Vaccine 41 (2023) 7096–7102

Contents lists available at ScienceDirect

Vaccine

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

Adverse events following immunization (AEFIs) with anti-meningococcus type B vaccine (4CMenB): Data of post-marketing active surveillance program. Apulia Region (Italy), 2019–2023

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ARTICLE INFO

Keywords:
Pharmacovigilance
Children
Meningitis
Vaccination
Safety

ABSTRACT

The four-component recombinant-DNA anti-meningococcus B vaccine (4CMenB) has been approved by the European Medicines Agency in 2013. In Italy, 4CMenB is recommended since 2017 for use in infants under one year of age. Due to the strong evidence of increased risk of fever after administration, surveillance of adverse events following immunization (AEFIs) is a priority for 4CMenB.

This cross-sectional prospective study aims at investigating 4CMenB's safety profile. The study population is represented by infants under twelve months of age vaccinated with 4CMenB in selected ambulatories in Apulia, a region in South-Eastern Italy, from October 1st, 2020, to March 31st, 2023. Parents were provided with a post-vaccination diary covering up to seven days after immunization and were contacted one week after the vaccination day. Information about AEFIs was collected, and reactions were classified following World Health Organization guidelines. For serious AEFIs, causality assessment was carried out. AEFI risk determinants were investigated via logistic regression.

A total of 4,773 diaries were completed, with 78.13 % of them (3,729/4,773) containing one or more AEFI reports. Systemic reactions such as malaise, drowsiness/insomnia and fatigue were the most common ones, followed by fever and local pain, tenderness, redness and swelling.

Twenty-three cases of serious AEFIs were reported. Following causality assessment, 78.26 % of serious adverse events (18/23) were deemed to have a consistent causal association with the administration of 4CMenB (reporting rate: 0.38 %). Three infants were hospitalized following vaccination, but no cases of death or permanent/severe impairment were reported. Prophylactic paracetamol administration showed a significant protective effect against the risk of manifesting fever within the first 24 h after administration (OR: 0.75; $p < 0.005$).

Our data confirms existing evidence regarding the safety of 4CMenB vaccination in babies under 2 years of age, but also highlight a significant risk of fever after vaccination. Prophylactic paracetamol administration could represent a protective factor against fever, especially during the first 24 h after vaccination.

1. Introduction

Two vaccines are currently available for the prevention of diseases associated with *Neisseria meningitidis*' B serogroup (meningococcus B) in the European Union. The first one to be approved for marketing by the European Medicines Agency (EMA) was a four-component recombinant-DNA vaccine (4CMenB), which was released in 2013 [1]. A second, two-component product based on meningococcus B factor H binding protein (fHbp-MenB) was approved in 2017 by EMA [2,3].

Italy's Vaccination Schedule for Life strongly recommends anti-meningococcus B (anti-menB) vaccination for all newborns since 2017. The schedule may vary between three and four doses according to the first administration's timing, but in both cases the vaccine should be administered during the subject's first year. Subjects with a high risk of meningococcus B infection, such as patients with asplenia or other forms of immune depression/suppression, laboratory workers handling

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https://doi.org/10.1016/j.vaccine.2023.09.061
Received 26 July 2023; Received in revised form 6 September 2023; Accepted 29 September 2023
Available online 26 October 2023

meningococcal specimens and healthcare providers working with infants and/or critical patients, are also targeted by anti-menB vaccination, although with different schedules based on their age [4–8]. All target categories are offered 4CMenB actively and free-of-charge.

Since the start of the post-marketing life of 4CMenB, special attention has been requested about the safety profile of this vaccine, because pre-marketing evidence seemed to suggest a high incidence of adverse events following immunization [9–11]. The expression "adverse event following immunization" (AEFI) refers to any untoward medical occurrence which happens after immunization. Therefore, AEFIs are not necessarily causally related with the administered vaccine. Surveillance of AEFIs is strongly recommended by the World Health Organization (WHO), as part of the pre-licensure trials but also in the post-marketing life of vaccines, as this practice allows to thoroughly investigate new products' safety profile as well as to increase the public's thrust towards vaccination itself [12]. In Italy, AEFI reporting is mandatory for any healthcare professional witnessing one, and nationwide surveillance of AEFIs is managed by the Italian Drug Authority's National Pharmacovigilance Network (NPN) [13].

As of now, 4CMenB safety profile has been investigated only via passive surveillance. A study highlighted a reporting rate about 26.5 AEFIs per 100,000 vaccine administrations in Apulia, a Region in South-Eastern Italy, from 2014 to 2019, a number much lower than the AEFI risk reported in pre-marketing experimentation. Data reported in this study, if compared with pre-marketing published data [9,10], seem to suggest a significant impact of under-reporting, especially in consideration of the recent release of the vaccine, thus calling for more intense safety investigation [14].

Since fever and hyperpyrexia have been described among the most frequent AEFIs detected among 4CMenB immunized infants [9–11,14], special attention has been dedicated to the interaction of prophylactic paracetamol administration after vaccination with 4CMenB in order to prevent fever and the vaccine's safety and immunogenicity profile. In fact, 4CMen B is associated with a significant risk of fever during the first 24–72 h after immunization [15].

