Vaccine 37 (2019) 5899–5908

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Meningococcal-group B (MenB) vaccine series completion and adherence to dosing schedule in the United States: A retrospective analysis by vaccine and payer type

Elizabeth Packnett [a,*], Debra E. Irwin [a], Patricia Novy [b], Philip S. Watson [b], Jane Whelan [c], Laura Moore-Schiltz [a], Matthew Lucci [a], Cosmina Hogea [b]

[a] IBM Watson Health, 7700 Old Georgetown Rd, Suite 650, Bethesda, MD 20814, USA
[b] GSK, 5 Crescent Drive, Philadelphia, PA 19112, USA
[c] GSK, Hullenbergweg 83-85, 1101 CL Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 26 February 2019
Received in revised form 19 June 2019
Accepted 20 June 2019
Available online 20 August 2019

Keywords:
Meningitis B
Completion
Compliance
Adherence
Vaccine
Retrospective

ABSTRACT

Background: Two MenB vaccines with different dosing schedules are approved in the US: MenB-4C (2 doses) and MenB-FHbp (2–3 doses). Both vaccines were licensed on the basis of immunogenicity demonstrated after vaccine series completion. We evaluated vaccination completion and adherence to dosing schedules.

Methods: This retrospective analysis used data from MarketScan Commercial Claims and Encounters Database (Commercial) January 1, 2015 - February 28, 2018 and Multi-State Medicaid Database (Medicaid) January 1, 2015 - December 31, 2017 to examine vaccine series completion and adherence to dosing schedule in individuals who initiated a MenB series at ages 16–23 years. Vaccine series completion and dose schedule adherence were assessed during a 15-month follow-up period after the first dose. Completion was defined as individual receipt of the recommended number of doses, with current recommendations applied retroactively to allow individuals who initiated the MenB-FHbp series to be complete with either the 2- or the 3-dose schedule.

Results: The study population comprised 65,205 commercially-insured individuals (36,118 initiated MenB-4C; 29,087 initiated MenB-FHbp) and 13,535 Medicaid-covered individuals (10,153 initiated MenB-4C; 3382 initiated MenB-FHbp). In Commercial, 63% of individuals who initiated MenB-4C and 52% of individuals who initiated MenB-FHbp completed vaccination within 15 months; dosing schedule adherence was 62% for MenB-4C initiators and 18% for MenB-FHbp initiators. In Medicaid, 15-month completion rates for MenB-4C and MenB-FHbp initiators were 49% and 31%, respectively, with corresponding dosing schedule adherence of 48% and 8%. Among individuals who completed the series, median time to completion was 68 days for MenB-4C versus 258 days for MenB-FHbp in Commercial and 88 days for MenB-4C versus 309 days for MenB-FHbp in Medicaid.

Conclusion: During the study period, MenB vaccine series completion was suboptimal. However, completion was significantly higher for MenB-4C, with notably shorter time to completion. This may reflect the flexible dosing schedule of MenB-4C.

1. Introduction

Invasive meningococcal disease is a serious illness caused by the bacterium *Neisseria meningitidis*, which is categorized into serogroups based on the structure of its polysaccharide capsule [1]. Serogroup B meningococcal (MenB) disease is the most common cause of meningitis and septicemia in developed countries [2]. Although meningococcal disease is rare in developed countries, it is clinically dangerous because of its rapid progression and the risk of long-term sequelae [1]. In a study of children who had survived MenB disease, approximately one-tenth had major disabling deficits and more than a third had one or more deficits in physical, cognitive or psychological functioning [2]. Each case of meningitis

* Corresponding author.
E-mail addresses: packnett@us.ibm.com (E. Packnett), debirwin@us.ibm.com (D.E. Irwin), patricia.l.novy@gsk.com (P. Novy), philip.s.watson@gsk.com (P.S. Watson), jane.x.whelan@gsk.com (J. Whelan), schiltz@us.ibm.com (L. Moore-Schiltz), matthew.lucci@ibm.com (M. Lucci), cosmina.s.hogea@gsk.com (C. Hogea).

https://doi.org/10.1016/j.vaccine.2019.06.065
0264-410X/

is life-threatening [3] and, despite available treatment, the case-fatality rate is estimated at 10–20% [1]. MenB disease is estimated to cause approximately 5–10 deaths per year in the United States (US), mainly among older adolescents and young adults aged 16–23 years [3].

Two MenB vaccines are licensed in the US for use in individuals aged 10–25 years, MenB-FHbp (*Trumenba*, Pfizer), licensed in October 2014 [4] and MenB-4C (*Bexsero*, GSK), licensed in January 2015 [5]. In February 2015, the Advisory Committee on Immunization Practices (ACIP) recommended routine (category A) MenB vaccination in persons aged 10 years and older who are at increased risk of MenB disease, including persons with functional or anatomic asplenia, persons with persistent complement component deficiencies (including persons receiving eculizumab therapy), microbiologists routinely exposed to isolates of *N. meningitidis*, and persons at risk due to a MenB outbreak [6]. In June 2015, the ACIP further recommended that adolescents and young adults aged 16–23 years may be vaccinated with a MenB vaccine to provide short-term protection against most strains of MenB disease, with preferred age for vaccination at 16–18 years (recommendation category B, i.e. recommended for individual clinical decision-making) [3].

MenB vaccines are not interchangeable. Both vaccines require more than one dose for series completion and there may be inadequate protection against MenB disease until the series is completed. Current licensure and recommendations are based on the correct number of doses administered with the appropriate timing to ensure optimal protection. The two vaccines have different recommended dosing schedules, and the recommended schedule for MenB-FHbp has been revised over time. The ACIP recommended schedule for MenB-4C is two doses administered at least one month apart [3]. There is no specific upper time limit for administration of the second dose of MenB-4C. The original ACIP recommended schedule for MenB-FHbp was three doses with the second and third doses administered 2 and 6 months after the first dose [3]. Changes to the dosing and administration of MenB-FHbp were approved by the Food and Drug Administration (FDA) in April 2016, and the ACIP recommendation was updated in October 2016 [7]. The revised schedule includes two options. For individuals at increased risk or during serogroup B outbreaks, a three-dose series is recommended with the second dose administered 1–2 months and the third dose 6 months after the first dose. For healthy individuals, a two-dose series is recommended with the second dose being administered 6 months after the first one [7].

Completion of the full vaccine series and adherence to the recommended dosing schedule (receiving all the doses with the recommended time interval between doses), are important to achieve optimal vaccination protection against MenB disease. Both vaccines were recommended based on immunogenicity demonstrated after vaccine series completion. The objective of this study was to evaluate series completion and adherence to dosing schedule for MenB-4C and MenB-FHbp vaccines among individuals aged 16–23 years in the US, in the first few years following vaccine licensing and recommendations. No such data was previously published.

2. Materials and methods

2.1. Study design

This study was a retrospective analysis of pre-existing de-identified healthcare claims data from the Commercial Claims and Encounters (CCAE) and the Multi-State Medicaid MarketScan Research Databases, both maintained by IBM Watson Health.

This study focused on age-based vaccination among persons aged 16–23 years. The same definition of completion (see 'Study outcomes' section below) was used for all individuals regardless of risk status, even though the ACIP recommends a three-dose MenB-FHbp schedule for individuals at increased risk, low-numbered compared to the general population [8].

