.1	59.4	64.7			
2 or more	35.9	34.2	37.5	34.1	30.4	37.9	34.7	32.1	37.3	37.9	35.3	40.6			
Type of vaccination providers for child													<.001	<.001	.002
Private	56.1	54.4	57.8	71.9	68.3	75.4	56.1	53.5	58.7	49.1	46.4	51.8			
Public	12.9	11.7	14.2	6.4	4.8	8.0	13.7	11.6	15.8	15.0	13.1	16.9			
Other[f]	31.0	29.4	32.5	21.7	18.4	25.1	30.2	28.0	32.4	35.9	33.3	38.5			
Child covered by SCHIP or Medicaid													<.001	<.001	.04
No	50.3	48.6	51.9	60.7	56.7	64.7	46.2	43.8	48.7	50.0	47.3	52.7			
Yes	49.8	48.1	51.4	39.3	35.3	43.3	53.8	51.3	56.2	50.0	47.3	52.7			

[a]SAO: Received at least one single-antigen hepatitis B vaccine and no type of combination vaccine by 24 months of age.
[b]NBC: Received at least one single-antigen hepatitis B vaccine and at least one non-hepatitis B combination vaccine by 24 months of age.
[c]BC: Received at least one hepatitis B combination vaccine by 24 months of age.
[d]Never married, widowed, divorced, separated or deceased.
[e]Interviewees who did not respond to household size or income questions during the household interview were assigned a poverty status "Unknown."
[f]"Other" provider types include those from the following facility types: multiple facilities; hospitals; military; Women, Infants and Children (WIC) clinics and unknown facility types.
BC indicates hepatitis B combination vaccine cohort; LCL, 95% lower confidence limit; NBC, non-hepatitis B combination vaccine cohort; SAO, single-antigen hepatitis B vaccine only cohort; SCHIP, State Children's Health Insurance Program; UCL, 95% upper confidence limit.

Compliance

Overall, 61.8% of children in the sample completed all 3 HepB doses at age-appropriate windows, 12.4% received 2 doses on time, 20.7% received one dose on time and 5.1% received no doses on time (Table 4). The NBC cohort had the highest proportion of children receiving all 3 doses on time (69.4%) compared with 57.5% ($P < .001$) in the BC and 53.0% ($P < .001$) in the SAO cohorts. The proportion of children who received 3 doses on time in the BC cohort did not significantly differ from the SAO cohort ($P = .06$). However, the BC cohort had a significantly smaller proportion of children who received 2 doses on time (10.0%) compared with the SAO cohort (18.3%; $P < .001$).

The mean time undervaccinated for the entire sample was 62.11 days [standard error (SE): 2.32]. The mean time undervaccinated in the SAO cohort was 107.70 days (SE: 7.50), more than twice that of the NBC (53.13 days, SE: 3.50, $P < .001$) and BC cohorts (51.63 days, SE: 2.90, $P < .001$). Among all children, 38.2% had at least 1 day of undervaccination. The SAO cohort had a significantly

TABLE 3. Hepatitis B Vaccine Completion by Vaccine Type

Completion at 18 Months	Total			SAO[a]			NBC[b]			BC[c]			SAO vs. NBC	SAO vs. BC	NBC vs. BC
	%	LCL	UCL	%	LCL	UCL	%	LCL	UCL	%	LCL	UCL	*P* Value	*P* Value	*P* Value
All doses	91.2	90.2	92.1	83.6	80.7	86.6	90.8	89.4	92.2	94.9	93.6	96.2	<.001	<.001	<.001
1–2 doses	8.6	7.6	9.5	15.9	13.0	18.8	9.0	7.6	10.4	4.9	3.6	6.2	<.001	<.001	<.001
None[d]	0.3	0.1	0.4	0.5	0.1	0.8	0.2	0.0	0.4	0.2	0.0	0.5	.23	.33	.88

[a]SAO: Received at least one single-antigen hepatitis B vaccine and no type of combination vaccine by 24 months of age.

[b]NBC: Received at least one single-antigen hepatitis B vaccine and at least one non-hepatitis B combination vaccine by 24 months of age.

[c]BC: Received at least one hepatitis B combination vaccine by 24 months of age.

[d]All children included in the overall sample were required to have at least one dose of hepatitis B by 24 months of age. Completion was assessed at 18 months; therefore, children who have 0 doses by 18 months received their first dose of hepatitis B vaccine sometime between 18 and 24 months.