Paracetamol given shortly before vaccination and subsequently at 4–6 and 8–12 h after the product's administration has been proven to significantly lower the risk of fever in infants, while not impacting on 4CMenB's immunogenicity [10,16]. No shared guidelines exist regarding prophylactic paracetamol administration before or shortly after 4CMenB vaccination, although the United Kingdom's Health Security Agency and the South Australia Government currently recommend administering paracetamol to infants under two years of age shortly after or before the vaccine [17,18].

This study investigates the real-life safety profile of 4CMenB via an active surveillance program. Our aim is to verify whether the real-world characteristics of this product is aligned with those identified by pre-registration clinical trials, while also testing the impact of prophylactic paracetamol administration on the vaccine's safety.

2. Materials and methods

This is a cross-sectional prospective study, carried out in Apulia Region, South-East of Italy (around 4 million inhabitants) [19].

The study population was made up of infants born in Apulia who received the first dose of anti-MenB vaccine with 4CMenB in one of the ambulatories taking part to the study.

As already mentioned, all infants born after 2017 are routinely offered 4CMenB in Italy; during the study period, two different schedules for 4CMenB have been employed. The first one, enforced until the end of 2021, provided for:

- Four vaccine doses for infants starting vaccination before six months of age, with the second dose one month after the first one, the third one after an additional two months and the fourth one at fifteen months of age;
- Three vaccine doses for infants starting vaccination after the sixth month of life, with two doses during the first year of life with a one-month interval and the third dose at fifteen months of age [4].

The second schedule, employed since 2022, provided for three doses for all infants, with two doses during the first year of life at a two-month interval and the third dose during the second year of life.

The enrollment lasted from October 1st, 2020, to March 31st, 2023.

Regional Health Service in Apulia is organized in 6 health trusts, one for each district. In each trust, Public Health Department cared the offer of vaccines for newborns, infants and adolescents and there is almost one vaccination clinic for town. Sixteen ambulatories were selected in Apulia, covering both large city centers and small towns and equally distributed across the region's territory. These ambulatories collectively serve an estimated 993,869 people according to the most recent Italian Statistics Institute's survey, and are representative of the whole Apulian territory [19].

The enrollment phase was planned at the time of the first dose of 4CMenB vaccine, routinely at 76 days of life. The infant's parents and/or legal tutors were asked to provide written consent both to vaccination and to the infant's participation to the study. The consent form included the infant's personal data and their parents'.

All infants aged less than twelve months who had received the first dose of 4CMenB and whose parents had given their consent to have the infant participate to the study were included. Exclusion criteria were:

a) Not the target age for active and free vaccination offered for the first dose of the 4CMenB vaccine;
b) Contraindications (conditions in a recipient that increase the risk for a serious adverse reaction) and precautions to vaccination.

Information about the infant's paediatrician, pathological anamnesis and history of drug administration was also gathered, as well as details related to the anti-MenB vaccination such as the product's batch and expiration date, the date of administration and injection site.

Appropriate informative for the treatment of personal data was given to the parents of infants enrolled by authorized personnel.

After vaccination, the parents consenting to the study were given a post-vaccination diary for AEFI surveillance. This diary covered the seven days after the vaccine's administration and included a comprehensive list of AEFIs. Parents were also instructed to note if and when drugs were required to control the AEFIs, if paracetamol was administered within two hours after vaccination and if hospitalization or emergency room access were needed. Prophylactic paracetamol administration was suggested, but ultimately left to the parents' decision.

After the first seven days following immunization, parents were contacted via phone call by operators of the Local Pharmacovigilance Service. Staff members recorded information contained in the post-vaccination diaries and entered it into an informatized database. In case parents reported symptoms/signs not to have resolved by the end of the week, a second phone contact occurred 30 days after vaccination in order to verify that all symptoms/signs had undergone resolution.

All AEFIs were thereafter signaled by entering them into the Italian Pharmacovigilance Network (RNF), as per Italian regulation.

AEFIs were classified as "serious" or "non-serious" according to their clinical features, following WHO definition. In particular, the "serious" label was used for adverse events resulting in death or in a life-threatening condition, requiring in-patient hospitalization or prolongation of existing hospitalization, resulting in persistent and/or significant disability/incapacity, or consisting in a congenital anomaly or birth defect [12,20]. In addition to this, AEFIs included in the EMA important medical events list were defined as serious events [21]. In case of access to the structures of the National Health Service, the health documentation was acquired (hospital discharge card, laboratory, and/or instrumental test reports, specialist consultations, etc.). The data were

stored in accordance with Italian privacy regulation [22].

For serious AEFIs, 1 month after notification, a follow up has been carried out in order to guarantee a supplemental surveillance of vaccine safety. For these patients, a close-up surveillance protocol was activated for the second vaccine dose administration.

All serious AEFIs underwent causality assessment, which was performed independently by two physicians with specific expertise in vaccine safety and with the support of a multidisciplinary team of specialists with various fields of expertise (paediatrics, neurology, immunology, etc.). Causality assessment is the systematic review of data about AEFI cases, aiming at determining the likelihood of a causal association between the event and the vaccination, and is recommended by WHO. For AEFIs that required hospitalization, we reviewed the causality assessment using additional data from the medical record [20].

