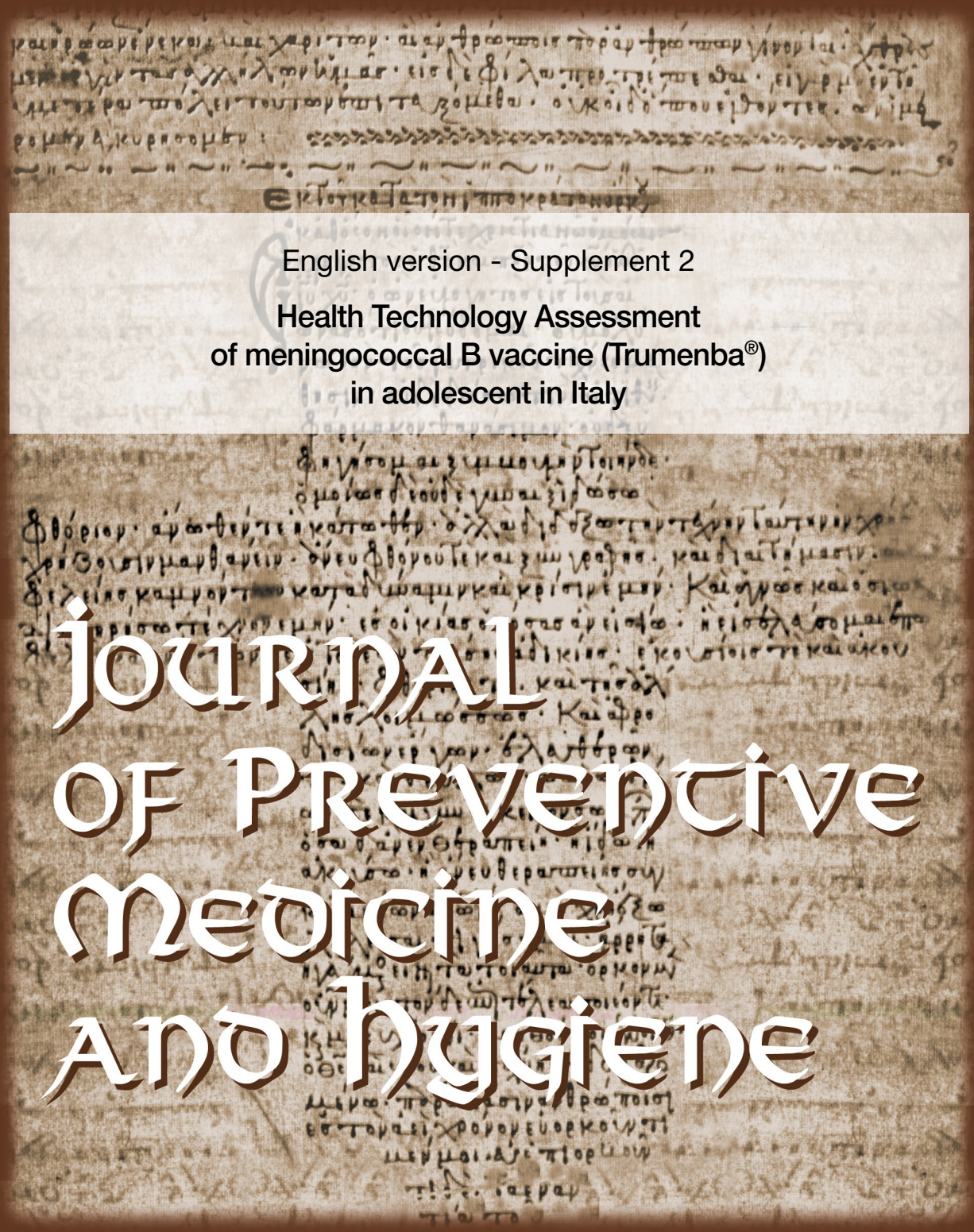
vol. 60 n. 3

September 2019

Cited in Index Medicus / Medline
NLM ID 921440 (Pub-Med)



English version - Supplement 2

Health Technology Assessment of meningococcal B vaccine (Trumenba®) in adolescent in Italy

Journal of Preventive Medicine and Hygiene

The Journal has been accreditated, on occasion of the 17th December 2004 Meeting of the Executive and Scientific SItI Councils, by the Italian Society of Hygiene, Preventive Medicine and Public Health

PACINI EDITORE MEDICINA

JOURNAL OF PREVENTIVE MEDICINE AND HYGIENE

http://www.jpmh.org

Managing Editor: Patrizia Alma Pacini
Publisher: Pacini Editore Srl, Via Gherardesca 1, 56121 Pisa, Italy

Published online December 2019
English version published online April 2020

Authorization Tribunal of Genoa, Italy n. 507 - 10/6/1960
Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

Health Technology Assessment of meningococcal B vaccine (Trumenba®) in adolescent in Italy

Department of Health Sciences, University of Florence, Italy
S. Boccalini, A. Bechini, G. Sartor, D. Paolini, M. Innocenti, P. Bonanni

UNIVERSITÀ DEGLI STUDI DI GENOVA

Department of Health Sciences, University of Genoa, Italy
D. Panatto, P.l. Lai, F. Zangrillo, F. Marchini, E. Lecini, M. Iovine, D. Amicizia

Department of Economics, University of Genoa, Italy
P. Landa

https://doi.org/10.15167/2421-4248/jpmh2019.60.3s2eng

This project was made possible by an unconditional contribution by Pfizer Vaccines Italy

Contents

Chapter 1

Rationale of a health technology assessment of an anti-meningococcal B vaccine for adolescents in Italy

S. BOCCALINI, P. BONANNI
Department of Health Sciences, University of Florence, Italy

Introduction

In the epidemiology of invasive meningococcal diseases, adolescents and young adults constitute a particularly important segment of the population, in that a significant number of cases are registered in this age-group. Furthermore, in some adolescents, the symptoms of meningococcal disease are recognized late; consequently, treatment is delayed and hospitalization is prolonged. The range of physical and psychological outcomes following invasive meningococcal disease is very broad and severe in adolescents and young adults. Indeed, among non-elderly subjects (< 65 years), the case fatality rate is highest in those aged between 15 and 24 years. In addition, owing to the typical behaviors of adolescents and young adults, these subjects have the highest rates of *N. meningitidis* carrier status, which means that they can spread the infection throughout the population.

Although the incidence of meningococcal disease is not particularly high, its considerable morbidity and case fatality rate in adolescents and young adults provide the rationale for adopting anti-meningococcal vaccination in this age-group. For this reason, anti-meningococcal C or ACYW135 vaccination has already been incorporated into the 2017-2019 National Vaccine Prevention Plan (NVPP). To date, however, there is no national recommendation to vaccinate adolescents against meningococcus B, though the possibility of its introduction in the future will hopefully be evaluated [1].

Meningococcus B is the most frequently identified serogroup in Italy, accounting for about 36% of cases of invasive disease due to *N. meningitidis* in the period 2011-2017, despite an upsurge of meningococcus C in 2015-2016 and the increasing percentage of cases due to other serogroups. According to the national surveillance of invasive bacterial diseases, coordinated by the *Istituto Superiore di Sanità* (ISS), meningococcus B is responsible for about 62 cases of invasive disease per year in the general population, including 3 cases in the 10-14-year age-group and 11 cases in the 15-24-year age-group.

A new anti-meningococcal B vaccine (Trumenba® - Pfizer) has recently been approved for use in subjects aged ≥ 10 years. This is a recombinant vaccine, with the addition of a lipid component (with an adjuvant effect). It contains two variants of the subfamilies A and B of the complement factor H binding protein (fHBP). Of the meningococcal B strains circulating in the USA and Europe, 96% express a variant belonging to one of the two subfamilies of fHBP. Administered according to a 2- or 3-dose schedule, this vaccine has proved to be immunogenic and able to elicit a robust bactericidal response to the most prevalent heterologous variants. The two-dose schedule is recommended in the healthy population [2], while the three-dose schedule is preferable in situations of epidemiological and clinical risk. The vaccine can be co-administered with all the main vaccines used in adolescence.

The possibility of instituting an anti-meningococcal B vaccination program for adolescents could therefore be evaluated by decision-makers and stakeholders in Italy in the near future. In this context, a specific Health Technology Assessment (HTA) report by experts in vaccination and health economics, and HTAs applied to immunization programs, could be of great use. Indeed, the HTA is acknowledged to be the best approach to evaluating the introduction of new vaccinations or new vaccination strategies in prevention programs [1, 3, 4].

Given the increasing availability of new vaccines and the extension of indications for some vaccines already available, it is important to draw up and use clear, solid and shared criteria to guide decision-making processes; this will enable National and Regional Health Services to rationalize their use of the limited resources available and to optimize the effects on public health. The best approach to establishing such criteria is to conduct HTAs, as envisaged by the WHO [4] and the 2017-2019 NVPP [1].

According to the HTA approach, a range of issues should be evaluated before any new vaccine or vaccination strategy is introduced. These include: the epidemiology of infections and diseases, the disease burden, the preventive and therapeutic interventions available, the efficacy and safety of the vaccines available, economic evaluations, and the ethical, legal, social and organizational aspects related to the introduction of vaccination [5]. Carrying out an HTA therefore involves collecting and critically examining the scientific evidence available, in order to make a thorough assessment of the possible impact of the introduction of the new vaccine or vaccination strategy.

Thus, in the light of the 2017-2019 NVPP [1] indication regarding the need to evaluate the appropriateness of extending anti-meningococcal B vaccination to adolescents, and in anticipation of the next update of this document, the present HTA report was conducted with the specific objective of evaluating anti-meningococcal B vaccination with the vaccine Trumenba® in adolescents

(12th year of life). A thorough review of the national and international scientific literature was carried out, in accordance with the principal domains indicated by EUnetHTA [6], on: the epidemiology of meningococcal disease; the burden of invasive disease, with particular reference to the clinical and economic impact of sequelae; the immunogenicity, efficacy and safety of the vaccine Trumenba®; the preventive measures currently adopted to combat meningococcal infection in adolescents; and the organizational impact that this vaccination may have on regional healthcare systems. No less important was the ethical evaluation. Finally, an economic assessment was carried out by means of a static Markov model of cost-effectiveness, in order to compare the strategy of "vaccination" with that of "non-vaccination".

References

[1] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-2019. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf

[2] Azzari C, Bonanni P. A new meningococcal B vaccine for adolescents and adults: characteristics and methods of use. J Prev Med Hyg 2018;59:E257-60. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1096

[3] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale (PNPV) 2012-2014. Gazzetta Ufficiale n. 47 (12 marzo 2012). Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_1721_allegato.pdf

[4] World Health Organization (WHO). Vaccine introduction guidelines. Adding a vaccine to the national immunization programme. Decision and implementation. 2005. Available at: http://whqlibdoc.who.int/hq/2005/WHO_IVB_05.18.pdf

[5] La Torre G, de Waure C, Chiaradia G, Mannocci A, Specchia ML, Nicolotti N, Ricciardi W. The future of best investing in vaccines: the Health Technology Assessment approach. Vaccine 2008;26(13):1609-10. https://doi.org/10.1016/j.vaccine.2008.01.009

[6] EUnetHTA. HTA Core Model®. Available at: http:// www.eunethta.eu/hta-core-model

Epidemiology of meningococcal disease in Italy

G. SARTOR[1], A. BECHINI[2], P. BONANNI[2], S. BOCCALINI[2]
[1] Medical School of Specialization in Hygiene and Public Health, University of Florence, Italy; [2] Department of Health Sciences, University of Florence, Italy

Disease due to *Neisseria meningitidis*

Meningitis, inflammation of the membranes that envelop the central nervous system, is generally of infectious origin (bacterial, viral or fungal). The main organisms responsible for bacterial meningitis are: *Neisseria meningitidis* (meningococcus), *Streptococcus pneumoniae* and *Haemophilus influenzae*. These bacteria are also associated with other serious forms of systemic infections, including sepsis.
The bacterium *N. meningitidis* is transmitted via the air, and is found in the upper respiratory tract, even in healthy subjects. The prevalence of healthy carriers (those who host the bacterium in the nasopharynx and can therefore be a source of contagion) varies with age: from 4-5% in children to over 20% in subjects aged about 20 years, and then declining again with age [1]. A recent study conducted in Milan (Italy) found that 5.3% of the adolescent population aged between 14 and 21 years were healthy carriers [2].
Although there are predisposing risk factors (e.g. diabetes, immunodeficiency, some genetic polymorphisms, etc.), it is the healthy population, especially children and young adults, who are mostly affected by invasive diseases (meningitis, bacteremia, bacteremic pneumonia and others) caused mainly by five serogroups of the bacterium (A, B, C, W, Y).
The symptoms are initially nonspecific (fever, headache, loss of appetite). As the disease progresses, however, more specific signs appear (stiffness of the neck and other signs of meningeal irritation). The disease has a rapid course (hours - days) and frequently causes complications (including septicemia, septic shock, coma) and invalidating sequelae (neurological disability, deafness, limb amputations, disfiguring scars etc. - see chapter 3). According to a recent Italian study, about 13% of pediatric patients die [3]. For these reasons, it is essential to reach an early diagnosis, in order to initiate proper antibiotic therapy with broad-spectrum antibiotics, such as third-generation cephalosporins or vancomycin, as soon as possible.
The standard technique for the diagnosis of bacterial meningitis is cerebrospinal fluid culture, which is also important in order to determine the susceptibility of the bacterial strain to antibiotics. However, this test has low sensitivity and takes a long time; moreover, administering antibiotics to the patient can alter the result. In recent years, real-time PCR has proved more sensitive than cerebrospinal fluid culture, and its use has increased the diagnosis rate of invasive bacterial meningococcal disease by up to 3 times [4].

Surveillance of invasive diseases due to meningococcus in Italy

Invasive bacterial diseases generally display a high frequency of serious complications and, from the clinical standpoint, the symptoms caused by each etiological agent are poorly specific. It is extremely important to ascertain the etiology of these diseases, not only for therapeutic purposes, but also with a view to prevention (possible prophylaxis for persons in contact with the patient, vaccination strategies).
In Italy, the surveillance of invasive bacterial diseases is coordinated by the Istituto Superiore di Sanità (ISS) [5] and requires that all cases of invasive bacterial diseases caused by *N. meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* be reported. Surveillance covers cases diagnosed in Italy, in people present in the country regardless of their nationality, residence or domicile. The objectives of the surveillance system are to monitor the trends in cases according to pathogen, serogroup, region and age-group, and to evaluate cases of antibiotic resistance and cases of vaccine failure and vaccine replacement.
With regard to invasive meningococcal diseases, surveillance is carried out only in cases of microbiological confirmation that meet the case definitions adopted by the European Commission [6]. This means cases that are confirmed: by isolating *N. meningitidis* from a normally sterile site or from purpuric skin lesions; by detecting the presence of nucleic acid of *N. meningitidis* in a normally sterile site or in purpuric skin lesions; by detecting *N. meningitidis* antigens in the cerebrospinal fluid; or by detecting Gram-negative diplococci in the cerebrospinal fluid on microscopy.
Every case of invasive bacterial disease, as defined according to the above criteria, is reported by the diagnosing physician to the competent Public Health Service through a specific report form. The competent Local Health Agency (*Azienda Sanitaria Locale*: ASL) checks that the data are complete and registers the case on the computerized platform of Invasive Bacterial Diseases (Malattie Batteriche Invasive: MaBI). At the same time, the healthcare professional or facility that has observed and notified the case collects and sends the strain isolated, or the clinical sample in the event of a negative culture test, for laboratory confirmation to a Regional Reference Laboratory and/or to the National Reference Laboratory at the ISS, which integrate the information entered by the ASL into the MaBI platform. The data are then uploaded, together with those of the other European

states, into the European information system, The European Surveillance System (TESSy) [7].

Incidence of invasive meningococcal diseases

Meningococcal disease occurs in both epidemic and endemic forms; the latter displays a seasonal trend, with the majority of cases being reported in the winter months.
Italy has one of the lowest notification rates in Europe [8], probably owing to the under-utilization of real-time PCR methods [4]. While the average European notification rate was between 0.5 and 0.7 cases per 100,000 inhabitants in the period 2011-2016, Italy registered rates between 0.2 and 0.4 cases per 100,000 inhabitants in the same period [9] (Tab. I).
Table II reports the annual trend in the incidence of meningococcal disease in Italy in the period 1996-2017. This reveals an average incidence of 0.35 cases per 100,000 inhabitants (min. 0.22 in 2006 and max. 0.61 in 2005), with an average of about 200 cases per year being reported [10, 11].

Tab. I. Incidence of invasive meningococcal disease per 100,000 inhabitants per year in Europe (2012-2016). Source: ECDC [9].

Country	2012	2013	2014	2015	2016
Austria	0.7	0.7	0.4	0.3	0.4
Belgium	1.1	1.2	0.8	0.9	0.9
Bulgaria	0.1	0.2	0.2	0.1	0.1
Croatia	1.0	0.6	0.8	1.0	0.7
Cyprus	0.7	0.2	0.5	0.5	1.4
Czech Rep.	0.6	0.6	0.4	0.5	0.4
Denmark	1.0	1.0	0.8	0.4	0.7
Estonia	0.5	0.5	0.2	0.3	0.2
Finland	0.6	0.4	0.4	0.4	0.3
France	0.8	0.9	0.6	0.7	0.8
Germany	0.4	0.4	0.3	0.4	0.4
Greece	0.5	0.5	0.5	0.5	0.5
Hungary	0.5	0.5	0.3	0.4	0.5
Iceland	0.3	0.3	0.3	1.2	0.0
Ireland	1.3	1.7	1.7	1.5	1.8
Italy	0.2	0.3	0.3	0.3	0.4
Latvia	0.2	0.3	0.3	0.5	0.2
Lithuania	1.8	2.6	1.8	1.9	2.4
Luxemburg	0.6	0.6	0.5	0.2	0.2
Malta	0.7	2.8	3.1	1.2	1.4
Netherlands	0.7	0.6	0.5	0.5	0.9
Norway	0.5	0.5	0.4	0.4	0.5
Poland	0.6	0.7	0.5	0.6	0.4
Portugal	0.7	0.6	0.5	0.6	0.4
Romania	0.4	0.3	0.3	0.3	0.3
Slovakia	0.6	0.3	0.4	0.4	0.4
Slovenia	0.4	0.5	0.4	0.8	0.3
Spain	0.7	0.6	0.3	0.5	0.6
Sweden	1.1	0.8	0.5	0.5	0.6
United Kingdom	1.4	1.3	1.2	1.4	1.3
EU/EEA	0.7	0.7	0.5	0.6	0.6

Tab. II. Incidence of invasive meningococcal disease in Italy, by year (1996-2017). Source: MaBi [10, 11].

Year	Incidence per 100,000	Year	Incidence per 100.000
1996	0.45	2007	0.30
1997	0.36	2008	0.30
1998	0.28	2009	0.30
1999	0.42	2010	0.25
2000	0.33	2011	0.25
2001	0.32	2012	0.23
2002	0.38	2013	0.29
2003	0.49	2014	0.27
2004	0.55	2015	0.31
2005	0.61	2016	0.38
2006	0.22	*2017**	0.32
		Average	0.35

* Data not consolidated.

The various Italian regions display considerable differences in incidence rates [10], probably as a result of under-reporting and/or under-diagnosis in some areas of the country (Tab. III). Until 2014, some Italian regions registered higher notification rates (Emilia Romagna, Friuli-Venezia-Giulia, Lombardy, PA Trento, PA Bolzano, Piedmont, Veneto). In 2015, however, owing to the weight of the cases reported in Tuscany, a region in which a meningococcal C epidemic occurred and in which real-time PCR is used systematically for diagnosis, the situation was reversed: the national incidence rate exceeded that of the seven regions that had historically had the highest notification rate, as shown in Table IV [12].
Figure 1 [10] shows that both in the 10-14-year age-group (average of 0.39 cases per 100,000 in the period 2011-2017) and in the 15-24-year age-group (0.54 cases per 100,000), the incidence of invasive meningococcal disease was generally higher than the overall incidence (0.29 cases per 100,000) [10]. This finding is in line with the European data, which indicate that the age-groups with the highest incidence rates in the period 2015-2016 were, in descending order: < 1 year, 1-4 years, 15-24 years, and 10-14 years [9].
It must, however, be pointed out that the notification system has become more sensitive over the years: indeed, failure to identify the causative agent (meningococcus, pneumococcus or *Haemophilus influenzae*) in the case of suspected invasive bacterial disease was 1% in 2016, < 3% in 2015 and < 6% in 2014.