BC indicates hepatitis B combination vaccine cohort; LCL, 95% lower confidence limit; NBC, non-hepatitis B combination vaccine cohort; SAO, single-antigen hepatitis B vaccine only cohort; UCL, 95% upper confidence limit.

TABLE 4. Hepatitis B Vaccine Timeliness by Vaccine Type

Characteristics	Total			SAO[a]			NBC[b]			BC[c]			SAO vs. NBC	SAO vs. BC	NBC vs. BC
		LCL	UCL		LCL	UCL		LCL	UCL		LCL	UCL	*P* Value	*P* Value	*P* Value
Compliance with the ACIP-recommended schedule (%)															
All 3 doses received according to schedule	61.8	60.2	63.4	53.0	49.0	56.9	69.4	67.0	71.7	57.5	54.8	60.2	<.001	.06	<.001
2 of 3 doses received according to schedule	12.4	11.3	13.4	18.3	15.2	21.5	12.1	10.6	13.6	10.0	8.5	11.5	<.001	<.001	.05
1 of 3 doses received according to schedule	20.7	19.3	22.1	22.4	19.1	25.8	13.5	11.5	15.4	27.9	25.5	30.2	<.001	.01	<.001
No doses received according to schedule	5.1	4.3	5.9	6.3	4.5	8.0	5.1	4.0	6.2	4.7	3.3	6.0	.25	.16	.64
Days undervaccinated (d)															
Mean	62.11	57.57	66.65	107.70	93.00	122.40	53.13	46.27	59.98	51.63	45.95	57.30	<.001	<.001	.74
Standard error	2.32			7.50			3.50			2.90					
Total number of days undervaccinated (%)															
0 days	61.8	60.2	63.4	53.0	49.0	56.9	69.4	67.0	71.7	57.5	54.8	60.2	<.001	.06	<.001
1–7 days	1.5	1.2	1.8	2.7	1.5	4.0	1.3	0.9	1.8	1.1	0.7	1.5	.01	.002	.50
8–31 days	2.3	1.8	2.8	4.0	2.4	5.6	2.1	1.5	2.7	1.8	1.1	2.4	.009	.002	.48
32 days to 2 months	16.1	14.9	17.3	12.7	10.3	15.1	11.5	9.9	13.2	22.6	20.4	24.8	.42	<.001	<.001
3–6 months	10.8	9.7	11.9	13.8	10.6	17.0	8.2	6.8	9.7	12.2	10.4	14.1	<.001	.39	<.001
7–12 months	3.1	2.5	3.7	2.6	1.5	3.7	3.8	2.8	4.7	2.6	1.5	3.8	.13	.97	.15
More than 12 months	4.4	3.7	5.0	11.1	8.9	13.4	3.7	2.7	4.6	2.2	1.4	2.9	<.001	<.001	.02
Severe delay (%)	7.5	6.6	8.4	13.7	11.3	16.2	7.4	6.1	8.7	4.8	3.5	6.1	<.001	<.001	.009
Vaccinated late (%)	38.2	36.6	39.8	47.0	43.1	51.0	30.6	28.3	33.0	42.5	39.8	45.2	<.001	.06	<.001

[a]SAO: Received at least one single-antigen hepatitis B vaccine and no type of combination vaccine by 24 months of age.

[b]NBC: Received at least one single-antigen hepatitis B vaccine and at least one non-hepatitis B combination vaccine by 24 months of age.

[c]BC: Received at least one hepatitis B combination vaccine by 24 months of age.

ACIP indicates Advisory Committee on Immunization Practices; BC, hepatitis B combination vaccine cohort; LCL, 95% lower confidence limit; NBC, non-hepatitis B combination vaccine cohort; SAO, single-antigen hepatitis B vaccine only cohort; UCL, 95% upper confidence limit.

higher proportion of children with more than 12 months undervaccinated (11.1%), compared with the NBC cohort (3.7%; $P < .001$) and the BC cohort (2.2%; $P < .001$). Severe delay among the SAO cohort (13.7%) was twice that of the NBC (7.4%; $P < .001$) and nearly 3 times that of the BC cohorts (4.8%; $P < .001$).

Characteristics Associated With the Likelihood of Full Completion, Severe Delay and Late Vaccination

Multivariable analyses (Table 5) revealed multiple factors were related to key completion and compliance measures. In Model 1, children in the SAO cohort [odds ratio (OR) = 0.25, 95% CI: 0.17–0.35] or NBC cohort (OR = 0.50, 95% CI: 0.37–0.69) were less likely to complete 3 HepB doses by 18 months than children in the BC cohort (reference group). Other factors significantly associated with completion of all 3 doses of HepB included living in the South (OR = 1.42, $P = .03$) and having 4 or more children in the household (OR = 0.59, $P = .006$).