2.2. Data sources

Healthcare claims data were obtained from the CCAE database, including Early View (EV) data, for the period between 1 January 2015 and 28 February 2018 for the commercially-insured (Commercial) population, and from the Multi-State Medicaid database for the period between 1 January 2015 and 31 December 2017 for the Medicaid population. These were the most recent data available at the time of starting the analysis.

The CCAE database contains the inpatient, outpatient, and outpatient prescription-drug experiences of several million employees and their dependents (annually) across all US regions, covered under a variety of fee-for-service and capitated health plans, including exclusive provider organizations (EPO), preferred provider organizations (PPOs), point of service (POS) plans, indemnity plans, and health maintenance organizations (HMOs). The MarketScan EV Database is released monthly and captures healthcare services incurred as late as approximately 45 days before data release. The overall age distribution of the CCAE population is similar to that of a nationally representative population of persons with employer-sponsored health insurance. The database also includes information on enrollee demographic characteristics (e.g., age and sex) and details on enrollment periods.

The MarketScan Multi-State Medicaid Database (Medicaid) contains records of inpatient services, inpatient admissions, outpatient services prescription-drug claims and information on long-term care for Medicaid enrollees in fee-for-service and managed care programs in 10–13 geographically dispersed states. The database also includes information on enrollee demographic characteristics (e.g., age, sex and race), eligibility category (e.g., elderly individual, blind/disabled individual), and details on Medicaid enrollment periods.

2.3. Study population

The study population included individuals aged 16–23 years who initiated either the MenB-4C or MenB-FHbp vaccine series between 1 July 2015 and either 30 November 2016 (Commercial population) or 30 September 2016 (Medicaid population) (Supplementary Fig. 1). This time window for initiation was selected to capture individuals who initiated vaccination after the age-based ACIP recommendations were issued, and to satisfy the 15-month continuous enrollment condition working backwards from the end of data availability in each database at the time of the study (31 December 2017 in the Medicaid population and 28 February 2018 in the Commercial population). Any individuals receiving both MenB-4C and MenB-FHbp vaccinations were excluded from the study.

Individuals included in the study were required to have continuous health plan enrollment for 6 months before (baseline period) and 15 months after (follow-up period) the index date. The 6-month baseline period was selected to permit assessment of baseline characteristics. The 15-month follow-up period was a pragmatic choice to capture individuals who might initiate and complete the vaccine series during consecutive summer vacations, for example college students.

The index date was defined as the date of first MenB vaccine claim and considered to be the date of vaccine series initiation.

Individuals were assigned to each vaccine cohort based on initial vaccination claims using corresponding procedure code (CPT) or National Drug Code (NDC) for MenB-4C and MenB-FHbp (details of the codes used are provided in Supplementary Table 1). The MenB-4C and MenB-FHbp vaccine cohorts consisted of individuals who had at least one claim for MenB-4C or MenB-FHbp, respectively, during the study period. All analyses were conducted separately for the Commercial and Medicaid populations.

Demographic characteristics were assessed on the index date and clinical characteristics during the 6-month baseline period.

2.4. Study outcomes

The main outcomes of interest were the proportion of subjects who completed each vaccine series and corresponding time to completion, as well as the proportion of subjects who adhered to the ACIP recommended dose schedule for each vaccine during the 15-month observation period after the date of first vaccination claim.

Vaccine series completion was defined as an individual's receipt of the appropriate number of MenB vaccine doses within the 15-month follow-up period. A MenB-4C series was considered complete if the individual had at least one additional claim during the follow-up period, indicating that MenB-4C was administered after the index claim. The most recent ACIP recommendations [7] were applied retroactively to individuals who initiated MenB-FHbp, so the series could be considered complete with either two or three doses. MenB-FHbp completion was defined according to the following criteria:

- Individuals received two doses of MenB-FHbp with a second claim indicating MenB-FHbp was administered at least 6 months (≥168 days, using a conservative lower bound of 28 days per month) after the index claim, OR;
- Individuals received 3 doses of MenB-FHbp series with a second MenB-FHbp claim occurring less than 6 months (<168 days) after the series initiation claim followed by a third MenB-FHbp claim during the observation period.

Vaccine dose schedule completion and adherence to dosing schedules were defined based on the corresponding prescribing information and ACIP guidelines for the timing of doses in relation to the index dose. For each timing window, the minimum number of days was defined assuming 28 days (4 weeks) per month, in accordance with ACIP Best Practice Guidelines [9], and the maximum number of days assuming 31 days per month. The timing criteria used for each vaccine are summarized in Table 1.

2.5. Statistical analysis

Demographic and clinical characteristics were analyzed using descriptive statistics by vaccine and payer type, with categorical variables represented by counts and proportions and cumulative frequency. Continuous variables were represented by mean, median, standard deviation, and interquartile range.

Differences across vaccine cohorts were tested for statistical significance using chi-square tests for categorical variables and t-tests for continuous variables. For categorical variables with more than two levels, pairwise chi-square tests at each level were conducted. The threshold for statistical significance was 0.05.

Log-binomial regression models were used to estimate adjusted risk ratios (RR) to compare vaccine series completion and adherence to dosing schedule in the MenB-4C and MenB-FHbp cohorts while adjusting for baseline characteristics. For the schedule adherence analyses, two different log-binomial models were created: the first compared overall schedule adherence between the two vaccine cohorts; the second focused on comparing schedule adherence in individuals who completed the MenB-4C series versus individuals completed the MenB-FHbp with two doses specifically. The outcomes were adjusted RR, 95% confidence intervals (CI) and p-values for each explanatory variable.

Logistic regression modeling was used to explore factors associated with each vaccine series completion and schedule adherence separately. The outcomes were adjusted odds ratios (OR) indicating increased or decreased likelihood of vaccine series completion/adherence to dosing schedule, 95% CI and p-values for each independent variable included in the model.

Factors included in the regression modeling were age, sex, health plan type, race, geographic region, residence density (rural vs urban), month and year of initiation, type of encounter at initiation, provider type at initiation, administration of MenACWY, influenza and other vaccinations, baseline healthcare costs and MenB risk status.

Table 1
Timing between vaccine doses used to define vaccine dose schedule completion and adherence [a].

Vaccine	Dose 2	Dose 3
Completion		
MenB-4C	Anytime after index dose during follow-up	N/A
MenB-FHbp (two-dose)	≥6 months (≥168 days) after index dose	N/A
MenB-FHbp (three-dose)	<6 months (<168 days) after index dose	Anytime after dose 2 during follow-up
Adherence to dosing schedule		
MenB-4C	At least one month (28 days) after index dose	N/A
MenB-FHbp (two-dose)	6 months (168–216 days) after index dose	N/A
MenB-FHbp (three-dose)	1–2 months (28–92 days) after index dose	6 months (168–216 days) after index dose

N/A, not applicable.
[a] Vaccine dose schedule completion and adherence were defined based on the ACIP guidelines for the timing of doses in relation to the index dose. For each timing window, the minimum number of days was defined assuming 28 days (4 weeks) per month, in accordance with ACIP Best Practice Guidelines. The maximum number of days was defined assuming 31 days per month. These definitions are permissive for MenB-FHbp. For example, a dose given six months after the index dose would be adherent to the vaccination schedule if administered on or after day 168 (the last day of the sixth month assuming 28 days per month) and before day 217 (the last day of the seventh month assuming 31 days per month). There is no specific upper time limit for administration of the second dose of MenB-4C. The follow-up period was limited to 15 months post-index for all patients, regardless of vaccine initiation type.

