

RESEARCH PAPER



Spontaneous demand for meningococcal b vaccination: Effects on appropriateness and timing

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ABSTRACT

When the meningococcus B vaccine was introduced into Italy in 2017, it was recommended for newborns based on national epidemiological data indicating that they were at greater risk. However, the vaccination service of the local health authority of L'Aquila had already been receiving spontaneous parental requests to provide vaccination for children in lower-risk age groups from the beginning of 2016. We therefore decided to use a self-administered questionnaire in order to investigate the parents' socio-demographic data; their children's history of other recommended vaccinations (against measles, mumps and rubella, varicella, meningococcus C and, for females, human papilloma virus); the information sources concerning meningococcal vaccination; and the timing of its administration.

The questionnaire was completed by 565 parents, and the results showed that the requests mainly came from the parents of children aged 5–11 years. The children whose mothers had received a high school education and were >35 years old were more likely to have received the first dose after the age of one year and to have perceived pain at the inoculation site, and less likely to have experienced mild general reactions. The requests were mainly triggered by the recommendations of healthcare professionals, and the overloading of the vaccination service led to delays in the administration of the doses after the first. The delays (reported by 74.07% of the parents) were mainly due to organisational problems in the service itself, which led 61.52% of the doses being more appropriately administered by staff working as private physicians inside public health facilities, albeit at extra cost.

These findings indicate that organisational factors and excessive demand had a considerable impact on both the efficacy of the immunisation and its appropriateness.

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Introduction

Bacterial meningitis caused by *Neisseria meningitidis* is an important cause of morbidity and mortality. The main serogroups circulating in Europe are B (which accounts for 60–72% of cases and mainly affects children aged 0–5) and C (which is responsible for 16% of cases and mainly affects 25–44-year olds),^{1–4} serogroup Y, which affects older subjects is less frequent.³

In Italy, meningitis is reported by hospital discharge records (HDRs) and by Invasive Bacterial Disease (IBD) surveillance system. Between 2007 and 2012 a study carried out in two Italian regions found that 341 cases of IBDs of which 202 were of serogroup B.⁵ In the same period in Italy the *Istituto Superiore di Sanità* (ISS, Italian National Health Institute) reported 991 cases IBDs, of which 455 were caused by serogroup B.⁶ Overall, 81% of all cases of meningitis occurring during the first year of life are caused by serotype B,⁶ and more than half occur in 4–8 months old infants.⁷ Stefanelli reported that in children younger than 1 year an incidence of IMD (invasive meningococcal disease) was 10 times higher (3.6/100,000) than the population rate (0.28/100,000),⁸ and serogroup B accounted for 65% of the cases. Recent data published by ISS show that 67 cases of

serotype B were reported 2016,⁹ with an incidence of 0.78/100,000 in children 0–4 years, and 0.11/100,000 in all age groups. However, underreporting can be as high as 23% as found by Neri,¹⁰ and failure to identify the serogroup can reach 19% of cases (unknown serogroup).⁹ As in 2016 when three cases of IMD due to *N. meningitidis* with an unspecified serogroup were reported in Abruzzo (0.23/100,000).⁹

The Italian National Health Service (NHS) provides free of charge the vaccinations included in the vaccination schedule including Men B vaccine which was included in May 2017.

At the time of this survey, the meningococcus B (MenB) vaccination was not yet included in the schedule, thus 50% of the vaccine cost would be charged to anyone requesting vaccination according Abruzzo regional law.¹¹ Alternatively, they could choose to pay the total cost in order to access what is called the *intramoenia* regimen, which allows physicians to carry out their own freelance activities in public hospitals outside institutional hours, to avoid long waits due to high demand in the public services.

The Italian National Vaccination Prevention Plan (NVPP) 2017–2019.¹² approved by the Ministry of Health in February

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2017, introduced free of charge MenB vaccinations with the following schedules: newborns should receive three initial doses at the ages of three, four and six months, with a fourth dose at the age of 13 months; infants aged >6 months should receive three doses, with the first two given at seven and nine months of age.