In Model 2, children in the SAO cohort were 3.45 times as likely to have severe delay compared with children in the BC cohort ($P < .001$), whereas children in the NBC cohort were 1.69 times as likely ($P = .003$). In addition, those who had 4 or more children in the household were more likely to have severe delay compared with those with only one child (OR = 1.61, 95% CI: 1.07–2.41).

In Model 3, children in the NBC cohort had reduced odds of having at least one late dose (OR = 0.60, $P < .001$) compared with children in the BC cohort. In addition, having a mother with 12 years of education compared with <12 years (OR = 0.76, $P = .03$) and living in the Midwest (OR = 0.68, $P < .001$) or the South (OR = 0.71, $P < .001$) compared with the Northeast were associated with a reduced likelihood of having at least one late dose. Whereas having 4 or more children in the household was associated with an increased likelihood of having at least one late dose (OR = 1.37, $P = .009$).

TABLE 5. Factors Associated With Completion and Compliance

	Model 1 (Completion): Completed 3 Doses by 18 Months[a]				Model 2 (Compliance): Severe Delay[b]				Model 3 (Compliance): At Least One Late Dose[c]			
Characteristics	OR	LCL	UCL	*P* Value	OR	LCL	UCL	*P* Value	OR	LCL	UCL	*P* Value
Vaccine type												
BC[d]	1.00				1.00				1.00			
SAO[e]	0.25	0.17	0.35	<.001	3.45	2.37	5.03	<.001	1.21	0.99	1.47	.06
NBC[f]	0.50	0.37	0.69	<.001	1.69	1.19	2.39	.003	0.60	0.51	0.70	<.001
Maternal age, years												
19 years or less	1.00				1.00				1.00			
20–29 years	0.60	0.19	1.89	.38	1.56	0.42	5.73	.51	1.64	0.97	2.80	.07
30 years or more	0.59	0.18	1.90	.38	1.66	0.44	6.24	.45	1.37	0.80	2.35	.26
Maternal marital status												
Not married[g]	1.00				1.00				1.00			
Married	1.34	0.96	1.86	.08	0.82	0.57	1.17	.27	1.12	0.92	1.35	.26
Maternal education												
<12 years	1.00				1.00				1.00			
12 years	1.32	0.89	1.96	.16	0.75	0.49	1.14	.18	0.76	0.60	0.97	.03
>12 years, noncollege graduated	0.89	0.58	1.37	.60	1.06	0.66	1.69	.81	0.88	0.69	1.13	.32
College graduate	1.31	0.85	2.04	.22	0.83	0.51	1.34	.44	0.93	0.71	1.22	.62
Census region												
Northeast	1.00				1.00				1.00			
Midwest	1.42	1.00	2.02	.05	0.72	0.49	1.05	.09	0.68	0.56	0.82	<.001
South	1.42	1.03	1.94	.03	0.74	0.53	1.05	.09	0.71	0.60	0.85	<.001
West	0.83	0.56	1.23	.35	1.29	0.85	1.97	.23	1.01	0.81	1.27	.93
Poverty status												
Below poverty line	1.00				1.00				1.00			
Above poverty line	1.02	0.70	1.47	.92	0.87	0.57	1.32	.51	0.83	0.67	1.02	.08
Unknown[h]	0.52	0.31	0.90	.02	1.84	1.04	3.25	.04	1.15	0.79	1.68	.46
Number of children in household												
1	1.00				1.00				1.00			
2 or 3	0.76	0.55	1.05	.09	1.26	0.90	1.77	.18	1.05	0.88	1.25	.59
4 or more	0.59	0.40	0.86	.006	1.61	1.07	2.41	.02	1.37	1.08	1.74	.009
Child's race/ethnicity												
Non-Hispanic white only	1.00				1.00				1.00			
Non-Hispanic black only	0.91	0.62	1.33	.61	1.08	0.70	1.67	.73	1.09	0.87	1.36	.47
Non-Hispanic other and multiple race	1.30	0.82	2.08	.27	0.85	0.52	1.39	.51	0.97	0.76	1.25	.81
Hispanic	1.29	0.88	1.89	.19	0.83	0.55	1.25	.38	0.89	0.73	1.09	.26
Child's sex												
Female	1.00				1.00				1.00			
Male	0.95	0.76	1.20	.68	0.99	0.78	1.27	.95	0.97	0.84	1.11	.62
Number of vaccination providers for child												
1	1.00				1.00				1.00			
2 or more	0.84	0.65	1.09	.19	1.08	0.81	1.44	.59	0.98	0.84	1.15	.81
Type of vaccination providers for child												
Private	1.00				1.00				1.00			
Public	0.72	0.49	1.05	.09	1.32	0.86	2.03	.20	1.27	1.00	1.60	.05
Other[i]	0.83	0.62	1.11	.20	1.37	1.00	1.88	.05	1.05	0.89	1.25	.56
Child covered by SCHIP or Medicaid												
No	1.00				1.00				1.00			
Yes	1.22	0.83	1.78	.31	0.72	0.48	1.10	.13	0.82	0.67	1.00	.05