The algorithm we employed for causality assessment was the 2019 version; each AEFI report was evaluated separately by two clinicians with specific expertise in vaccinology, and differences in causality assessment's outcomes were resolved via consensus [23,24]. For serious AEFIs, the WHO causality assessment algorithm was applied to classify AEFI as 'consistent causal association', 'inconsistent causal association', 'indeterminate', or 'not-classifiable'.

The adverse events reported were grouped into the following categories:

- Local reactions (pain, redness, swelling, induration at the injection site)
- Allergic reaction (anaphylaxis, allergic/urticarial reaction)
- Gastrointestinal symptoms (vomiting, diarrhea)
- Systemic reaction (malaise, drowsiness/insomnia, skin rash, anomalous crying, irritability/nervousness, convulsions)
- Fever/hyperpyrexia.

Reporting rates of AEFIs was calculated as:

$$Reportingrate = \frac{AEFIreports}{Totalnumberofadministeredvaccinedoses} \times 100patients$$

A multivariate logistic regression model was fitted to investigate the effect of various potential determinants on the risk of AEFIs. In particular, we studied the impact of age, sex, chronic diseases, anti-rotavirus vaccine simultaneous administration and paracetamol administration within two hours. A two-sided p-value < 0.05 was identified as an indicator of statistical significance. All data was entered into a database built with software Microsoft Excel®. Statistical analysis was conducted via software STATA MP17®.

The research conducted for this study was carried out in accordance with the Helsinki Declaration and was approved by the Ethical Committee in charge for study protocols for Apulia Region.

The project was conceived and coordinated by Apulia's Regional Administration and approved and funded by the Italian Drug Authority.

3. Results

3.1. Descriptive statistical analysis

During the study period, an estimated 22,500 infants received 4CMenB vaccine in the selected ambulatories. 23.45 % of parents (5,277 enrolled subjects/22,500 children) accepted to have their infant participate to the study. Out of these subjects, 4,773 answered the seven-day phone contact attempt (response rate: 90.45 %), each accounting for one completed post-vaccination diary. Males were slightly more numerous than females, adding up to 52.19 % of the sample (2,491/4,773). Females represented therefore 47.81 % (2,282/4,773). The study population's mean age at vaccination time was 106.73 (±31.60) days.

Only 0.40 % of all vaccinated infants were affected by one or more chronic illnesses (19/4,773). 4CMenB was administered with anti-rotavirus vaccine to 14.58 % (696/4,773) of infants. Paracetamol was administered shortly before vaccination or within two hours after vaccination to 27.72 % (1,323/4,773) of subjects.

After post-vaccination diary examination, 78.13 % (3,729/4,773) of infants were reported to have manifested one or more AEFIs. Information about adverse event starting and resolution times is provided in Table 1.

It is apparent that in 95.01 % of cases (3,543/3,729), infants experiencing one or more AEFIs started manifesting them within the first 24 h after 4CMenB administration. On the other hand, the distribution of adverse events' ending times is more uniform throughout the follow-up period. It is also relevant to notice that 17.24 % (643/3,729) of all AEFIs had not undergone full resolution by the seventh follow-up day. However, during the 30-day phone contact, it was possible to ascertain that all symptoms had spontaneously met resolution before that time.

Table 2 describes the prevalence of adverse events in the study population by type, while Graph 1 highlights their distribution over time. Systemic reactions were the most common ones (reporting rate: 54.43 %), followed by fever (reporting rate: 52.46 %) and local reactions of pain, redness, swelling and induration (reporting rate: 45.15 %). Gastrointestinal manifestations (reporting rate: 12.57 %) and allergic reactions (reporting rate: 0.15 %) were much less frequent.

In 38 cases (0.80 %), parents reported that the infant required paediatrician evaluation due to one or more AEFIs, and 23 cases of serious AEFIs were reported (reporting rate: 0.48 /100 administered doses). Following causality assessment, 78.26 % of serious adverse events (18/23) were deemed to have a consistent causal association with the administration of 4CMenB (reporting rate: 0.38 %). The remaining 5 AEFIs, on the other hand, were considered not to have consistent causal association with the vaccine. Four infants accessed the emergency room within the first seven days after vaccination, and 3 of these infants were subsequently hospitalized.

The eighteen adverse reaction episodes which were deemed consistently causally associated with 4CMenB administration occurred in 7 female (38.89 %) and 11 male infants (61.11 %). They occurred on average in infants with an age of 109.67 ± 24.80 days (range: 79–171 days), and 27.78 % of them (5/18) was observed in infants who had received prophylactic paracetamol either shortly before or within two hours after vaccination. All of these cases were characterized by fever, with 16 cases of hyperpyrexia (highest body temperature above 39 °C). Of the two remaining infants, one had fever at 38.5 °C and muco-hematic diarrhea, the other had fever at 38.4 °C and febrile seizure. In eight instances, parents called for a paediatrician to provide assistance, and one of the subjects accessed the emergency room and was hospitalized due to persisting hyperpyrexia.

Only one out of the 23 infants was not administered the 2nd dose of 4CMenB vaccine, whereas the remaining 22 kept following the vaccination cycle.

A more in-depth description of the three hospitalization cases is

Table 1
Time of beginning and ending of symptoms or signs reported after 4CMenB administration.

