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Association of Number of Doses With Hepatitis B Vaccine Series Completion in US Adults

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Abstract

IMPORTANCE Receipt of hepatitis B virus vaccine is important to prevent infection. However, adherence to the hepatitis B vaccine series among adults at risk of infection has been low.

OBJECTIVE To assess whether recipients of a 2-dose hepatitis B vaccine with cytosine phosphoguanine adjuvant (HepB-CpG vaccine; Heplisav-B) are more likely to complete their series compared with recipients of a 3-dose vaccine with alum adjuvant (comparator vaccine; Engerix-B [HepB-alum]).

DESIGN, SETTING, AND PARTICIPANTS This nested cohort study was conducted from August 7 to December 31, 2018, at Kaiser Permanente Southern California, an integrated health care system with a diverse population of approximately 4.6 million members. Adults not receiving dialysis who received a first dose of a hepatitis B vaccine series in family practice or internal medicine departments of 15 Kaiser Permanente Southern California medical centers were followed up through electronic health records for up to 1 year after receipt of the first dose. Data were analyzed from March 16 to September 23, 2020.

EXPOSURES Receipt of a first dose of the HepB-CpG vaccine (2-dose vaccine) vs receipt of a first dose of the HepB-alum vaccine (3-dose vaccine).

MAIN OUTCOMES AND MEASURES Series completion within the recommended vaccine schedule plus 3 months (primary outcome) and series completion within 1 year after receipt of the first dose (secondary outcome).

RESULTS Of 4727 individuals who initiated the HepB-CpG vaccine series and 6161 individuals who initiated the HepB-alum vaccine series included in the study, 2876 (60.8%) and 3789 (61.5%), respectively, were ages 40 to 59 years, 2415 (51.1%) and 3113 (50.5%) were male, and 2364 (50.0%) and 2881 (46.8%) were Hispanic. The vaccine series was completed within the recommended schedule plus 3 months for 2111 (44.7%) individuals who initiated the HepB-CpG vaccine series and 1607 (26.1%) individuals who initiated the HepB-alum vaccine series, and within 1 year for 2858 (60.5%) and 1989 (32.3%) individuals, respectively. The individuals who initiated the HepB-CpG vaccine series were significantly more likely to complete the series (adjusted relative risk, 1.77; 95% CI, 1.68-1.87). Results were consistent across clinical and demographic strata.

CONCLUSIONS AND RELEVANCE In this study, use of the HepB-CpG vaccine was associated with hepatitis B vaccine series completion, but tailored strategies to increase completion of hepatitis B vaccine series are warranted.

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Key Points

Question Is completion of an adult hepatitis B virus vaccine series higher among recipients of a 2-dose vaccine compared with recipients of a 3-dose vaccine?

Findings In this cohort study of 10 888 adults who initiated a hepatitis B virus vaccine series, 45% of adults who initiated the 2-dose vaccine vs 26% of those who initiated the 3-dose vaccine completed the series, representing a significant difference.

Meaning The study's findings indicate that use of the 2-dose vaccine may be associated with better adherence; however, tailored strategies are needed to increase completion of hepatitis B vaccine series.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Hepatitis B vaccines are important for the prevention of hepatitis B, a liver infection caused by the hepatitis B virus that can lead to cirrhosis and liver cancer. Approximately 22 000 new cases of hepatitis B occur each year in the US.[1] Most new hepatitis B infections occur in adults aged 30 years and older. The younger population (<30 years) has largely been protected since 1991 with universal hepatitis B vaccination of infants and catch-up vaccination of adolescents.[2] Hepatitis B vaccination of adults is recommended for those at higher risk of virus exposure, including sexual exposure, percutaneous or mucosal exposure (eg, via intravenous drug use, work in a health care setting, receipt of dialysis, and insulin injection to treat diabetes), travel to countries with a high prevalence of hepatitis B virus, incarceration, and some chronic medical conditions (eg, chronic liver disease, hepatitis C virus infection, and HIV infection).[3-5]

Coverage of hepatitis B vaccination among adults in the US has been low, even among those at high risk of hepatitis B infection. In a study using National Health Interview Survey data from 2009, 50% of adults ages 18 to 49 years with hepatitis B risk factors and 40% without risk factors had received at least 1 dose of hepatitis B vaccine, and 42% and 34%, respectively, completed a 3-dose series.[6] In another National Health Interview Survey study from 2015, 32% of all adults ages 19 to 49 years and 16.5% of those age 50 years or older had completed a 3-dose hepatitis B vaccine series.[7] Other studies using electronic health records (EHRs) or administrative claims data have also found suboptimal levels of adherence.[8-10]

