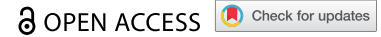


RESEARCH PAPER



Safety profile of MenB-FHBp vaccine among adolescents: data from surveillance of Adverse Events Following Immunization in Puglia (Italy), 2018–2020

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ABSTRACT

MenB-FHBp was licensed in Europe in 2017 from the age of 10. In the “postmarketing life” of a new vaccine, surveillance of Adverse Events Following Immunization (AEFI) is crucial, to better understand the pattern of safety and the effectiveness. This paper describes the MenB-FHBp AEFIs notified in Puglia in 2018–2021, to take a picture of the safety profile of this vaccine in the real life, four years after its introduction in Italy. This is a retrospective observational study. Data were collected from the list of AEFIs notified after MenB-FHBp vaccine administration in Puglia in 2018–2020, and the number of doses of this vaccine administered in the same period. AEFIs were classified according to WHO’s algorithm, and causality assessment was carried out for serious AEFIs. From January 2018 to December 2020, in Puglia, 43,061 doses of MenB-FHBp were administered and 42 MenB-FHBp AEFIs (reporting rate: 97.5 per 100,000 doses administered) were reported. Among these, 12 were classified as severe (28.6%; reporting rate 27.9 per 100,000 doses). Overall, the male/female ratio in AEFIs was 1:1. The median age of people who suffered from AEFIs was 12 years (range 11–13). For the 11 serious AEFIs for which the classification was “consistent causal association,” the diagnosis was hyperpyrexia (reporting rate 13.9 per 100,000 doses), fainting (rate 4.6 per 100,000 doses), urticaria (rate 2.3 per 100,000 doses), convulsions (rate 2.3 per 100,000 doses), and vomit (rate 2.3 per 100,000 doses). No deaths or impairment were notified in studied AEFIs. The picture of MenB-FHBp vaccine supports that the risk of AEFIs is in line with previous published data and in general acceptable.

ARTICLE HISTORY

Received 13 October 2021
Revised 22 January 2022
Accepted 9 February 2022

KEYWORDS

Aefis; causality assessment; Trumenba; vaccination confidence

Introduction

Neisseria meningitidis is a leading cause of meningitis and septicemia and epidemiologists estimated that there are around 1.2 million cases of meningococcal infection per year worldwide, with a death toll of ~135,000.¹

Out of 13 currently described distinct meningococcal serogroups, 6 (A, B, C, W-135, X, Y) have been demonstrated as causes of human diseases.^{1,2} The pattern of circulating meningococcal serotypes is changing according to the different geographical areas; in particular, serogroup B is the most important cause of endemic disease in developed countries.¹

In 2017, 3,221 confirmed cases of invasive meningococcal disease, including 282 deaths, were reported in 30 EU/EEA Member States, 1,527 of which (51% of 2,979 cases for which information about the serogroup was available) were caused by serogroup B. The percentage of cases related to serogroup B *N.meningitidis* was around 70% for cases detected among 0–4-year-old and 60% among 5–14- and 15–24-year-old people.³

Serogroup B polysaccharide is poorly immunogenic⁴ and in the past several attempts to prepare a specific anti-B meningococcal vaccination based on subcapsular polysaccharides have failed.

The first multicomponent MenB vaccine (4CMenB, Bexsero, GSK) was licensed in 2013 in Europe and was based on a new approach to vaccines’ preparation, named “reversed vaccinology.”^{5,6}

A second MenB vaccine, MenB-FHBp (Trumenba, Pfizer), was licensed in the United States in 2014, originally approved for usage in a 3-dose schedule (administered at 0, 1–2, and 6 months), and later as a two-dose schedule (0 and 6 months) in 10–25-year-olds.⁷ MenB-FHBp was licensed in Europe in 2017 for use in a two-dose (0, 6 months) or three-dose (0, ≥1, and ≥4 months postdose 2) schedule from the age of 10.⁸ In Italy, the use of MenB-FHBp has been authorized on 20 July 2017 by the Italian Drug Authority (AIFA, <https://www.aifa.gov.it/>) for “the prevention of meningococcal disease caused by *Neisseria meningitidis* serogroup B, among subjects aged at least 10 years”; additional surveillance activities about this drug’s safety pattern were also recommended.⁹