Time after vaccination	N. of diaries reporting beginning of symptomatology	N. of diaries reporting symptomatology resolution
Day 0, within 6 h	2,437	177
Day 0, 6 to 12 h	935	530
Day 0, 12 to 24 h	171	571
Day 1	157	642
Day 2	19	449
Day 3	4	279
Day 4	3	159
Day 5	0	92
Day 6	1	97
Day 7	2	90

Table 2
Prevalence of AEFIs, by type.

Type of adverse event	N.	Reporting rate (per 100 subjects)	% (/3,729)
Systemic reaction	2,598	54.43	69.67 %
Fever	2,504	52.46	67.15 %
Local reaction	2,155	45.15	57.79 %
Gastrointestinal symptoms	600	12.57	16.09 %
Allergic reaction	7	0.15	0.19 %

provided in the following paragraphs.

Case 1

Four-point-one months old baby boy who received paracetamol three hours after vaccination. Between six and twelve hours after 4CMenB administration, the infant started manifesting significant crying and fever reaching up to 39 °C and unresponsive to further paracetamol administration. The infant was therefore brought to the emergency room and hospitalized due to the diagnosis of "hyperpyrexia during acute pharyngitis". Slight meningeal signs were identified by clinicians, likely due to high body temperature, and the infant was treated with antibiotics (amoxicillin/clavulanic acid) and antipyretics (paracetamol). The subject was discharged after three days without any residual signs/symptoms. Causality assessment did not highlight a consistent causal association.

Case 2

Two-point-eight months old baby girl who did not receive paracetamol after vaccination. Within the first six hours after immunization, the infant started manifesting pain, reddening and swelling near the injection site and irritability, due to which the parents administered her with paracetamol nearly 24 h after vaccine administration. During the first day after vaccination, the infant started presenting vomit and muscle stiffness of the left side of the body, and was therefore brought to the emergency room. She was subsequently hospitalized with diagnosis of "suspected sepsis, torticollis" and treated with antibiotics (amoxicillin/clavulanic acid). She was discharged after two days without any residual signs/symptoms. Causality assessment did not highlight a consistent causal association.

Case 3

Four-point-two months old baby girl who did not receive paracetamol after vaccination. Approximately ten hours after the vaccine's administration, the infant manifested an episode with sudden and unjustified crying, followed by hypotonia-hyporesponsiveness with cyanosis and pallor. No loss of conscience occurred, and the episode resolved after tactile stimulation in a short time.

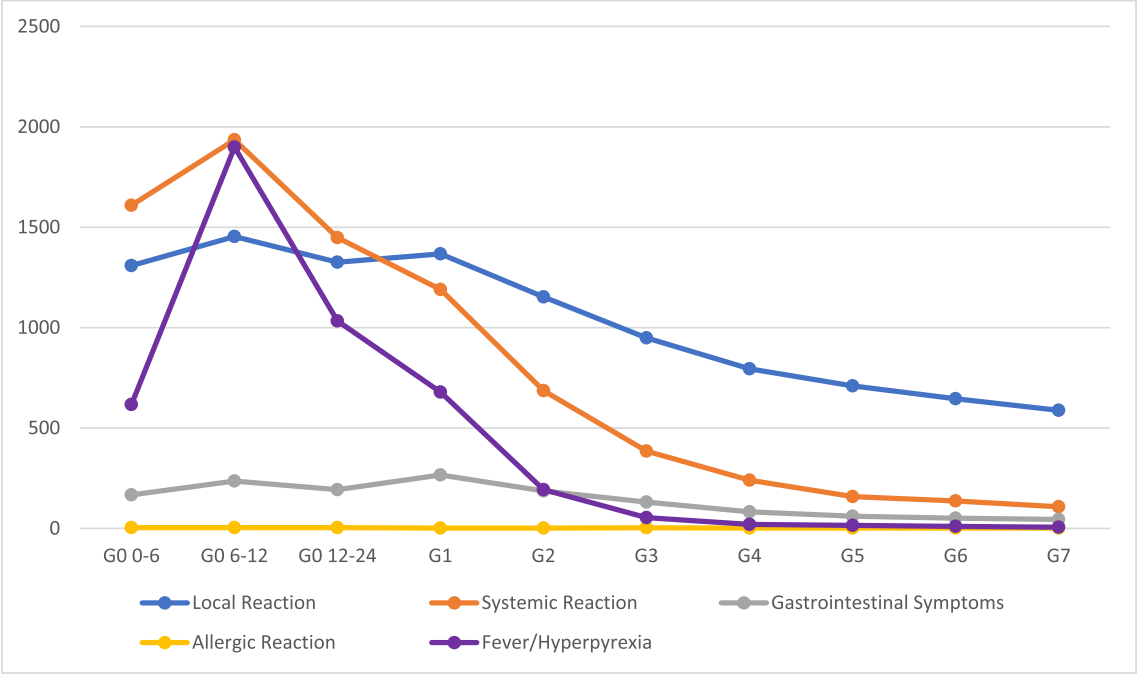
Due to this crisis, the infant was carried shortly after to the emergency room of Bari's "Giovanni XXIII" Paediatric Hospital and thereafter admitted to the Paediatrics' ward of the same hospital. While entering the ward, the infant was in good general conditions, with neither sensory anomalies nor fever and with normal, pink skin color. Cardio-respiratory function was normal, the abdomen was flat and treatable in all quadrants. Routine blood exams highlighted increased white blood cell count (30,510/mm^3) with 67.2 % neutrophils. During hospital stay, the following exams were carried out: *trans*-fontanel echography, which did not highlight any morphological alterations; electrocardiogram, within normal limits.