Although the low incidence of IMD, and the fact that the cost of vaccination would be substantial for parents as still not provided free of charge, the vaccination service of the local health authority of L'Aquila (ASL 01, Abruzzo, Italy) experienced an unexpected increase of the demand for MenB vaccination between the end of 2015 and the beginning of 2016.

We performed the present study to characterise the profile of the parents wishing to have their children vaccinated against meningococcus B, (4CMenB; Bexsero), their sources of information, and their compliance to other recommended vaccinations as measles, rubella and mumps, Varicella MenC, HPV for adolescents girls.

Results

The investigation lasted seven months, during which we interviewed the children's parents after having administered 4CMen B vaccinations. Out of 600 questionnaires administered, 565 were considered valid for the analysis. As showed in Table 1 the valid questionnaires were compiled mainly by the mothers (78.33%) than the fathers (21.67%) in great majority of Italian nationality (94.34% of mothers and 98.05% of fathers); the majority was older than 35 years, and mothers had higher education than fathers (55.22% and 33.27% had a university degree, respectively). More men than women were employed (94.66% vs 78.47%), and 1.78% and 5.34% of these worked in the healthcare sector, respectively. The gender distribution of their children was 52.39% of males and 47.61% of females. Their age group was distributed as follows: 42.30%

Table 1. Characteristics of the parents and children.

	Parents n = 565	
	Mothers, n (%)	Fathers, n (%)
Age, years		
21–30	38 (6,73)	21 (3,72)
31–35	97 (17,17)	68 (12,04)
>35	430 (76,11)	476 (84,25)
Education		
Middle school	25 (4,42)	50 (8,85)
High school	228 (40,35)	327 (57,88)
University	312 (55,22)	188 (33,27)
Nationality		
Italian	533 (94,34)	554 (98,05)
Non-Italian	32 (5,66)	11 (1,95)
Occupational status		
Employed	441 (78,47)	532 (94,66)
Unemployed/students	91 (16,19)	20 (3,56)
Healthcare workers	30 (5,34)	10 (1,78)
Children characteristics		
Gender	n (%)	
Male	296 (52,39)	
Female	269 (47,61)	
Age, years		
<1	52 (9,20)	
1–4	188 (33,27)	
5–11	239 (42,30)	
≥12	86 (15,22)	

Table 2. Age ranges of the children receiving MenB vaccination, the timing of its administration, and reasons for any delays

	n (%)
Ages of the children receiving the first vaccine dose	
<1 years	112 (19,82)
1–4 years	146 (25,84)
5–11 years	227 (40,18)
≥12 years	80 (14,16)
Time between first and second dose	
2 months	126 (38,18)
3–6 months	182 (55,15)
≥7 months	22 (6,67)
Time between second and third dose	
2–6 months	23(42,59)
7–12 months	18(33,33)
>12 months	13(24,07)
Reasons for not respecting the times of administration	
Child's recurrent illnesses	59 (19,87)
Timing imposed by Vaccination Service	220 (74,07)
Parental commitments/Fear of adverse events	18 (6,06)

were 5–11 years, 33.27% aged 1–4 years, 15.22% aged ≥12 years, and 9.20% aged <1 year.

Table 2 shows the ages of the children receiving the first dose MenB vaccine, the timing of the administrations, and the reasons for not respecting the recommended timing. Of the 565 children receiving the vaccination, 40.18% were aged 5–11 years, 25.84% were aged 1–4 years, 19.82% were aged <1 year, and 14.16% were aged ≥12 years. The results VAS showed that the mother's opinion weighed "a great deal" more frequently than that of the father (83.96% vs 69.98%) (data not shown).

The time between the first and second dose was 3–6 months in 55.15% of cases, two months in 38.18%, and more than seven months in 6.67%, and the time between the second and third dose (among those who needed it) was 2–6 months in 42.59% of cases, 7–12 months in 33.33%, and >12 months in 24.07%. The main reason for the delays in administering the doses after the first (74.07% of cases) was the timing imposed by the vaccination service, followed by delays due to illness of the child (19.87%), and other reasons (6.06%).