During this new vaccine’s development, LP2086, a conserved surface-exposed bacterial lipoprotein that functions as a human complement factor H-binding protein, has been identified as a vaccine target.¹⁰ Epidemiologic studies suggested that a vaccine containing a factor H-binding protein (FHBp) variant from each of the two immunologically distinct protein subfamilies (A and B) would protect against

diverse, disease-causing meningococcal B strains.^{11,12} These findings spurred the development of MenB-FHbp, which consists of one factor H-binding protein variant from each subfamily. Two phase 3 studies assessed the safety of the vaccine and its immunogenicity against diverse strains of group B meningococcus; a postlicensure study showed that MenB-FHbp elicited bactericidal responses against diverse meningococcal B strains after doses 2 and 3, and was associated with more reactions at the injection site than the hepatitis A virus vaccine and saline.¹³ A 2020 study carried out in UK seems to support the ability of MenB-FHbp to provide broad coverage against MenB strains expressing diverse FHbp variants.¹⁴

In the “postmarketing life” of a new vaccine, surveillance of the occurrence of Adverse Events Following Immunization (AEFI), as recommended by World Health Organization, is crucial to better understand the new drug’s safety pattern and effectiveness.¹⁵ In particular, postmarketing surveillance could help Public Health Authorities in detecting rare sanitary events not described in prelicensure studies, reviewing the reporting rate and having a picture of the vaccine’s safety profile in subgroups not represented in its premarketing life.^{16,17} These goals could be achieved using the standardized Causality Assessment methodology and avoiding the “emotional” approach on emerging AEFIs, that was in the past one of the most important causes of vaccine hesitancy.¹⁸

4CMenB and MenB-FHbp were licensed on the basis of safety and immunogenicity using serum bactericidal antibody assays in clinical trials, with the expectation that evidence of effectiveness would be gathered after licensure; safety data in prelicensure trials were deemed acceptable for both vaccines.⁶ However, at the time of writing, MenB-FHbp has not been included in national immunization programs in any country and few postmarketing data are available about the safety of this vaccine in the real world.

Since 1978, in Italy, healthcare is guaranteed by the National Health Service, founded on public initiative and on the universality of the access. Immunization strategies are designed by the Ministry of Health (Ministero della Salute, <https://www.salute.gov.it/portale/home.html>) and reported in the National Immunization Plan (NIP) and vaccine are in general offered actively and free of charge by public initiative, that cover all the population. Vaccine are not administered in private sector. Each of the 20 Italian Regions has to adhere to the strategies described in the NIP, but is also free to add new vaccination offers for target population not covered by the National Plan. MenB Vaccine is offered since 2017 actively and free-of-charge to all Italian newborns, but there are no national strategies concerning adolescents, for whom there is an important burden of meningococcal disease.^{3,19}

Puglia is a region in the South-East of Italy with around 4 million inhabitants. In 2018, Apulian Health Authority (Regione Puglia, Assessorato alle Politiche della Salute, <https://www.sanita.puglia.it/>) approved the Regional Immunization Plan that provided the active and free-of-charge offer of MenB vaccines also for 11–12-year-old people (approximately 38,000 people per years); vaccines are administered by the Public Health Services and there is at least one vaccination clinic in almost each of 257 Apulian cities.

4CMenB and MenB-FHbp were judged as equivalent for the immunization of adolescents and adults; MenB-FHbp were offered by vaccination clinics in 2018–2021 in Puglia.²⁰

According to Italian Law, postmarketing surveillance of AEFIs is mandatory and each healthcare worker who diagnosed a suspected or confirmed AEFI has to make a notification to the Italian Drug Authority.

This paper aims to describe the MenB-FHbp-related AEFIs notified in Puglia in 2018–2021, to take a picture of this vaccine’s safety profile in the real life, four years after its introduction in Italy.

Patients and methods

This is a retrospective observational study.

Data were collected from the list of AEFIs notified after MenB-FHbp vaccine administration in Puglia in 2018–2020, and the number of doses of this vaccine administered in the same period.

The list of MenB-FHbp AEFIs was obtained from AIFA’s database. In Italy, in fact, it is mandatory for all Healthcare Workers to report every case of AEFIs occurred in their patients to the National Pharmacovigilance Network (RNF), a platform managed by AIFA. AEFIs may also be reported directly by the person who experimented them or by their legal representatives.