The novel hepatitis B vaccine with cytosine phosphoguanine adjuvant (HepB-CpG vaccine; Heplisav-B) was licensed for use in adults in 2017 and recommended by the Advisory Committee on Immunization Practices in 2018.[11] The hepatitis B vaccine with alum adjuvant (comparator vaccine; Engerix-B [HepB-alum]) requires 3 doses (at 0, 1, and 6 months), and the HepB-CpG vaccine requires 2 doses (at 0 and 1 month). In prelicensure clinical trials,[12,13] the HepB-CpG vaccine indicated significantly greater and earlier seroprotection than the HepB-alum vaccine and had a similar safety profile. The lower number of doses and shorter time for completion of the HepB-CpG vaccine series have the potential to increase hepatitis B vaccine adherence. In this study, we assessed and compared series completion among adults who initiated the HepB-CpG vaccine series (HepB-CpG initiators) and the HepB-alum vaccine series (comparative vaccine initiators) as part of a large postlicensure cohort study conducted in an integrated health care system.

Methods

Study Setting

The study was conducted at Kaiser Permanente Southern California (KPSC), an integrated health care organization serving more than 4.6 million members. The diverse demographic characteristics of KPSC members are similar to the Southern California population.[14] The KPSC EHRs capture all aspects of patient care, including receipt of vaccinations. Because KPSC members are offered recommended vaccinations free of charge at every visit and at convenient walk-in locations, they have incentive to seek care within the organization; however, vaccinations received outside of KPSC with appropriate documentation are routinely incorporated into KPSC EHRs. The study protocol was reviewed and approved by the KPSC Institutional Review Board, which waived the requirement for informed consent based on meeting criteria for very low risk to study participants. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study Design and Population

The study was nested in a larger postlicensure safety study conducted among adult KPSC members not receiving dialysis who received a dose of hepatitis B vaccine in family medicine and internal medicine departments, where approximately 88% of all hepatitis B vaccine doses at KPSC are

administered. In the umbrella study, 7 of 15 KPSC medical centers used only the HepB-CpG vaccine in their family medicine and internal medicine departments, while the remaining 8 medical centers continued to use the HepB-alum vaccine. The default EHR order sets associated with adult hepatitis B vaccination in the family medicine and internal medicine departments were changed from the HepB-alum vaccine to the HepB-CpG vaccine for the 7 medical centers using the HepB-CpG vaccine. Individuals from the larger cohort were included in the present adherence study cohort if they received their first dose of hepatitis B vaccine between August 7 and December 31, 2018. These individuals were followed up through the EHRs for up to 1 year after the first dose to assess their receipt of subsequent doses of the HepB-CpG or HepB-alum vaccines.

Study Measures

The primary adherence outcome for the study was series completion based on the recommended schedule for the vaccine series plus 3 months (4 months after the date of the first dose of the HepB-CpG vaccine and 9 months after the date of the first dose of the HepB-alum vaccine). We allowed 3 months after the recommended schedule to account for real-world variation in health care seeking, as vaccines are often delivered during routine follow-up visits for patients' convenience. A secondary adherence outcome was series completion at 1 year after the date of the first dose, allowing 11 months after the recommended schedule for the HepB-CpG vaccine and 6 months after the recommended schedule for the HepB-alum vaccine. We included this outcome to address the public health importance of whether the 2-dose HepB-CpG vaccine was associated with higher and earlier series completion compared with the 3-dose HepB-alum vaccine. Demographic and clinical covariates, including age, sex, race and ethnicity, median household income of census block, educational level of census block (measured as the proportion of individuals with a high school education or higher), and health care use in the year before the first dose, were extracted from the EHRs. In addition, test orders for sexually transmitted infection in the year before the first dose and a diagnosis of diabetes (beginning on January 1, 2010) before the first dose were also included, as these conditions trigger alerts and reminders in the KPSC EHR system for the practitioner to order hepatitis B vaccine.

Statistical Analysis

For both the HepB-CpG and HepB-alum vaccine, characteristics of initiators were described based on both the primary and secondary adherence outcomes. The distribution of characteristics among those who completed the series (completers) and those who did not complete the series (noncompleters) for each vaccine group was compared using χ^2 P values. The cumulative incidence of series completion was estimated using the Kaplan-Meier method, comparing receipt of the second dose of the HepB-CpG vaccine, the second dose of the HepB-alum vaccine, and the third dose of the HepB-alum vaccine. Unadjusted relative risks (RRs), adjusted RRs (aRRs), and their 95% CIs comparing series completion among recipients of the HepB-CpG and HepB-alum vaccines were estimated using Poisson regression with robust error variance, adjusting for potential confounders. Variables identified a priori that were significantly associated with series completion in the bivariable analyses were included in the models. For the primary outcome, RRs stratified by demographic and clinical characteristics were also estimated. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute). Data were analyzed from March 16 to September 23, 2020.