Incidence of invasive meningococcal B diseases

From 2011 to 2017 in Italy, meningococcus B was the serogroup most frequently identified in most years [10], both in adolescents and in all age-groups, although the proportion of meningococcus B generally decreased with increasing age, as shown in Table V. On average, in the period considered (2011-2017), about 36% of cases of invasive bacterial meningococcal disease were caused

Tab. III. Cases and incidence rates (per 100,000 inhabitants) of invasive meningococcal disease in Italy, by region (2011-2017). Source: MaBi [10]).

	2011		2012		2013		2014		2015		2016		2017*	
Region	Cases	Incidence	Cases	Incidence	Cases	Incidence	Cases	Incidence	Cases	Incidence	Cases	Incidence	Cases	Incidence
Abruzzo	3	0.22	2	0.15	0	0.00	1	0.07	4	0.30	3	0.23	3	0.23
Basilicata	0	0.00	0	0.00	1	0.17	1	0.17	1	0.17	2	0.35	1	0.18
Calabria	3	0.15	0	0.00	1	0.05	1	0.05	1	0.05	3	0.15	0	0.00
Campania	12	0.21	16	0.28	10	0.17	15	0.26	11	0.19	33	0.56	21	0.36
ER	17	0.38	15	0.35	15	0.34	16	0.36	14	0.31	18	0.40	25	0.56
FVG	2	0.16	2	0.16	3	0.25	0	0.00	2	0.16	2	0.16	1	0.08
Lazio	10	0.17	8	0.15	16	0.29	13	0.22	16	0.27	22	0.37	21	0.36
Liguria	0	0.00	0	0.00	0	0.00	1	0.06	2	0.13	5	0.32	10	0.64
Lombardy	30	0.30	34	0.35	42	0.43	45	0.45	34	0.34	46	0.46	30	0.30
Marche	1	0.06	1	0.06	8	0.52	0	0.00	2	0.13	8	0.52	3	0.20
Molise	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.32
PA BZ	5	0.98	4	0.79	3	0.59	3	0.58	5	0.96	1	0.19	5	0.95
PA TN	1	0.19	2	0.38	4	0.75	2	0.37	3	0.56	1	0.19	0	0.00
Piedmont	17	0.38	10	0.23	13	0.30	10	0.23	9	0.20	15	0.34	14	0.32
Puglia	1	0.02	2	0.05	19	0.47	9	0.22	12	0.29	5	0.12	8	0.20
Sardinia	2	0.12	4	0.24	1	0.06	3	0.18	4	0.24	5	0.30	4	0.24
Sicily	11	0.22	3	0.06	6	0.12	11	0.22	13	0.26	8	0.16	9	0.18
Tuscany	12	0.32	18	0.49	11	0.30	16	0.43	38	1.01	41	1.09	17	0.45
Umbria	2	0.22	3	0.34	4	0.45	1	0.11	4	0.45	0	0.00	4	0.45
V. Aosta	1	0.78	0	0.00	0	0.00	1	0.78	2	1.56	1	0.79	0	0.00
Veneto	22	0.45	13	0.27	15	0.31	15	0.30	12	0.24	13	0.26	19	0.39
TOTAL	**152**	**0.25**	**137**	**0.23**	**172**	**0.29**	**164**	**0.27**	**189**	**0.31**	**232**	**0.38**	**196**	**0.32**

* Data not consolidated.

Tab. IV. Incidence of invasive meningococcal disease in the 0-4-year age-group and in the general population, in Italy and in some Regions (2008 and 2016) [12].

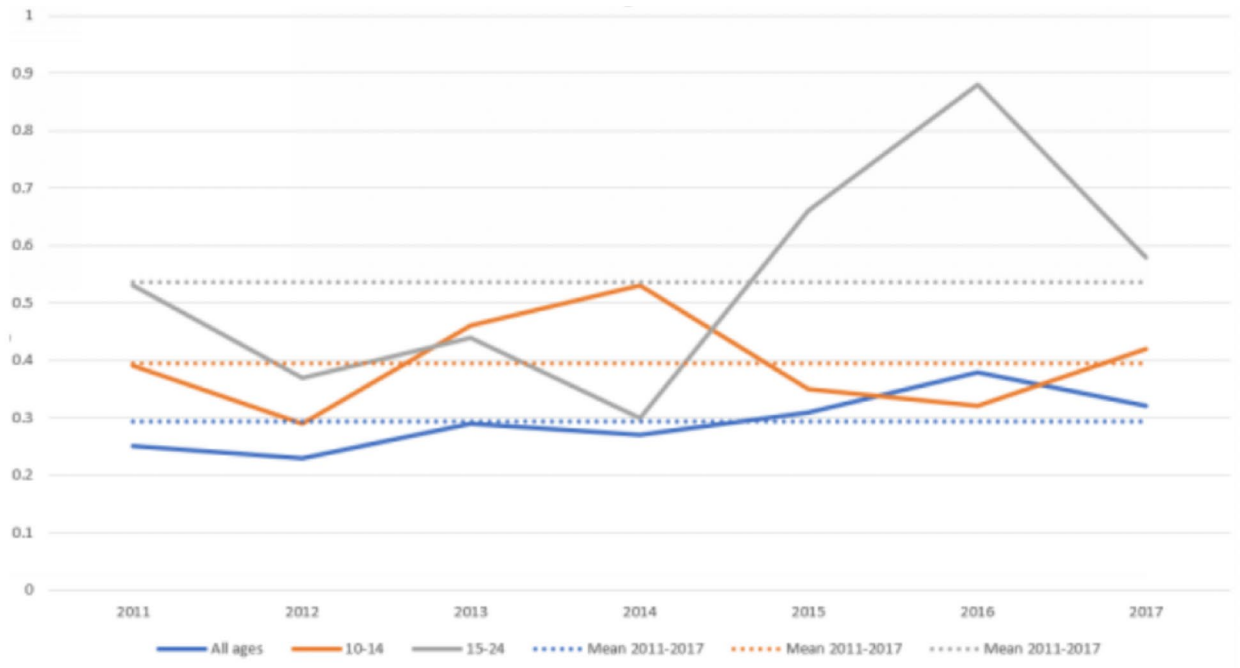
	2008 0-4 years	2016 0-4 years	2008 General population	2016 General population
Meningococcus	Incidence per 100,000		Incidence per 100,000	
Italy	1.64	1.83	0.30	0.38
Emilia Romagna, Friuli-Venezia-Giulia, Lombardy, PA Trento, PA Bolzano, Piedmont, Veneto	2.34	1.7	0.44	0.37
Meningococcus B	Incidence per 100,000		Incidence per 100,000	
Italy	0.96	0.78	0.13	0.11
Emilia Romagna, Friuli-Venezia-Giulia, Lombardy, PA Trento, PA Bolzano, Piedmont, Veneto	1.67	1.07	0.20	0.15
Meningococcus C	Incidence per 100,000		Incidence per 100,000	
Italy	0.32	0.31	0.09	0.13
Emilia Romagna, Friuli-Venezia-Giulia, Lombardy, PA Trento, PA Bolzano, Piedmont, Veneto	0.42	0.18	0.15	0.11

by serogroup B, which was responsible for about 62 cases per year in the general population, three of which in the 10-14-year age-group and 11 in the 15-24-year age-group. In the same period, the average percentage of meningococcal B cases, out of the total cases of invasive bacterial meningococcal disease, was similar in the general population and in the 15-24-year age-group (about 32%), while in the 10-14-year age-group it was lower (about 28%). The European data generally reported higher percentages of cases attributable to meningococcus B, especially in the age-groups under 25 years, in which this serogroup was responsible for more than 50% of cases in both 2015 and 2016 [9].

The period 2015-2016 in Italy saw a reversal of the trend in meningococcal diseases in favor of meningococcus C; this was probably due to the cases recorded during the meningococcal C epidemic in Tuscany, a region in which real-time PCR is systematically used for diagnosis [13]. Indeed, this turnaround did not occur elsewhere in Europe, according to ECDC data [9]. In 2017 in Italy, the trend again reversed in favor of the B strain.

Recent years have seen an increase in the percentage of cases of meningococcal disease attributed to other serogroups, particularly W and Y, both in the general population and among adolescents, and today about 17% of *N. meningitidis* cases in the general population are caused

Fig. 1. Rate of incidence (per 100,000 inhabitants) of invasive meningococcal disease by age-group (2011-2017) [10].



Tab. V. Number and percentage of cases of invasive meningococcal disease (including non-typed meningococcal cases), by serogroup and year (2007-2017) in all age-groups and in the 10-14 and 15-24 age-groups [10].

	All age-groups					10-14 years					15-24 years				
	B	C	Others	Non-typed	Total	B	C	Others	Non-typed	Total	B	C	Others	Non-typed	Total
2011	76 (50%)	20 (13%)	21 (14%)	35 (23%)	152	4 (37%)	0 (0%)	4 (37%)	3 (27%)	11	16 (50%)	5 (16%)	2 (6%)	9 (28%)	32
2012	55 (40%)	32 (23%)	20 (15%)	30 (22%)	137	3 (38%)	2 (25%)	2 (25%)	1 (12%)	8	8 (36%)	7 (32%)	3 (14%)	4 (18%)	22
2013	56 (32%)	36 (21%)	24 (14%)	57 (33%)	173	2 (16%)	1 (8%)	5 (39%)	5 (38%)	13	11 (42%)	3 (11%)	3 (11%)	9 (35%)	26
2014	55 (33%)	36 (22%)	24 (15%)	49 (30%)	164	4 (27%)	3 (20%)	2 (13%)	6 (40%)	15	3 (17%)	5 (28%)	5 (28%)	5 (28%)	18
2015	49 (26%)	64 (34%)	30 (16%)	45 (24%)	188	3 (30%)	3 (30%)	3 (30%)	1 (10%)	10	8 (20%)	17 (43%)	6 (15%)	8 (21%)	39
2016	67 (29%)	80 (35%)	40 (17%)	44 (19%)	231	1 (10%)	2 (20%)	7 (70%)	0 (0%)	10	14 (26%)	17 (32%)	9 (17%)	13 (25%)	53
2017	74 (38%)	54 (28%)	47 (24%)	19 (10%)	194	4 (37%)	3 (27%)	1 (9%)	3 (27%)	11	17 (50%)	5 (15%)	11 (32%)	1 (3%)	34
Average	**62 (36%)**	**46 (25%)**	**30 (16%)**	**39 (23%)**	177	**3 (28%)**	**2 (19%)**	**3 (32%)**	**3 (22%)**	11	**11 (32%)**	**8 (27%)**	**6 (15%)**	**8 (26%)**	32

by non-B-non-C strains. A similar pattern has been observed in other European countries [9].

Figure 2 reports the incidence rates of meningococcal B invasive bacterial disease in Italy by age-group. No significant differences in incidence are seen between the general population and the 10-14-year age-group (0.11 cases per 100,000). This can be explained by the fact that the incidence in the general population is the average of very high incidence rates in very young age-groups and lower incidence rates in the elderly. It is also important to consider the high percentage of cases attributed to other serogroups in this age-group. The incidence of invasive bacterial meningococcal B disease in subjects aged 15-24 years is higher (0.18 cases per 100,000).

If, however, we add to the incidence of invasive meningococcal disease B a proportion of non-typed cases equal to the percentage of B cases among those typed, we obtain rates of 0.12 cases per 100,000 inhabitants in the general population and in the 10-14-year age-group, and of 0.21 in the 15-24-year age-group. Finally, if we apply a corrective factor of 3.28 [4] to offset the underestimation due to diagnosis by means of culture methods, we

obtain incidence rates of 0.40 cases per 100,000 inhabitants in the general population, 0.41 in the 10-14-year age-group and 0.69 in the 15-24-year age-group.

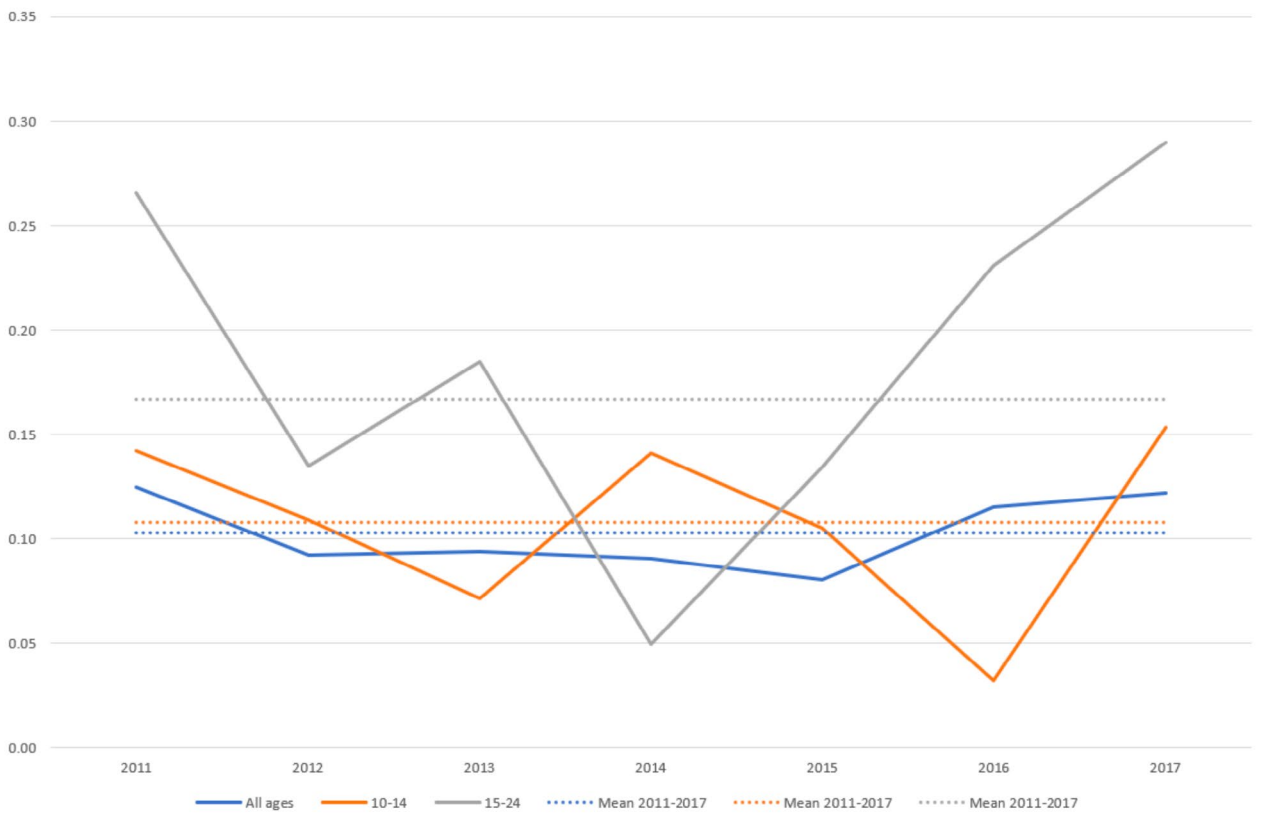
Healthy carriers and risk factors

Healthy carriers are the main source of the disease; indeed, secondary cases due to contagion from a sick individual are very few.
In this regard, it should be borne in mind that the highest prevalence of healthy carriers is seen in adolescents and young adults, with a peak around the age of 20 years [1].
A very recent meta-analysis reports that the overall prevalence of carriers in Europe varies from one country to another, ranging from 5.3% in Italians aged 14-21 years to 61.9% among university students in the UK. In most European countries, the main serogroups are B, Y and "other type". Moreover, subjects aged 18-24 years are more frequently carriers than 11-17-year-olds, and the serogroups most commonly found in this older age-group are of groups B (5.0%, 95% CI 3.0% to 7.5%), Y (3.9%, 95% CI from 1.3% to 7.8%) and "others" (6.4%, 95% CI from 3.1% to 10.8%) [14].
As healthy carriers are a major source of infection for the population, it is not surprising that meningococcal B epidemics are described among adolescents and young people, particularly in settings of intense social aggregation (schools, universities), both in Italy and internationally [15]. In Italy, for example, seven cases of meningitis due to *N. meningitidis* type B were reported in Sardinia at the beginning of 2018; these were caused by a particularly virulent strain and occurred in subjects who had attended a discotheque [16].

Conclusions

Italy has one of the lowest rates of notification of meningococcal diseases in Europe, and displays marked differences in incidence among its various regions. These data, however, are underestimated, mainly as a result of the diagnostic techniques used.
Meningococcus B is the serogroup most frequently identified by the Invasive Bacterial Disease Surveillance System and is responsible for approximately 62 cases per year in the general population (36%), three of which in the 10-14-year age-group (28%) and 11 in the 15-24-year age-group (32%). Given the underestimation in diagnoses, however, the real incidence is probably about 3 times higher than the official statistics. Moreover, although the incidence of the disease is not particularly high, it should be emphasized that it is a serious and often lethal pathology. In addition, as a high proportion of adolescents are healthy carriers of the bacterium, they are a source of contagion of others, especially in settings of social aggregation, as is highlighted by the epidemics that have occurred both in Italy and elsewhere.

Fig. 2. Incidence (per 100,000 inhabitants) of invasive meningococcal B disease by age-group.



References

[1] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(12):853-61. https://doi.org/10.1016/S1473-3099(10)70251-6

[2] Terranova L, Principi N, Bianchini S, Di Pietro G, Umbrello G, Madini B, Esposito S. Neisseria meningitidis serogroup B carriage by adolescents and young adults living in Milan, Italy: prevalence of strains potentially covered by the presently available meningococcal B vaccines. Hum Vaccines Immunother 2018;14(5):1070-4. https://doi.org/10.1080/21645515.2018.1450121

[3] Azzari C, Canessa C, Lippi F, Moriondo M, Indolfi G, Nieddu F, Martini M, de Martino M, Castiglia P, Baldo V, Resti M; Italian Group for the Study of Invasive Bacterial Disease. Distribution of invasive meningococcal B disease in Italian pediatric population: Implications for vaccination timing. Vaccine 2014;32(10):1187-91. https://doi.org/10.1016/j.vaccine.2013.09.055.