[a]The reduced model included vaccine series type, marital status, education, poverty status, number of children in the household and census region.
[b]The reduced model included vaccine series type, poverty status and census region. Severe delay is defined as 7 months or more of undervaccination.
[c]The reduced model included vaccine series type, poverty status, maternal age, number of children in the household, insurance type and census region.
[d]BC: Received at least one hepatitis B combination vaccine by 24 months of age.
[e]SAO: Received at least one single-antigen hepatitis B vaccine and no type of combination vaccine by 24 months of age.
[f]NBC: Received at least one single-antigen hepatitis B vaccine and at least one non-hepatitis B combination vaccine by 24 months of age.
[g]Never married, widowed, divorced, separated or deceased.
[h]Interviewees who did not respond to household size or income questions during the household interview were assigned a poverty status "Unknown."
[i]"Other" provider types include those from the following facility types: multiple facilities; hospitals; military; Women, Infants and Children (WIC) clinics and unknown facility types.
BC indicates hepatitis B combination vaccine cohort; LCL, 95% lower confidence limit; NBC, non-hepatitis B combination vaccine cohort; OR, odds ratio; SAO, single-antigen hepatitis B vaccine only cohort; SCHIP, State Children's Health Insurance Program; UCL, 95% upper confidence limit.

DISCUSSION

Overall, we found the vast majority of children received all 3 doses of vaccine by 18 months of age. Those who received the HepB combination vaccine (BC cohort) were demographically similar to those who received a non-HepB combination vaccine (NBC cohort). However, the demographics of children receiving only single-antigen

vaccine (SAO cohort) differed significantly from both groups. A higher proportion of children receiving single-antigen vaccine only were living above the poverty level, receiving vaccines from private providers and not enrolled in public health insurance. These characteristics are consistent with the profile of unvaccinated children[19] and parents who intentionally refuse or delay their child's vaccines.[4,20–22]

In the United States, the completion rate of 3 HepB doses by 18 months of age has remained above 90% over the past several years, which is consistent with the present study's findings. As expected, when stratified by vaccine type, completion rates were much higher for children who received at least one combination vaccine than for those who received only single-antigen vaccine. Furthermore, multivariable logistic regression analyses indicated the effect of receiving HepB combination vaccine was associated with a greater likelihood of completing all 3 doses by 18 months compared with the other groups. Happe et al[10,11] found that the DTaP-HepB-IPV combination vaccine was associated with greater completion and compliance of the recommended childhood vaccination series and specific antigens when compared with children who did not receive that combination vaccine. A study by Marshall et al[9] reported any HepB combination vaccine (DTaP-HepB-IPV or HepB-Hib) was associated with increased coverage of several individual vaccines and the full recommended childhood vaccination series. However, these studies did not take into account the potential effect of non-HepB combination vaccines on compliance measures, thus making interpretation of the association between HepB combination vaccines and compliance difficult.

In the present study, we found that although the NBC group had reduced odds of completion compared with the BC group, the odds of completion for the SAO group compared with the BC group was even lower. This suggests the use of non-HepB combination vaccine may improve compliance outcomes, but with a smaller effect than that of the HepB combination vaccine. These results also revealed a significantly lower proportion of children who were missing 1 or 2 doses among those who received the HepB or non-HepB combination vaccines compared with those who received the single-antigen vaccine only. Although these children are not fully protected against HepB, our findings indicate combination vaccines are associated with improved coverage, including increased partial coverage.