The number of MenB-FHbp vaccine doses administered per year in Puglia was obtained from the regional online immunization database (GIAVA); reporting vaccination to GIAVA is mandatory and vaccinations must be registered in the same day of the administration for all healthcare workers of public service.

For every person who experienced one or more AEFIs, a specific form was filled in including information on date of birth, gender, date of vaccine administration, other vaccines administered during the same visit and information about the AEFIs (date of onset and date of computing in National Pharmacovigilance Network, clinical characteristics of the adverse events, case description, duration and treatment, hospitalization or emergency room access, final outcome).

An Excel spreadsheet was used to build the database and perform the required analyses.

The total reporting rate was calculated as the total number of reported AEFIs/the number of MenB-FHbp doses administered, while the annual reporting rate was calculated as the number of AEFIs occurred in a year/the number of MenB-FHbp doses administered during the same year.

World Health Organization (WHO) guidelines were used to classify AEFIs as “serious” or “not serious.” An AEFI is considered serious, if: it results in death; it is life-threatening; it requires in-patient hospitalization or prolongation of existing hospitalization; it results in persistent or significant disability/incapacity; it is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage. Additionally, in 2016 AIFA published a list of particular health conditions that must be considered as serious AEFIs, if they occur after vaccination. This list is the Italian edition of the European Medicine Agency (EMA) Important Medical Events (IME) list.^{21,22}

For serious AEFIs, we retrospectively applied the WHO causality assessment algorithm to classify AEFIs as “consistent causal association,” “inconsistent causal association,” “indeterminate” or “non-classifiable”; in particular, for AEFIs that required hospitalization, we examined data from the medical record.²³ Causality assessment is carried out by two different physicians expert in vaccinology and results are compared; in case of different results of the algorithm, a review of the literature is carried out and a third physician was consulted.

To describe the association between the experience of a serious AEFI after the first dose of MenB-FHBP and missing the second dose, a univariate model was designed. The null hypothesis was no difference in missing the second dose after a serious AEFI; the alternative hypothesis was that the experience of serious AEFI could change the attitude for the second dose.

Cases were defined as people who experienced an AEFI following the prior doses of MenB-FHBP vaccine and missed the second dose; controls were people who experienced an AEFI but completed the vaccination cycle. The exposition investigated regarded the type of AEFI; we defined exposed the person who experienced a serious AEFI and non-exposed the person who reported a non-serious AEFI. Data were put in a 2 × 2 table, odds ratio (OR) was calculated and chi-square test was used. Statistical significance was set for $p > .05$. An OR of 1 suggested absence of association; $OR > 1$ suggested that the experience of serious AEFIs increased the risk of missing the second dose while and $OR < 1$ indicated a decrease of this risk.

Ethical approval and patient consent were not requested for this study, because it regarded data routinely and anonymously collected and yet available in AIFA’s database.

Results

From January 2018 to December 2020, 43,061 doses of MenB-FHBP were administered in Puglia. The distribution of the doses administered per year, the number of people who experimented at least an AEFIs and the AEFIs reporting rate per 100,000 doses is presented in Table 1.

During the study period, a total of 42 people experienced at least one MenB-FHBP AEFIs (reporting rate: 97.5 per 100,000 doses administered) were reported in Puglia. Among these, 12 (28.6%) were classified as serious and 30 (71.4%) as non-serious, according to the latest WHO guidelines.¹⁵ Of 12 serious AEFIs, 2 lead to hospitalization. The reporting rate was 27.9 per 100,000 doses for serious AEFIs and 69.7 per 100,000 doses for not serious AEFIs.

Among the 42 reports of AEFIs, 34 (80.9%) occurred after the first dose and 6 (14.3%) after the second dose. For 2 reports information about the AEFI’s timing was not available.

Table 1. Distribution of MenB-FHBP vaccine doses administered per year, of the subjects for which an AEFI was notified and of the AEFIs reporting rate per 100,000 doses.

	2018	2019	2020
Number of doses of MenB-FHBP vaccine administered	2,969	29,213	10,879
People with at least an AEFI notified	4	28	10
Reporting rate per 100,000 doses	134.7	95.8	91.9

Overall, the male/female ratio in AEFIs was 1:1; in fact, 21 AEFIs regarded males and 21 AEFIs regarded females. The median age of people who experienced AEFIs was 12 years (range 11–13).