Table 3 shows the organisational regimen under which the vaccination was administered (ordinary or *intramoenia*). It can be seen that the parents of newborns aged <1 year more frequently used the ordinary regimen (30.72%), whereas those of

Table 3. Percentage distribution of MenB vaccine by children's age, and the timing and organisational type of administration

	Ordinary regimen	<i>Intramoenia</i> regimen ^o	p-value*
Age at time of first dose	n (%)	n (%)	<0.001
<1 year	106 (30,72)	6 (2,76)	
1–4 years	94 (27,25)	51 (23,50)	
5–11 years	103 (29,86)	122 (56,22)	
≥12 years	42 (12,17)	38 (17,51)	
Time between first and second dose			<0.001
2 months	61 (27,48)	65 (60,19)	
3–6 months	144 (64,86)	38 (35,19)	
≥7 months	17 (7,66)	5 (4,63)	

^oadministration by a doctor working full-time in a public healthcare facility but acting in his/her private capacity.

*χ test

the children aged >5 years more often had recourse to the *intramoenia* regimen (73.73%). The time between the first and second dose was respected more frequently by the parents who paid for the administration (60.19% vs 27.48%), whereas intervals of >3 months were more frequent under the ordinary regimen (72.52% vs 39.82%). There were therefore significant differences between the two regimens in terms of the children's age ($p < 0.001$) and the time interval between the two vaccine doses ($p < 0.001$).

Table 4 compares the parents' socio-demographic characteristics and their information sources, and the side effects of Men B vaccination in the children who received their first vaccine dose in the first year of life (group A) and those who received it later (group B). There was a statistically significant between-group difference in the percentage of mothers and fathers aged >35 years (50.00% vs 82.56%; $p < 0.001$), and (66.96% vs 88.52%; $p < 0.001$). The percentage of mothers with a university degree was higher in group A (68.75% vs 51.88) and, although the percentage of fathers with a degree was similar in the two

groups, the frequency of fathers with a medium-low level of education was lower in group A. The percentage of mothers who were healthcare workers was significantly higher in group A (21.62% vs 14.86%; $p = 0.002$). There were also significant between-group differences in the side effects reported after the vaccination: pain at the inoculation site ($p < 0.001$) and functional impotence ($p = 0.002$) were most frequently reported in group B, whereas mild general reactions were more frequent in group A ($p < 0.001$). Finally, the sources of information regarding MenB vaccinations were more frequently institutional in group A ($p = 0.018$).

Multiple logistic regression analysis (Table 5) showed that the children with mothers aged 31–35 years (OR 7.38, 95% CI 1.83–29.87; $p = 0.005$) and >35 years (OR 32.80, 95% CI 7.17–50.05; $p < 0.001$), and those whose mothers had had a high school education (OR 3.72, 95% CI 1.73–8.03; $p = 0.001$) were at higher risk of receiving their first MenB dose after the age of one year, whereas children with fathers aged >35 years were at lower risk of receiving their first MenB dose after the age of one year (OR 0.17, 95% CI 0.03–0.92; $p = 0.040$).

The children who received their first vaccine dose after the age of one year were more likely to have perceived pain at the inoculation site (OR 4.82, 95% CI 1.99–11.70; $p = 0.001$), and less likely to have experienced mild general reactions (OR 0.32, 95% CI 0.14–0.72; $p = 0.006$).

With the aim of assessing compliance to the use of vaccinations in general, we investigated the self-reported adherence to the other recommended vaccinations. The results indicated 99.80% adherence for MMR, 65.74% for varicella, 92.83% for Men C, and 72.60% for HPV (girls only) Two of the main reasons for non-adherence to varicella vaccinations were its high cost (20.81%) and the fact that it was not considered necessary (16.77%).