Results

From August 7 to December 31, 2018, there were 4727 HepB-CpG initiators and 6161 HepB-alum vaccine initiators. Of these, 2876 (60.8%) HepB-CpG initiators and 3789 (61.5%) HepB-alum vaccine initiators were age 40 to 59 years, 2415 (51.1%) and 3113 (50.5%) were male, and 2364 (50.0%) and 2881 (46.8%) were Hispanic (**Table 1**).

Table 1. Comparison of Participants Who Completed and Did Not Complete the HepB-CpG Vaccine and HepB-Alum Vaccine

Characteristic	No. (%)							
	HepB-CpG vaccine group				HepB-alum vaccine group			
	Initiated series[a] (n=4727)	Completed series[b] (n=2111)	Did not complete series (n=2616)	*P* value	Initiated series[a] (n=6161)	Completed series[b] (n=1607)	Did not complete series (n=4554)	*P* value
Age at first dose, y								
18-29	677 (14.3)	267 (12.6)	410 (15.7)	<.001	769 (12.5)	197 (12.3)	572 (12.6)	<.001
30-39	712 (15.1)	284 (13.5)	428 (16.4)		928 (15.1)	199 (12.4)	729 (16)	
40-49	1233 (26.1)	517 (24.5)	716 (27.4)		1552 (25.2)	338 (21.0)	1214 (26.7)	
50-59	1643 (34.8)	768 (36.4)	875 (33.4)		2237 (36.3)	614 (38.2)	1623 (35.6)	
≥60	462 (9.8)	275 (13.0)	187 (7.1)		675 (11.0)	259 (16.1)	416 (9.1)	
Sex								
Male	2415 (51.1)	1023 (48.5)	1392 (53.2)	.04	3113 (50.5)	722 (44.9)	2391 (52.5)	<.001
Female	2312 (48.9)	1088 (51.5)	1224 (46.8)		3048 (49.5)	885 (55.1)	2163 (47.5)	
Race/ethnicity[c]								
White	746 (15.8)	380 (18.0)	366 (14)	<.001	1790 (29.1)	544 (33.9)	1246 (27.4)	<.001
Hispanic	2364 (50.0)	1031 (48.8)	1333 (51)		2881 (46.8)	666 (41.4)	2215 (48.6)	
Black	436 (9.2)	122 (5.8)	314 (12)		439 (7.1)	99 (6.2)	340 (7.5)	
Asian/Pacific Islander	841 (17.8)	421 (19.9)	420 (16.1)		691 (11.2)	216 (13.4)	475 (10.4)	
Other	340 (7.2)	157 (7.4)	183 (7)		360 (5.8)	82 (5.1)	278 (6.1)	
Median household income of census block, $								
<40 000	521 (11.0)	178 (8.4)	343 (13.1)	.004	630 (10.2)	158 (9.8)	472 (10.4)	.06
40 000-69 999	2148 (45.4)	936 (44.3)	1212 (46.3)		2695 (43.7)	662 (41.2)	2033 (44.6)	
70 000-99 999	1340 (28.3)	637 (30.2)	703 (26.9)		1768 (28.7)	476 (29.6)	1292 (28.4)	
≥100 000	717 (15.2)	359 (17.0)	358 (13.7)		1056 (17.1)	311 (19.4)	745 (16.4)	
Missing	1 (0)	1 (0)	0		12 (0.2)	0	12 (0.3)	
Proportion of census block with ≥ high school educational level, %								
<50	342 (7.2)	128 (6.1)	214 (8.2)	.10	147 (2.4)	33 (2.1)	114 (2.5)	.52
50-75	1703 (36.0)	726 (34.4)	977 (37.3)		1785 (29.0)	462 (28.7)	1323 (29.1)	
>75	2681 (56.7)	1256 (59.5)	1425 (54.5)		4219 (68.5)	1112 (69.2)	3107 (68.2)	
Missing	1 (0)	1 (0)	0		10 (0.2)	0	10 (0.2)	
Test order for STI in year before first dose								
No	3752 (79.4)	1677 (79.4)	2075 (79.3)	.95	5160 (83.8)	1340 (83.4)	3820 (83.9)	.72
Yes	975 (20.6)	434 (20.6)	541 (20.7)		1001 (16.2)	267 (16.6)	734 (16.1)	
Diagnosis of diabetes between January 1, 2010, and first dose								
No	2297 (48.6)	1143 (54.1)	1154 (44.1)	<.001	3027 (49.1)	896 (55.8)	2131 (46.8)	<.001
Yes	2430 (51.4)	968 (45.9)	1462 (55.9)		3134 (50.9)	711 (44.2)	2423 (53.2)	
Outpatient encounters in year before first dose, No.								
0	397 (8.4)	132 (6.3)	265 (10.1)	.003	439 (7.1)	70 (4.4)	369 (8.1)	<.001
1	634 (13.4)	261 (12.4)	373 (14.3)		699 (11.3)	147 (9.1)	552 (12.1)	
2-4	1623 (34.3)	713 (33.8)	910 (34.8)		1993 (32.3)	467 (29.1)	1526 (33.5)	
5-9	1209 (25.6)	566 (26.8)	643 (24.6)		1694 (27.5)	493 (30.7)	1201 (26.4)	
≥10	864 (18.3)	439 (20.8)	425 (16.2)		1336 (21.7)	430 (26.8)	906 (19.9)	
Emergency department encounters in year before first dose, No.								
0	3906 (82.6)	1740 (82.4)	2166 (82.8)	.86	4993 (81.0)	1308 (81.4)	4993 (81)	.93
1	562 (11.9)	262 (12.4)	300 (11.5)		782 (12.7)	205 (12.8)	782 (12.7)	
2-4	236 (5.0)	98 (4.6)	138 (5.3)		336 (5.5)	81 (5.0)	336 (5.5)	
≥5	23 (0.5)	11 (0.5)	12 (0.5)		50 (0.8)	13 (0.8)	50 (0.8)	
Inpatient encounters in year before first dose, No.								
0	4509 (95.4)	2012 (95.3)	2497 (95.5)	.75	5813 (94.4)	1516 (94.3)	4297 (94.4)	.88
1	167 (3.5)	72 (3.4)	95 (3.6)		265 (4.3)	67 (4.2)	198 (4.3)	
≥2	51 (1.1)	27 (1.3)	24 (0.9)		83 (1.3)	24 (1.5)	59 (1.3)	