Reliance on completion rates alone as an indicator of population-level protection against HepB can mask susceptibility during the first 2 years of life. Although a child may complete all 3 doses by age 2 years, some or all of these doses may have been delayed, leaving the child temporarily undervaccinated. Evidence suggests few children receive all vaccinations on time.[16,18,23,24] Overall, we found approximately 1 in 3 children missed or delayed at least one dose of vaccine. When stratified by vaccine type, those who received a non-HepB combination vaccine had the greatest proportion of children who were vaccinated on time. In the single-antigen group, close to half were delayed or missing at least one dose. Children who had received only single-antigen vaccine had twice the mean number of total days undervaccinated when compared with the other groups. In addition, the single-antigen group also had the highest proportion of severe delay. Those who had received the HepB combination vaccine had the lowest proportion of severe delay. These results indicate that many children are in fact underimmunized against hepatitis B during the first 24 months of life. Although they may catch up by their second birthday, more than one-third of children are insufficiently protected for some time before reaching that milestone. It is particularly worrisome for those with severe delay. A long period of undervaccination may point to issues with accessing preventive care, vaccine delivery or intentional refusal to complete the ACIP-recommended dosing series.

These findings should be interpreted in light of several limitations. First, the NIS telephone survey methodology relies on the household respondent to identify all vaccine providers, and for each of those providers to accurately report the child's vaccination history. There is potential bias due to households without landline or cell phone service and nonresponse. It is also possible some providers were not identified or those who were identified did not report the child's entire vaccine history. This could result in some children being misclassified in our study with regard to vaccination type, completion or compliance.

Second, child and household characteristics are subjected to the child's caregiver's interpretation. The total number of vaccine providers is also reported by the child's caregiver. As many children receive the HepB birth dose from hospital staff before discharge and subsequent vaccines from primary care providers (eg, pediatric practices), the fact that the majority of patients had a single vaccine provider is likely due to the caregiver's perception that the hospital staff is not a "vaccine provider." However, this misclassification likely does not greatly impact reporting of vaccinations as birth doses are well recorded in the medical record that is subsequently reviewed by the infant's primary care provider (eg, vaccine provider).

The analyses conducted in this study do not test for causality. Although we found a significant association between receipt of combination vaccines and improved outcomes, we were unable to account other mediating, confounding and moderating variables that may have substantial effect on the association and thus interpretation of the findings. For example, as described previously, children who received single-antigen vaccine only had a similar demographic profile to unvaccinated children and children of parents who intentionally refuse or delay childhood vaccines (ie, vaccine hesitant). It is possible vaccine hesitancy, manifested by lack of vaccination, vaccine delay, seeking of providers who supply single-antigen vaccine and use of alternative schedules, is contributing to low completion and compliance rates among single-antigen only recipients. A study by Nadeau et al[25] reported that approximately 1 in 4 children followed an alternative vaccination schedule, which resulted in a significantly lower completion rate at 9 months of age. As we did not examine such external influences on completion and compliance, there may be unaccounted selection bias affecting the present study's findings. This study provides new information on HepB completion and compliance among children who received HepB combination vaccine compared with those who did not. Although completion rates were high, a large proportion of children remain undervaccinated for some time before age 2 years, leaving them at risk during one of their most vulnerable periods in life. However, the use of combination vaccine was associated with higher completion and compliance outcomes compared with single-antigen HepB vaccine only. These findings suggest the use of combination vaccines should be encouraged among children who are undervaccinated or receiving single-antigen vaccines to increase compliance with the ACIP-recommended schedule. Future research on parental and provider barriers to using HepB combination vaccines is warranted.

Ms. Kurosky analyzed the data, interpreted results, drafted the manuscript, and approved the final manuscript as submitted. Mr. Davis conceptualized and designed the study, interpreted results, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Galindo conceptualized and designed the study, interpreted results, reviewed and revised the manuscript, and approved the final manuscript as submitted.

ACKNOWLEDGMENTS

The authors thank Cristina Masseria (at that time employed by GSK) for her contribution to the original study design, Daniel

Siepert of RTI Health Solutions for editorial review of the manuscript, and Julia Donnelly (freelance publication manager, United Kingdom, on behalf of GSK) and Grégory Leroux (publication manager, Business & Decision Life Sciences on behalf of GSK) for editorial assistance and manuscript coordination.

Comvax is a trademark of Merck and Co., Inc. Pediarix is a trademark of the GSK group of companies.