3. Results

3.1. Demographic and baseline characteristics

The study population meeting all the inclusion criteria comprised 65,205 commercially-insured individuals (36,118 initiated MenB-4C; 29,087 initiated MenB-FHbp), and 13,535 Medicaid-insured individuals (10,153 and 3382 of whom initiated MenB-4C and MenB-FHbp, respectively) (Supplementary Table 2).

Fig. 1 shows the distribution of age at MenB vaccination initiation for each vaccine cohort. There was little difference between both vaccines in age at initiation, however in the Commercial population the age at initiation was approximately one year older than in the Medicaid population for both vaccines. Most individuals initiated vaccination at age 16–18 years (Fig. 1), consistent with the ACIP-recommended preferred age for MenB vaccination [3].

Demographic characteristics for the vaccine cohorts are summarized in Table 2. There were no differences in sex distribution between the cohorts, and most subjects were in urban areas.

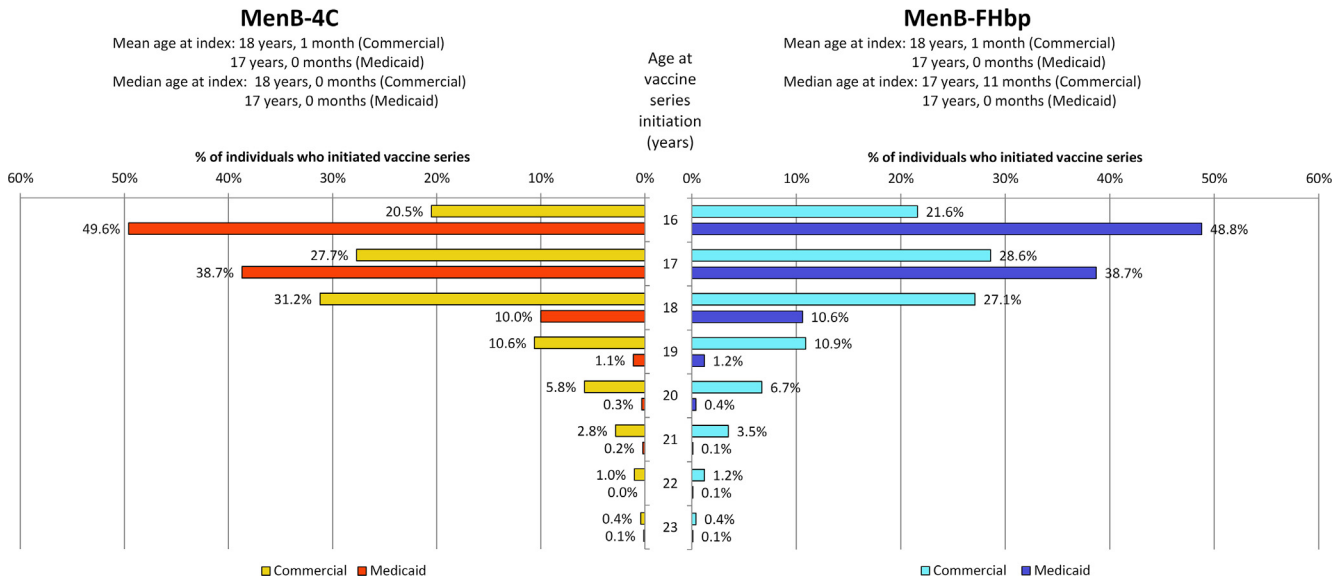

Fig. 1. Age at vaccine series initiation by vaccine and payer type.

Table 2
Demographic characteristics by vaccine cohort and payer population.

	Commercial			Medicaid		
	MenB-4C	MenB-FHbp	p-value*	MenB-4C	MenB-FHbp	p-value*
Number of individuals	36,118	29,087		10,153	3382	
Sex (%)						
Male	48.8%	48.5%	0.8145	48.5%	50.3%	0.0671
Female	51.2%	51.5%		51.5%	49.7%	0.0671
Residence Density (%)						
Urban	92.5%	94.7%	<0.0001	80.2%	84.7%	<0.0001
Rural	6.2%	4.9%	<0.0001	19.6%	14.9%	<0.0001
Unknown	1.4%	0.5%	<0.0001	0.2%	0.4%	0.0408
Geographic Region (%)						
Northeast	29.2%	42.3%	<0.0001	–	–	–
North Central	22.3%	16.9%	<0.0001	–	–	–
South	33.6%	30.4%	<0.0001	–	–	–
West	13.6%	9.9%	<0.0001	–	–	–
Unknown	1.4%	0.5%	<0.0001	–	–	–
Race (%)						
White	–	–	–	36.3%	36.8%	0.6533
Black	–	–	–	41.9%	41.4%	0.5725
Hispanic	–	–	–	6.9%	10.1%	<0.0001
Other	–	–	–	4.8%	1.9%	<0.0001
Missing	–	–	–	10.0%	9.9%	0.8774
Year of Index MenB Vaccination (%)						
2015	6.8%	10.9%	<0.0001	3.5%	4.8%	0.0006
2016	93.2%	89.1%	<0.0001	96.5%	95.2%	0.0006
Age 16–18 Years on Index Date (%)	79.3%	77.3%	<0.0001	98.3%	98.2%	0.5607
Type of Visit of Index Vaccination (%)						
Preventive care or well-child visit	74.3%	74.2%	0.9281	76.1%	77.9%	<0.0001
Vaccine-only visit	15.0%	15.6%	0.0401	9.6%	8.7%	0.1121
Other visit	10.7%	10.2%	0.0223	14.2%	13.5%	0.2530
Provider Type of First Vaccination (%)						
Family medicine	9.0%	9.7%	0.0061	1.3%	3.5%	<0.0001
Pediatrician	77.1%	77.2%	0.6984	31.3%	48.7%	<0.0001
Internal medicine	2.2%	3.0%	<0.0001	0.8%	0.5%	0.1091
Obstetrician/gynecologist	0.1%	0.1%	0.0335	0.0%	0.0%	1.0000
Other	6.8%	6.0%	<0.0001	37.8%	22.4%	<0.0001
Unknown	4.7%	4.0%	<0.0001	28.8%	24.8%	<0.0001

Variables unavailable in the database are noted with '-'.
* The p-values refer to the comparison between vaccine cohorts for each payer population.

In both payer populations, baseline vaccine events characteristics between vaccine cohorts were relatively similar, most index vaccinations occurred at a physician office visit, and more than 58% of all index vaccinations occurred in June, July or August (Supplementary Table 3).

3.2. Vaccine completion and adherence to dosing schedule

Across both vaccines, the completion rate at 15 months after initiation was 58% in the Commercial population and 44% in the Medicaid population.