[4] Azzari C, Nieddu F, Moriondo M, Indolfi G, Canessa C, Ricci S, Bianchi L, Serranti D, Poggi GM, Resti M. Underestimation of invasive meningococcal disease in Italy. Emerg Infect Dis 2016;22(3):469-75. https://doi.org/10.3201/eid2203.150928

[5] Istituto Superiore di Sanità (ISS). Protocollo per la sorveglianza nazionale delle malattie invasive da meningococco, pneumococco ed emofilo e delle meningiti batteriche in Italia. 2017. Available at: http://old.iss.it/binary/mabi/cont/Protocollo_MIB06102017.pdf

[6] Gazzetta ufficiale dell'Unione Europea. Decisione di esecuzione della commissione dell'8 agosto 2012 recante modifica della decisione 2002/253/CE che stabilisce la definizione dei casi ai fini della dichiarazione delle malattie trasmissibili alla rete di sorveglianza comunitaria istituita ai sensi della decisione n. 2119/98/CE del Parlamento europeo e del Consiglio. Available at: http://eur-lex.europa.eu/legal-content/IT/TXT/PDF/?uri=CELEX:32012D0506&from=IT

[7] European Centre for Disease Prevention and Control (ECDC). The European Surveillance System (TESSy) [internet, cited 2017 Dec 7]. Available at: https://ecdc.europa.eu/en/publications-data/european-surveillance system-tessy

[8] European Centre for Disease Prevention and Control (ECDC). Invasive meningococcal disease - Annual Epidemiological Report for 2015. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-meningococcal-disease.pdf

[9] European Centre for Disease Prevention and Control (ECDC). Invasive meningococcal disease - Annual Epidemiological Report for 2016. Available at: https://ecdc.europa.eu/en/publications-data/invasive-meningococcal-disease-annual-epidemiological-report-2016

[10] Istituto Superiore di Sanità (ISS). Dati di sorveglianza delle malattie batteriche invasive aggiornati al 19 marzo 2018. Available at: http://old.iss.it/binary/mabi/cont/InterimReport2017.pdf

[11] Commissione Europea. European Core Health Indicators (ECHI). Available at: https://ec.europa.eu/health/communicable_diseases/indicators_it

[12] Istituto Superiore di Sanità (ISS). Dati di sorveglianza delle malattie batteriche invasive aggiornati al 3 aprile 2017. Available at: http://www.iss.it/binary/mabi/cont/Report_MBI_20170403_finale.pdf

[13] Stefanelli P, Miglietta A, Pezzotti P, Fazio C, Neri A, Vacca P, Voller F, D'Ancona FP, Guerra R, Iannazzo S, Pompa MG, Rezza G. Increased incidence of invasive meningococcal disease of serogroup C/clonal complex 11, Tuscany, Italy, 2015 to 2016. Eurosurveillance 2016;21(12). https://doi.org/10.2807/1560-7917.ES.2016.21.12.30176

[14] Peterson ME, Li Y, Shanks H, Mile R, Nair H, Kyaw MH; Meningococcal Carriage Group. Serogroup-specific meningococcal carriage by age group: a systematic review and meta-analysis. BMJ Open 2019;9(4):e024343. https://doi.org/10.1136/bmjopen-2018-024343

[15] National Foundation for Infectious Diseases. Meningococcal serogroup B cases and outbreaks on US college campuses. Available at: http://www.nfid.org/idinfo/meningococcal/meningococcal-b-college-outbreaks.html

[16] Stefanelli P, Fazio C, Vacca P, Palmieri A, Ambrosio L, Neri A, Piana A, Castiglia P, Argiolas F, Santus S, Masala L, Steri G, Riccardo F, Iannazzo S, Maraglino FP, D'Amario C, Rezza G. An outbreak of severe invasive meningococcal disease due to a capsular switched Neisseria meningitidis hypervirulent strain B:cc11. Clin Microbiol Infect 2019;25(1):111.e1-111.e4. https://doi.org/10.1016/j.cmi.2018.07.014

Chapter 3

The disease burden and sequelae of meningococcal disease

F. ZANGRILLO, D. AMICIZIA, F. MARCHINI, E. LECINI, M. IOVINE, P.L. LAI, D. PANATTO
Department of Health Sciences, University of Genoa, Italy

Introduction

Neisseria meningitis is an aerobic, Gram-negative bacterium that exclusively infects the human species and is the leading cause of invasive bacterial disease in the world [1]. Transmission of the micro-organism occurs via the air, mainly through direct contact or respiratory secretions. The micro-organism usually inhabits the nasopharyngeal mucosa, where it is among the commensal bacteria. Indeed, many people are asymptomatic carriers of meningococcus [2, 3]. Only occasionally does it cause invasive disease, and the greatest risk being associated with the first episode of infection [4, 5].
The incidence of invasive meningococcal disease varies greatly according to the geographical area, weather and age [6]. Of the 13 serogroups currently known, only 6 are able to cause invasive disease (A, B, C, W-135, Y and X) [5, 6], and the distribution of serogroups varies from one geographical area to another [6-8]. Pathogenic meningococci are generally surrounded by a polysaccharide capsule, which is the main virulence factor of the pathogen and is responsible for its complex antigenic variability [7-9].
Although the disease is rare in developed countries, it imposes a heavy clinical, social and economic burden, owing to its high lethality (8-15%) [9-12] (in the event of sepsis, the lethality rate can reach 40% [9]) and the large number of survivors (up to 60%) who suffer transient and/or permanent sequelae [10]. Furthermore, many survivors have multiple permanent sequelae, such as amputations, mental retardation, deafness, motor impairments and speech disorders, that impact heavily on their quality of life and that of their family members [10, 11].
This chapter deals with the burden of meningococcal disease, its acute phase, its lethality and its complications. We also evaluate its social impact, chiefly with regard to severe complications, which also engender considerable costs for various sectors of the state (e.g. special education, disability pensions, invalidity benefits and accompaniment allowances) and for society as a whole (loss of productivity of both patient and caregiver).

Clinical aspects of invasive meningococcal disease (outcomes, acute phase, diagnosis and therapy)

Invasive meningococcal disease displays a rapid evolution and is sometimes difficult to diagnose. The initial symptoms are non-specific and often mimic those of influenza, such as fever, sore throat and general malaise [9, 13].
The incubation period of the disease ranges from 1 to 14 days [13] and the clinical picture is variable, the most common being the meningitis that follows hematogenous dissemination of the meningococcus. The specific symptoms of meningitis appear, on average, 12-15 hours after the onset of the disease; later symptoms, such as loss of consciousness, convulsions and delirium, occur after about 15 hours in infants and 24 hours in older children. A study by Thompson et al. revealed that some early symptoms in children and adolescents appear even within the first 12 hours; these are leg pains, cold hands and abnormal skin color [14].
The clinical presentation of meningococcal meningitis is similar to that of forms of purulent meningitis: rapid-onset fever, headache, stiffness of the neck, nausea, vomiting, photophobia, and alteration of the mental state. Meningococcal sepsis (or meningococcemia) occurs in 5-20% of patients and is characterized by rapid-onset fever, petechiae, purpuric rash, often associated to the typical signs of shock, with hypotension, acute adrenal hemorrhage and multiorgan failure [9]. Less frequent clinical manifestations are pneumonia (5-15%), arthritis (2%), otitis media (1%) and epiglottitis (< 1%) [9].
The latest report by the Invasive Bacterial Disease Surveillance System in Italy [15] stated that, in the period 2015-2017, the most frequent clinical presentation of meningococcal disease was meningitis (39%-45% of cases), followed by sepsis/bacteremia not associated to any other clinical picture (25%-30% of cases) and by meningitis associated to sepsis/bacteremia (23%-30% of cases). Other clinical manifestations were rare [15]. When divided by age-class, the data revealed that the most frequent clinical picture in adolescents was meningitis (40% in 2015 and 56% in 2016), followed by sepsis/bacteremia and meningitis and sepsis. The report did not describe the clinical picture associated to the various serogroups [15]. Similarly, the association between the acute-phase clinical presentation and the probability of developing sequelae was not reported. To date, no study reporting this information has been published.
Only a few international studies have reported clinical presentations subdivided by age-class and serogroup, and have also considered the length of hospitalization. A study by Lecocq et al. estimated that the most frequent clinical presentation in children aged 5-14 years was meningitis (46.9%), followed by sepsis and meningitis

(35.3%) and sepsis (16.3%); in adolescents aged from 15 to 19 years, meningitis was present in 56.5% of cases, sepsis and meningitis was diagnosed in 31.3% of cases, and sepsis was documented in 11.8% of cases [16].
Rivero-Calle et al. analyzed surveillance system data on children/adolescents aged less than 15 years. These authors reported that 38% of these patients had a clinical presentation corresponding to sepsis and meningitis, while 37.1% had sepsis, and 24.9% had meningitis. From their study, it emerged that the mean duration of hospitalization of patients with invasive disease due to serogroup B was 12.4 days, and that most patients required therapy in intensive care for a mean of 4.2 days [17].
A study by Sadarangani et al. examined the association between clinical presentation and death/complications. The highest mortality rate was recorded in adults, especially in those who had presented with septic shock without meningitis (33%), as opposed to those who had presented with meningitis alone (2.2%). The study reported a median hospital stay of 8 days (range 1 day - 9 months). Children suffered a higher rate of complications than adults, especially those children who had presented with septic shock without meningitis in the acute phase (38%) [11].
Viner et al. analyzed 246 cases of invasive meningococcal disease due to serogroup B in children aged from 0 to 16 years. The most frequent clinical manifestation was septicemia (63%), followed by septicemia and sepsis (18%) and meningitis (14%). The authors reported a median duration of hospitalization of 5 days; 29% of patients required admission to the intensive care unit, where they remained for a median of 3 days (range 1-26 days) [18]. Similar results emerged from a study by Wang et al., who analyzed cases of invasive meningococcal B disease in children and adolescents aged less than 18 years. The study reported 41.6% of cases with septicemia, 32.5% with sepsis and meningitis, and 26% with meningitis alone. Admission to intensive care was needed in 41.6% of patients [19].
Stoff et al. conducted a retrospective study of invasive meningococcal disease in the Netherlands between 1999 and 2011 and found that 48% of patients had presented a clinical picture of meningitis. Septic shock (with or without meningitis) was more frequent in children. In their study, the median duration of hospitalization was subdivided by age-group: 0-6 months: 11 days; 6-24 months: 9 days; 2-4 years: 9 days; 5-9 years: 8 days; 10-19 years: 9 days. The proportion of patients hospitalized in the intensive care unit was higher among those aged > 10 years (45%, with a stay of 2-5 days) than among those aged < 10 years. The percentage of admissions to intensive care was 35% in cases caused by serogroup B [20].
In a study of 1654 patients observed over a three-year period (1999-2001), O'Brien J.A. et al. calculated the mean length of hospitalization and the related costs by age-group. On the basis of their clinical presentation, the patients were divided into two groups: those with meningitis alone and those with meningococcemia. The authors recorded a longer mean hospital stay in patients with meningococcemia (9.2 days) than in those with meningitis alone (7.5 days). In patients with meningitis alone, the mean age-related duration was: < 1 year: 8.6 days; 1-10 years: 6.2 days; 11-17 years: 7 days; 18-22 years: 6.8 days; 23-49 years: 8.3 days; ≥ 50 years: 9 days. In those with meningococcemia, the mean duration was: < 1 year: 7.5 days; 1-10 years: 9.3 days; 11-17 years: 10.3 days; 18-22 years: 9.1 days; 23-49 years: 10.2 days; ≥ 50 years: 8.8 days [21].
In general, clinical manifestations of septic shock are associated with greater lethality and a higher probability of suffering temporary and/or permanent sequelae [10, 20].

Risk factors

The risk factors associated with the development of meningococcal disease are related both to the host and to the environment. Host-related factors comprise immunological defects, particularly impairment of the complement cascade, anatomical or functional asplenia, and the presence of chronic diseases. Subjects affected by acquired immunological diseases, such as HIV-positive patients, are also at increased risk. With regard to the environment, the main risk factor is frequentation of crowded enclosed spaces. Moreover, exposure to tobacco smoke, whether active or passive, seems to be a risk factor; indeed, children exposed to passive smoking have a higher risk of contracting invasive meningococcal disease [22]. Finally, it has been observed that previous viral infections of the airways can increase the risk of meningococcal disease [23].
Regarding adolescents and young adults, the risk of invasive disease increases if they attend colleges (being higher among matriculation students [24]) or frequent crowded pubs and bars, owing to the close interpersonal contact [25]. The risk is also increased by intimate kissing, especially if promiscuous, as adolescents and young adults are much more likely to be carriers than subjects of other age-groups [3, 22]. Indeed, adolescents and young adults are considered to be the principal vehicles of meningococcus [20, 26].

Lethality

Although the disease is rare in developed countries, it imposes a heavy clinical, social and economic burden, owing to its high lethality (8-15%) [9-12]; in the event of sepsis, the lethality rate can reach 40% [9]. With regard to Europe, the latest report by the European Centre for Disease Prevention and Control (ECDC) provides data on invasive meningococcal disease in the period 2011-2015. The overall rate of lethality in the period was 9%, while among serogroup B cases, the rate was 8% [12]. The figures for the various age-groups are not reported in detail; the report only indicates that subjects aged ≥65 years have the highest lethality rate, followed by those aged 50-64 years [12].

Similar results emerged from the study by Sadarangani et al. [11], who reported an overall lethality rate of 8.4%. Their study, which was conducted in Canada between 2002 and 2011, analyzed the data by serogroup and subdivided into two age-groups: 0-18 years (children) and > 18 years (adults). The authors recorded a lethality rate of 4.1% in children and 12.5% in adults. When the data were subdivided by serogroup, the lethality rate due to meningococcus B was 4.4% among children and 8.6% among adults [11].
Similarly, the above-mentioned Netherlands study, which was conducted from 1999 to 2011, revealed an overall rate of lethality due to invasive meningococcal B disease of 8%. The authors reported values subdivided by age-group but not by serogroup: 0-6 months: 2%; 6-24 months: 7%; 2-4 years: 5%; 5-9 years: 4%; 10-19 years: 4%; 20-64 years: 8%, and ≥ 65 years: 39% [20].
A review published in 2016 reported that 10-20% of subjects who contracted the disease died. The global lethality rate for meningococcus B was between 5.3 and 12.5%. On subdividing the patients by age-class, the authors reported the following values: 8.1% in infants aged < 1 year; 2.7% in children aged 1-4 years; 16.6% in those aged 5-9 years; 10-19 years: data not available; 20-64 years: 9.5% and ≥ 65 years: 41.3% [25].
A Spanish study published in 2016 evaluated the burden of invasive meningococcal disease in subjects of pediatric age (0-14 years) in the period 2008-2013. The overall rate of lethality was 3.5% (< 1 year: 2.5%; 1-4 years: 4.2%; 5-9 years: 4% and 10-14 years: 3.2%), a lower value than the data published in the literature [17].
Another 2016 study assessed the impact and cost-effectiveness of introducing anti-meningococcus B vaccination for infants in France. The authors took the lethality rates for meningococcus B from the French surveillance system and subdivided these by age-class. The rates reported were: 9.7% in infants aged < 1 year; 10.7% in children aged 1-4 years; 5.7% in those aged 5-14 years; 7.8% in subjects aged 15-24 years; 6.6% in the 25-59-year class and 21.3% in adults aged ≥ 60 years [16].
To date, no data on meningococcus B lethality rates subdivided by age-class in Italy have been published. The only partial data available have been provided by surveillance systems in a few regions, such as Piedmont and Emilia Romagna. In Piedmont, a 2016 report indicated a rate of about 14%, with a mean of 2 deaths per year [27]. In Emilia Romagna, overall lethality due to meningococcal diseases was 9.7%. The lethality rates indicated that serogroup C (15.1%) was more aggressive than serogroup B (8.6%) [28].

The sequelae of meningococcal disease

Invasive meningococcal disease has a particularly heavy impact on health, as a high percentage of survivors, especially children and adolescents, suffer permanent sequelae. Sequelae may be physical, neurological and/or psychological, and may be single or multiple. Survivors may therefore suffer severe impairment of their quality of life, not only in the early period after the acute phase, but for the rest of their lives.
In order to trace scientific articles that would be of use in drawing up the present HTA report, we conducted bibliographic searches by means of the search engine PubMed (www.ncbi.nlm.nih.gov/pubmed). Initially, we used the following research string: (Meningitis OR meningococcal disease) AND adolescent* AND (meningococcus B OR meningococcus type B OR Neisseria meningitidis B OR Neisseria meningitidis type B) AND (complication* OR sequelae) and restricted the search to the period 2000-2018. This choice was prompted by the fact that studies carried out before 2000 reported only global data on sequelae, without indicating the types (physical, neurological, psychological sequelae); they were therefore unsuitable for the present report. Both Italian and international studies were deemed eligible, though international articles were only admitted if published in English; studies carried out in countries with a high incidence of meningitis (e.g. the African meningitis belt) were excluded. As the studies conducted exclusively on adolescents were few and not exhaustive, the search was subsequently broadened to take in all age-classes.
A manual search was then carried out by examining the bibliographies of the papers included in the present overview, in order to bring to light any sources that were not identified through the automatic search. Subsequently, each manuscript was reinserted into the search engine of Google Scholar (https://scholar.google.it/schhp?hl=it), in order to identify articles that cited the studies included. Once duplicates had been eliminated, the titles and abstracts of the articles were evaluated. Subsequently, the full texts were examined.
A total of 27 articles were included in the present overview.
We considered three distinct categories of sequelae (physical, neurological and psychological). First, we examined the systematic reviews; then, we analyzed the results of the single studies deemed suited to the objectives of the present report.

Physical sequelae

Invasive meningococcal disease is associated with numerous physical sequelae. These include: dermatological consequences (skin scars, necrosis, eczema and psoriasis); musculoskeletal consequences/conditions (amputations, limb deformities, arthritis and arthralgia); kidney diseases (acute and chronic renal insufficiency, urinary retention); cardiovascular diseases (Raynaud's phenomenon, venous thrombosis and vasculitis) and other conditions (adrenal insufficiency, anemia, pulmonary diseases, autoimmune diseases, chronic fatigue and cardiorespiratory insufficiency).
The data reported in the published studies are very variable and present a broad range.
In 2018, a systematic review by Olbrich et al. [1] analyzed 31 studies conducted from 2001 to 2016 in high-income countries. The results of the various studies were subdivided according to clinical presentation and, when

possible, were stratified by age. Most of the studies were conducted on children and adolescents and reported the probability of suffering sequelae, regardless of the serogroup involved; only a few stratified cases according to serogroup. The most frequent physical sequelae reported were amputations (up to 8% in children and up to 3% in adolescents/adults) and skin scars (up to 55% in children, 18% in adolescents and 2% in adults). Other physical sequelae were limb deformities, various skin diseases and kidney damage. Sometimes, however, damage to bones and joints emerges several years after the acute phase, especially during adolescence, when subjects undergo a rapid growth spurt [29].

Another review was published in 2016 [25]. The authors stressed the need to modify the approach to evaluating the devastating consequences of invasive meningococcal disease; indeed, they also examined aspects that are frequently underestimated, including the impact on the subject's family and on society. The most frequent physical sequelae recorded were skin scars (6.4-48%) and amputations (0.8-14%), both of which displayed variable percentages according to the patient's age and the severity of the acute phase of the disease. Other physical sequelae, such as arthritis and vasculitis (4.7%), renal dysfunction (2-8.7%) and growth disorders (6-13.1%), were also recorded.

In 2013, Vyse et al. [30] published the results of a review aimed at assessing the impact of invasive meningococcal disease in terms of mortality, complications and long-term sequelae. Highly variable percentages in the probability of suffering sequelae were reported by these authors, too [30].

The single studies deemed suitable for inclusion in the present HTA report on anti-meningococcus B vaccination with Trumenba® in adolescents were examined, described and listed according to their publication date (from the most recent to the least recent).

In Spain, a retrospective multi-center cohort study of the 2008-2013 data from a surveillance system on children under the age of 15 years was conducted. The authors identified 368 patients with laboratory-confirmed invasive meningococcal disease. Serotyping was carried out in 269 cases and detected serogroup B in 95.2% (256/269); 12.9% of the patients suffered at least one sequela. Sequelae were subdivided on the basis of both the clinical presentation of the disease and the age of the subject (< 1 year, 1-4 years, 5-9 years, 10-14 years). The most frequent sequelae were: neurological impairment, neurosensory deafness, physical and cognitive disabilities, chronic headache, focal neurological signs, severe mental retardation and epilepsy. With regard to physical sequelae, the study revealed that, among infants aged < 1 year, the most frequent complications were: severe skin lesions (19%), other skin lesions (9.5%), amputations (14.3%), renal complications (4.8%) and moderate pulmonary hypertension (9.5%). In children aged 1-4 years, the most frequent complications were: severe skin lesions requiring skin grafting (25.9%), moderate skin lesions (11.1%), amputations (22.2%) and renal complications (22.2%). Among those aged 5-9 years, severe skin lesions and renal complications were most frequently recorded (both 12.5%). In the 10-14-year age-class, the most frequent sequelae were amputations (33.3%); the authors observed that amputations were mostly associated with sepsis [17].