Abbreviations: HepB-alum, hepatitis B with alum adjuvant; HepB-CpG, hepatitis B with cytosine phosphoguanine adjuvant; STI, sexually transmitted infection.

[a] Individuals who initiated the hepatitis B vaccine series and received their first dose between August 7 and December 31, 2018.

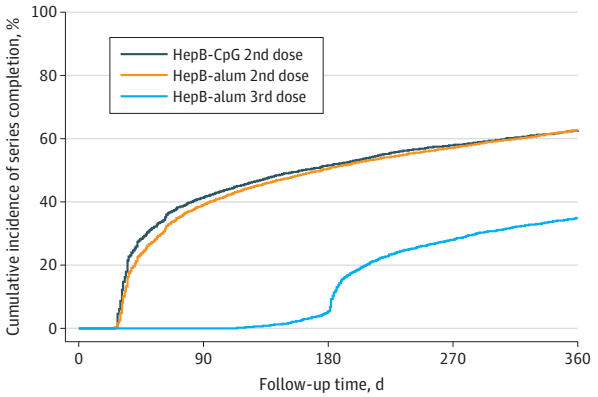
[b] Individuals who initiated and completed the hepatitis B vaccine series within the recommended schedule plus 3 months.

[c] All categories, with the exception of Hispanic, were non-Hispanic.

By the primary adherence outcome (recommended schedule plus 3 months), 2111 (44.7% of HepB-CpG initiators) and 1607 (26.1% of HepB-alum vaccine initiators) completed the series (Table 1). By the secondary adherence outcome (1 year after first dose), 2858 (60.5% of HepB-CpG initiators) and 1989 (32.3% of HepB-alum vaccine initiators) completed the series (eTable in the Supplement). Approximately 57 individuals who initiated the HepB-CpG series and 3 individuals who initiated the HepB-alum vaccine received subsequent doses of the other vaccine and were not considered to have completed the series. Cumulative incidence curves for the 2 vaccines tracked together for the second dose, but the curves separated for completion of the series (**Figure**). The cumulative incidence of completion of the second dose of HepB-CpG was 41.4%, 51.5%, 57.9%, and 62.6% at 90, 180, 270, and 360 days, respectively. The cumulative incidence of completion of the second dose of HepB-alum vaccine was 39.1%, 50.5%, 57.1%, and 62.7%, and the cumulative incidence of completion of the third dose of HepB-alum vaccine was 0.0%, 5.5%, 28.0%, and 34.9% at the same points.