In the Commercial population, 63% of individuals who initiated the MenB-4C vaccine series and 52% of individuals who initiated Men-FHbp vaccine series completed the vaccine series within 15 months, with schedule adherence rates at 62% versus 18%, respectively (Fig. 2). The trend was similar in the Medicaid population, where the 15-month completion rate for MenB-4C and MenB-FHbp initiators was 49% and 31%, respectively, and the schedule adherence rate was 48% and 8%, respectively (Fig. 2). The differences in completion and schedule adherence between MenB-4C and MenB-FHbp were statistically significant ($p < 0.0001$) in both Medicaid and Commercial populations. In the Commercial population, 59% of those who completed the MenB-FHbp vaccine series completed a two-dose schedule, and 41% completed a three-dose schedule. In the Medicaid population 71% of those who completed the MenB-FHbp vaccine schedule completed a two-dose schedule, and 29% completed a three-dose schedule.

In both payer populations, the cumulative proportion of individuals who completed the vaccine series was significantly ($p < 0.05$) higher for MenB-4C than MenB-FHbp at all time points during the follow-up period (Fig. 3). At 7 months after series initiation, 46.9% of subjects in the Commercial population who initiated with MenB-4C were fully vaccinated, compared with only 19.2% of subjects who initiated MenB-FHbp ($p < 0.0001$), and in the Medicaid population 32.7% of subjects who initiated MenB-4C had completed their series compared with only 8.9% of those who initiated MenB-FHbp ($p < 0.0001$).

In both payer populations, the mean time to completion among individuals who completed the vaccine series was significantly ($p < 0.0001$) shorter for individuals initiating MenB-4C compared with those initiating MenB-FHbp. Among the individuals who completed each vaccine series, median time to series completion was 68 days for MenB-4C and 258 days for MenB-FHbp in the Commercial population, and 88 days for MenB-4C and 309 days for MenB-FHbp in the Medicaid population (Fig. 4).

3.3. Multivariable analyses

Log-binomial multivariable regression models confirmed that after controlling for age, sex, health plan type, geographic region (in the Commercial database), race (in the Medicaid database), residence density, month and year of index MenB vaccination, index visit type, provider type and baseline costs, the probability of vaccine series completion remained 22% higher for MenB-4C than MenB-FHbp in the Commercial population (adjusted RR 1.22, 95% CI 1.20, 1.23, $P < 0.0001$) and 48% higher in the Medicaid population (adjusted RR 1.48, 95% CI 1.40, 1.56, $P < 0.0001$) (Table 3).

In the Commercial and Medicaid payer populations, each additional year of age at vaccine series initiation was significantly associated with a decreased likelihood of vaccine series completion in both the MenB-4C and MenB-FHbp vaccine cohorts. No differences were observed by sex, and there were no notable differences by commercial health plan type. In the Commercial population, all geographic regions had decreased likelihood of completion compared to the Northeast. Residence in a rural area in the Commercial population was associated with decreased likelihood of completion for both MenB-4C and MenB-FHbp, while in the Medicaid population, rural residence was associated with higher likelihood of completion only in the MenB-FHbp cohort. In the Commercial MenB-4C cohort, individuals who received their initial vaccination from family medicine were 21% less likely to complete the vaccination series while those initiating with an "other" or "unknown" provider type were 19% and 26%, respectively, less likely to complete the vaccine series compared with those receiving the initial vaccination from a pediatrician. In the Commercial MenB-FHbp cohort, individuals who received their initial vaccination from family medicine were 19% less likely to complete the vaccination series while those initiating with an "other" or "unknown" provider type were 29% and 36%, respectively, less likely to complete the vaccine series compared to those receiving the initial vaccination from a pediatrician. The Medicaid MenB-4C cohort showed a similar result regarding family medicine providers versus pediatricians: individuals initiating with a family medicine provider were 52% less likely to complete the vaccination series. This was not observed in the Medicaid MenB-FHbp cohort where no significant differences in likelihood of completion were observed by provider type. Receipt

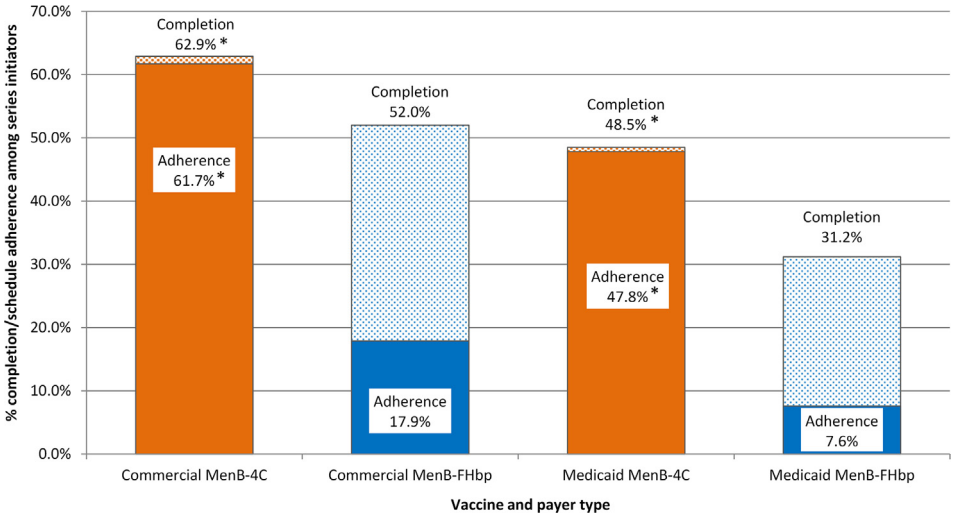

Fig. 2. Vaccine series completion and dosing schedule adherence rates at 15 months after vaccine series initiation by vaccine and payer type. *$p < 0.0001$ MenB-4C vs MenB-FHbp (chi-square test).