A Canadian study conducted by Sadarangani et al. between 2002 and 2011 analyzed clinical data on 868 subjects (48% aged < 18 years; 52% aged ≥ 18 years) hospitalized for invasive meningococcal disease; 55% of cases were due to serogroup B. On considering only the patients with serogroup B infection, the authors found that 19% suffered sequelae: 21.8% of the patients aged < 18 years and 14.6% of the adults. Moreover, in 37% of cases, these sequelae were multiple: 33% in patients aged < 18 years and 42% in adults. On stratifying the types of sequelae by age-group, the authors found that patients aged < 18 years more frequently suffered amputations (7.6%), skin scars (4.3%), renal dysfunction (1.4%) and joint problems (1%). Among subjects aged ≥ 18 years, the most frequent complications were renal dysfunction (3.6%), amputations (3.1%), skin scars (2.4%) and joint problems (1.6%) [11].

Between 1999 and 2000, a British study observed a cohort of adolescents and young adults (aged 16-18 years and 19-22 years; mean age: 19.3 years) affected by invasive meningococcal disease who were evaluated 18-36 months after the acute phase. A total of 202 subjects were recruited (101 cases and 101 sex- and age-matched controls); 84 cases were laboratory-confirmed as meningococcus, 47 (56%) of which as meningococcus B. Meningitis and sepsis were recorded in 39.6% of cases, meningitis alone in 32.7% and septicemia alone in 26.7%. At least one sequela was reported in 57.4% of cases. Regarding physical sequelae, the authors reported that 31% of subjects who suffered sequelae had skin scars, 6.9% had impaired function of the upper limbs and 5.2% had suffered at least one amputation [31].

Stoof et al. [20] conducted a retrospective study on 879 isolates collected by the Dutch sentinel surveillance system between 1999 and 2011. In 99% of the isolates, the serogroup was determined; serogroup B proved to be prevalent (77%). On subdividing the data by age-class, the percentage of cases caused by meningococcus B was about 90% in children aged 0-4 years and about 70% among adolescents. The overall lethality rate was 8%. Among the survivors, 29% had at least one sequela, and complications were seen to be dependent on age and the clinical manifestation in the acute phase. The percentage of patients with sequelae was higher among adults than among children. Sequelae on discharge or in the year following hospitalization were subdivided into: severe (vegetative state, mental retardation, skin necrosis requiring transplantation, amputation, deafness requiring cochlear implant, renal insufficiency, adrenal insufficiency, epilepsy or peripheral paralysis/paresis) and moderate. In the 10-19-year age-class, 24.7% of patients suffered moderate sequelae and 4.5% suffered severe sequelae [20].

An Australian study analyzed cases of invasive meningococcal disease in children aged <18 years between 2000

and 2011, in order to evaluate sequelae following acute disease and their related costs. A total of 109 cases were identified, 102 of which were typed; 70.6% involved serogroup B. Sequelae were documented in 37.6%. Of the patients with sequelae, 75.6% had been infected by meningococcus B. On considering only those patients with sequelae caused by serogroup B, 25.8% had joint and bone problems, 6.4% had suffered amputations, and 32.2% had skin complications (necrosis and scarring) [19].

Data from the system of surveillance of hospital admissions from 2002 to 2011 in Canada were analyzed in a study aimed at assessing the impact of invasive disease caused by serogroup B. A total of 769 cases of invasive disease (356 adults aged ≥ 20 years and 413 children) were analyzed. In all age-groups, the most frequently identified serogroup was serogroup B, accounting for 53.7% of cases (413 cases: 278 children and 135 adults); 24% of patients were aged between 5 and 19 years, 13.6% of whom were adolescents between 15 and 19 years of age. Among the adults, 9% of cases were recorded in subjects aged 20-24 years. Of the 391 survivors, 18.9% had at least one sequela, and 23.3% of those with sequelae had multiple sequelae. Of the 278 children with invasive meningococcal disease caused by serogroup B, 266 survived; among the adults, 125 survived. The authors also stratified sequelae due to meningococcus B on the basis of age. On considering only infants aged < 1 year with sequelae and evaluating only physical sequelae, they found that 15% had suffered amputations, 15% had skin scars and 5% had renal insufficiency. Among children aged 1- 4 years, 26.9% had suffered amputations, 50% had skin scars, and 3.8% had renal insufficiency. In the group of subjects aged between 5 and 19 years, 40% had skin scars. Finally, among the adults (>20 years) 27.7% had suffered amputations, 27.7% had skin scars and 33.3% suffered from renal insufficiency [32].

In the United Kingdom, Viner et al. [18] conducted a case-control study in the period 2008-2010 in order to assess the impact of sequelae in children who survived invasive disease due to meningococcus B. The mean age of the cases was 6.5 years. With regard to physical sequelae, the authors reported that 1% of patients had suffered amputations.

Gottfredsson et al. conducted two studies in Iceland: one retrospective (1975-2004) and one follow-up study (January 2007-April 2008). During the follow-up study, 120 survivors from invasive meningococcal disease were interviewed, 70 of whom had been infected by meningococcus B. Considering only the subjects affected by meningococcus B, their mean age at the time of the interview was 29.1 years (standard deviation ± 13.3), while their mean age at the time of the acute phase had been 9.3 years (standard deviation ± 11.7). Regarding physical sequelae, 21.4% of the subjects reported skin complications, and 2.8% arthritis [33].

In 2010, Buysse MP et al. published the results of a follow-up study (mean follow-up period: 9.8 years; range: 3.7-17.4 years) conducted in the Netherlands on survivors from invasive meningococcal disease aged between 1 month and 18 years, the objective being to evaluate the association between long-term sequelae (physical and/or psychological) and quality-of-life impairment. The authors subdivided the subjects into 4 categories: those with major physical sequelae (extensive scarring and/or limb amputations); those with moderate neurological damage (hearing loss, chronic headache, focal neurological damage); those with behavioral problems, and those with an intelligence quotient (IQ) < 85. The study involved 120 subjects (79% of whom had been affected by *Neisseria meningitidis* B). Overall, 73/120 (61%) suffered from one or more sequelae; of these, 47 (64.4%) had major sequelae subdivided into: 13 (27.6%) major physical sequelae; 19 (40.4%) moderate neurological problems; 7 (14.9%) severe behavioral problems, and 8 (17%) IQ < 85. Moreover, 26 (35%) of the 73 subjects with sequelae had multiple sequelae. The following combinations were reported: 8 subjects with major physical sequelae and neurological damage (8/26 = 30.8%), 2 with major physical sequelae and behavioral problems (2/26 = 7.7%), 4 with major physical sequelae and IQ < 85 (4/26 = 15.4%), 4 with neurological damage and behavioral problems (4/26 = 15.4%), 5 with neurological damage and IQ < 85 (5/26 = 19.2%), 2 with major physical sequelae, neurological damage and behavioral problems (2/26 = 7.7%), and 1 with neurological damage, behavioral problems and IQ < 85 (1/26 = 3.9%). One patient with chronic renal insufficiency had also suffered the amputation of a leg, had extensive scarring and focal neurological signs. A subject with severe mental retardation (IQ < 70) also had extensive scarring and amputations; another had major scarring and a difference of 13 cm between the length of one leg and the other. Overall, 48% had skin scars, 8% had suffered amputations, 6% presented a discrepancy in the growth of the legs, 35% had neurological damage (mental retardation with epilepsy, hearing loss, chronic headache, focal neurological signs) and 13.3% had suffered acute kidney damage, 6% of whom had chronic renal impairment [10].

Vermunt et al. conducted a study in the Netherlands to evaluate the psychological outcomes of 179 patients (aged 8-17 years) affected by invasive meningococcal disease. These authors also assessed the association between the gravity of the patients' physical sequelae and their psychosocial problems. The most frequent physical sequelae were: skin scarring (52% of subjects aged 8-11 years and 50% of those aged 12-17 years), amputations (7% of children aged 8-11 years and 8% of adolescents aged 12-17 years) and other orthopedic complications (7% in children) [34].

An American study conducted by Kaplan et al. [35] collected data from 10 hospitals between 2001 and 2005, and focused on cases of invasive meningococcal disease in pediatric patients. The authors identified 159 cases, 44% of which were caused by meningococcus serogroup B. The study described the distribution of the disease by age-class: 25.7% of patients were infants aged < 12 months; 13.8% were children aged 12-24 months; 24.5% were children aged 2-4 years, and 35.8% were children/adolescents from 5 to 19 years of age. The study re-

ported that 91.8% of the subjects survived (146/159) and that the most common physical sequelae were scarring (9.5%) and amputations (1.3%). However, the authors also stressed the fact that sequelae involving the musculoskeletal apparatus and renal system could emerge even several years after the acute phase [35].
Table I shows the probability of suffering physical sequelae according to the results of the studies included in the present overview.

Neurological sequelae

The neurological sequelae caused by invasive meningococcal disease are numerous and include: impairment of the sensory system (deafness, blindness, cranial nerve paralysis, exotropia, tinnitus, sluggishness, paresthesia, sensitivity to light); motor deficits (paralysis, cerebral paralysis, muscle weakness, monoparesis/hemiparesis, spasticity, mobility problems, severe neuromotor deficit, coordination deficit); communication problems (aphasia, stuttering, difficulty in language and communication); cognitive problems (severe mental retardation with intelligence quotient (IQ) < 70, moderate mental retardation with IQ 70-85, learning difficulties, cognitive deficit); altered cerebral activity (epileptic and non-epileptic fits, chronic headache, migraine, vegetative state, dizziness); other neurological disorders (cranial nerve damage, hydrocephalus, fever convulsions, radiculopathy, subdural empyema, multi-cerebral infarction, retarded development, sleep disorders, lethargy).
The published studies dealing with neurological sequelae report very varied data.
In their systematic review, Olbrich et al. reported that deafness was the most frequent neurological sequela (up to 19% in infants, 13% in children, 12% in adolescents and 8% in adults). They also considered other sequelae, such as convulsions, cognitive impairment, motor deficit and visual deficit [1].
The review by Martinon-Torres et al. [25] listed memory deficits, unilateral and bilateral deafness, convulsions and chronic pain among the neurological sequelae. The rates reported by the authors ranged between 2% and 9.3% for deafness, 1.4-13.9% for convulsions, 2.9-7.5% for cognitive impairment, 1.2-8.1% for neuromotor disability, and 2.4-10.1% for neurological damage in children and 13.5% in adults. Moreover, epilepsy was diagnosed in 2% of the children who survived invasive disease due to serogroup B. Many subjects with sequelae also suffered moderate or severe cognitive impairment associated with difficulty in concentration; this was reflected in poor scholastic performance, with repercussions in adulthood. In this regard, a Danish study revealed that survivors from meningococcal meningitis were less likely to complete high school (only 11%) than the general population and to become financially independent in adulthood [36].
On analyzing the probability of suffering neurological sequelae, Vyse et al. [30] also found that the data were very variable and covered a broad range of probability.
In a British study of survivors from invasive serogroup B meningococcal disease aged < 16 years (period of observation: November 2012-May 2013) Kennedy et al. reported that 20.2% of subjects had suffered hearing loss, 9.2% had convulsions and 5.5% memory impairment [37].
The Spanish study conducted by Rivero-Calle et al. is one of the few that examined the distribution of sequelae according to age. On considering only survivors with sequelae, the authors found that neurological sequelae had struck 57.1% of infants aged < 1 year, 29.6% of children aged 1-4 years, 25% of those between the ages of 5 and 9 years, and 33% of those aged 10-14 years. They also

Tab. I. Principal physical sequelae and probabilities.

Type of sequelae	(Ref.)	Age	Probability (%)	Note
Skin scars	Buysse [10]	Range: 1 month-18 years; mean age: 3.1 years; median age on follow-up 14.5 years (range 5.3 -31.1)	48%	79% of subjects were affected by serogroup B invasive disease
	Sadarangani [11]	< 18 years ≥ 18 years	4.3% 2.4%	55% of cases were caused by serogroup B
	Wang [19]	< 18 years	32.2%	70.6% of cases were due to serogroup B; 37.6% of subjects had sequelae; 75.6% of patients with sequelae were affected by meningococcus B
	Kaplan [35]	0-19 years	9.5%	44% of cases were due to serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	9.5% 11.1% - -	95.2% of cases were due to serogroup B
	Bettinger [32]	< 1 year 1-4 years 5-19 years > 20 years	15% 50% 40% 27.7%	Only sequelae due to meningococcus B
	Borg [31]	Mean age 19.3 years	31%	56% of cases were caused by meningococcus B
	Vermut [34]	8-11 years 12-17 years	52% 50%	

(continues)

Tab. I. Principal physical sequelae and probabilities (*follows*).

Type of sequelae	(Ref.)	Age	Probability (%)	Notes
Skin grafts	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	19% 25.9% 12.5% -	95.2% of cases were due to serogroup B
Amputations	Buysse [10]	Range: 1 month-18 years; mean age: 3.1 years; median age on follow-up 14.5 years (range 5.3 -31.1)	8%	79% of subjects were affected by invasive disease due to serogroup B
	Sadarangani [11]	< 18 years ≥ 18 years	7.6% 3.1%	55% of cases were due to serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	14.3% 22.2% - 33.3%	95.2% of cases were due to serogroup B.
	Viner [18]	0-16 years (mean age 6.5%)	1%	The authors analyzed only sequelae in survivors from invasive disease due to meningococcus B
	Kaplan [35]	0-19 years	1.3%	44% of cases were due to serogroup B
	Wang [19]	< 18 years	6.4%	70.6% of cases were due to serogroup B; 37.6% of subjects had sequelae; 75.6% of those with sequelae were affected by meningococcus B
	Bettinger [32]	< 1 year 1-4 years 5-19 years > 20 years	15% 26.9% - 27.7%	Only sequelae due to meningococcus B
	Borg [31]	Mean age 19.3 years	5.2%	56% of cases were due to meningococcus B
	Vermut [34]	8-11 years 12-17 years	7% 8%	
Limb deformity	Buysse [10]	Range: 1 month-18 years; mean age: 3.1 years; median age on follow-up 14.5 years (range 5.3 -31.1)	6%	79% of subjects were affected by invasive disease due to serogroup B
	Borg [31]	Mean age 19.3 years	6.9%	56% of cases were due to meningococcus B
Renal insufficiency	Buysse [10]	Range: 1 mese-18 years; mean age: 3.1 years; median age on follow-up 14.5 years (range 5.3 -31.1)	13.3% of patients reported acute kidney damage. 6% of whom had chronic kidney damage	79% of subjects were affected by invasive disease due to serogroup B
	Sadarangani [11]	< 18 years ≥ 18 years	1.4% 3.6%	55% of cases were due to serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	4.8% 22.2% 12.5% -	95.2% of cases were due to serogroup B
	Bettinger [32]	< 1 year 1-4 years 5-19 > 20 years	5% 3.8% - 33.3%	Only sequelae due to meningococcus B
Joint and bone problems	Sadarangani [11]	< 18 years ≥ 18 years	1.0% 1.6%	Il 55% of cases were due to serogroup B
	Wang [19]	< 18 years	25.8%	70.6% of cases were due to serogroup B; 37.6% of subjects had sequelae; 75.6% of those with sequelae were affected by meningococcus B
	Gottfredsson [33]	Mean age at time of acute phase: 9.3 years; age at time of interview: 29.1 years	2.8%	Sequelae due to meningococcus B

found an association between the onset of neurological sequelae and the acute clinical presentation of meningitis [17].
In their study conducted between 2002 and 2011 on 868 subjects (48% aged < 18 years and 52% aged ≥ 18 years) who had had meningococcal disease (55% of cases due to serogroup B), Sadarangani et al. found that 21% of those aged <18 years and 15.4% of those aged ≥ 18 years had neurological sequelae, and that some had multiple sequelae. On considering only subjects with sequelae, the authors observed that among those aged < 18 years, 7.4% had suffered deafness, 4.1% motor deficit, 0.7% convulsions, 2.1% visual defects, 0.2% cognitive impairment, and 1.4% undefined neurological problems. Among the subjects aged ≥ 18 years, 3.3% presented deafness, 0.9% motor deficit, 1.3% convulsions, 3.6% visual defects, 0.9% cognitive impairment, and 2.2% undefined neurological problems [11].
On analyzing patients with sequelae, Borg et al. found that 29.3% suffered from chronic dizziness, 22.4% had language problems, 20.7% hearing impairment, and 3.5% convulsions [31].
Wang et al. focused only on subjects with sequelae due to meningococcus B. Their study revealed that neurological sequelae appeared in 25.8% of cases, and that deafness, convulsions/epilepsy, chronic lethargy and headache were each present in 12.9% of cases [19].
Bettinger et al. analyzed sequelae on the basis of age. On considering only subjects with sequelae, and on analyzing only sequelae of a neurological nature, they observed that 45% of infants aged <1 year presented deafness, 40% had convulsions, and 20% had undefined neurological complications. In children aged between 1 and 4 years, 34.6% presented deafness, 7.7% had convulsions, and 11.5% had other undefined neurological complications. In subjects between the ages of 5 and 19 years, 30% presented deafness and 20% had other undefined neurological complications [32].
The outcomes of children and adolescents (from 1 month to 13 years) affected by invasive meningococcal disease in the United Kingdom between 2008 and 2010 were investigated in a case-control study by Viner et al. The study involved 245 survivors from meningococcal disease (mean age: 6.5 years) and 328 control subjects (mean age: 6.9 years). The authors analyzed physical, psychological, neuro-cognitive and educational sequelae. With regard to neurological sequelae, severe bilateral hearing loss was documented in 2% of cases, and moderate bilateral hearing loss in 5%; visual defects were observed in less than 1% of cases; 2% had had convulsions, and 4% communication problems. In the cognitive sphere, it emerged that survivors from meningococcal disease had lower IQ scores. In their assessment of memory, the authors considered various indicators: short-term verbal memory (100.4 in cases vs 106.5 in controls), long-term verbal memory (102.6 vs 106.9), procedural memory (97.8 vs 104.7), planning and organization (16.4 vs 18.5) and long-term visual memory (8.2 vs 10.1). The authors concluded that 30% of the cases presented memory problems, as against 17% of controls. Moreover, although severe mental retardation was rare, 11% of the cases displayed low or borderline IQ (< 85); these subjects needed educational support [18].
In a follow-up study (January 2007-April 2008), Gottfredsson et al. reported that 5.7% of survivors had convulsions, 24.2% cognitive difficulties, 4.3% muscular deficit, 12.8% hearing impairment and 10% migraine [33].
Buysse MP et al. reported that 35% of subjects had neurological damage, and that 17% presented IQ scores < 85 [10].
Finally, Kaplan et al. found that 9.5% of survivors presented deafness (4.1% monolateral and 5.5% bilateral), and that hearing loss was more common in infants and young babies than in children aged >2 years. Moreover, the authors reported that 6.2% of subjects had convulsions, 2.7% ataxia and 2% hemiplegia [35].
Table II reports the probability of suffering neurological sequelae according to the results of the studies included in the present overview.