For the whole duration of her hospital stay, the patient was in good clinical conditions, with neither desaturation episodes nor further crises. She was discharged four days after admission and finally diagnosed with Brief Resolved Unexplained Events (BRUE). The adverse event was classified as "undetermined" following causality assessment, as the increased white blood cell count may indicate an infectious origin of the episode, despite no microorganism having been identified in the infant. The parents refused the infant to be administered with the second 4CMenB dose following this event.

3.2. *Inferential statistical analysis*

The multivariate logistic regression model fitted to study the impact of age, sex, chronic diseases, anti-rotavirus vaccine simultaneous administration and paracetamol administration within two hours on the risk of adverse events highlighted no significant impact of any of the independent variables ($p > 0.05$) (Table 3).

On the other hand, when only fever within the first 24 h after administration was taken into consideration as the dependent variable, a significant protective effect was shown for paracetamol administration



Graph 1. Distribution during the study period of AEFIs, by type and time of insurgence.

Table 3
Characteristics of subjects who did and did not experience AEFIs.

		Mean age (days, ±SD)	Sex		Paracetamol dministration		Chronic illnesses		Anti-rotavirus vaccinecoadministration	
			Male	Female	Yes	No	Yes	No	Yes	No
AEFI reports	Yes	105.20 ± 28.69	1,966	1,763	1,032	2,697	16	3,713	524	3,205
	No	112.18 ± 39.85	525	519	291	753	3	1,041	172	872

within the first two hours after vaccination (OR: 0.75; 95CI: 0.66–0.86; $p < 0.001$). None of the other independent variables was shown to significantly impact the risk of developing a fever during the first 24 h ($p > 0.05$) (Table 4). Further details about the logistic regression models fitted for AEFIs in general and fever during the first 24 h are provided in Table 5 and Table 6, respectively.

4. Discussion

During the study period, 4,773 post-vaccination diaries were completed after administration of 4CMenB to infants. The reporting rate of AEFIs was 78.13 % with 3,729 diaries out of 4,773 containing one or more adverse event reports. The most commonly reported symptoms were systemic reactions, fever and injection-site reactions of pain, redness, swelling and induration. Only a small amount of all AEFIs were identified as serious (23/3,729), with 4 emergency room accesses and 3 infants requiring hospitalization due to clinical manifestations occurring after vaccination.

Our data are coherent with pre-marketing and post-marketing evidence, which identified systemic manifestations, injection site reactions, and fever as common AEFIs, occurring in >10.00 % of paediatric patients administered with 4CMenB. They also confirmed the limited risk of allergic adverse events following vaccination. It should however be taken into consideration that the quoted document generally refers to infants "up to 10 years of age", and can therefore investigate symptoms which are difficult to observe in infants under 2, such as headache and eating disorder [25–27].

The significant risk of fever after 4CMenB administration is well-known. A comprehensive review of safety data coming from both clinical studies and real-world observations has highlighted the fact that injection site tenderness and erythema, fever and irritability were the most common AEFIs observed in infants younger than two after this vaccine's administration, and that co-administration of 4CMenB with other vaccines significantly increased the risk of fever compared with vaccination with the other product alone [28].

As already stated, the prophylactic use of antipyretics shortly after vaccination has already been investigated, proving that paracetamol does not interfere with 4CMenB immunogenicity while significantly reducing the risk of fever [15,16,29,30]. Our study confirms the value of prophylactic antipyretics, as we observed a significant association of paracetamol administration within two hours after vaccination and a lower risk of fever (OR: 0.75; 95CI: 0.66–0.86; $p < 0.001$).

A single hypotonic-hyporesponsive episode was notified: in line with the previously published literature regarding the benignity of the episodes, it resolved briefly and the infant returned to the prevaccination status with no alteration in neuropsychomotor development. Therefore parents refused the infant to be administered with the second 4CMenB dose following this event [31].

Interestingly, data from the aforementioned post-marketing surveillance study in Apulia carried out by our research group highlighted a much lower reporting rate (26.5 AEFIs per 100,000 doses), with a much higher percentage of serious adverse events (27.1 %) [14]. This phenomenon is likely related to the different surveillance method employed, as the present study performed an active surveillance of adverse events. The former, on the contrary, used passive surveillance, which is known to be associated with under-reporting and with an alteration of the serious-to-non-serious adverse reaction ratio [32–34].

The main strengths of our study are the large population size we addressed, which covers a large part of infants vaccinated against serogroup B *N. meningitidis*, and the active surveillance method. We also gathered information regarding paracetamol administration, which allowed us to infer the effect of this practice on the risk of fever. Finally, the use of causality assessment provides additional information and is able to further increase the precision of a surveillance system [35].