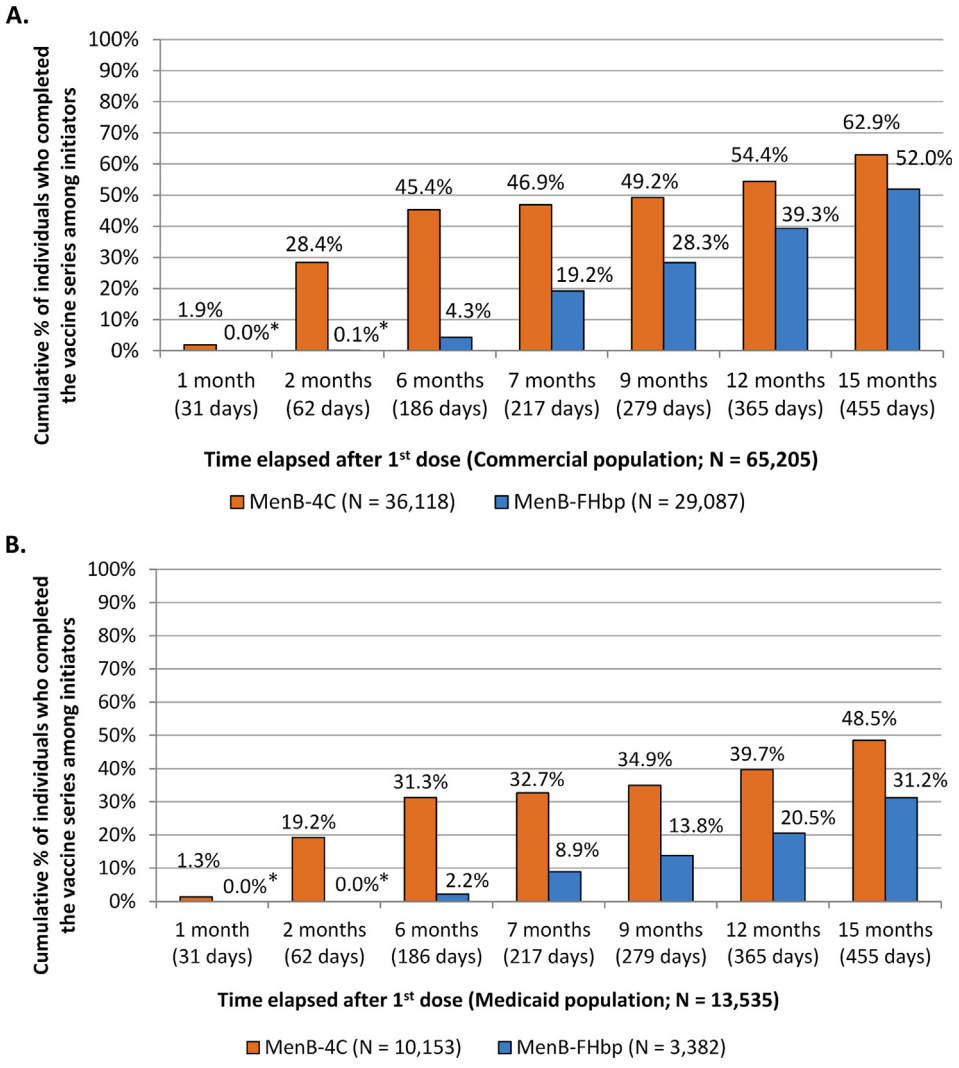

Fig. 3. Vaccine series completion over time for MenB-4C and MenB-FHbp in (A) the Commercial population and (B) the Medicaid population. $p < 0.05$ MenB-4C vs MenB-FHbp (chi-square test) at all time points in both populations. *Low MenB-FHbp series completion was expected prior to the '6 months' mark inherently due to recommended dosing schedule.

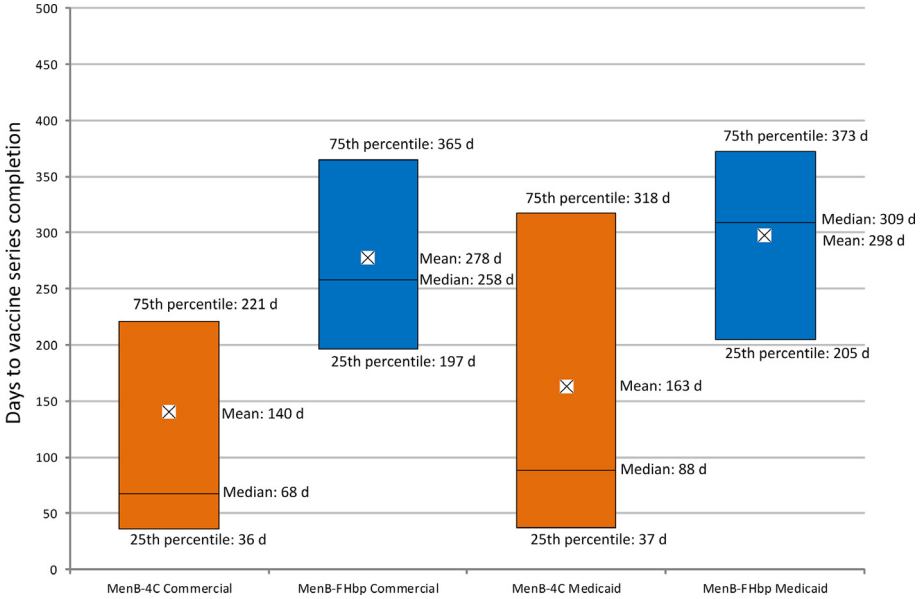

Fig. 4. Time to series completion (days) by vaccine and payer type d, days $p < 0.0001$ mean time to completion MenB-4C vs MenB-FHbp in both populations (t-test).

Table 3
Adjusted risk ratio (RR) of vaccine series completion in the Commercial and Medicaid populations based on a log-binomial regression model.

Covariate		Commercial		Medicaid	
		RR	95% CI	RR	95% CI
Vaccine Type (Ref: MenB-FHbp)	MenB-4C	**1.22**	**(1.20, 1.23)**	**1.48**	**(1.40, 1.56)**
Age	One-year increase in age	**0.92**	**(0.92, 0.93)**	**0.81**	**(0.79, 0.84)**
Sex (Ref: Male)	Female	**1.03**	**(1.02, 1.04)**	1.03	(0.99, 1.07)
Health Plan (Ref: EPO/PPO)	Comprehensive /Indemnity	**0.95**	**(0.91, 0.99)**	1.12	(0.88, 1.42)
	POS/POS with capitation	0.99	(0.97, 1.02)	–	–
	HMO	**0.97**	**(0.95, 0.99)**	1.14	(0.89, 1.45)
	CDHP/HDHP	**1.04**	**(1.02, 1.05)**	–	–
	Missing/ Unknown	1.06	(1.00, 1.13)	–	–
Geographic Region (Ref: Northeast)	West	**0.85**	**(0.83, 0.87)**	–	–
	South	**0.82**	**(0.81, 0.83)**	–	–
	North Central	**0.88**	**(0.86, 0.89)**	–	–
Race (Ref: White)	Black	–	–	**0.95**	**(0.91, 0.99)**
	Hispanic	–	–	**1.15**	**(1.08, 1.23)**
	Other	–	–	1.03	(0.97, 1.10)
	Unknown	–	–	1.07	(0.99, 1.16)
Residence Density (Ref: Urban)	Rural	**0.91**	**(0.89, 0.94)**	0.98	(0.93, 1.03)
Month of Initiation (Ref: January)	December	**0.92**	**(0.86, 0.99)**	1.22	(0.90, 1.65)
	November	0.95	(0.90, 1.00)	1.30	(0.96, 1.77)
	October	**0.93**	**(0.89, 0.98)**	1.09	(0.78, 1.52)
	September	**0.89**	**(0.85, 0.93)**	**0.89**	**(0.79, 1.00)**
	August	**0.90**	**(0.86, 0.94)**	**0.86**	**(0.76, 0.96)**
	July	0.98	(0.94, 1.02)	0.90	(0.80, 1.01)
	June	1.04	(1.00, 1.09)	1.00	(0.89, 1.12)
	May	1.00	(0.95, 1.05)	0.95	(0.84, 1.08)
	April	**0.92**	**(0.87, 0.97)**	**0.85**	**(0.74, 0.97)**
	March	**0.93**	**(0.88, 0.99)**	0.94	(0.82, 1.07)
	February	0.96	(0.90, 1.01)	0.93	(0.80, 1.08)
Year of Initiation (Ref: 2015)	2016	**0.95**	**(0.92, 0.97)**	1.19	(0.94, 1.51)
Type of Encounter at Initiation (Ref: Preventive/ Well Child)	Other visit	1.00	(0.98, 1.02)	**1.12**	**(1.06, 1.17)**
	Vaccine-only visit	1.00	(0.99, 1.02)	**0.91**	**(0.84, 0.98)**
Provider Type at Initiation (Ref: Pediatrician)	Family medicine	**0.89**	**(0.87, 0.91)**	**0.68**	**(0.55, 0.85)**
	Internal medicine	**0.93**	**(0.88, 0.97)**	1.01	(0.78, 1.32)
	Other	**0.89**	**(0.87, 0.92)**	**1.21**	**(1.14, 1.27)**
	None/Unknown	**0.86**	**(0.83, 0.89)**	**1.07**	**(1.01, 1.14)**
Cost	10% increase in baseline cost	**1.00**	**(1.00, 1.00)**	**1.00**	**(1.00, 1.00)**