Psychological sequelae

Psychiatric and psychological effects often ensue following hospitalization, and these are frequently underestimated in the medium and long term. Most survivors suffer from post-traumatic stress disorders; however, owing to the heavy impact of physical complications, these psychological sequelae may well be overlooked [38].
Psychological and behavioral sequelae can be classified as: anxiety disorders (generalized anxiety, anxiety due to separation, social dysfunction, and specific phobias); behavioral disorders (oppositional defiant disorder, conduct disorder); other psychological/emotional/behavioral disturbances (depression, attention deficit, attention deficit/hyperactivity disorder, post-traumatic stress disorder, autism spectrum disorder, and eating disorders).
In their systematic review, Olbrich et al. reported that psychological sequelae (anxiety, learning difficulties, emotional and behavioral disorders) afflicted most survivors from invasive meningococcal disease, their family members and caregivers in both the short and long terms [1].
Martinon-Torres et al. [25] evaluated both the short-term and long-term psychiatric and psychological effects of meningococcal disease. They observed that long-term consequences were more frequent in pediatric patients and in their parents. Similarly, the review published in 2013 by Vyse et al. documented post-traumatic stress disorders in patients, parents and caregivers, and highlighted the importance of the effects of stress in the long period [30].
In the study conducted by Viner et al., 26% of children who survived serogroup B meningococcal disease displayed psychological disorders, as against 10% of control subjects. In 22% of cases, significant psychological disorders, mainly anxiety and behavioral disorders, emerged 3-5 years after the acute phase of the disease. The authors concluded that the probability of developing mental disorders, anxiety, behavioral problems and

Tab. II. Main neurological sequelae and probabilities.

Type of sequela	Study	Age	Probability of sequelae	Notes
Deafness	Sadarangani [11]	< 18 years ≥ 18 years	7.4% 3.3%	55% of cases caused by serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	14.3% 22.2% 25% 33.3%	95.2% of cases caused by serogroup B
	Viner [18]	0-16 years	2% (severe bilateral) 5% (moderate bilateral)	Sequelae due to meningococcus B
	Kennedy [37]	0-16 years	20.2%	Sequelae due to meningococcus B
	Kaplan [35]	0-19 years	4.1% unilateral deafness 5.5% bilateral deafness	
	Bettinger [32]	< 1 year 1 – 4 years 5 – 19 >20 years	45% 34.6% 30% 38.9%	Sequelae due to meningococcus B
	Wang [19]	< 18 years	12.9%	Sequelae due to meningococcus B
	Borg [31]	Mean age 19.3 years	20.7%	56% of cases caused by meningococcus B
	Gottfredsson [33]	Mean age at time of acute phase: 9.3 years; Mean age at time of interview: 29.1 years	12.8%	Sequelae due to meningococcus B
Visual defects	Sadarangani [11]	< 18 years ≥ 18 years	2.1% 3.6%	55% of cases caused by serogroup B
	Viner [18]	0-16 years	< 1%	Sequelae due to meningococcus B
Convulsions/ epilepsy	Sadarangani [11]	< 18 years ≥ 18 years	0.7% 1.3%	55% of cases due to serogroup B
	Viner [18]	0-16 years	2%	Sequelae due to meningococcus B
	Kennedy [37]	0-16 years	9.2%	Sequelae due to meningococcus B.
	Wang [19]	< 18 years	12.9%	Sequelae due to meningococcus B
	Bettinger [32]	< 1 year 1-4 years 5-19 years > 20 years	40% 7.7% - -	Sequelae due to meningococcus B
	Kaplan [35]	0-19 years	6.2%	
	Borg [31]	Mean age 19.3 years	3.5%	56% of cases caused by meningococcus B
	Gottfredsson [33]	Mean age at time of acute phase: 9.3 years; mean age at time of interview: 29.1 years	5.7%	Sequelae due to meningococcus B
Cognitive impairment	Sadarangani [11]	< 18 years ≥ 18 years	0.2% 0.9%	55% of cases caused by serogroup B
	Gottfredsson [33]	Mean age at time of acute phase: 9.3 years; mean age at time of interview: 29.1 years	24.2%	Sequelae due to meningococcus B
Impaired memory and concentration	Kennedy [37]	0-16 years	5.5%	Sequelae due to meningococcus B
Communication problems	Viner [18]	0-16 years	4%	Sequelae due to meningococcus B
	Borg [31]	Mean age 19.3 years	22.4%	56% of cases caused by serogroup B
Motor deficit	Sadarangani [11]	< 18 years ≥ 18 years	4.1% 0.9%	55% of cases caused by serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	- 3.7% - -	95.2% of cases caused by serogroup
	Kaplan [35]	0-19 years	2.7%	

(continues)

Tab. II. Main neurological sequelae and probabilities (*follows*).

Type of sequela	Study	Age	Probability of sequelae	Notes
Chronic headache/ migraine	Wang [19]	< 18 years	12.9%	Sequelae due to meningococcus B
	Gottfredsson [33]	Mean age at time of acute phase: 9.3 years; mean age at time of interview: 29.1 years	10%	Sequelae due to meningococcus B
Lethargy	Wang [19]	< 18 years	12.9%	Sequelae due to meningococcus B
Undefined neurological damage	Sadarangani [11]	< 18 years ≥ 18 years	1.4% 2.2%	55% of cases caused by serogroup B
	Rivero-Calle [17]	< 1 year 1-4 years 5-9 years 10-14 years	57.1% 29.6% 25% 33.3%	95.2% of cases caused by serogroup B
	Wang [19]	< 18 years	25.8%	Sequelae due to meningococcus B
	Bettinger [32]	< 1 year 1-4 years 5-19 > 20 years	20% 11.5% 20% 27.8%	Sequelae due to meningococcus B
	Buysse [10]	Range: 1 month-18 years; mean age: 3.1 years. median age on follow-up: 14.5 years (range 5.3 -31.1)	35%	79% of subjects affected by invasive disease due to serogroup B
IQ < 85	Buysse [10]	Range: 1 month-18 years; mean age: 3.1 years. median age on follow-up: 14.5 years (range 5.3 -31.1)	17%	79% of subjects affected by invasive disease due to serogroup B
	Viner [18]	0-16 years	11%	Sequelae due to meningococcus B

attention deficit/hyperactivity disorder was 50% higher in cases than in controls [18].

In their follow-up study (January 2007-April 2008), Gottfredsson et al. reported that 20% of survivors from serogroup B meningococcal disease had mental problems (5.7% depression, 7.1% anxiety and 2.8% anxiety/depression). The probability of having psychiatric and psychological problems was significantly higher than in the general population [33].

The study conducted by Borg et al. analyzed symptoms of depression 18-36 months after the acute phase of disease by means of the test "Beck Depression Inventory II" (BDI-II), in which scores >13 indicate clinical symptoms of depression; 20% of patients reported depressive symptoms, as opposed to 12% of control subjects [31].

In the UK between 1999 and 2000, Shears et al. [39] recruited 60 children aged 3-16 years who had survived meningococcal disease, together with 60 mothers, 45 fathers and several teachers. The aim of their study was to assess the short-term psychological consequences of invasive meningococcal disease. To this end, they administered the "Strength and Difficulties Questionnaire" (SDQ) to the family members and teachers at the time of the child's hospitalization and after three months. The SDQ, a short questionnaire for the behavioral screening of children/adolescents aged 3-16 years, assesses 25 indicators subdivided into 5 areas of interest: emotional symptoms, behavioral problems, hyperactivity/poor attention, relationships with peers, and pro-social behavior. To each of the 25 items, the respondent answers on a 3-point Likert scale ("not true", "partly true", "completely true"), indicating the extent to which each of the behaviors listed describes the child considered. The four sub-scales that evaluate problem behaviors, i.e. excluding the scale concerning pro-social behaviors (which measures the child's strengths), yield a total score indicating difficulties (higher scores indicate greater difficulty). Another questionnaire was also administered to children aged < 8 years, in order to evaluate post-traumatic stress disorder. From the SDQ, it emerged that, in the spheres of emotivity, hyperactivity and behavioral problems, the children had higher scores during follow-up (3 months) than at the time of the acute phase. Subsequently, the same patients were interviewed after 12 months, in order to evaluate long-term psychiatric sequelae. These interviews revealed difficulties in the spheres of emotivity and behavior, and especially in the sphere of everyday life. At 12 months, about 11% of the children were deemed to be at risk of post-traumatic stress disorder [40].

In 2002, Judge et al. published the results of a study conducted in the UK on children/adolescents who had survived meningococcal disease, the aim of which was to assess the risk of psychiatric disorders in patients and their parents. The authors observed 29 subjects aged between 2 and 16 years (mean age: 5.7 years) and interviewed 27 couples of parents. The patients were followed up for a period of 3-12 months (mean 8.9 months). Following hospital discharge, 62% of the patients experienced symptoms due to stress, the most common being nightmares and hyper-excitation. During follow-up, 10% of subjects suffered marked post-traumatic stress disorder. The overall risk of psychiatric disorders was twice as high in patients as in the general population [41].

Psychosocial problems and quality of life in parents and caregivers

Shears et al. [39] also evaluated the psychosocial problems suffered by the parents of children who had survived invasive meningococcal disease (60 children aged 3-16 years). The study involved 60 mothers, 45 fathers, and several teachers. From the results of the questionnaires administered to the parents, it emerged that the mothers suffered mental stress both at the time of the child's hospitalization (59%) and during follow-up (3 months later) (43%), while 42% of the fathers suffered mental stress at the time of hospitalization and 24% during follow-up. It was estimated that about 38% of the mothers and 19% of the fathers were at risk of post-traumatic stress disorder. Moreover, a correlation emerged between the length of the child's stay in intensive care and the parents' post-traumatic stress disorders [39]. The authors prolonged the study in order to evaluate the impact of the disease at 12 months, and concluded that 24% of the mothers and 15% of the fathers were at risk of post-traumatic stress disorder. The parents were asked to fill in a "Parental Assessment Questionnaire". This brought to light a change in their behavior, in that they had become more protective towards their children, worried more about their children's health, and tended to be more permissive [40].

The psychiatric problems suffered by the parents of children who had survived meningococcal disease were also assessed by Judge et al. These authors observed that 40% of mothers had an increased risk of psychiatric disorders, 48% suffered from clinically significant post-traumatic stress disorder, and 29% required psychological support. The mothers' symptoms of stress were significantly associated to the severity of their children's disease [41].

Ehrlich et al. also conducted a study aimed at evaluating psychological stress among the parents of children with invasive meningococcal disease. The parents completed the "Goldberg General Health Questionnaire-30" (GHQ); in this study, the cut-off was set at a level of 5 points, scores of > 5 being indicative of psychological stress. The mean GHQ scores of the mothers were: 8.71 at 3 months after the acute phase; 10.7 after 6 months; 6.96 after 12 months; 7.17 after 2 years and 4.9 after 3 years. The percentages of mothers suffering from psychological stress were also calculated: 50% presented signs of psychological stress after 3 months; 69% after 6 months, 39% after 12 months; 33% after 2 years, and 31% after 3 years. Among the fathers, the mean GHQ scores were: 7.17 after 3 months; 6.69 after 6 months; 5.9 after 12 months; 6.25 after 2 years and 5.43 after 3 years. The percentages of fathers who suffered from psychological stress were: 41% after 3 months; 58% after 6 months; 45% after 12 months; 50% after 2 years and 29% after 3 years [42].

Impaired quality of life associated with meningococcal disease

The concept of quality of life was introduced in the 1980s within the framework of studies on the consequences of chronic diseases in adults; more recently, it has also been applied to children. The assessment of quality of life involves evaluating physical, cognitive, social and emotional functions. The term "Health-related quality of life" (HRQoL) refers to the specific impact of disease, of the damage suffered and of treatments on patients and their quality of life. In pediatric patients, the effect of the disease and its treatment often increases their dependence on parents and reduces their participation in school and recreational activities. This has a negative influence on the development of subjects' abilities, impairing their quality of life (QoL) [43].

The two following sections describe the impact of meningococcal disease and its possible sequelae on the quality of life of patients, family members and caregivers. The quality of life of patients is reduced, according to the severity of the acute phase of the disease and the type of temporary and/or permanent sequelae [38].

In their systematic review, Olbrich et al. [1] stressed that meningococcal disease affected the quality of life of all patients (including those without sequelae) and their families for very long periods of time [1]. The 2013 review by Vyse et al. also documented a lower quality of life among survivors from meningococcal disease than in the general population, with effects being observed throughout the patient's entire life [30].

Quality of life in the acute phase of meningococcal disease and in the short term

A study conducted in the UK by Kennedy et al. on subjects aged < 16 years who had survived invasive meningococcal B disease (observation period: November 2012-May 2013) utilized the EQ-5DY questionnaire (a 5-dimensional questionnaire for youth developed by EuroQoL) to evaluate QoL impairment during the worst period of the disease and over the subsequent months (mean period: 134 days). This questionnaire, which is the pediatric version of the EQ-5D (children aged 8-15 years), investigates various aspects of everyday life, such as mobility, independence, the performance of daily activities, pain and the emotional sphere. Each domain is subdivided into three levels: "no problems", "moderate problems" and "severe problems". The results are then transformed by applying pre-established weights to the individual domains. The second (follow-up) assessment considers a single value on a scale from 0 to 100, where 0 indicates the worst situation. The authors surveyed 109 families. Sequelae were recorded in 36.7% of the respondents, the most frequent being hearing loss (20.2%). From the results it emerged that, on the worst days of the disease, 69% of patients had severe mobility problems, 74% had severe independence-related problems, 75% were unable to perform daily activities, 77% suffered considerable pain, and 80% were sad and unhappy. Scores on the VAS (Visual Analogic Scale, which evaluates pain intensity, where 0 indicates the worst pain) recorded on the worst day and on the day of follow-up examination (on average, after 134 days) were 6.5/100 and 95/100, respectively. On follow-up evaluation, subjects with long-term sequelae presented a significantly

worse state of health than subjects without sequelae. At this time-point, 93% of the patients stated that they had no mobility problems, 92% managed to take care of themselves, 91% were able to carry out normal daily activities, 86% reported not having any pain, and 93% reported that they were not worried or unhappy [37].

Quality of life in the medium and long term

Few studies have evaluated long-term health-related quality of life in survivors from meningococcal disease. Although the psychosocial impact of meningococcal disease is important, QoL assessments are also influenced by the socio-economic consequences of the disease. These aspects were examined in a study conducted in Denmark on 2,902 patients diagnosed with meningococcal meningitis. 2,077 patients were followed up until their 20th birthday, and 1,028 of whom, until their 30th birthday. The respective control groups consisted of 9,032 and 4,452 subjects. The areas assessed were: education, work and social and economic security. In the assessment of education, the average of the marks obtained during the last year of the primary school were considered; the patients had obtained an average of 5.7 vs 5.9 among control subjects (OR= 1.58, 95% CI = 0.90-0.99). On comparing patients and controls at the age of 20 years, it emerged that a greater number of control subjects than patients had completed secondary school (43.8% vs 37.5%). At the age of 30 years, 33.4% of patients had attended university vs 36% of controls. With regard to the sphere of work, at the age of 20 years, more of the patients had received social assistance (OR 1.39, 95% CI = 1.00-1.93) and a higher percentage were receiving a disability pension (OR = 2.52, 95% CI = 1.62-3.95). Moreover, at the age of 30 years, the patients had a significantly lower income than the controls (p =0.001) [44].

Borg et al. [31] conducted a cohort study of adolescents and young adults (aged 16-18 years;19-22 years; mean age: 19.3 years) affected by invasive meningococcal disease, and evaluated QoL 18-36 months after the acute phase; 56% of cases were caused by meningococcus B. In all subjects, the authors assessed QoL (Short Form 36 Health Survey – SF-36), daily tiredness (11-item Chalder Fatigue Scale), life stress (Family Inventory of Life Events), educational level reached (General Certificate of Secondary Education) and cognitive functions. QoL was assessed by considering the overall scores of the physical component (48.4 in patients vs 51.8 in controls) and the psychological component (46.6 in patients vs 53.5 in controls); higher scores indicated a better state of health. With regard to the level of tiredness, the test evaluated physical fatigue (scored from 0 to 21), psychological fatigue (scored from 0 to 12) and overall fatigue (scored from 0 to 33); higher scores indicated a worse condition. The patients scored 9 on the scale of physical fatigue vs 8.3 among the controls, and 4.6 on the scale of psychological fatigue vs 4 among controls; regarding overall fatigue, the scores were 13.6 among patients and 12.4 among controls. To evaluate the level of stress, the authors considered the experience of the patients over the 12 months prior to the interview (higher scores indicated a higher level of stress); the scores obtained by the patients were not significantly higher than those obtained by the controls (6 vs 7.1). Finally, the educational and scholastic sphere was investigated; among patients, a score of 8 was assigned, as opposed to 9 among controls. Moreover, 64% of patients had not reached an advanced level of education, while among controls the figure was 50%; the percentage of patients who had not passed their examinations during the previous year was 19%, while among controls it was 8% [31].

In a study conducted in Holland (1988-2001) Buysse et al. [45] evaluated the QoL of 140 survivors from meningococcal disease by means of the HRQoL indicator, which consists of a scale that assigns a score from 0 to 100 to the various health domains; lower scores correspond to a worse state of health. The authors also assessed the QoL of both patients and their families by means of the "Child Health Questionnaire" (CHQ) (< 18 years) and the SF-36 for subjects aged >18 years. The CHQ measures the global health profile of the child with reference to the physical and psychosocial domains, including those concerning lifestyle habits, self-esteem and the effects of the child's state of health on the family. The structure of the questionnaire is similar to that of the SF-36 used for adults. The study recruited subjects who had had invasive disease between the ages of 1 month and 18 years, who were interviewed after a median period of 10 years. In the case of patients aged between 4 and 17 years, the CHQ was completed by family members; in addition, patients aged between 12 and 17 years also completed the questionnaire themselves. In the case of subjects aged ≥ 18 years, the SF-36 questionnaire was completed by both the patients and their family members. A total of 140 questionnaires were collected: 54 concerning patients aged 4-11 years, 38 concerning those aged 12-17 years and 48 on subjects aged ≥18 years; the mean age of the patients at the time of the survey was 14.6 years. The scores of the subjects enrolled were then compared with those obtained by a control group of healthy children and adolescents. In the 14-17-year age-group (questionnaires completed by parents), the scores were lower among patients than among healthy children, particularly with regard to the physical domain (92/100 vs 99/100), psychosocial domain (76/100 vs 79/100) and overall perception of health (64/100 vs 83/100). The patients aged 12-17 years had lower scores than their healthy peers in the perception of their general state of health (66/100 vs 74/100). Among patients aged ≥ 18 years, scores were lower in the domains of vitality (63/100 vs 71/100) and global state of health (49/100 vs 55/100). Among patients aged < 18 years, the perceived state of global health was worse according to the scores assigned both by the patients themselves and by their family members; this result may be correlated not only with the experience of health during the acute phase, but also with concerns regarding the future state of health. The results of the analysis of the scores assigned by the patients' parents revealed that they assigned higher scores than their children. A possible explanation for this

may be that, after the great stress caused by the acute phase of the disease and the fear that their child might die, the parents may have tended to underestimate the sequelae, especially if they were mild [39]. Overall, QoL, particularly that associated with the physical domains, was lower among patients than among control subjects in all age-groups; indeed, the authors suggested that patients with severe physical sequelae (amputations and extensive scars) were at higher risk of experiencing worse QoL over time. To investigate the issue in greater depth, the authors prolonged the study by following up the patients for a longer period. The results obtained in the follow-up study, which were published in 2010, revealed that the lower levels of QoL were associated with behavioral and emotional problems [10].

Vermunt et al. evaluated the possible impact of meningococcal septic shock (the main sequela being scars) on the self-esteem of children and adolescents aged between 8 and 17 years at least 4 years after the acute phase. In their study, self-esteem was assessed by means of the Dutch version of "Harter's Self-Perception Profile for Children" (SPP-C) in children aged 8-11 years, and by means of "Harter's Self-Perception Profile for Adolescents" (SPP-A) in adolescents between 12-17 years. Each questionnaire investigated specific domains: scholastic skills, social acceptance, athletic skill, physical appearance, behavior and overall self-esteem; higher scores indicated a better situation. Male adolescents from 12 to 17 years obtained lower scores than their control-group peers in the domains of scholastic skills (13.4 vs 14.5), social acceptance (13.1 vs 15.3), athletic skill (12.3 vs 14.8), physical appearance (12.7 vs 14.7), friendship (12.1 vs 16.6) and global self-esteem (12 vs 16). Adolescents aged 12-17 years had lower scores with regard to social acceptance (13.2 vs 15.4), friendship (12.3 vs 17.7) and global self-esteem (11.6 vs 14.9). In addition, the authors also assessed the association between severe physical sequelae and the level of self-esteem. It emerged that children with skin scars had lower scores in the domain of social acceptance. By contrast, adolescents with skin scars had lower scores in the domain of friendship. Overall, the study revealed that adolescents had worse results than children. This may be explained by the fact that experiencing such a severe disease engenders in adolescent patients a state of vulnerability that impacts negatively on self-esteem [34].