Table 2 shows the distribution of signs and symptoms described in MenB-FHBP AEFIs reports and the reporting rate ×100,000 doses administered.

For 11 out of 12 serious MenB-FHBP vaccine AEFIs, the classification was “consistent causal association” and for 1 “inconsistent causal association.” The latter regarded an 11-year-old child who reported fever, oral mucosal reaction, headache, and nausea after immunization; in this case, a revision of the subject’s medical history described the presence of an intercurrent infection as a possible alternative cause of the signs and symptoms.

For the 11 AEFIs for which the classification was “consistent causal association,” the diagnosis was fever/hyperpyrexia (6/11–54.5% reporting rate 13.9 per 100,000 doses), neurological symptoms (fainting: 2/11–18.2% rate 4.6 per 100,000 doses; convulsions: 1/11–9.1% rate 2,3 per 100,000 doses; vomit: 1/11–9.1% rate 2,3 per 100,000 doses), and allergic reactions (urticaria: 1/11–9.1% rate 2,3 per 100,000 doses).

We focused on the relationship between adverse events and the interruption of the vaccination course, aiming to explore the causes of the lack of adherence to proper vaccination schedule.

Data showed that 13 people (38.2% of 34 who experimented an AEFI after the first dose) didn’t complete the vaccination schedule; of these, 5 experienced a serious AEFI and 8 a non-serious one. Of 21 people who continued the schedule, 5 suffered from a serious AEFI and 16 a nonserious one. The association between the experience of a serious AEFI and missing the second dose did not achieve statistical significance (Odds Ratio = 2; p -value = .36); so the observation failed to reject H_0 under the given target of $p = .05$.

For 71.4% (30/42) of AEFIs the outcome was “healed” and for 14.3% (6/42) “healing in course”; for another 14.3% the outcome was not available. No deaths or impairments were notified in studied AEFIs.

These data are globally in line with prelicensure evidence. EMA summary product characteristics for MenB-FHBP vaccine described that the most common adverse reaction in prelicensure studies, with a frequency >10% of immunized people, were

Table 2. Distribution of signs and symptoms described in AEFIs MenB-FHBP reports and reporting rate per 100,000 doses.

Sign/symptom	n	Reporting rate per 100,000 doses
Fever/hyperpyrexia	20	46.4
Neurological symptoms	19	44.1
Local reactions	15	34.8
Allergic reactions	4	9.3
Asthenia	4	9.3
Chills	4	9.3
Hypotension	3	7.0
Hypoglycemia	1	2.3
Hypothermia	1	2.3
Oral mucosal reaction	1	2.3
Pain at the limbs	1	2.3
Pallor	1	2.3
Sweating	1	2.3
Syncope	1	2.3
Tachycardia	1	2.3

headache, diarrhea, nausea, myalgia, arthralgia, chills, fatigue, redness, swelling, and pain at injection site. The frequency of fever ranged from 1 to 10%.⁸ In our results, fever seemed more frequent than other signs/symptoms, even if in general the reporting rate was lower. This difference could be explained considering the source of data; in prelicensure studies information about AEFIs are collected by active surveillance (phone-recall, web-based system, etc.) while in our study data are from passive surveillance, which implies a major risk of under-reporting.²³

In a 2016 prelicensure study on the safety of MenB-FHBp among adolescents and young adults, individuals aged 10–25 years enrolled at sites across the United States, South America, Europe and Australia were randomly assigned to receive MenB-FHBp or HAV/saline at 0, 2, and 6 months. Serious AEFIs during the vaccination phase were rare both in control and MenB-FHBp-vaccinated people (1.8% and 1.2%, respectively). The most commonly reported sign/symptoms in MenB-FHBp recipients were injection site pain (19.0%), headache (6.2%), and pyrexia (6.1%).²⁴ In addition, these results are globally in line with our data, considering the yet discussed differences between passive and active surveillance models.