On the other hand, a few limitations are to be acknowledged. First of all, we contacted parents seven days after vaccination, which might account for at least some degree of recall bias. However, our data is in line with available evidence, suggesting that no significant distortion of data has been caused. Secondly, although numerous, our population is below 10,000 subjects, therefore making us unable to detect very rare adverse events occurring in less than one case in ten thousand. Further investigation is required, possibly expanding the study population.

An additional bias might be related to prophylactic paracetamol administration being left to the parents to decide. In fact, families with one or more healthcare professionals and/or in closer contact with their infant's paediatrician might have been more prone to use pharmacological prophylaxis to prevent symptoms. Finally, it should be considered that the years 2020 and 2021 were characterized by the Coronavirus Disease-2019 (COVID-19) pandemic, which according to WHO significantly hindered routine vaccination activities in most countries worldwide. This might have contributed to a reduction in the numerosity of our population, possibly lowering our study's power [36].

In conclusion, our data confirms existing evidence regarding the safety of 4CMenB vaccination in babies under 2 years of age. The only two hospitalization cases were then identified by causality assessment as not having a consistent causal association with vaccination, consolidating the identity of this product as safe for use even in young infants. It is important to stress this aspect when confronting parents' worries regarding their sons and daughters' safety and well-being, in order to tackle vaccination hesitancy and increase compliance to vaccination practice [37–39]. Finally, the strategic role of HCW in counselling and post-immunization follow up should be encouraged and included in routine activities. In futurea common vaccination schedule should be implemented both country-wide and at the European level in order to increase the sense of coherent policies, thus encouraging adhesion to vaccination programs [40–43].

Table 4
Characteristics of subjects who did and did not experience fever during the first 24 h after vaccination.

		Mean age (days, ±SD)	Sex		Paracetamol administration		Chronic illnesses		Anti-rotavirus vaccinecoadministration	
			Male	Female	Yes	No	Yes	No	Yes	No
Fever	Yes	104.56 ± 25.44	1,310	1,170	609	1,871	9	2,471	324	2,156
	No	109.07 ± 36.99	1,181	1,112	714	1,579	10	2,283	372	1,921

Table 5
Univariate and multivariate analysis for experiencing AEFIs during the first 24 h after vaccination.

	Univariate (crude)	CI95[]	p-value	Multivariate (adjusted)	CI95[]	p-value
Age (days)	0.99	0.95–1.04	0.168	0.99	0.95–1.04	0.172
Sex (M)	1.10	0.96–1.26	0.164	1.11	0.96–1.27	0.148
Paracetamol administration	0.99	0.85–1.15	0.899	1.05	0.89–1.22	0.571
Chronic Illnesses	1.49	0.43–5.14	0.523	1.54	0.45–5.35	0.492
Anti-rotavirus vaccine coadministration	0.83	0.69–1.00	0.050	0.84	0.69–1.02	0.077

Table 6
Univariate and multivariate analysis for experiencing fever during the first 24 h after vaccination.

	Univariate (crude)	CI95[]	p-value	Multivariate (adjusted)	CI95[]	p-value
Age (days)	0.99	0.98–1.01	0.062	0.99	0.98–1.01	0.067
Sex (M)	1.05	0.94–1.18	0.362	1.06	0.94–1.18	0.352
Paracetamol administration	0.72	0.63–0.82	0.000	0.75	0.66–0.86	**0.000**
Chronic Illnesses	0.83	0.34–2.05	0.689	0.81	0.33–2.01	0.652
Anti-rotavirus vaccine coadministration	0,7760339	0.66–0.91	0,002	0.86	0.73–1.01	0.070

Funding

The project was conceived and coordinated by Apulia's Regional Administration and approved and funded by the Italian Drug Authority.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