A subsequent study by Vermunt et al. evaluated the emotional and behavioral problems of survivors after several years (median 13 years). The authors administered the "Groninger Intelligence Test 2" to these subjects in order to assess their intellectual functioning. Most patients achieved good results on the test and displayed good recovery of their daily activities and school or work attendance. Nevertheless, 5-20% of survivors reported still having behavioral problems, intellectual difficulties and social consequences related to the outcome of their disease [46].

In the Netherlands, Groothenhuis et al. conducted a study on 38 children aged 8-11 years who had survived severe meningococcal disease and who were followed up for 1-7 years after their hospitalization in the intensive care unit. From the seven domains analyzed in order to assess health-related quality of life, it emerged that 45% of the subjects had motor difficulties, and that 40% had independence-related problems. Comparison with a control group of healthy children revealed statistically significant differences [43].

In 2005, Koomen et al. published the results of a study aimed at assessing the QoL of children who had survived bacterial meningitis and examining the association between scholastic impairment and behavioral problems. They compared 182 children aged 9.7 years on average (range 5.3-14.2) with a control group of healthy children. The study-group children had not had "severe" disease during the acute phase and did not suffer from serious invalidating sequelae. QoL was evaluated, on average, 7.4 years after the acute phase by means of the "Academic Achievement Test", while their parents completed the "Child Behavior Checklist", the "Child Health Questionnaire" and the "Health Utilities Index". The long-term incidence of limitations in the scholastic and behavioral spheres was 32%. Overall, the QoL of the survivors was below that of the reference pediatric population, especially with regard to psychosocial, cognitive and family life aspects. The negative effects on QoL were not significantly influenced by age, sex, causal pathogen or the presence of neurological sequelae [47].

Focus on a clinical case with permanent severe sequelae

The amputation of all four limbs is an extremely rare occurrence which may become inevitable when sepsis gives rise to coagulopathy, extensive thromboses and gangrene.

In 2004, Lowe et al. [48] reported the case of a 14-month-old Australian child who underwent numerous amputations as a result of meningococcal disease. Following the infection, he was hospitalized in the intensive care unit and, three weeks later, underwent amputation of all four limbs. To close the wounds and to replace the necrotic tissues, numerous skin grafts were required. Three months after surgery, prostheses were applied. The child rapidly adapted to his condition, attempting to perform everyday actions, such as walking or grasping objects without the prostheses or help, though he was unable to follow the rehabilitative therapy proposed. His toys were adapted to his condition and his capabilities. It proved difficult to understand the child's psychological needs and to judge whether the prostheses could help him to move and to accept his new body image. After six months of hospitalization, he returned home, where, with the aid of specialized personnel, his family managed to look after him. When the boy was three years old, his mother obliged him to use a wheelchair whenever he went out; this, however, was not helpful from either a physical or psychological point of view. Whenever possible, the child was allowed to move without his prostheses, which were nevertheless adapted as he grew.

It is not known what the future holds for this child. What is certain, however, is that this case required a multidisciplinary approach involving several professionals (from surgeons to psychologists) in order to support the child and his family, in addition to considerable financial commitment.

Conclusions

To date, no study has analyzed the impact of sequelae due to meningococcal disease in Italy. The results presented in the following HTA report have therefore been taken from studies conducted in various other high-income countries. The main physical sequelae reported in these studies are: skin scars, amputations (single and multiple), limb deformities and renal dysfunction. With regard to neurological sequelae, the most frequent and severe are: deafness (unilateral or bilateral) and cognitive, communicative and motor deficits. However, psychiatric and psychological damage suffered by both patients and their families as a result of meningococcal disease is also very important; indeed, many survivors (up to 62% of patients) suffer from post-traumatic stress disorders. Anxiety and depression are the most serious psychiatric sequelae. Moreover, about 60% of mothers and 40% of fathers report suffering from psychiatric/psychological disorders that require specialist support during the acute and post-acute phases of their children's disease.
Thus, although meningococcal disease displays a low incidence in developed countries, it generates a heavy clinical, economic and social impact owing to its elevated lethality (8-15%), the gravity of the acute phase and its numerous sequelae, both single (up to 60%) and multiple (about 30-35%). Moreover, it should be pointed out that this heavy impact also stems from the fact that the disease mainly strikes children, adolescents and young adults.

Bibliografia

[1] Olbrich KJ, Müller D, Schumacher S, Beck E, Meszaros K, Koerber F. Systematic review of invasive meningococcal disease: sequelae and quality of life impact on patients and their caregivers. Infect Dis Ther 2018;7(4):421-38. https://doi.org/10.1007/s40121-018-0213-2

[2] McNamara LA, Thomas JD, MacNeil J, Chang HY, Day M, Fisher E, Martin S, Poissant T, Schmink SE, Steward-Clark E, Jenkins LT, Wang X, Acosta A; Oregon Meningococcal Carriage Team. Meningococcal carriage following a vaccination campaign with menB-4C and menB-FHbp in response to a university serogroup B meningococcal disease outbreak-Oregon, 2015-2016. J Infect Dis 2017;216(9):1130-40. https://doi.org/10.1093/infdis/jix446

[3] Gasparini R, Comanducci M, Amicizia D, Ansaldi F, Canepa P, Orsi A, Icardi G, Rizzitelli E, De Angelis G, Bambini S, Moschioni M, Comandi S, Simmini I, Boccadifuoco G, Brunelli B, Giuliani MM, Pizza M, Panatto D. Molecular and serological diversity of Neisseria meningitidis carrier strains isolated from Italian students aged 14 to 22 years. J Clin Microbiol 2014;52(6):1901-10. https://doi.org/10.1128/JCM.03584-13

[4] Guzzetta G, Manfredi P, Gasparini R, Panatto D, Edmunds WJ. On the relationship between meningococcal transmission dynamics and disease: remarks on humoral immunity. Vaccine 2009;27(25-26):3429-34. https://doi.org/10.1016/j.vaccine.2009.01.092

[5] Gasparini R, Amicizia D, Domnich A, Lai PL, Panatto D. Neisseria meningitidis B vaccines: recent advances and possible immunization policies. Expert Rev Vaccines 2014;13(3):345-64. https://doi.org/10.1586/14760584.2014.880341

[6] Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine 2009;27(Suppl 2):B51-63. https://doi.org/10.1016/j.vaccine.2009.04.063

[7] Hammerschmidt S, Müller A, Sillmann H, Mühlenhoff M, Borrow R, Fox A, van Putten J, Zollinger WD, Gerardy-Schahn R, Frosch M. Capsule phase variation in Neisseria meningitidis serogroup B by slipped-strand mispairing in the polysialyltransferase gene (siaD): correlation with bacterial invasion and the outbreak of meningococcal disease. Mol Microbiol 1996;20(6):1211-20. https://doi.org/10.1111/j.1365-2958.1996.tb02641.x

[8] Panatto D, Amicizia D, Lai PL, Gasparini R. Neisseria meningitidis B vaccines. Expert Rev Vaccines 2011;10(9):1337-51. https://doi.org/10.1586/erv.11.103

[9] Center for Disease Control and Prevention (CDC). Epidemiology and prevention of vaccine-preventable diseases, The Pink Book, 13th Edition, 2015, chapter 14: Meningococcal Disease. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/index.html [Accessed 31 December 2018].

[10] Buysse CM, Vermunt LC, Raat H, Hazelzet JA, Hop WC, Utens EM, Joosten KF. Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care 2010;14(3):R124. https://doi.org/10.1186/cc9087

[11] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program, ACTive (IMPACT). Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028

[12] European Centre for Disease Prevention and Control (ECDC). Invasive meningococcal disease - Annual Epidemiological Report for 2015. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-meningococcal-disease.pdf [Accessed 31 December 2018].

[13] Bosis S, Mayer A, Esposito S. Meningococcal disease in childhood: epidemiology, clinical features and prevention. J Prev Med Hyg 2015;56(3):E121-4.

[14] Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, Harnden A, Mant D, Levin M. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367(9508):397-403. https://doi.org/10.1016/s0140-6736(06)67932-4

[15] Dipartimento Malattie Infettive, Istituto Superiore di Sanità. Sorveglianza delle malattie batteriche invasive. Rapporto "Interim" 2017. Roma, aprile 2018. Available at: http://old.iss.it/binary/mabi/cont/InterimReport2017.pdf [Accessed 31 December 2018].

[16] Lecocq H, Parent du Châtelet I, Taha MK, Lévy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine 2016;34(19):2240-50. https://doi.org/10.1016/j.vaccine.2016.03.020

[17] Rivero-Calle I, Vilanova-Trillo L, Pardo-Seco J, Salvado LB, Quinteiro LI, Martinon-Torres F; MENDICOS Research Network. The burden of pediatric invasive meningococcal disease in Spain (2008-2013). Pediatr Infect Dis J 2016;35(4):407-13. https://doi.org/10.1097/INF.0000000000001048

[18] Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, Kaczmarski E, Rajput K, Ramsay M, Christie D. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study.

Lancet Neurol 2012;11(9):774-83. https://doi.org/10.1016/S1474-4422(12)70180-1

[19] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine 2014;32(37):4791-8. https://doi.org/10.1016/j.vaccine.2014.05.069

[20] Stoof SP, Rodenburg GD, Knol MJ, Rümke LW, Bovenkerk S, Berbers GA, Spanjaard L, van der Ende A, Sanders EA. Disease burden of invasive meningococcal disease in the Netherlands between June 1999 and June 2011: a subjective role for serogroup and clonal complex. Clin Infect Dis 2015;61(8):1281-92. https://doi.org/10.1093/cid/civ506

[21] O'Brien JA, Caro JJ, Getsios D. Managing meningococcal disease in the United States: hospital case characteristics and costs by age. Value Health 2006;9(4):236-43. https://doi.org/10.1111/j.1524-4733.2006.00113.x

[22] Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, Booth C, Klein N, Kaczmarski E, Booy R. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. BMJ 2006;332(7539):445-50. https://doi.org/10.1136/bmj.38725.728472.BE

[23] Watson JM, Nicholas S, James P. Meningococcal infection and influenza: do surveillance data support an association? Options for the control of influenza III. Amsterdam: Elsevier Science 1996; pp. 82-4.

[24] Bruce MG, Rosenstein NE, Capparella JM, Shutt KA, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. JAMA 2001;286(6):688-93. https://doi.org/10.1001/jama.286.6.688

[25] Martinón-Torres F. Deciphering the burden of meningococcal disease: conventional and under-recognized elements. J Adolesc Health 2016;59(2 Suppl):S12-20. https://doi.org/10.1016/j.jadohealth.2016.03.041

[26] Christensen H, May M, Bowen L. Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:853-61. https://doi.org/10.1016/S1473-3099(10)70251-6

[27] Lombardi D, Pasqualini C. Malattie batteriche invasive in Piemonte nel 2016. SEREMI, Regione Piemonte. Available at: https://www.seremi.it/sites/default/files/REPORT%20MIB%202017%20ed%202018_0.pdf [Accessed 31 December 2018].

[28] Frasca G, Pascucci MG, Gualanduzzi C. Servizio Prevenzione Collettiva e Sanità Pubblica, Regione Emilia-Romagna. Malattie invasive da meningococco in Emilia Romagna. 2017. Available at: https://salute.regione.emilia-romagna.it/documentazione/rapporti/rapporto-meningococco-2017/at_download/file/meningococc-aprile-2017.pdf [Accessed 31 December 2018].

[29] Judelsohn R, Marshall GS. The burden of infant meningococcal disease in the United States. J Pediatric Infect Dis Soc 2012;1(1):64-73. https://doi.org/10.1093/jpids/pir003

[30] Vyse A, Anonychuk A, Jäkel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther 2013;11(6):597-604. https://doi.org/10.1586/eri.13.42.

[31] Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics 2009;123(3):e502-9. https://doi.org/10.1542/peds.2008-0581

[32] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R; Members of Canadian Immunization Monitoring Program, Active (IMPACT). The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J 2013;32(1):e20-5. https://doi.org/10.1097/INF.0b013e3182706b89

[33] Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, Schneerson R, Robbins JB, Miller MA. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis 2011;53(9):e117-24. https://doi.org/10.1093/cid/cir500

[34] Vermunt L, Buysse CM, Joosten KF, Oranje AP, Hazelzet JA, Verhulst FC, Utens EM. Self-esteem in children and adolescents after septic shock caused by Neisseria meningitidis: scars do matter. J Adolesc Health 2008;42(4):386-93. https://doi.org/10.1016/j.jadohealth.2007.09.026

[35] Kaplan SL, Schutze GE, Leake JA, Barson WJ, Halasa NB, Byington CL, Woods CR, Tan TQ, Hoffman JA, Wald ER, Edwards KM, Mason EO Jr. Multicenter surveillance of invasive meningococcal infections in children. Pediatrics 2006;118(4):e979-84. https://doi.org/10.1542/peds.2006-0281

[36] Roed C, Omland LH, Skinhoj P, Rothman KJ, Sorensen HT, Obel N. Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis. JAMA 2013;309(16):1714-21. https://doi.org/10.1001/jama.2013.3792

[37] Kennedy ITR, van Hoek AJ, Ribeiro S, Christensen H, Edmunds WJ, Ramsay ME, Ladhani SN. Short-term changes in the health state of children with group B meningococcal disease: a prospective, national cohort study. PLoS One 2017;12(5):e0177082. https://doi.org/10.1371/journal.pone.0177082 eCollection 2017

[38] Erickson L, De Wals P. Complications and sequelae of meningococcal disease in Quebec, Canada, 1990-1994. Clin Infect Dis 1998;26(5):1159-64.

[40] Shears D, Nadel S, Gledhill J, Garralda ME. Short-term psychiatric adjustment of children and their parents following meningococcal disease. Pediatr Crit Care Med 2005;6(1):39-43. https://doi.org/10.1097/01.PCC.0000144705.81825.EE

[41] Garralda ME, Gledhill J, Nadel S, Neasham D, O'Connor M, Shears D. Longer-term psychiatric adjustment of children and parents after meningococcal disease. Pediatr Crit Care Med 2009;10(6):675-80. https://doi.org/10.1097/PCC.0b013e3181ae785a

[42] Judge D, Nadel S, Vergnaud S, Garralda ME. Psychiatric adjustment following meningocpoccal disease treated on a PICU. Intensive Care Med 2002;28:648-50. https://doi.org/10.1007/s00134-002-1237-2

[43] Ehrlich TR, Von Rosenstiel IA, Grootenhuis MA, Gerrits AI, Bos AP. Long-term psychological distress in parents of child survivors of severe meningococcal disease. Pediatr Rehabil 2005;8(3):220-4. https://doi.org/10.1080/13638490400022246

[44] Grootenhuis MA, Koopman HM, Verrips EGH, Vogels AGC, Last BF. Health-related quality of life problems of childre aged 8-11 years with a chronic disease. Dev Neurorehabil 2007;10(1):27-33. https://doi.org/10.1080/13682820600691017

[45] Pickering L, Jennum P, Ibsen R, Kjellberg J. Long-term health and socioeconomic consequences of childhood and adolescent onset of meningococcal meningitis. Eur J Pediatr 2018. https://doi.org/10.1007/s00431-018-3192-0

[46] Buysse CM, Raat H, Hazelzet JA, Vermunt LC, Utens EM, Hop WC, Joosten KF. Long-term health-related quality of life in survivors of meningococcal septic shock in childhood and their parents. Qual Life Res 2007;16(10):1567-76. https://doi.org/10.1007/s11136-007-9271-8

[47] Vermunt L, Buysse CM, Joosten KF, Duivenvoorden H, Hazelzet JA, Verhlust FC, Utens EM. Survivors of septic shock caused by Neisssria meningitides in childhood: psycosocial outcomes in young adulthood. Pediatr Crit Care Med 2011;12(6):e302-9. https://doi.org/10.1097/PCC.0b013e3182192d7f

[48] Koomen I, Raat H, Jennekens-Schinkel A, Grobbee DE, Roord JJ, van Furth M. Academic and behavioral limitations and health-related quality of life in school-age survivors of bacterial meningitis. Qual Life Res 2005;14(6):1563-72. https://doi.org/10.1007/s11136-004-7706-z

[49] Lowe KG and Boyce JM. Rehabilitation of a child with meningococcal septicemia and quadrilateral limb loss: a case report. Arch Phys Med Rehabil 2004;85(8):1354-7. https://doi.org/10.1016/j.apmr.2003.09.030

Chapter 4

The costs of invasive disease due to *Neisseria meningitidis*

D. PANATTO, F. ZANGRILLO, F. MARCHINI, E. LECINI, M. IOVINE, P.L. LAI, D. AMICIZIA
Department of Health Sciences, University of Genoa, Italy

Introduction

Invasive disease due to *Neisseria meningitidis* generates a high clinical, social and economic impact (see chapter 3).
Despite the availability of adequate antibiotic therapies, invasive meningococcal disease still displays a high lethality rate and causes temporary and/or long-term complications in a considerable percentage of survivors [1-5]. Indeed, it is estimated that up to 60% of those who survive, especially children and adolescents, suffer permanent sequelae, which may be extremely debilitating and impair the quality of life (QoL) of both patients and their family members [2, 6, 7]. QoL impairment in survivors from meningococcal disease varies according to the type and gravity of these sequelae (see chapter 3).
The percentage of subjects who suffer complications varies according to age [8], the severity of the acute phase and the serogroup involved; infections caused by serogroups B and C are the most severe, as demonstrated by numerous studies [9, 10]. Sequelae may be physical, neurological, cognitive or psychiatric [10] and of variable gravity, and generate high direct and indirect costs.
Direct costs consist of the costs borne by the National Health Service (NHS). These can be subdivided into: acute-phase costs (hospitalization, rehabilitation and public health response); costs incurred during the post-acute phase (up to 6 months after the acute phase), and healthcare costs related to temporary or permanent sequelae (Fig. 1).
Indirect costs consist of: the cost of death; costs due to loss of productivity of patients and family members and to psychiatric and psychological support needed during the acute phase of disease; the costs of managing the patient during the post-acute phase (psychiatric/psychological support for family members, loss of productivity of the patient and of a parent); the costs of long-term management of patients with sequelae (patient's loss of productivity, special education, private medical examinations, disability pensions, invalidity benefits and accompaniment allowances, long-term psychiatric and psychological support for patients and family members) (Fig. 2).
In the present HTA, a search was carried out by means of the main search engines (Pubmed, Embase, Scopus) in order to identify studies that reported the costs associated to meningococcal disease; in this phase, particular attention was devoted to studies conducted in Italy and on adolescents.
To date, no exhaustive studies have evaluated all the costs of meningococcal disease in Italy. Indeed, the pharmacoeconomic studies conducted in Italy on the prevention of meningococcal disease report cost data that have been extrapolated from international contexts [11-13].