Discussion

This study was carried out in response to an unusually high parental demand for MenB vaccination in 2016. Although only three cases of IMD had occurred in our region,⁹ none of which involved our local health authority, the unexpected demand for vaccination prompted us to investigate the profile of the parents who spontaneously requested the vaccination, their sources of information, and whether they had adhered to the other recommended childhood vaccinations. The results of our study showed that the demand for vaccination with MenB vaccine mainly concerned children aged 5–11 years (42% of the sample), whereas those aged <1 year, considered to be at highest risk, accounted for only 9% of the total.

The choice of vaccination was most likely motivated by the parents' perception of the severity of meningitis as almost all of them answered the specific question affirmatively, with the mothers' opinions more prevalent in the determining the request than those of the fathers (83.96% vs 69.98%). It is also possible that the many cases of meningitis caused by meningococcus C reported in Italy in 2016 prompted the parents to immunise their children also against meningococcus B.⁹

The parents participating in this study showed a positive attitude towards vaccination in general, as demonstrated by

Table 4. Comparison of the parents' socio-demographic characteristics, their sources of information, and the reactions to MenB vaccination in the group of children who received the first vaccine dose in their first year of life (group A) and those who received it later (group B)

	Group A (n = 112)	Group B (n = 453)	p-value*
Mother's age (years)	n (%)	n (%)	< 0,001
21–30	21 (18.75)	17 (3.75)	
31–35	35 (31.25)	62 (13.69)	
>35	56 (50.00)	374 (82.56)	
Father's age (years)			< 0,001
21–30	12 (10.71)	9 (1.99)	
31–35	25 (22.32)	43 (9.49)	
>35	75 (66.96)	401 (88.52)	
Mother's education			0,006
Primary/middle school	3 (2.68)	22 (4.86)	
High school	32 (28.57)	196 (43.27)	
University	77 (68.75)	235 (51.88)	
Father's education			0,034
Primary/middle school	3 (2.68)	47 (10.38)	
High school	71 (63.39)	256 (56.51)	
University	38 (33.93)	150 (33.11)	
Mother's occupational status			0,002
Employed	75 (67.57)	366 (81.15)	
Unemployed/student	12 (10.81)	18 (3.99)	
Healthcare workers	24 (21.62)	67 (14.86)	
Father's occupational status			0,502
Employed	103 (92.79)	429 (95.12)	
Unemployed/student	6 (5.41)	14 (3.10)	
Healthcare workers	2 (1.80)	8 (1.77)	
Reactions to MenB vaccination			
None	26 (30.23)	57 (22.62)	0,191
Pain at inoculation site	11 (12.79)	96 (38.10)	<0,001
Functional impotence	0 (0.00)	23 (9.13)	0,002
Mild general reactions	37 (43.02)	26 (10.32)	<0,001
Two or more previous reactions	12 (13.95)	50 (19.84)	0,261
Source of information concerning MenB vaccination			
One or more institutional source (Vaccination Service, pediatrician, GP, pre-partum course)	78 (69.64)	256 (57.14)	0,018
One or more non-institutional source (word of mouth, Internet, mass media)	16 (14.29)	85 (18.97)	0,274
Multiple sources	18 (16.07)	107 (23.88)	0,077

* χ^2 test or Fisher's exact test

Table 5. Multivariate logistic regression analysis of the factors associated with receiving the first dose of Men B vaccination after the age of one year

	OR ^o	95% CI	p-value
Mother's age (years)			
21–30*	1		
31–35	7.38	1.83–29.87	0.005
>35	32.80	7.17–50.05	<0.001
Father's age (years)			
21–30*	1		
31–35	0.35	0.07–1.81	0.213
>35	0.17	0.03–0.92	0.040
Mother's education			
Primary/middle school	2.89	0.57–14.65	0.199
High school	3.72	1.73–8.03	0.001
University*	1		
Mother's occupational status			
Employed	2.25	0.95–5.34	0.066
Unemployed/student	0.89	0.21–3.76	0.869
Healthcare workers*	1		
Reactions to MenB vaccination			
None*	1		
Pain at inoculation site	4.82	1.99–11.70	0.001
Mild general reactions	0.32	0.14–0.72	0.006
Two or more previous reactions	2.29	0.92–5.70	0.075
Source of information concerning MenB vaccination			
One or more institutional source (Vaccination Service, paediatrician, GP, pre-partum course)*	1		
One or more non-institutional source (word of mouth, Internet, mass media)	2.03	0.80–5.13	0.134
Multiple sources	1.52	0.67–3.48	0.319