CDHP, consumer-driven health plan; CI, confidence interval; EPO, exclusive provider organization; HDHP, high-deductible health plan; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; Ref, referent group; RR, risk ratio.
Variables unavailable in the database are noted with '-'.
Bold text indicates $p < 0.05$.

of vaccinations other than MenB in the post-index period was consistently a significant factor in completing each vaccine series: receipt of MenACWY and influenza vaccination in the post-index period was significantly associated with increased likelihood of vaccine series completion, while receipt of other catch-up vaccinations was associated with decreased likelihood of completion (Table 4).

Vaccine series adherence to dosing schedule was also higher for individuals initiating MenB-4C than those initiating MenB-FHbp in the Commercial population (adjusted RR 3.48, 95% CI 3.39, 3.57, $P < 0.0001$), and in the Medicaid population (adjusted RR 6.06, 95% CI 5.38, 6.83, $P < 0.0001$), after adjusting for demographic and index vaccination characteristics (Supplementary Table 4).

In the Commercial population, those who completed the MenB-4C vaccine series were more likely to be adherent to the recommended vaccination schedule compared with those who completed the MenB-FHbp vaccine series with two doses (adjusted RR 3.69, 95% CI 3.56, 3.82, $P < 0.0001$). In the Medicaid population, those who completed the MenB-4C series were more likely to be adherent to the vaccination schedule compared with those who completed the two-dose MenB-FHbp series (adjusted RR 5.40, 95% CI 4.61, 6.32, $P < 0.0001$). There were no notable effects on series schedule adherence due to other covariates in the model after adjusting for vaccine type (Supplementary Table 5).

Similar to vaccine series completion, each additional year of age was associated with decreased likelihood of vaccine series adherence to dosing schedule in all models. In the MenB-4C cohorts, factors associated with vaccine series schedule adherence were almost identical in significance and effect size to factors associated with completion, as adherence to dosing schedule among completers was close to 100 percent in both payer populations. In the MenB-FHbp cohorts, notable factors impacting likelihood of schedule adherence included the month of vaccine series initiation (Supplementary Table 6).

4. Discussion

To our knowledge, this is the first study to evaluate vaccine series completion and dosing schedule adherence for the two MenB vaccines currently licensed and recommended for use in the US, MenB-4C and MenB-FHbp.

Overall, the completion rates at 15 months of follow-up were only moderate for both vaccines, at 58% across both vaccines in the Commercial population and 44% across both vaccines in the Medicaid population, although completion was higher in individuals who initiated MenB-4C than those who initiated Men-FHbp in both payer populations. This indicates that additional efforts are needed to improve the completion rate for MenB vaccine series

Table 4
Adjusted OR of vaccine series completion by vaccine in the Commercial and Medicaid populations.

Covariate		MenB-4C				MenB-FHbp			
		Commercial		Medicaid		Commercial		Medicaid	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	One-year increase in age	**0.84**	**(0.82, 0.86)**	**0.75**	**(0.70, 0.79)**	**0.76**	**(0.74, 0.77)**	**0.62**	**(0.55, 0.70)**
Sex	Female	1.05	(1.00, 1.09)	1.02	(0.94, 1.11)	1.00	(0.95, 1.05)	1.03	(0.88, 1.20)
(Ref: Male)									
Geographic Region	West	**0.67**	**(0.62, 0.73)**	–	–	**0.59**	**(0.54, 0.64)**	–	–
(Ref: Northeast)	South	**0.58**	**(0.54, 0.61)**	–	–	**0.65**	**(0.61, 0.69)**	–	–
	North Central	**0.70**	**(0.66, 0.75)**	–	–	**0.70**	**(0.65, 0.75)**	–	–
Race	Black	–	–	**0.90**	**(0.82, 0.99)**	–	–	**1.22**	**(1.02, 1.47)**
(Ref: White)	Hispanic	–	–	1.13	(0.95, 1.35)	–	–	**1.67**	**(1.26, 2.21)**
	Other	–	–	1.01	(0.87, 1.18)	–	–	**1.49**	**(1.12, 1.99)**
	Unknown	–	–	1.20	(0.98, 1.46)	–	–	1.50	(0.86, 2.63)
Residence Density	Rural	**0.87**	**(0.80, 0.96)**	0.91	(0.82, 1.01)	**0.81**	**(0.72, 0.91)**	**1.30**	**(1.03, 1.62)**
(ref: Urban)									
Month of Initiation	December	0.85	(0.64, 1.11)	1.05	(0.53, 2.09)	0.81	(0.62, 1.07)	2.28	(0.51, 10.21)
(Ref: January)	November	0.93	(0.75, 1.14)	1.28	(0.63, 2.62)	**0.79**	**(0.63, 0.98)**	1.81	(0.38, 8.58)
	October	0.89	(0.73, 1.08)	0.80	(0.39, 1.66)	**0.69**	**(0.55, 0.85)**	1.76	(0.35, 8.81)
	September	**0.77**	**(0.64, 0.93)**	0.80	(0.58, 1.09)	**0.67**	**(0.55, 0.83)**	0.51	(0.28, 0.94)
	August	**0.78**	**(0.65, 0.93)**	0.82	(0.60, 1.13)	**0.74**	**(0.61, 0.90)**	0.55	(0.30, 1.01)
	July	1.14	(0.95, 1.37)	0.97	(0.71, 1.33)	**0.80**	**(0.66, 0.98)**	0.68	(0.37, 1.25)
	June	**1.46**	**(1.22, 1.76)**	1.32	(0.96, 1.82)	0.97	(0.79, 1.19)	0.74	(0.40, 1.35)
	May	**1.35**	**(1.11, 1.64)**	1.14	(0.81, 1.59)	0.86	(0.69, 1.07)	0.66	(0.35, 1.26)
	April	1.06	(0.86, 1.31)	0.97	(0.69, 1.37)	**0.71**	**(0.56, 0.90)**	0.47	(0.24, 0.93)
	March	1.12	(0.90, 1.39)	1.00	(0.71, 1.42)	**0.70**	**(0.55, 0.88)**	0.53	(0.28, 1.03)
	February	0.94	(0.74, 1.19)	0.93	(0.64, 1.36)	0.95	(0.73, 1.24)	0.68	(0.34, 1.37)
Type of Encounter at Initiation	Other visit	1.01	(0.94, 1.09)	**1.20**	**(1.06, 1.37)**	**0.84**	**(0.77, 0.92)**	**0.78**	**(0.60, 0.99)**
(Ref: Preventive/Well Child)	Vaccine-only visit	**1.15**	**(1.07, 1.23)**	0.95	(0.81, 1.11)	0.95	(0.88, 1.02)	0.81	(0.59, 1.11)
Provider Type at Initiation	Family medicine	**0.79**	**(0.73, 0.85)**	**0.48**	**(0.32, 0.73)**	**0.81**	**(0.75, 0.89)**	0.83	(0.52, 1.35)
(Ref: Pediatrician)	Internal medicine	0.88	(0.76, 1.03)	1.18	(0.73, 1.93)	**0.79**	**(0.68, 0.91)**	0.42	(0.09, 1.94)
	Other	**0.81**	**(0.74, 0.88)**	**1.38**	**(1.23, 1.56)**	**0.71**	**(0.64, 0.79)**	**1.65**	**(1.34, 2.03)**
	None/Unknown	**0.74**	**(0.66, 0.82)**	1.06	(0.93, 1.20)	**0.64**	**(0.56, 0.74)**	1.04	(0.83, 1.31)
MenACWY Vaccination	On index date	**0.80**	**(0.76, 0.84)**	1.09	(0.99, 1.21)	**0.72**	**(0.67, 0.76)**	1.04	(0.86, 1.26)
(Ref: Not Administered)	After index date	**1.89**	**(1.61, 2.21)**	**4.44**	**(3.31, 5.96)**	**1.66**	**(1.44, 1.91)**	**2.50**	**(1.69, 3.71)**
	Before index date	**0.83**	**(0.73, 0.94)**	1.25	(0.99, 1.60)	**0.87**	**(0.77, 0.99)**	1.38	(0.92, 2.05)
Influenza Vaccination	Before/on index but not post index	1.13	(0.97, 1.31)	1.17	(0.90, 1.52)	**1.27**	**(1.07, 1.51)**	0.91	(0.56, 1.49)
(Ref: Not Administered)	Post index but not before/on index	**2.54**	**(2.40, 2.69)**	**3.11**	**(2.77, 3.49)**	**2.13**	**(2.00, 2.26)**	**2.63**	**(2.17, 3.19)**
	Before/on index and post index	**1.62**	**(1.50, 1.76)**	**1.76**	**(1.51, 2.05)**	**1.64**	**(1.52, 1.78)**	**2.57**	**(1.91, 3.45)**
Other Vaccinations	After/on index date	**0.92**	**(0.87, 0.96)**	**0.74**	**(0.68, 0.81)**	NS	NS	**0.78**	**(0.66, 0.92)**
(Ref: Not Administered)	Before index date	0.92	(0.81, 1.05)	**0.56**	**(0.42, 0.75)**	NS	NS	0.63	(0.37, 1.07)
High Risk[*]	High risk condition during baseline	NS	NS	**1.69**	**(1.07, 2.67)**	0.69	(0.31, 1.52)	NS	NS