REFERENCES

1. Strikas RA; Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP); ACIP Child/Adolescent Immunization Work Group. Advisory committee on immunization practices recommended immunization schedules for persons aged 0 through 18 years–United States, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:93–94.
2. Centers for Disease Control and Prevention (CDC). In: Atkinson W, Hamborsky J, Wolfe S, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 12th ed., second printing. Washington, DC: Public Health Foundation; 2012.
3. Elam-Evans LD, Yankey D, Singleton JA, et al; Centers for Disease Control and Prevention (CDC). National, state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2014;63:741–748.
4. Gust DA, Darling N, Kennedy A, et al. Parents with doubts about vaccines: which vaccines and reasons why. *Pediatrics*. 2008;122:718–725.
5. Luthy KE, Beckstrand RL, Peterson NE. Parental hesitation as a factor in delayed childhood immunization. *J Pediatr Health Care*. 2009;23:388–393.
6. Smith PJ, Humiston SG, Parnell T, et al. The association between intentional delay of vaccine administration and timely childhood vaccination coverage. *Public Health Rep*. 2010;125:534–541.
7. Wallace AS, Mantel C, Mayers G, et al. Experiences with provider and parental attitudes and practices regarding the administration of multiple injections during infant vaccination visits: lessons for vaccine introduction. *Vaccine*. 2014;32:5301–5310.
8. National Center for Immunization and Respiratory Diseases. General recommendations on immunization–recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60:1–64.
9. Marshall GS, Happe LE, Lunacsek OE, et al. Use of combination vaccines is associated with improved coverage rates. *Pediatr Infect Dis J*. 2007;26:496–500.
10. Happe LE, Lunacsek OE, Marshall GS, et al. Combination vaccine use and vaccination quality in a managed care population. *Am J Manag Care*. 2007;13:506–512.
11. Happe LE, Lunacsek OE, Kruzikas DT, et al. Impact of a pentavalent combination vaccine on immunization timeliness in a state Medicaid population. *Pediatr Infect Dis J*. 2009;28:98–101.
12. US Department of Health and Human Services (DHHS). National Center for Health Statistics. *The 2011 National Immunization Survey*. Hyattsville, MD: Centers for Disease Control and Prevention; 2012.
13. Smith PJ, Battaglia MP, Huggins VJ, et al. Overview of the sampling design and statistical methods used in the National Immunization Survey. *Am J Prev Med*. 2001;20(4 suppl):17–24.
14. Zell ER, Ezzati-Rice TM, Battaglia MP, et al. National Immunization Survey: the methodology of a vaccination surveillance system. *Public Health Rep*. 2000;115:65–77.
15. NORC at the University of Chicago. National Immunization Survey. A user's guide for the 2011 Public-Use Data File. Centers for Disease Control and Prevention (CDC), National Center for Immunization and Respiratory Diseases, National Center for Health Statistics: Oct 2012. 187 p.
16. Luman ET, Barker LE, McCauley MM, et al. Timeliness of childhood immunizations: a state-specific analysis. *Am J Public Health*. 2005;95:1367–1374.
17. Luman ET, Barker LE, Shaw KM, et al. Timeliness of childhood vaccinations in the United States: days undervaccinated and number of vaccines delayed. *JAMA*. 2005;293:1204–1211.
18. Luman ET, McCauley MM, Stokley S, et al. Timeliness of childhood immunizations. *Pediatrics*. 2002;110:935–939.
19. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? *Pediatrics*. 2004;114:187–195.
20. Salmon DA, Moulton LH, Omer SB, et al. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. *Arch Pediatr Adolesc Med*. 2005;159:470–476.
21. Wei F, Mullooly JP, Goodman M, et al. Identification and characteristics of vaccine refusers. *BMC Pediatr*. 2009;9:18.
22. Dorell C, Yankey D, Jeyarajah J, et al. Delay and refusal of human papillomavirus vaccine for girls, national immunization survey-teen, 2010. *Clin Pediatr (Phila)*. 2014;53:261–269.
23. Dombkowski KJ, Lantz PM, Freed GL. Risk factors for delay in age-appropriate vaccination. *Public Health Rep*. 2004;119:144–155.
24. Dombkowski KJ, Lantz PM, Freed GL. The need for surveillance of delay in age-appropriate immunization. *Am J Prev Med*. 2002;23:36–42.
25. Nadeau JA, Bednarczyk RA, Masawi MR, et al. Vaccinating my way–use of alternative vaccination schedules in New York State. *J Pediatr*. 2015;166:151–156.
26. Centers for Disease Control and Prevention (CDC). Recommended immunization schedules for persons aged 0 through 18 years—United States, 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60;1–4.