Direct costs

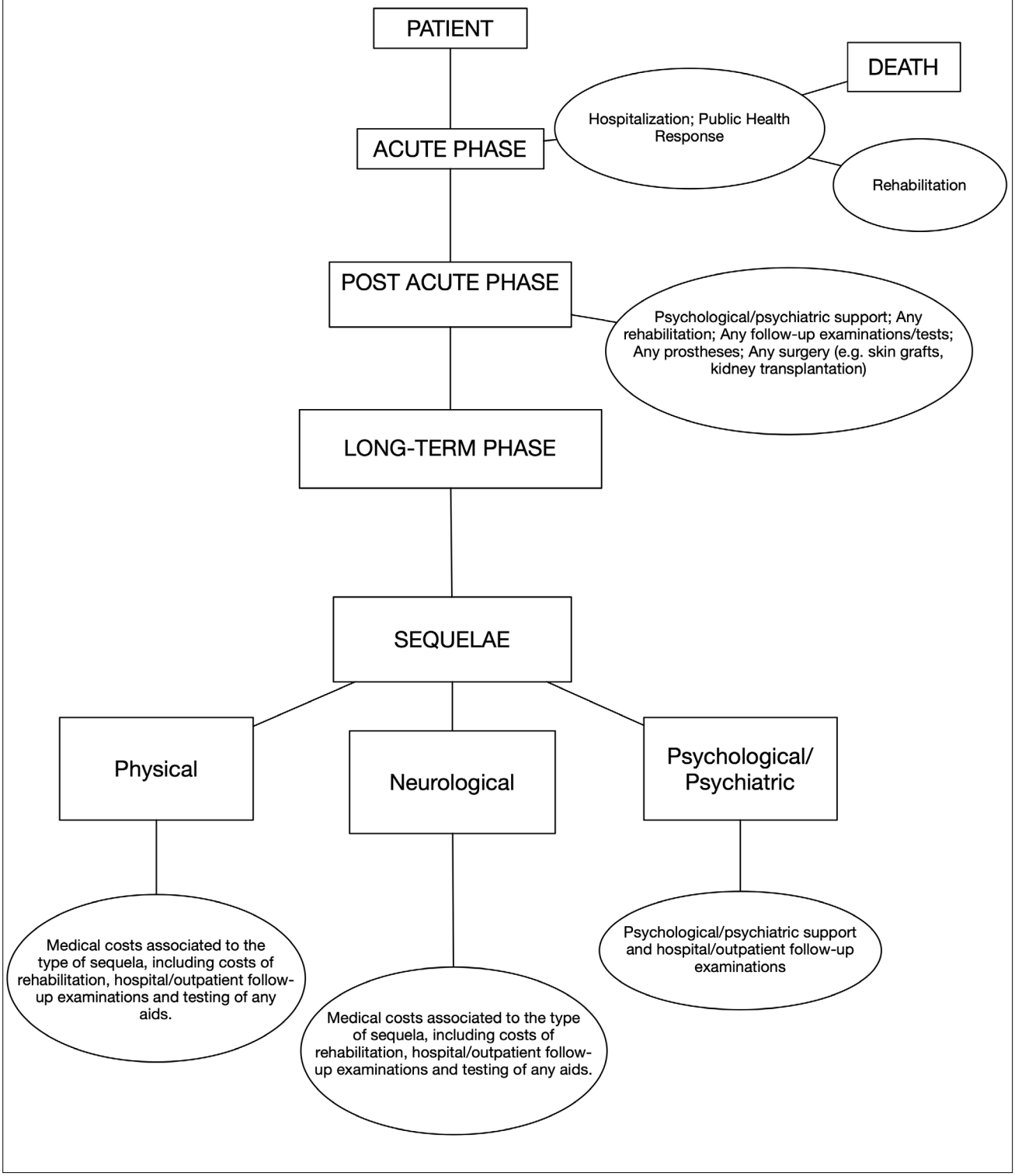
Acute-phase costs

The main cost items associated to the acute phase of disease are the costs of the public health response, hospitalization and rehabilitation.

Costs of the Public Health response

The management of a case of meningococcal disease places a considerable financial burden on public health agencies, which are called upon to mitigate the effects of the disease at both the individual and population levels and to prevent possible secondary cases. The costs involved mainly concern the management of subjects who have come into contact with the patient affected by invasive disease; this means tracing these subjects and then providing chemoprophylaxis and vaccination. This pathway begins from the notification of invasive meningococcal disease, which is mandated by a 1990 Ministerial Decree. As a class II infectious disease is involved, the necessary forms must be filled in and sent to the pertinent Local Health Agency (*Azienda Sanitaria Locale*: ASL) within 48 hours of identification of the case [14]. The reporting of a suspected case triggers the immediate implementation of specific prophylactic measures; the first action undertaken is epidemiological investigation, which consists of tracing persons who have been in contact with the patient during the 7 days prior to the date of diagnosis, and evaluating the risk to any other possible contacts [15]. Contacts are subdivided into "high-risk" and "low-risk" categories. The first category comprises persons who cohabit with the patient (particular attention being devoted to children aged < 3 years) and, in the case of children, adolescents and young people, school contacts. In infant schools, these "school contacts" are children who attend the same section and those who have shared the same facilities (rest area, refectory, etc.) with the index case. In primary schools and in first- and second-grade secondary schools, these are the patient's classmates, teachers and service staff. Moreover, individuals who have been exposed to the patient's bodily secretions (by kissing, using toothbrushes, etc.) or who have eaten or slept in the same room as the patient are also regarded as "high-risk contacts". Finally, risk evaluation has to be carried out among workmates, persons who have engaged in recreational activities and/or frequented enclosed spaces

Fig. 1. Direct costs of invasive meningococcal disease.

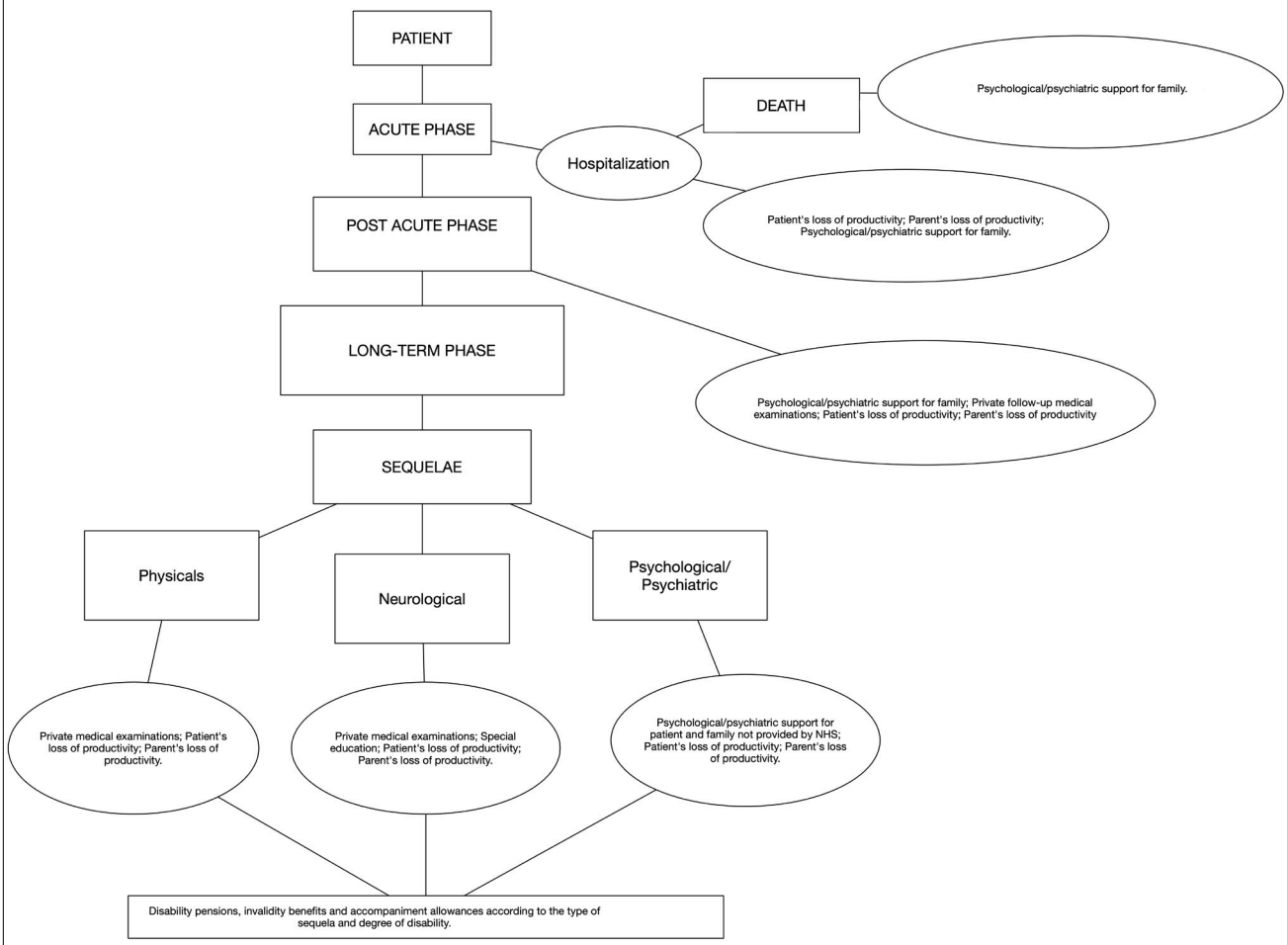


(restaurants, swimming pools, discotheques, etc.) with the patient, and among healthcare personnel and other individuals who may have been present during the patient's hospitalization (emergency department, outpatient clinic, etc.).

The "low-risk" category comprises occasional contacts. The mean number of contacts per case varies markedly and, if the patient has frequented public places, the number of individuals exposed will increase enormously.

A 2019 study conducted in Germany by Scholz et al. reported a mean number of 16.4 contacts per case [16]. In Italy, the number may well be higher, given that, for example, classes in Italian schools are generally larger than in German

Fig. 2. Indirect costs of invasive meningococcal disease.



schools. The data provided by ISTAT (Italian National Institute of Statistics), updated to 2014, indicate the number of pupils attending first-grade secondary school as 1,743,587 individuals, divided into 81,443 classes throughout Italy. The mean number of pupils per class is therefore 21.4 [17]. In addition, the mean number of persons per household is 2.4 (updated to 2016-2017) [17]. Thus, if we also consider possible contacts outside of school and the family, the number of contacts per case of invasive disease could range from 30 to 35.

Guidelines for the prophylaxis of contacts do not differ according to age or serogroup; the only difference concerns therapy, i.e. the type of antibiotic administered, which varies according to the age and condition of the subject (e.g. during pregnancy). According to the 2016 ESCMID guidelines, the proposed therapy is: rifampicin (dosage according to age and weight; duration of therapy: 2 days; may be administered during pregnancy, but only after the first 3 months); or ciprofloxacin (adults only; duration of therapy: 1 day; not to be administered during pregnancy); or ceftriaxone (single dose for children, adults and pregnant women) [18]. The mean cost of the antibiotic treatment of contacts is about € 4.24 per person [19].

On completion of antibiotic prophylaxis, the administration of anti-meningococcal vaccine may be considered [20]. The vaccination schedule varies according to the age of the subject [21, 22].

The costs of the public health response also include the costs related to the mean working time spent tackling the emergency by the healthcare personnel of the Departments of Prevention and Public Health of the ASLs. As exhaustive Italian data are not currently available, the data from international studies have been analyzed in the present HTA report. The costs regarding the prevention of secondary cases vary greatly according to the type of healthcare system in each country. They do not differ, however, according to the serogroup; thus, economic studies concerning vaccination with the anti-meningococcus C vaccine and with the quadrivalent ACWY vaccine were also analyzed in the present report.

A recent Canadian study assessed the cost-effectiveness of alternative strategies for vaccinating children against meningococcal disease with the monovalent C vaccine and the quadrivalent conjugate ACWY vaccine [23]. With regard to the cost of the public health response, the authors took as a reference the value reported in a previous cost-effective-

ness analysis conducted in the United States [24]. This cost, which referred to 2014, amounted to $CAN 4,250.
A US study published in 2005 reported an overall public health cost of $ 4,317 (referred to 2003). The study considered the mean number of contacts who required chemoprophylaxis, the mean cost of a course of chemoprophylaxis, and the mean time spent by the healthcare personnel of the public health departments per case of meningococcal disease [25].
In 2013, Anonychuk et al. published a systematic review of the public health costs and the burden generated by epidemics of meningococcal disease. The authors analyzed the data from several articles that quantified the public health response in the event of an epidemic. Specifically, in a Canadian study that they analyzed, the costs of chemoprophylaxis for close contacts and of vaccinations at school amounted to $5,014 (US$ updated to 2010); this included the costs for nursing staff, administrative staff and public relations staff. Moreover, the authors also quoted a study which considered the management of an outbreak in Switzerland; the public health response required $ 54,483 (US$ updated to 2010) [26].
An Italian study conducted in 2016 by Gasparini et al. calculated the cost to public health of a case of invasive meningococcal disease. For each case of disease, the authors considered the mean number of contacts that required chemoprophylaxis, the mean cost of a course of chemoprophylaxis and the mean working time devoted to managing an individual case by public health personnel. The mean cost of a single case was € 3,223 (referred to 2013) [11].
The 2019 study by Scholz et al. also analyzed public health costs on taking into account the cost of staff and post-exposure prophylaxis. The authors calculated the cost of each case of invasive meningococcal disease to be € 824, at 2015 values [16].

Costs of hospitalization

In the present HTA report, the costs of hospitalization were calculated on the basis of Diagnosis Related Groups (DRG). For details, see chapter 6 and, in particular, the table of the input data of the model.
With regard to this cost parameter, Italian data are available, though these are not exhaustive. Thus, for the sole purpose of broadening the evidence, we also analyzed international data from recent studies conducted in high-income countries.
An Australian study published in 2014 estimated the hospital costs of invasive meningococcal disease in 109 children hospitalized between 2000 and 2011. The authors considered both the costs of hospitalization during the acute phase in all patients and the costs of readmission to hospital in patients with sequelae. The costs of hospitalization were evaluated according to serogroup, age, sex, clinical presentation, and absence/presence of sequelae. The costs of hospital readmission of patients with sequelae were calculated according to serogroup, age, sex and clinical presentation in the acute phase. The costs were reported in A$ (Australian Dollars) at 2011 values. The mean cost of hospitalization per patient was estimated to be A$ 12,311.50. The mean cost of cases involving serogroup B was more than twice as high as that of cases involving other serogroups (B: A$ 23,774.1 vs non-B: A$10,329.6); moreover, the cost was significantly higher among patients with sequelae than those without (sequelae: A$ 35,323.5 vs no sequelae: A$8,250.0). Specifically, the cost of hospitalization was related to the clinical picture; higher costs were recorded among patients with meningitis and septicemia (A$ 24,076.2) than among those with meningitis alone (A$ 18,701.1) or septicemia alone (A$ 19,300.4). Costs were expressed in 2011 values [7].
In a French study published in 2016, all hospital admissions with main diagnoses of meningococcal meningitis (ICD-10 A39.0) and septicemia (ICD-10 A39.1, A39.2 and A39.4) were scrutinized in order to assess the costs of invasive disease due to meningococcus B. These costs were broken down by age-group. In the 5-14-year age-group, costs of € 5,919 and € 9,230 were recorded for meningitis and septicemia, respectively; in patients with both clinical pictures, the cost was estimated to be € 9,230. Costs were expressed in 2011 values [27].
The 2018 review by Wang et al. analyzed the costs incurred during the acute phase of invasive meningococcal disease in various countries. All the costs (referred to 2014) were converted into weighted estimates to achieve purchasing power parity (international dollars: I$) by means of the "Campbell and Cochrane Economic Methods" and the cost converter. The mean acute-phase cost of each case ranged from I$ 1,629 (Colombia) to I$ 50,796 (USA). Key variables, such as the presence of sequelae, were associated with higher costs and longer duration of hospitalization [28].
The 2019 study by Scholz et al. evaluated the costs of invasive meningococcal disease due to serogroup B by analyzing a cohort of 343 patients, which was reconstructed from the database of the German National Institute of Public Health in the period 2001-2016. For each case, the authors analyzed the costs of the acute phase by considering the costs of hospitalization in patients of different ages; these were: € 9,439 in the 10-14-year age-group, € 7,837 in patients aged 15-19 years, and € 7,374 in those aged 20-24 years. It emerged that the costs were higher among younger patients; this was attributed to the cost of managing long-term sequelae and to the loss of productivity of patients and their parents [16].

Costs of temporary and/or permanent sequelae

As reported in chapter 3, sequelae can be subdivided into: physical, neurological, and psychiatric/psychological.
According to the UK study conducted by Wright et al. in 2013, the costs generated by a severe case of meningitis were estimated to range between £ 160,000 and £ 200,000 (2008-2009 prices indexed to 2010-2011) in the first year after hospital discharge. Moreover, the study underlined the fact that rehabilitation would be required for the patient's entire lifetime, and especially in the first few years after hospital discharge, and that the cost of rehabilitation must be taken into account in economic assessments [29]. From this analysis it emerged that the most costly sequelae were neurological – especially severe neurological damage and hearing impairment – followed by psychological and physical sequelae, as indeed has been shown by numerous other

studies, such as those by Shepard [25], Gasparini [11] and Scholz [16].

Costs of physical sequelae

Invasive meningococcal disease is associated with numerous physical sequelae, including: dermatological outcomes (skin scars, necrosis, eczema and psoriasis); musculoskeletal problems (amputations, limb deformities, arthritis and arthralgia); kidney diseases (acute and chronic renal insufficiency, urinary retention); vascular complications (Raynaud's phenomenon, venous thrombosis and vasculitis), and other physical conditions (adrenal insufficiency, anemia, pulmonary diseases, autoimmune diseases, chronic fatigue, and cardio-respiratory insufficiency).

The 2005 study by Shepard et al. considered the total cost generated by a few sequelae: $ 5,698 for skin scars, $ 166,317 for single amputations and $ 199,317 for multiple amputations. The cost of amputation comprised both that of the surgical procedure and the long-term cost (including rehabilitation). These costs were expressed in US dollars and referred to 2003 [25].

Wright et al. reported a cost of £ 21,793 (referred to 2008-2009) for skin scars and grafts. Their calculation was based on the evaluation of a clinical case of a 12-month-old child with septicemia due to meningococcus, severe septic shock, severe acute respiratory syndrome and renal insufficiency. The patient had developed gangrene of the limbs, caused by *purpura fulminans*, and suffered major skin necrosis [29].

In 2016, Gasparini et al. calculated the annual cost of physical sequelae as: € 7,339 for amputation with substantial disability, €1,184 for arthritis, € 1,066 for skin necrosis, € 533 for scars, and € 56,126 for kidney damage. Some considerations regarding this study, however, should be borne in mind: the cost of amputation also included the long-term cost (e.g. of prosthesis maintenance, rehabilitation, etc.); the cost attributed to arthritis covered only one year, as this complication frequently resolves within a relatively short time; the cost of kidney damage included both that of dialysis and that of permanent organ damage requiring kidney transplantation, assuming life expectancy of five years [11].

A Canadian study conducted in 2017 estimated the cost of a few long-term physical sequelae: skin scars $ 6,827; amputation $ 146,871, and kidney damage $ 1,001,960. However, it was not specified whether these calculations also included indirect costs. The prices, referred to 2015, were expressed in Canadian dollars [30].

The 2019 study by Scholz et al. analyzed the costs of sequelae over time. To avoid any confusion, it must be borne in mind that the German National Health System is structured differently from the Italian system. In their study, the authors subdivided the costs of the various sequelae into costs incurred during the first year and those incurred during subsequent years. Regarding the first year, the costs were: € 13,023 for amputation; € 2,026 for skin scars, and € 10,181 for kidney damage. Over the subsequent years, the annual costs were: € 2,413 for amputation; € 20 for skin scars, and € 4,532 for kidney damage [16].

Costs of neurological sequelae

Neurological sequelae are the most numerous and the most complex. Moreover, they place the heaviest cost burden on the NHS, especially in the long term. For details on the individual neurological sequelae, see chapter 3.

The 2005 study by Shepard et al. estimated the total cost of a few sequelae: $ 68,640 for deafness (this included the cost of a cochlear implant and its maintenance), and $ 2,503,677 for neurological disability, including the cost of residential care [25].