CI, confidence interval; NS, variable not selected for inclusion in the final model; OR, odds ratio; Ref, referent group.
Variables unavailable in the database are noted with '-'.
Covariates for which adjusted ORs were non-statistically significant or close to 1 not shown; these included the health plan type, the year of initiation, the total baseline healthcare costs, the total follow-up healthcare costs and the number of outpatient visits during follow-up.
Bold text indicates $p < 0.05$.
[*] High risk group here included individuals with medical or pharmacy claims for conditions with category A recommendation for MenB vaccination (asplenia, sickle cell anemia, complement component deficiency, or eculizumab use) and also individuals with medical claims for HIV infection during the six-month baseline period.

in order to ensure full protective benefits of MenB vaccination. The results of this study suggest that individuals who initiated vaccination with MenB-4C were more likely to complete the series than those who initiated with MenB-FHbp. The definition of completion comprised two or three doses for MenB-FHbp (two doses with the second dose at least 6 months after the first one, or three doses with the second dose < 6 months after the first and the third at any time during follow-up) and two doses for MenB-4C at least one month apart. The difference in completion rates between vaccines was consistent across both Commercial and Medicaid populations, even after adjusting for individual characteristics in multivariable analyses. Adherence to the recommended vaccine dose schedule was also significantly higher for MenB-4C than for MenB-FHbp, regardless of payer population, and this difference also persisted in multivariable analyses. The time to completion of the vaccine series was substantially shorter for MenB-4C compared with MenB-FHbp, in both the Commercial and Medicaid populations. These observed differences may be due in part to the flexible dosing schedule of MenB-4C which allows for administration of the second dose at any interval at least one month after the first dose, whereas the MenB-FHbp schedule requires two doses 6 months apart or three doses at 0, 1–2 and 6 months. While higher completion rates were to be expected for MenB-4C compared to MenB-FHbp within the first 6 months after dose 1, inherent to their specific dosing schedules, this trend remained significant throughout the rest of the follow-up period.

While currently there is no upper limit for administration of dose 2 of MenB-4C, it is important to note that the degree of protection afforded during the inter-dose period is uncertain. A Phase 3 study in adolescents showed that hSBA titers ranged from 93 to 96% after a single dose, however waning of all antibody titers was evident by 2 months and titers continued to decline after 6 months in participants who did not receive a second dose [10]. For MenB-FHbp, there are no published data relating to the immunogenicity or protection of a single vaccine dose. It is therefore critical to optimize protection against MenB disease by ensuring vaccine series completion in line with the respective licensed indication for each vaccine.

The rates of vaccine series completion reported in this study are consistent with other vaccines in older adolescents in the US. A

systematic review of studies of multi-dose vaccination in adolescents reported completion rates ranging from 27% to over 90% [11]. A previous study of hepatitis B vaccination in a high-risk cohort found that an accelerated vaccination schedule and shorter time between visits were significant predictors of vaccine completion rate [12], consistent with our observations of higher completion for the shorter MenB-4C schedule (two doses > 1 month apart) compared with the longer MenB-FHbp schedule (two doses 6 months apart or three doses at 0, 1–2 and 6 months) in the present study.

The mean age at vaccination initiation in the Commercial population was older than in the Medicaid population, for both vaccines. The age at vaccination in the Commercial population may reflect individuals being vaccinated prior to beginning college. There may be more individuals in the Medicaid population than the Commercial population who take advantage of the earlier vaccination platform at age 16 years that aligns with the MenACWY booster dose, as Medicaid providers attempt to maximize vaccination opportunity and administer vaccines sooner rather than later. In the Commercial population, series completion was significantly higher among individuals who initiated MenB-4C vaccination in June, which may indicate that the flexible MenB-4C dosing schedule allows individuals to receive all necessary doses before beginning college. Each additional year of age of vaccine series initiation was associated with a statistically significant decreased probability of vaccine completion and adherence to dosing schedule, regardless of vaccine type, in both the Commercial and Medicaid payer populations. This finding is consistent with previous studies that have reported higher completion rates in younger adolescents compared with older adolescents [11], and suggests that interventions aimed at improving series completion should give consideration to vaccine timing for series initiation. To maximize the potential vaccine benefit, it is important that the MenB vaccine series is completed as recommended by the ACIP to maximize the likelihood of protection lasting into the period of highest age-related risk [3].