For both vaccines, the distribution of demographic and clinical characteristics was different for completers by the primary outcome compared with noncompleters. Significantly greater proportions of individuals who completed their series were older (eg, aged ≥60 years; HepB-CpG, 275 of 2111 [13.0%] completers and 187 of 2616 [7.1%] noncompleters; HepB-alum vaccine, 259 of 1607 [16.1%] completers and 416 of 4554 [9.1%] noncompleters), female (HepB-CpG, 1088 of 2111 [51.5%] completers and 1224 of 2616 [46.8%] noncompleters; HepB-alum vaccine, 885 of 1607 [55.1%] completers and 2163 of 4554 [47.5%] noncompleters), White (HepB-CpG, 380 of 2111 [18.0%] completers and 366 of 2616 [14.0%] noncompleters; HepB-alum vaccine, 544 of 1607 [33.9%] completers and 1246 of 4554 [27.4%] noncompleters), Asian or Pacific Islander (HepB-CpG, 421 of 2111 [19.9%] completers and 420 of 2616 [16.1%] noncompleters; HepB-alum vaccine, 216 of 1607 [13.4%] completers and 475 of 4554 [10.4%] noncompleters), living in a census block with higher median income (eg, ≥$100 000; HepB-CpG, 359 of 2111 [17.0%] completers and 358 of 2616 [13.7%] noncompleters; HepB-alum vaccine, 311 of 1607 [19.4%] completers and 745 of 4554 [16.4%] noncompleters), and living in a census block with more than 75% of individuals with high school education or higher (HepB-CpG, 1256 of 2111 [59.5%] completers and 1425 of 2616 [54.5%] noncompleters; HepB-alum vaccine, 1112 of 1607 [69.2%] completers and 3107 of 4554 [68.2%] noncompleters). Significantly greater proportions of individuals who completed their series did not have diabetes prior to the first dose (HepB-CpG, 1143 of 2111 [54.1%] completers and 1154 of 2616 [44.1%] noncompleters; HepB-alum vaccine, 896 of 1607 [55.8%] completers and 2131 of 4554 [46.8%] noncompleters), and had more outpatient encounters in the year before the first dose (eg, ≥10 encounters; HepB-CpG, 439 of 2111 [20.8%] completers and 425 of 2616 [16.2%]

Figure. Cumulative Incidence of Hepatitis B Vaccine Series Completion



No. at risk

HepB-CpG 2nd dose	4727	2672	2122	1782	1530
HepB-alum 2nd dose	6161	3629	2832	2355	1984
HepB-alum 3rd dose	6161	5928	5412	3958	3465

HepB-alum indicates hepatitis B with alum adjuvant; HepB-CpG, hepatitis B with cytosine phosphoguanine adjuvant.

noncompleters; HepB-alum vaccine, 430 of 1607 [26.8%] completers and 906 of 4554 [19.9%] noncompleters). For both vaccines, there was no significant difference between completers and noncompleters in the proportion of individuals who had a test order for sexually transmitted infection (HepB-CpG, 434 of 2111 [20.6%] completers and 541 of 2616 [20.7%] noncompleters; HepB-alum vaccine, 267 of 1607 [16.6%] completers and 734 of 4554 [16.1%] noncompleters) (Table 1).

In adjusted analyses, HepB-CpG initiators were significantly more likely to complete the vaccine series compared with HepB-alum vaccine initiators. By the primary outcome (recommended schedule plus 3 months), HepB-CpG initiators were 77% more likely than HepB-alum vaccine initiators to complete the series (aRR, 1.77; 95% CI, 1.68-1.87) (**Table 2**). In a sensitivity analysis in which initiators without 1 year of complete follow-up were excluded (300 [6.3%] HepB-CpG initiators and 707 [11.5%] HepB-alum vaccine initiators excluded), similar results were observed for the primary outcome (aRR, 1.68; 95% CI, 1.59-1.77). By the secondary outcome (1 year after first dose), HepB-CpG initiators were 92% more likely than HepB-alum vaccine initiators to complete the series (aRR, 1.92; 95% CI, 1.84-2.01). Results across demographic and clinical strata were consistent with the overall finding that HepB-CpG initiators were more likely than HepB-alum vaccine initiators to complete the series (**Table 3**). For example, among individuals aged 40 to 49 years, the HepB-CpG initiators were 93% more likely than HepB-alum vaccine initiators to complete the series (RR, 1.93; 95% CI, 1.72-2.16). Among Hispanic individuals, HepB-CpG initiators were 89% more likely than HepB-alum vaccine initiators to complete the series (RR, 1.89; 95% CI, 1.74-2.05). Among individuals with diabetes, HepB-CpG initiators were 76% more likely than HepB-alum vaccine initiators to complete the series (RR, 1.76; 95% CI, 1.62-1.90).