^oOdds ratio adjusted for the other factors in the model

(Akaike information criterion, AIC)

*Reference category

the high rate of immunisation against MMR, meningococcus C, varicella and HPV that were higher than the national and regional averages.^{13,14,15,16,17} HPV coverage was higher than that. The most frequent time interval between the first and second dose of MenB vaccine was 3–6 months (up to seven months in some cases), and about 47% of the newborns were not immunised within the recommended.¹² A number of studies have found that there is a more or less marked, dose-related decrease in the persistence of antibody titres in adolescents after six months,^{18,19} in adults after 12 months²⁰ and in newborns and infants up to the age of two years.^{21–24} A large proportion of parents (74.07%) reported that the delays were mainly due to the organisational needs of the vaccination service, in fact more than half of the vaccinations (61.52%) were given under

the *intramoenia* regimen in an attempt to overcome the long waiting times in ordinary regimen.

We therefore considered the type of administration regimen (ordinary or *intramoenia*) in relation to the children's age and the time interval between the first and second dose, and found some significant differences. The time between the first two doses was longer under the ordinary regimen than with the *intramoenia* regimen (72.52% vs 39.82%). It can therefore be said that the vaccination health service satisfied the requests of parents whose children were aged <1 year by postponing the vaccination of older children, whose parents resorted to the *intramoenia* regimen even though their children were not at risk.

MenB vaccinations were first authorised in Italy in 2015 but, before they were included in the free-of-charge NVPP in 2017, it was necessary to pay in order ensure regular scheduled immunisation. As the age of the children at the time of the first dose varied, we investigated the difference between those who received it during the first year of life (group A) and those who received it later (group B) in terms of their parents' socio-demographic characteristics and sources of information, and the side effects of the vaccinations on the children. Both parents of the children in group A were younger and had a higher educational level than those of the children in group B, and a higher proportion of the mothers worked in the healthcare sector. Mothers with a university education were well represented in both groups, which contrasts with the finding of Mameli²⁶ and Anello²⁷ that a willingness to have children vaccinated inversely correlates with their parents' educational level but is in line with those of Morrone.¹⁵ Comparison of the adverse effects reported by the parents showed that the children in group B significantly more frequently experienced pain with functional impotence and pain at the inoculation site, whereas those in group A more frequently experienced mild general reactions such as restlessness, fever, headache and diarrhea. These findings are in line with those of many studies of MenB^{21,28,29} and other vaccinations^{30–32} and indicate that the onset of adverse events is age related. No serious side effects were reported.

There was also a statistically significant between-group difference in the parents' sources of information. As found in other studies,^{26,33–36} the main source was healthcare professionals. The willingness to bear 50% of the cost of the vaccine (€ 82.00 a dose) is in line with data showing that parents are prepared to pay in order to ensure the immunisation of their children.³⁷

It can therefore be seen that these parents were well disposed to vaccination protection, sensitive to indications of healthcare professionals, and free of economic and organisational problems. Under such favourable conditions, the appropriateness and efficacy of vaccinations for the people involved and society as a whole is in the responsibility of public healthcare services and healthcare professionals.

The present study has some limitations. First of all, we could not evaluate the differences in opinions between the fathers who were alone and those who were with mothers at the moment of vaccination because the questionnaire was distributed at the time of vaccination when only one parent is present and was returned after the 20-minute period

needed to observe possible acute adverse events. Secondly, given the recent introduction of MenB vaccination, it was difficult to compare our findings with those of others because of the lack of similar studies in Italy. The only data accessible to us came from the Ministry of Health and related to coverage in 2014 cohort,¹³ which showed that coverage in Abruzzo was below the national average. Thirdly, our findings relate to a specific group of people who spontaneously requested the MenB vaccination before it was introduced into the childhood immunisation schedule, and so our data may not apply to the general population. Finally, as more than 60% of the parents opted for the *intramoenia* regimen, the economic factor might be a bias.