Although both payer populations showed statistically significantly higher completion and adherence rates for MenB-4C than MenB-FHbp after adjusting for covariates, the differences were greater in the Medicaid than in the Commercial population. The adjusted RR for completion was 1.48 (95% CI 1.40, 1.56, $P < 0.0001$) in the Medicaid population compared with 1.22 (95% CI 1.20, 1.23, $P < 0.0001$) in the Commercial population, and the adjusted RR for adherence was 6.06 (95% CI 5.38, 6.83, $P < 0.0001$) and 3.48 (95% CI 3.39, 3.57], $P < 0.0001$), respectively. Time to completion was significantly shorter for MenB-4C than MenB-FHbp in both payer populations; however, the median time to completion was longer in the Medicaid than the Commercial population for both vaccines. The relationship between provider type at MenB vaccination series initiation and series completion/adherence to dosing schedule differed between the Commercial and Medicaid populations. In the Commercial population, individuals who initiated a MenB vaccine series with a pediatrician were significantly more likely to complete the series and adhere to the dose schedule, whereas in the Medicaid population those who initiated with provider types other than family medicine, internal medicine or pediatrician were more likely to complete the series and respect the schedule. The Commercial and Medicaid populations also differed in the distribution of provider type at time of vaccine initiation, possibly reflecting differences in healthcare utilization between the commercially-insured and Medicaid populations.

The main strengths of the present study include the large sample size and the use of routinely collected real-world data from national samples representing both commercially-insured individuals and individuals covered by Medicaid. The observations of improved completion and schedule adherence rates for MenB-4C compared with MenB-FHbp were consistent across both the Commercial and Medicaid populations, and persisted after adjusting for individual factors in multivariable analyses, suggesting that the results were not skewed by population differences in demographic or other characteristics. The criteria used for completion and schedule adherence have a positive bias for MenB-FHbp estimates, since MenB-FHbp was retroactively considered complete with either two or three doses and the time windows to define completion/adherence were permissive. This is likely to provide a conservative estimate of the difference between the vaccine cohorts.

This study has some limitations inherent in any retrospective study conducted using claims databases. Claims databases do not record information on social, cognitive or institutional factors that may influence vaccination behavior. The data are limited to health information included in reimbursement claims, and thus any vaccination that did not generate a claim would not be captured in this analysis. As the databases rely on administrative claims data for clinical detail, there is the potential for clinical characteristics to be miscoded or missing.

The study was limited by the time frame of data availability in conjunction with the continuous enrollment restrictions. The same definition of completion was used for all individuals regardless of risk status, even though the ACIP recommends a three-dose MenB-FHbp schedule for individuals at increased risk. It is therefore possible that some high-risk individuals may have been classified as completers in this study with only two doses, which could contribute to an overestimate of the completion rate for MenB-FHbp. The proportion of individuals identified in the 6-month baseline period at high-risk due to underlying medical conditions in the MenB-FHbp cohort was however very small in this study in both payer populations. Finally, individuals receiving mixed MenB-4C or MenB-FHbp vaccinations were excluded, so any subjects who switched vaccine product for any reason were not captured in this study, although the numbers were small.

Due to design constraints to allow for 15 months of follow-up with the most recent available data, this study only included subjects who initiated vaccination in 2015 or 2016, when the MenB vaccine recommendations were relatively new. It therefore provides a picture of vaccine use in the first 2–3 years after licensing and recommendations. Future studies may be helpful to understand how MenB vaccine use may evolve with time.

5. Conclusion

In this study, MenB vaccination completion and dose schedule adherence rates were suboptimal across vaccine and payer types, with ample room for improvement. Vaccine series completion and adherence to dosing schedule were higher for MenB-4C than MenB-FHbp, across commercially-insured and Medicaid-covered individuals and after adjusting for individual characteristics in multivariable analyses. The time to completion of the vaccine series was substantially shorter for MenB-4C compared with MenB-FHbp, in both the Commercial and Medicaid populations. These observed differences in completion and schedule adherence may reflect the flexible dosing schedule of MenB-4C, which allows for administration of the second dose at any interval at least one month after the first dose.

Acknowledgements

The authors would like to thank Carole Nadin (Fleetwith Ltd, on behalf of GSK) for medical writing support. The authors also thank Business & Decision Life Sciences platform for editorial assistance

and manuscript coordination, on behalf of GSK. Marie Cloes coordinated manuscript development and editorial support.

Trademark statement

Bexsero is a trademark owned by or licensed to the GSK group of companies. *Trumenba* is a trademark of Pfizer.

Author contributions

Involvement in the conception or design of the study: CH, JW, PSW, PN, DEI, EP, LMS, ML.

Participation in the collection or generation of the study data: CH, DEI, EP.

Involvement in the analyses or interpretation of the data: CH, JW, PSW, PN, DEI, EP, LMS, ML.

Disclosure

CH, PN, PSW and JW are employees of the GSK group of companies, and hold shares in it. EP, DEI, LMS and ML are employees of IBM Watson Health, which was contracted to conduct this study by the GSK group of companies.

Funding statement

GlaxoSmithKline Biologicals SA was the funding source (GSK study identifier: HO-17-18203) and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and agreed with the submission of the publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.06.065.

References

[1] Baccarini C, Ternouth A, Wieffer H, Vyse A. The changing epidemiology of meningococcal disease in North America 1945–2010. Hum Vaccin Immunother 2013;9:162–71.
[2] Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. Lancet Neurol 2012;11:774–83.
[3] MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep 2015;64:1171–6.
[4] Food and Drug Administration. October 29, 2014 Approval Letter - TRUMENBA. 2014. Available from: https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm421034.htm. Accessed: 1 January 2017.
[5] Food and Drug Administration. January 23, 2015 Approval Letter - BEXSERO. 2015. Available from: https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm431446.htm. Accessed: 1 January 2017.
[6] Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR. Use of serogroup B meningococcal vaccines in persons aged >/=10 years at increased risk for serogroup B meningococcal disease: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep 2015;64:608–12.
[7] Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for use of MenB-FHbp Serogroup B meningococcal vaccine - Advisory Committee on Immunization Practices, 2016. MMWR Morb Mortal Wkly Rep 2017;66:509–13.
[8] MacNeil J. Considerations for Serogroup B Meningococcal (MenB) Vaccine Booster Doses in Persons at Increased Risk for Serogroup B Meningococcal Disease. 2017. Available from: https://stacks.cdc.gov/view/cdc/58805/cdc_58805_DS1.pdf. Accessed: 14 February, 2019.
[9] Kroger AT, Duchin J, Vázquez M. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). 2017. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed: 26 January, 2018.
[10] Santolaya ME, O'Ryan ML, Valenzuela MT, Prado V, Vergara R, Munoz A, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet 2012;379:617–24.
[11] Gallagher KE, Kadokura E, Eckert LO, Miyake S, Mounier-Jack S, Aldea M, et al. Factors influencing completion of multi-dose vaccine schedules in adolescents: a systematic review. BMC Public Health 2016;16:172.
[12] Macdonald V, Dore GJ, Amin J, van Beek I. Predictors of completion of a hepatitis B vaccination schedule in attendees at a primary health care centre. Sex Health 2007;4:27–30.