Discussion

In this study, we found that series completion was higher among HepB-CpG initiators than HepB-alum vaccine initiators (44.7% vs 26.1% by the primary outcome [recommended schedule plus 3 months]). In adjusted analyses, HepB-CpG initiators were significantly more likely to complete the series than HepB-alum vaccine initiators. This finding was consistent across strata of demographic and clinical characteristics. By the secondary outcome (1 year after first dose), series completion was 60.5% among HepB-CpG initiators and 32.3% among HepB-alum vaccine initiators.

Similar levels of suboptimal adherence among adult recipients of hepatitis B vaccine have been reported by other studies using routinely collected data. In a study using EHRs in the UK from 2009 to 2016,[9] 22% of adults who initiated a 3-dose vaccine series had completed the series after 6 months, and 35% of adults had completed the series after 30 months. In the US, a similar study[8] reported that 31% of adults who initiated a 3-dose vaccine series had completed the series after 28 months. A study using earlier data (1996-2004) from the Vaccine Safety Datalink in integrated health care systems found higher series completion (approximately 60%) after 1 year among adults who initiated the vaccine series,[10] although indications for adult hepatitis B vaccination at the time were narrower than currently specified.[5]

Adherence to the full hepatitis B vaccine series schedule is important for protection against hepatitis B virus infection. Studies have shown lower antibody responses when fewer doses than recommended in a series are received for both the HepB-alum vaccine and HepB-CpG[12,15]; optimal seroprotection requires receipt of all recommended doses. Furthermore, delays in series completion prolong the time during which individuals are at risk of hepatitis B infection. Our results suggest that the receipt of 2 doses of the HepB-CpG vaccine over 1 month may be associated with significantly higher and earlier hepatitis B vaccination series completion than 3 doses of the HepB-alum vaccine over 6 months.

Our study also found that series completion was lower among some sociodemographic subgroups of the population. For both vaccines, series completion was lower among Black individuals and, to a lesser extent, Hispanic individuals compared with White individuals, consistent with the

Table 2. Adjusted Relative Risk of Series Completion for HepB-CpG Vaccine vs HepB-Alum Vaccine Groups