References

[1] European Medicine Agency. Bexsero: EPAR - product information. Amsterdam. 28/01/2013. Last updated: 12/10/2022.
[2] European Medicine Agency. Trumenba: EPAR - product information. Amsterdam. 06/06/2017. Last updated: 14/11/2022.
[3] Stefanizzi P, Bianchi FP, Martinelli A, et al. Safety profile of MenB-FHBp vaccine among adolescents: data from surveillance of Adverse Events Following Immunization in Puglia (Italy), 2018–2020. Hum Vaccin Immunother 2022;18(1):2041359. https://doi.org/10.1080/21645515.2022.2041359.
[4] Italian Republic. Ministry of Health. Permanent Conference for the relationships among the State, the Regions and Trento and Bolzano's autonomous provinces. Intesa, ai sensi dell'articolo 8, comma 6, della legge 5 giugno 2003, n. 131, tra il Governo, le regioni e le province autonome di Trento e Bolzano sul documento recante "Piano nazionale prevenzione vaccinale 2017-2019". General Series' Official Gazette n. 41, 18 February 2017.
[5] Lee GM. Preventing infections in children and adults with asplenia. Hematology Am Soc Hematol Educ Prog 2020;2020(1):328–35. https://doi.org/10.1182/hematology.2020000117.
[6] Crum-Cianflone N, Sullivan E. Meningococcal vaccinations. Infect Dis Ther 2016;5(2):89–112. https://doi.org/10.1007/s40121-016-0107-0.
[7] Maltezou HC, Botelho-Nevers E, Brantsæter AB, et al. Vaccination of healthcare personnel in Europe: update to current policies. Vaccine 2019;37(52):7576–84. https://doi.org/10.1016/j.vaccine.2019.09.061.
[8] Pollard AJ, Begg N. Meningococcal disease and healthcare workers. BMJ 1999;319(7218):1147–8. https://doi.org/10.1136/bmj.319.7218.1147.
[9] Gossger N, Snape MD, Yu LM, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized controlled trial. J Am Med Assoc 2012;307(6):573–82. https://doi.org/10.1001/jama.2012.85.
[10] Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials [published correction appears in Lancet. 2013 Mar 9;381(9869):804]. Lancet 2013;381(9869):825–35. https://doi.org/10.1016/S0140-6736(12)61961-8.
[11] Findlow J, Borrow R, Snape MD, et al. Multicenter, open-label, randomized phase II controlled trial of an investigational recombinant Meningococcal serogroup B vaccine with and without outer membrane vesicles, administered in infancy. Clin Infect Dis 2010;51(10):1127–37. https://doi.org/10.1086/656741.
[12] Stefanizzi P, Calabrese G, Infantino V, Del Matto G, Tafuri S, Quarto M. Systematic use of causality assessment in AEFI surveillance: a 2013–2016 pilot study in Puglia. EBMJ 2017;12(33):154–8. https://doi.org/10.3269/1970-5492.2017.12.33.
[13] Italian Republic. Ministry of Health. Decreto 30 april 2015. Procedure operative e soluzioni tecniche per un'efficace azione di farmacovigilanza adottate ai sensi del comma 344 dell'articolo 1 della legge 24 dicembre 2012, n. 228 (Legge di stabilità 2013). General Series' Official Gazette n. 143, June 23rd, 2015.
[14] Stefanizzi P, Bianchi FP, Spinelli G, et al. Postmarketing surveillance of adverse events following meningococcal B vaccination: data from Apulia Region, 2014–19. Hum Vaccin Immunother 2022;18(1):1–6. https://doi.org/10.1080/21645515.2021.1963171.
[15] Prymula R, Esposito S, Zuccotti GV, et al. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I). Hum Vaccin Immunother 2014;10(7):1993–2004. https://doi.org/10.4161/hv.28666.
[16] Dubus M, Ladhani S, Vasu V. Prophylactic paracetamol after meningococcal B vaccination reduces postvaccination fever and septic screens in hospitalized preterm infants. Pediatr Infect Dis J 2020;39(1):78–80. https://doi.org/10.1097/INF.0000000000002507.
[17] UK Health Security Agency. Guidance – MenB vaccine and paracetamol. Information about the meningococcal B (MenB) vaccine and paracetamol use. Published July 22nd, 2015. Last updated November 24th, 2022. Available online at https://www.gov.uk/government/publications/menb-vaccine-and-paracetamol. Last accessed on July 20th, 2023.
[18] Government of South Australia. SA Health. Meningococcal B Immunisation Program. Last updated on July 6th, 2023. Available online at https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/conditions/immunisation/immunisation+programs/meningococcal+b+immunisation+program. Last accessed on July 20th, 2023.
[19] Italian National Statistics Institute. Demografics. Available online at https://demo.istat.it/. Last accessed on July 18th, 2023.
[20] World Health Organization. Global manual on surveillance of adverse events following immunization. Geneva. 2014. Revised March 2016.
[21] European Medicines Agency. Inclusion/exclusion criteria for the "Important Medical Events" list. Amsterdam. 18 March 2021.
[22] Italian Republic. Decreto Legislativo 30 giugno 2003, n. 196. Codice in materia di protezione dei dati personali, ((recante disposizioni per l'adeguamento dell'ordinamento nazionale al regolamento (UE) n. 2016/679 del Parlamento europeo e del Consiglio, del 27 aprile 2016, relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali, nonché alla libera circolazione di tali dati e che abroga la direttiva 95/46/CE)). General Series' Official Gazette n. 174, July 29th, 2003 - Ordinary Supplement n. 123.
[23] Tafuri S, Fortunato F, Gallone MS, Stefanizzi P, Calabrese G, Boccalini S, et al. Systematic causality assessment of adverse events following HPV vaccines: analysis of current data from Apulia region (Italy). Vaccine 2018;36(8):1072–7. https://doi.org/10.1016/j.vaccine.2018.01.018. Epub 2018 Jan 19 PMID: 29358055.
[24] World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification second edition, 2019 update. Geneva. 2019. License: CC BY-NC-SA 3.0 IGO.
[25] Mentzer D, Oberle D, Keller-Stanislawski B. Adverse events following immunisation with a meningococcal serogroup B vaccine: report from post-marketing surveillance, Germany, 2013 to 2016. Eurosurveillance 2018;23(17). https://doi.org/10.2807/1560-7917.ES.2018.23.17.17-00468. PMID: 29717697.
[26] Stefanizzi P, Ferorelli D, Scazzi FL, Di Lorenzo A, Martinelli A, Trinchera C, et al. Allergic adverse events following immunization: data from post-marketing surveillance in Apulia region (South of Italy). Front Immunol 2023;27(14):1074246. https://doi.org/10.3389/fimmu.2023.1074246. PMID: 36923411; PMCID: PMC10008905.
[27] Leitzen S, Dubrall D, Toni I, Stingl J, Schulz M, Schmid M, et al. Analysis of the reporting of adverse drug reactions in children and adolescents in Germany in the time period from 2000 to 2019. PLoS One 2021;16(3):e0247446. https://doi.org/10.1371/journal.pone.0247446.