Conclusions

The introduction of a new vaccine is generally accompanied by an analysis of epidemiological data, the impact of the vaccination on health, and the cost/benefit ratio. The incidence of meningococcus B is low in Italy (and in Abruzzo), and the many studies of the vaccination's cost/benefit ratio (including direct and indirect costs, and the reduction in disease-related costs) agree in concluding that, when the incidence of the disease is low, the vaccination is good value for money only if it is cheap³⁸⁻⁴⁰ and if the children are <1 year old.⁴¹ All of this was confirmed by the recent Ministry of Health decree recommending MenB vaccinations only for children in their first year of life. It can therefore be said that the high level of parental compliance generated by the advice of pediatricians and GPs revealed in this study is not supported by epidemiological evidence or economic analyses. The willingness to bear half of the cost of the vaccine does not justify its inappropriate administration insofar as part of the cost is borne by the National Health Service. Furthermore, having recourse to the *intramoenia* regimen does not assure the equity underlying Italian healthcare. The failure to respect the administration schedule of a newly introduced vaccine whose medium- and long-term efficacy had not been defined may also have led to an inadequate level of protection. Our findings suggest that organisational factors had a determining impact on the efficacy of the immunisation: the vaccination service was overwhelmed by the excessive demand encouraged by the favourable attitude of pediatricians and responded in a manner that was inconsistent with the criteria of appropriateness. However, it is comforting that the opinions of pediatricians and GPs were considered important or very important in favouring compliance, and they should be involved in the implementation of any new vaccine in order to better adherence (see varicella coverage).

Methods

This was a study including 600 parents who spontaneously attended the Vaccination Service of the Department of Prevention of the local health authority (ASL 01) in L'Aquila, Abruzzo, Italy to have their children vaccinated against MenB and was conducted between April and November 2016. The study was approved by the Ethics Committee of ASL 01. A questionnaire was administered to each parent included into the study and asked to be compiled in anonymous way. The

questionnaire was adapted from a template previously used in other studies⁴² and before study start was validated with a sample of 25 parents. The test-retest results indicated a Cohen kappa coefficient of 0.92.

The items were designed to investigate the parents' socio-demographic characteristics (age, nationality, education level and employment status), the characteristics of the children receiving the vaccination (sex, age, and condition at birth), parental adherence to other recommended vaccinations, and the reasons for any non-adherence, the sources of information concerning MenB vaccination, the timing of its administration, and any adverse events related to its administration. The visual analogue scale (VAS) ranging from "not at all" to a "a great deal" used to answer the question "How much did the opinion of the mother and father weigh on the decision to have the MenB vaccination administered?" was used. Every questionnaire was accompanied by a description of the design and purpose of the study, and an informed consent form.

Statistical analysis

Descriptive statistics were used to describe the socio-demographic characteristics of the parents and children. Percentage adherence to the main vaccinations recommended for childhood and reasons for any non-adherence were calculated, as was the age distribution of the children receiving the vaccine. A record was also made of the timing of its administration and the reasons for any delays.

The sample was divided into two groups: one consisting of the children who started receiving the vaccination at an age of <1 year, when the incidence of the disease is greatest (group A), and the other of the children who started receiving the vaccination after the age of one year (group B). The two groups were compared in terms of their socio-demographic characteristics, the sources of information concerning MenB vaccination, and the adverse reactions occurring after its administration. The statistical significance of the differences in frequency distributions between the two groups were analysed using the χ^2 or Fisher's exact test, with a 5% level of significance. Backward stepwise selection using the Akaike information criterion (AIC) was used for the multiple logistic regression analysis of the factors associated with receiving the first dose of Men B vaccination after the recommended age of one year, which are reported as odds ratios (ORs) with their 95% confidence intervals (95% CIs). The analyses were made using the STATA/IC12.0 statistical package.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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