Variable	Recommended vaccine series schedule plus 3 mo (primary outcome)		1 Year after initiation of vaccine series (secondary outcome)	
	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]	Unadjusted RR (95% CI)	Adjusted RR (95% CI)[a]
HepB-CpG vaccine vs HepB-alum vaccine	1.71 (1.62-1.80)	1.77 (1.68-1.87)	1.87 (1.79-1.95)	1.92 (1.84-2.01)
Age at first dose, y				
18-29	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
30-39	0.92 (0.82-1.02)	1.04 (0.93-1.15)	0.97 (0.89-1.06)	1.05 (0.96-1.14)
40-49	0.96 (0.87-1.05)	1.12 (1.02-1.22)	1.11 (1.03-1.20)	1.21 (1.12-1.31)
50-59	1.11 (1.02-1.21)	1.33 (1.22-1.45)	1.24 (1.15-1.33)	1.37 (1.27-1.48)
≥60	1.46 (1.33-1.61)	1.53 (1.39-1.69)	1.40 (1.29-1.52)	1.44 (1.33-1.57)
Sex				
Male	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Female	1.17 (1.11-1.23)	1.14 (1.09-1.2)	1.11 (1.07-1.16)	1.11 (1.06-1.15)
Race/ethnicity[b]				
White	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Hispanic	0.89 (0.83-0.95)	0.90 (0.84-0.96)	0.98 (0.93-1.03)	0.93 (0.88-0.98)
Black	0.69 (0.61-0.79)	0.65 (0.57-0.73)	0.88 (0.80-0.96)	0.78 (0.71-0.85)
Asian/Pacific Islander	1.14 (1.06-1.23)	1.07 (0.99-1.15)	1.15 (1.07-1.23)	1.02 (0.96-1.09)
Other	0.94 (0.83-1.05)	0.93 (0.83-1.04)	0.98 (0.89-1.07)	0.92 (0.84-1.01)
Median household income of census block, $				
<40 000	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
40 000-69 999	1.13 (1.02-1.25)	1.08 (0.98-1.19)	1.04 (0.96-1.12)	1.01 (0.94-1.09)
70 000-99 999	1.23 (1.11-1.36)	1.11 (1.00-1.23)	1.10 (1.02-1.19)	1.04 (0.97-1.13)
≥100 000	1.29 (1.16-1.44)	1.14 (1.02-1.27)	1.09 (1.00-1.18)	1.03 (0.94-1.12)
Missing	0.26 (0.04-1.74)	0.29 (0.05-1.79)	0.37 (0.10-1.31)	0.43 (0.13-1.44)
Proportion of census block with ≥ high school educational level, %				
<50	1 [Reference]	NA	1 [Reference]	NA
50-75	1.03 (0.90-1.18)	NA	0.89 (0.81-0.98)	NA
>75	1.04 (0.91-1.19)	NA	0.86 (0.79-0.94)	NA
Missing	0.28 (0.04-1.80)	NA	0.36 (0.10-1.26)	NA
Test order for STI in year before first dose				
No	1 [Reference]	NA	1 [Reference]	NA
Yes	1.05 (0.98-1.12)	NA	0.99 (0.94-1.05)	NA
Diagnosis of diabetes between January 1, 2010, and first dose				
No	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Yes	0.79 (0.75-0.83)	0.76 (0.72-0.80)	0.94 (0.90-0.98)	0.88 (0.85-0.92)
Outpatient encounters in year before first dose, No.				
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.27 (1.10-1.46)	1.24 (1.08-1.43)	1.17 (1.05-1.32)	1.17 (1.05-1.31)
2-4	1.35 (1.19-1.54)	1.35 (1.19-1.53)	1.24 (1.12-1.37)	1.25 (1.14-1.38)
5-9	1.51 (1.33-1.72)	1.52 (1.34-1.72)	1.38 (1.25-1.53)	1.41 (1.28-1.55)
≥10	1.63 (1.43-1.86)	1.64 (1.44-1.86)	1.41 (1.27-1.56)	1.43 (1.30-1.58)
Emergency department encounters in year before first dose, No.				
0	1 [Reference]	NA	1 [Reference]	NA
1	1.01 (0.94-1.10)	NA	0.97 (0.91-1.04)	NA
2-4	0.91 (0.81-1.04)	NA	0.95 (0.86-1.05)	NA
≥5	0.96 (0.69-1.33)	NA	0.95 (0.72-1.24)	NA
Inpatient encounters in year before first dose, No.				
0	1 [Reference]	NA	1 [Reference]	NA
1	0.94 (0.82-1.08)	NA	0.92 (0.82-1.04)	NA
≥2	1.11 (0.90-1.38)	NA	1.04 (0.86-1.25)	NA

Abbreviations: HepB-alum, hepatitis B with alum adjuvant; HepB-CpG, hepatitis B with cytosine phosphoguanine adjuvant; NA, not applicable; RR, relative risk; STI, sexually transmitted infection.

[a] Adjusted for age, sex, race/ethnicity, median household income, diagnosis of diabetes, and number of outpatient visits in the year before first dose.

[b] All categories, with the exception of Hispanic, were non-Hispanic.

racial/ethnic disparities in adult vaccination reported in other studies.[7,16-18] Series completion was also lower among younger adults and those living in census blocks with lower levels of income or education. Previous research has identified barriers to adult vaccination, such as underinsurance and concerns about the costs of vaccines, perceptions of low disease risk, and low confidence in

Table 3. Stratified Analysis of Relative Risk of Series Completion for HepB-CpG Vaccine vs HepB-Alum Vaccine Groups