A study carried out using VAERS source of data for 2014–2018, showed a reporting rate of 69.8 per 100,000 doses of MenB-FHBp vaccine (2,106 AEFIs on 3,018,899 MenB-FHBp doses); with regard to serious AEFIs, the rate was 1.5 per 100,000 (44 serious AEFIs on 3,018,899 MenB-FHBp doses). In the same report, fever and headache were the most reported signs and symptoms after the vaccine.²⁵ The most important differences between this report and our data are the reporting rates (in our survey the rate is 1.5 times higher than in US data) and the percentages of serious AEFIs, 2% in VAERS (Vaccine Adverse Events Reporting System) data and 28.5% in our survey. This differences could be explained both considering hypothesizing different applications of WHO Causality Assessment Algorithm (that is routinely applied in Italy only since 2013) and with the attitude of Apulian healthcare workers in missing the notification of non-serious AEFIs, already discussed in other surveys of our research group.^{16,23,26}

Our research group recently published a survey about the risk of AEFIs among adolescents was presented, analyzing Puglia AEFIs data from 2016 to 2020 (including data about MenBFHBP discussed in this article). MenBFHBP vaccine showed a higher AEFI notification rate than the general picture from the adolescents population (97.5 per 100,000 doses versus 15.4 per 100,000 doses) and accounted the major parts of serious AEFIs notified (53.8%) among adolescents; for this reason, we focus our attention on this vaccine safety profile, considering a longer period of observation, that is the entire “real life” of this vaccine.²⁷ The two paper regarded a different period of observation and, formally, different target groups (only adolescents in the paper of Di Lorenzo et al; all people who received MenBFHBP vaccine in this paper); in this paper, we also considered in detail the serious AEFIs related to MenBFHBP vaccine and the specific reporting rate of sign and symptoms identified in AEFIs report.

The difference in the AEFIs reporting rate (MenBFHBP vaccine vs other vaccine administered among adolescents) could be related to the sensitivity of healthcare providers in

the notification of events reported after a “new vaccine,” neither used in the past. The rate is consequently decreasing in the three years of observation and this difference is not actually a concern for the regulatory authorities.

The most important strength of our study is the reference population (43,061 doses administered, around three times higher than population examined in prelicensure trials), the systematic use of causality assessment for serious AEFIs, the added value of examination of medical records¹⁷ and the double check of the results of causality assessment, carried out by two separate physicians. We have also to consider that the analysis is referred to the first three years of MenB-FHBp vaccine availability, in which the attention level toward safety concerns was particularly high both by physicians’ and by the patient’s parents’ point of view. This is also confirmed by our data, in which the reporting rate is decreasing over the course of the three years of observation.

The study’s weakness regarded the use of data from passive surveillance, that could be affected by underreporting, in particular for non-serious events. Another important weakness is the lack of information about the outcome for around 15% of AEFIs.

The general picture of MenB-FHBp vaccine emerging is in line with data previous published about the safety of this vaccine. In fact, the general risk of AEFIs is low (around 1% of administered doses) and the majority of AEFIs are mild and self-limiting. No deaths or impairments have been recorded after MenB-FHBp vaccine administration. The experience of a serious AEFIs could be associated with the discontinuation of the vaccination cycle but our observation, due to the small sample size, did not achieve statistical significance. So, future larger studies are needed to measure the frequency of missing schedules and the reason not to complete the vaccination cycle. The right communication about the plausibility of a relation between vaccine and AEFIs to the parents of adolescents and the correct knowledge of the contraindications to the immunization by Healthcare Workers are crucial for this progress.^{18,28}

The safety of vaccines is the most important accuse of antivaccination movements and the principal reason of vaccination skepticism of parents and adolescents,²⁹ as recently showed in Italy itself following the “AstraZeneca case.”³⁰ The analysis of AEFIs’ occurrence carried out by research groups of Regulatory Authorities and the right risk communication by Health Authorities are necessary in order to increase the general accountability of the “vaccine system” and the vaccination confidence by the general population.

Discussion

Our study reports the data about the safety profile of MenB-FHBp vaccine administered in 2018/2020 to adolescents of 11–13 years of age in Puglia. The vaccine was offered actively and free-of-charge and 43,061 doses were administered in the study period. Data from passive surveillance of AEFIs showed that around the general incidence of adverse events was 1 of 100 doses and 1 out of 300 for serious AEFIs. The most frequently reported events after MenB-FHBp vaccine were fever/hyperpyrexia and neurological symptoms, such as headache and convulsions.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Funding The author(s) reported there is no funding associated with the work featured in this article.

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