[28] Marshall GS, Abbing-Karahagopian V, Marshall HS, et al. A comprehensive review of clinical and real-world safety data for the four-component serogroup B meningococcal vaccine (4CMenB). Expert Rev Vaccines 2023;22(1):530–44. https://doi.org/10.1080/14760584.2023.2222015.
[29] Kent A, Beebeejaun K, Braccio S, et al. Safety of meningococcal group B vaccination in hospitalised premature infants. Arch Dis Childhood-Fetal Neonatal Ed 2019;104(2):F171–5. https://doi.org/10.1136/archdischild-2017-314152.
[30] De Serres G, Billard MN, Gariépy MC, et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada. Vaccine 2018;36(52):8039–46. https://doi.org/10.1016/j.vaccine.2018.10.095.
[31] Vigo A, Costagliola G, Ferrero E, Noce S. Hypotonic-hyporesponsive episodes after administration of hexavalent DTP-based combination vaccine: a description of 12 cases. Hum Vaccin Immunother 2017;13(6):1375–8. https://doi.org/10.1080/21645515.2017.1287642. PMID: 28301267.
[32] Stefanizzi P, De Nitto S, Spinelli G, Lattanzio S, Stella P, Ancona D, et al. Post-marketing active surveillance of adverse reactions following influenza cell-based quadrivalent vaccine: an Italian prospective observational study. Vaccines 2021;9(5):456. https://doi.org/10.3390/vaccines9050456.
[33] Tandon VR, Mahajan V, Khajuria V, Gillani Z. Under-reporting of adverse drug reactions: a challenge for pharmacovigilance in India. Indian J Pharmacol 2015;47(1):65–71. https://doi.org/10.4103/0253-7613.150344.
[34] Stefanizzi P, Stella P, Ancona D, et al. Adverse events following measles-mumps-rubella-varicella vaccination and the case of seizures: a post marketing active surveillance in Puglia Italian Region, 2017–2018. Vaccines (Basel) 2019;7(4):140. https://doi.org/10.3390/vaccines7040140.
[35] Lee H, Kang H-Y, Cho S, Park S, Kim A-Y, Jung S-Y, et al. Causality assessment guidelines for adverse events following immunization with a focus on Guillain-Barré syndrome. Vaccines 2020;8(1):101. https://doi.org/10.3390/vaccines8010101.
[36] SeyedAlinaghi S, Karimi A, Mojdeganlou H, Alilou S, Mirghaderi SP, Noori T, et al. Impact of COVID-19 pandemic on routine vaccination coverage of children and adolescents: a systematic review. Health Sci Rep 2022;5(2):e00516. https://doi.org/10.1002/hsr2.516.ù.
[37] Costantino C, Rizzo C, Rosselli R, Battista T, Conforto A, Cimino L, et al. Ten actions to counteract vaccine hesitancy suggested by the Italian Society of Hygiene, Preventive Medicine, and Public Health. Vaccines 2022;10(7):1030. https://doi.org/10.3390/vaccines10071030.
[38] Cataldi JR, O'Leary ST. Parental vaccine hesitancy: scope, causes, and potential responses. Curr Opin Infect Dis 2021;34(5):519–26. https://doi.org/10.1097/QCO.0000000000000774.
[39] Gianfredi V, Moretti M, Lopalco PL. Countering vaccine hesitancy through immunization information systems, a narrative review. Hum Vaccin Immunother 2019;15(11):2508–26. https://doi.org/10.1080/21645515.2019.1599675. Epub 2019 Jun 21.
[40] Tomietto M, Simonetti V, Comparcini D, Stefanizzi P, Cicolini G. A large cross-sectional survey of COVID-19 vaccination willingness amongst healthcare students and professionals: reveals generational patterns. J Adv Nurs 2022;78(9):2894–903. https://doi.org/10.1111/jan.15222. Epub 2022 Mar 17.
[41] Effraimidou E, Cassimos DC, Medic S, Topalidou M, Theodoridou M, Maltezou HC. Vaccination programs for children aged up to 18 years in Europe, 2020. J Child Health Care. 2021:13674935211055294. https://doi.org/10.1177/13674935211055294 [published online ahead of print, 2021 Nov 29].
[42] Moscara L, Venerito V, Martinelli A, Di Lorenzo A, Toro F, Violante F, Tafuri S, Stefanizzi P. Safety profile and SARS-CoV-2 breakthrough infections among HCWs receiving anti-SARS-CoV-2 and influenza vaccines simultaneously: an Italian observational study. Vaccine. 2023 Aug 31;41(38):5655–61. https://doi.org/10.1016/j.vaccine.2023.07.043.
[43] Bianchi FP, Stefanizzi P, Brescia N, Lattanzio S, Martinelli A, Tafuri S. COVID-19 vaccination hesitancy in Italian healthcare workers: a systematic review and meta-analysis. Expert Rev Vaccines 2022 Sep;21(9):1289–300. https://doi.org/10.1080/14760584.2022.2093723.