Variable	Recommended schedule plus 3 mo, unadjusted RR (95% CI)
Overall	1.71 (1.62-1.80)
Age at first dose, y	
18-29	1.54 (1.32-1.79)
30-39	1.86 (1.60-2.17)
40-49	1.93 (1.72-2.16)
50-59	1.70 (1.56-1.85)
≥60	1.55 (1.37-1.75)
Sex	
Male	1.83 (1.69-1.98)
Female	1.62 (1.51-1.74)
Race/ethnicity[a]	
White	1.68 (1.52-1.86)
Hispanic	1.89 (1.74-2.05)
Black	1.24 (0.99-1.56)
Asian/Pacific Islander	1.60 (1.41-1.82)
Other	2.03 (1.62-2.53)
Median household income of census block, $	
<40 000	1.36 (1.14-1.63)
40 000-69 999	1.77 (1.63-1.93)
70 000-99 999	1.77 (1.61-1.94)
≥100 000	1.70 (1.51-1.91)
Proportion of census block with ≥ high school educational level, %	
<50	1.67 (1.20-2.32)
50-75	1.65 (1.50-1.81)
>75	1.78 (1.67-1.90)
Test order for STI in year before first dose	
No	1.72 (1.62-1.82)
Yes	1.67 (1.47-1.89)
Diagnosis of diabetes between January 1, 2010, and first dose	
No	1.68 (1.57-1.80)
Yes	1.76 (1.62-1.90)
Outpatient encounters in year before first dose, No.	
0	2.09 (1.61-2.69)
1	1.96 (1.65-2.32)
2-4	1.87 (1.70-2.06)
5-9	1.61 (1.46-1.77)
≥10	1.58 (1.43-1.75)
Emergency department encounters in year before first dose, No.	
0	1.70 (1.60-1.80)
1	1.78 (1.54-2.06)
2-4	1.72 (1.35-2.20)
≥5	1.84 (0.98-3.46)
Inpatient encounters in year before first dose, No.	
0	1.71 (1.62-1.81)
1	1.71 (1.30-2.24)
≥2	1.83 (1.20-2.80)

Abbreviations: HepB-alum, hepatitis B with alum adjuvant; HepB-CpG, hepatitis B with cytosine phosphoguanine adjuvant; RR, relative risk; STI, sexually transmitted infection.

[a] All categories, with the exception of Hispanic, were non-Hispanic.

vaccines.[19-22] At KPSC, all members are insured and can receive recommended vaccines free of charge; however, other social needs may impact health care access.[23]

Kaiser Permanente Southern California also uses a system of electronic alerts and reminders for hepatitis B vaccination, which has increased coverage among patients with diabetes and those tested for sexually transmitted infections.[24,25] Despite this system, individuals with diabetes who initiated a hepatitis B vaccine series had lower series completion than those without diabetes, and individuals who received testing for sexually transmitted infections in the year before the first dose had similar levels of completion as those who did not receive testing. Further research is needed to understand barriers to hepatitis B vaccine series completion in these populations and to evaluate tailored interventions, such as disease-specific or culturally appropriate outreach, to encourage series completion.

Strengths and Limitations

This study has several strengths and limitations. We conducted a real-world study in which the hepatitis B vaccine was administered as part of routine clinical care, using primary and secondary definitions and analyses to compare series completion among those who initiated the HepB-CpG and HepB-alum vaccine series. We included individuals who initiated a hepatitis B vaccine series in the family medicine and internal medicine departments of medical centers, in which approximately 88% of hepatitis B vaccine doses were administered during the study period. The small proportion of individuals who initiated a hepatitis B vaccine series in other departments, such as the travel clinics, infectious disease, or obstetrics and gynecology departments, were not included in the study; series completion may have differed among these individuals. Approximately 57 HepB-CpG initiators and 3 HepB-alum vaccine initiators received subsequent doses of the other vaccine and were not considered to have completed the series. Because guidance from the Advisory Committee on Immunization Practices allows for a combination series of 1 dose of the HepB-CpG vaccine with 2 doses of a 3-dose vaccine,[11] our approach may have underestimated series completion (eg, by approximately 1% for those who initiated the HepB-CpG vaccine series). In addition, outcome misclassification could have occurred if hepatitis B vaccine doses were received outside of the KPSC system and were not documented in the KPSC EHRs; however, this potential bias is likely minimal, as KPSC members receive vaccines recommended by the Advisory Committee on Immunization Practices free of charge at any health care visit. Results of this study may have limited generalizability in settings with greater proportions of underinsured or uninsured individuals or in the absence of electronic reminders for hepatitis B vaccination; in these settings, lower series completion for both 2-dose and 3-dose vaccines might be observed.

Conclusions

Results from this cohort study suggest that series completion was significantly higher among adults who initiated the HepB-CpG vaccine series compared with those who initiated the HepB-alum vaccine series, and this result was consistent across demographic and clinical strata. Although the use of the HepB-CpG vaccine may be associated with better vaccine adherence, tailored strategies are needed to increase completion of hepatitis B vaccine series.

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SUPPLEMENT.

eTable. Characteristics of Hepatitis B Vaccine Initiators and Completers, 1 Year After Initiation