The 2013 HTA report by Di Pietro et al., which was based on the literature data, reported the annual costs of neurological sequelae as follows: € 23,679.47 for severe neurological disability; € 7,339.86 for mental retardation (cognitive disorders); € 1,914.96 for epilepsy/convulsions; € 1,114.85 for blindness; € 7,667.98 for motor deficit, and € 9,585.67 for severe communication disorders [13].

The 2016 study by Gasparini et al. calculated the annual cost of neurological sequelae as: € 7,682 for motor deficit; € 4,076 for blindness; € 2,272 for epilepsy/convulsions; € 94,880 for severe neurological disability; € 7,507 for mental retardation; € 6,327 for deafness requiring a cochlear implant; € 3,163 for moderate/severe bilateral/unilateral deafness; € 9,796 for severe communication disorders, and € 892 for migraine. Some features of these calculations, however, should be borne in mind. For example, the cost of deafness requiring cochlear implantation included not only the cost of the implant but also that of its long-term maintenance; moreover, the cost of severe neurological disability also included the cost of long-term institutional care [11].

A study conducted by De Wals in 2017 evaluated the total long-term costs of two neurological sequelae: deafness ($ 84,325) and neurological disability ($ 2,999,968). However, it was not specified whether these calculations also included indirect costs [30].

The German study conducted by Scholz et al. in 2019 subdivided the costs of neurological sequelae into costs incurred during the first year and those incurred during subsequent years. The first-year costs were: € 48,046 for deafness with cochlear implant; € 2,986 for moderate bilateral deafness; € 2,986 for moderate unilateral deafness; € 2,277 for severe neurological disability; € 2,003 for mental retardation/low IQ; €1,921 for communication impairment; € 486 for motor deficits; € 4,532 for epilepsy/convulsions, and € 742 for blindness/visual impairment. Over the subsequent years, the annual costs were: € 1,269 for deafness with cochlear implant; € 1,343 for moderate bilateral/unilateral deafness; € 122 for severe neurological disability; € 82 for mental retardation/low IQ; € 41 for communication impairment; € 41 for motor deficits; € 4,532 for epilepsy/convulsions, and € 742 for blindness/visual impairment [16].

Costs of psychological/psychiatric sequelae

In percentage terms, psychological sequelae are the most frequent, and are frequently associated to other types of sequelae. These are described in detail in chapter 3.

The above-mentioned HTA by Di Pietro et al. reported annual costs of € 2,923.16 for depression and € 1,065.68 for anxiety [13]. An Italian pharmaco-economic study conducted in 2016 calculated the annual costs of these sequelae as € 1,146 for anxiety and € 3,192 for depression [11]. Finally, in the study by Scholz et al., the costs of psychological sequelae in the first year and in the subsequent years were: € 1,538 for attention deficit hyperactivity disorder (ADHD; € 464 for depression; € 269 for anxiety, and € 2,487 for separation anxiety [16].

Indirect costs

Indirect costs comprise: the cost of death; costs due to loss of productivity of the patient and family members and psychiatric and psychological support for the family during the acute phase of the disease; the cost of patient management in the post-acute phase (psychiatric/psychological support for the family, loss of productivity of patients and parents), and the costs of managing a patient with sequelae (loss of patient's productivity, special education, private medical examinations, disability pensions, invalidity benefits, accompaniment allowances, costs of long-term psychiatric and psychological support for the patient and family members).

Social cost of death

To assess the social costs of the death of the patient, two approaches are generally adopted: "willingness to pay" and "human standard capital". As in previous studies, such as that by Gasparini et al. [11], these two approaches have been considered separately in this chapter. The cost was calculated on the basis of the patient's age at the time of death. The costs are expressed in € and updated to January, 2018 (Tab. I).

According to Scholz et al. [16] the cost of death, as calculated by means of the "Human Standard Capital" approach, varies greatly according to the patient's age at the time of death, being higher in the 1-4-year and 10-14-year age-groups and then decreasing significantly with the passing of time; the total capital lost over the entire mean lifespan is € 36,583 for each subject (prices updated to 2015).

Indirect cost of the acute phase

The only study found in which acute-phase indirect costs are reported was that by Scholz et al. [16], which calculated the mean cost of each individual case as € 1,322.

Cost of therapy for psychological/psychiatric sequelae

To date, no published studies have quantified the overall costs borne by families for psychological/psychiatric treatment sessions/pharmacological therapy needed by patients and their family members, and which are not covered by the NHS.

Cost of special education

Patients with invasive disease who suffer serious physical, neurological and psychological/psychiatric sequelae often require special educational support during school activities. In Italian schools, specialized teachers are available to assist pupils suffering from severe physical disabilities, learning difficulties, communication deficits and behavioral problems. Data from other countries, but which are nevertheless comparable, are also available in the literature.

According to the study by Wright et al. [29], the cost of special education amounts to € 5,311.67 for each school year, and employing a dedicated support teacher costs € 17,640.68 per year (costs converted to € and updated to January 2018). Educational support is guaranteed up to the age of 19 years. Gasparini et al. [11] reported the annual cost of special education as € 14,566, referred to 2013. In the study conducted by De Wals [30] in 2017, the cost of special education was calculated to be CAN$ 166,008 for the 10-17-year age-group.

The overall cost depends on the age of the patient and the type and gravity of the sequela.

Tab. I. Social cost of death, in Euro (data published in the study by Gasparini et al. [11].

Age	Willingness to pay (WTP) [11]	Human Standard Capital (HSC) [11]
10-14	1,961,403.81	232,730.43
15-24	2,162,446.39	375,007.29
25-64	1,284,407.72	343,070.81
> 64	98,005.38	41,144.16

Loss of productivity of the subject and of one parent

Loss of productivity of patients and their parents is difficult to quantify and can only be hypothesized. This value depends on the patient's age, on the gravity of his condition and on the social security system operating in the country.

In their Italian study, Gasparini et al. [11] hypothesized that the loss of productivity of one parent amounted to € 870 during the acute phase, and to € 24,500 annually over the subsequent years (differing according to the gravity of sequelae). They estimated that the patient's loss of productivity during the acute phase amount to € 1,426, while the annual cost over the subsequent years was equal to that of the parents (costs referred to January 2013).

Scholz et al. [16] estimated a mean number of 92 working days lost in the base-case. Moreover, on subdividing lost income by sex and age-group, they estimated that male subjects had a mean per capita income of € 16,728 in the 10-24-year age-group, € 43,070 in the 25-64-year age-group, and € 14,394 if aged over 65 years. The corresponding figures among females were: 10-24 years, € 14,107; 25-64 years, € 25,984.4; and > 65 years, € 8,382.

Italian Social Security System

In accordance with article 38 of the Italian Constitution, the Italian social security system is responsible for social security and assistance, and provides a range of services such as old-age pensions, retirement pensions, invalidity, disability and survivors' pensions, etc. The main Italian social security institution is the INPS (National Social Security Institute).

According to the INPS management, the *disability pension for civil invalids* constitutes an economic benefit, which is

paid on demand to subjects who are recognized as being totally (100%) and permanently unable to work and who are in a state of economic need. This economic benefit is paid to totally disabled persons aged between 18 and 67 years who meet the health and administrative requirements; 13 sums of € 285.66 are paid per year. Persons over the age of 67 years may also receive a *social allowance*, bringing the total amount to 13 sums of € 458.00 per year [31].

By contrast, the *ordinary disability allowance* is paid to those whose working capacity is reduced to less than a third, owing to physical or mental infirmity; at retirement age, it becomes an old-age pension. The amount is variable, being based on a calculation that considers both the contributions paid into the system by the individual and the remuneration received [31].

The *accompaniment allowance* is an economic benefit, payable on demand to persons who are totally disabled owing to physical or mental impairment, who are unable to walk without the aid of another person or who are unable to perform the normal activities of daily life. It is payable to citizens whose total (100%) disability has been ascertained and who reside permanently in Italy, regardless of their annual personal income and age. The amount is € 517.84 per month for 12 months. Moreover, the accompaniment allowance is also compatible and cumulative with the disability pension, other pensions and the accompaniment allowances for the totally or partially blind (multiply disabled persons) [31].

The *special allowance* is an economic benefit, payable on demand to those recognized as partially blind. This allowance is due only on account of the impairment, i.e., it is independent of age and income. The allowance is paid in 12 monthly installments; in 2016, the amount was € 206.59 per month [31].

The *communication allowance* is an economic benefit issued upon request to those who have been recognized as suffering from congenital or acquired deafness, regardless of age or income. Twelve monthly sums of € 256.89 are paid per year. The allowance is compatible with the performance of a work activity and with other direct allowances granted on account of disability due to war, work or service [31].

To date, no published studies have quantified the social security costs associated with meningococcal disease and its sequelae in Italy.

As it is very difficult to assess the social security cost of meningococcal disease in Italy, this cost item was not considered in the present HTA report. It should, however, be stressed that these costs could be very high in the case of severe sequelae (severe neurological damage, deafness, amputations, blindness, etc.). Indeed, these sequelae are highly invalidating and, in the most serious cases, the subjects require constant support in order to perform their normal everyday activities. In addition, many patients are totally unable to work.

Focus on some clinical cases and their costs

Bénard et al. described two scenarios involving patients with septicemia and *purpura fulminans* (case A) and meningococcal meningitis (case B). They estimated both direct and indirect costs (expressed in € and updated to 2013) incurred throughout each patient's lifetime (case A and case B).

Case A reports the clinical history of a 6-year-old boy who presents with septicemia and *purpura fulminans*, and who suffers bilateral amputation of the legs below the knee. After hospital discharge, the child attends a rehabilitation center 5 times a week for 4 months. Once the wounds have healed, the patient undergoes skin grafting in order to repair the dermatological damage caused by the amputation. After his return home, his parents employ a home help for 3 months. In addition, his wounds are medicated during home visits by a nurse. The boy undergoes several other operations owing to complications due to the amputation. Before the child's illness, his mother worked full-time, earning the French minimum wage, while his father, who also worked full-time, earned an average wage. When the child is taken ill, his mother gives up work for 6 months; she subsequently returns to work, but on a part-time schedule. The patient's family receive parental allowances for 6 months and, subsequently, a "Handicapped Child Education Aid" allowance until the patient reaches the age of 20 years. After taking his high-school diploma, the patient continues to study for another 3 years and, at the age of 21 years, takes up full-time employment in an office, and is no longer dependent on his parents. He dies at the age of 77 years. The main cost items regard: prostheses (€ 281,595), special equipment (€ 109,760), education (€ 100,315), domestic help (€ 82,099) and hospital care (€ 58,694). Loss of income is estimated as € 77,214. The total discounted cost of case A amounts to € 768,875. With regard to case A, the authors also hypothesized an alternative scenario in which the patient develops chronic renal insufficiency and needs 4 kidney transplants during his lifetime; in this scenario, the discounted cost comes to € 1,480,546.

Case B concerns a 3-year-old girl with a clinical presentation of meningococcal meningitis, who is hospitalized in the intensive care unit. The patient presents convulsions and complications due to severe encephalitis. After the disease, she presents cognitive impairment, hemiplegia, lateral hemianopia, behavioral disorders and hydrocephalus. Following hospital discharge, the child is transferred to a rehabilitation center for 5 months. During her lifetime, the patient undergoes neurosurgical ventriculoperitoneal shunt operations. Owing to her clinical condition, the patient needs to use a wheelchair and a corset throughout her life, to assist her mobility. With regard to schooling, she attends a specialized center (Medical-Educational Institute). Before the patient's illness, her parents both worked full-time and earned an average wage. When the child is taken ill, her mother gives up work for 7 months; she subsequently returns to work, but on a part-time schedule. The patient's family receive a parental allowance for 6 months and, subsequently, a "Handicapped Child Education Aid" allowance until the patient reaches the age of 20 years. At the age of 20 years, the patient is placed in full-time residential care, where she remains until her death at the age of 55 years. With regard to case B, the authors also hypothesized an alternative scenario in which the girl receives drugs to treat her epilepsy and a cochlear implant

to treat her severe deafness. In the original scenario, the total discounted cost is € 1,924,475, the main cost items being: education (€ 835,922), residential care (€ 669,308), loss of income (€ 159,244) and special equipment (€ 130,660); on adding the cost of treating deafness and epilepsy, the total becomes € 2,267,25 [32].

Darbà et al. assessed the medical, educational and social costs accruing to survivors from invasive meningococcal disease from the perspective of the Spanish health system. The authors described two different scenarios: patient A with septicemia and patient B with meningococcal meningitis. The non-discounted costs were expressed in € and updated to the 2012 consumer price index.

At the age of 12 months, patient A presents respiratory difficulty, renal problems and *purpura fulminans*; he subsequently undergoes amputation of both legs above the knee and of one arm above the elbow. The cost of the prostheses is € 934,186 and that of their revision and maintenance € 21,683. The patient spends 31 days in the intensive care unit and another 90 days in the pediatric department, the total cost amounting to € 139,269. After being discharged, he requires regular appointments with the pediatrician, orthopedic surgeon, physiatrist and plastic surgeon until he is 18 years old; he also undergoes periodic examinations of his prostheses (total € 13,400) and special equipment (€ 11,139). The patient attends primary and secondary school with the support of a specialized teacher (€ 33,449) and requires special transport to and from school (€ 6,013). Moreover, he needs psychotherapy sessions up to the age of 20 years (€ 34,934 for drugs). His family members also require psychological support. As one of the patient's parents gives up working in order to look after him, the family income decreases. For this reason, the family receives personal social services, an indemnity and an allowance for disabled persons (total cost: € 733,841). The patient attends university for four years and obtains a job, which enables him to become independent from his parents.

Patient B is struck by meningococcal meningitis at the age of 3 years, which leaves him with severe neurological sequelae, including epilepsy and deafness. He is hospitalized in the intensive care unit for 26 days, and then spends 100 days in the pediatric department (total cost € 112,840). Owing to his severe neurological sequelae, he requires regular examinations by that neurologist, physiatrist, pediatric surgeon and ophthalmologist (total cost € 43,126). Moreover, on account of his inability to walk, he has to use a wheelchair for the rest of his life and, because of his deafness, he requires two cochlear implants (replaced at the age of 13 years), the total cost being € 11,715. The patient attends a special school up to the age of 18 years and, subsequently, a day center for the disabled (€ 201,977). One of the patient's parents gives up working during the acute phase of the disease, in order to look after him; the family income therefore declines. For this reason, the family is granted an indemnity, personal social services and financial assistance for the patient's transport. The total cost of these benefits is € 1,240,281. After the age of 18 years, the patient receives a pension owing to his inability to work [33].

Conclusions

Although invasive meningococcal disease is rare in high-income countries, this pathology and its short-, medium- and long-term complications give rise to high direct and indirect costs.

In order to provide a detailed, in-depth assessment of these costs, we considered both direct costs – i.e. those borne by the NHS – and the indirect costs borne by society (costs accruing to other state institutions, the family and society in general). Moreover, in order to reach an even more accurate evaluation, we subdivided each cost category (direct and indirect) by the three phases of disease: acute phase, post-acute phase and long-term phase with sequelae. The main economic impact was seen to be driven by the direct and indirect costs associated with sequelae; specifically, the sequelae resulting in the greatest cost are neurological sequelae that involve the auditory apparatus and those which result in mental retardation. Among the indirect costs, we can highlight those of special education (borne by the state), which is needed in order to support patients in their school career. In addition, it is important not to overlook the costs resulting both from the loss of productivity of patients and their parents, who are often forced to give up working, and from the need to provide psychiatric/psychological support for patients and caregivers.

Finally, it should be stressed that, in Italy, costs may be markedly underestimated as a result of the shortage of data on the frequency of multiple sequelae and the association of these with each other, their consequences and the paucity of cost data. It therefore seems necessary to design Italian studies for the assessment of the direct and indirect costs of meningococcal disease.

Bibliografia

[1] CDC - Centre for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. The Pink Book, 13th Edition, 2015, chapter 14: Meningococcal Disease. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/mening.html [Accessed 28/02/2019].

[2] Buysse CM, Vermunt LC, Raat H, Hazelzet JA, Hop WC, Utens EM, Joosten KF. Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care 2010;14(3):R124. https://doi.org/10.1186/cc9087

[3] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program A. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028

[4] ECDC - European Centre for Disease Prevention and Control. Invasive meningococcal disease - Annual epidemiological report for 2015. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-meningococcal-disease.pdf [Accessed 28/02/2019].

[5] Bosis S MA, Esposito S. Meningococcal disease in childhood: epidemiology, clinical features and prevention. J Prev Med Hyg 2015;56):E121-4.

[6] Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-

cohort study. Pediatrics 2009;123(3):e502-9. https://doi.org/10.1542/peds.2008-0581

[7] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine 2014;32(37):4791-8. https://doi.org/10.1016/j.vaccine.2014.05.069

[8] Erickson L DWP. Complication and sequelae of meningococcal disease in Quebec, Canada 1990-1994. Clin Infect Dis 1998;26(5):1159-64.

[9] Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther 2013;11(6):597-604. https://doi.org/10.1586/eri.13.42

[10] Olbrich KJ, Muller D, Schumacher S, Beck E, Meszaros K, Koerber F. Systematic review of invasive meningococcal disease: sequelae and quality of life impact on patients and their caregivers. Infect Dis Ther 2018;7(4):421-38. https://doi.org/10.1007/s40121-018-0213-2

[11] Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, Tanfani E, Bonanni P, Lucioni C, Testi A, Panatto D. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero(R)) against meningococcal B disease: a cost-effectiveness analysis. Hum Vaccin Immunother 2016;12(8):2148-61. https://doi.org/10.1080/21645515.2016.1160177

[12] Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new MenB vaccine (Bexsero) into the Italian routine infant immunisation programme. PLoS One 2015;10(4):e0123383. https://doi.org/10.1371/journal.pone.0123383

[13] Di Pietro ML CS, Kheiraoui F, de Waure C, Quaranta G, Poscia A, Specchia ML, Veneziano MA, Di Nardo F, Cadeddu C, Lovato E, Ferriero AM, Mancuso A, Miglietta A, Delon M, Alicevjc M, La Torre G, Fantoni S, Bianchi A. Health Technology Assessment della vaccinazione contro Meningococco B. 2013.

[14] Decreto Ministeriale. Sistema informativo delle malattie infettive e diffusive. Pubblicato nella Gazz. Uff. 8 gennaio 1991, n. 6. 15 dicembre 1990.

[15] Regione Liguria. Dipartimento Salute e Servizi Sociali. Struttura Prevenzione, Igiene, Sanità Pubblica. Commissione Regionale Vaccini e Malattie Infettive. 2016. Sorveglianza delle malattie invasive da Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae tipo b. Protocollo operativo per le attività di Sanità Pubblica. Available at: http://www.alisa.liguria.it/index.php?option=com_docman&task=doc_download&gid=487&Itemid=116 [Accessed 12/04/2019].

[16] Scholz S, Koerber F, Meszaros K, Fassbender RM, Ultsch B, Welte RR, Greiner W. The cost-of-illness for invasive meningococcal disease caused by serogroup B Neisseria meningitidis (MenB) in Germany. Vaccine 2019;37(12):1692-701. https://doi.org/10.1016/j.vaccine.2019.01.013

[17] Istituto Nazionale di Statistica. ISTAT. Data available at: http://dati.istat.it [Accessed 01/03/19].

[18] Van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Sipahi OR, Brouwer MC, Brain ESGfIot. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22(Suppl 3):S37-62. https://doi.org/10.1016/j.cmi.2016.01.007

[19] Prices are taken from the site: www.federfarma.it. Accessed 28/02/2019.

[20] Dipartimento Salute e Servizi Sociali Settore Prevenzione, Sanità Pubblica, Sicurezza Alimentare e Sanità Animale. Regione Liguria. Protocolli operativi per la sorveglianza e la gestione diagnostico terapeutica delle malattie batteriche invasive da Neisseria Meningitidis, Streptococcus Pneumoniae, Haemophilus Influenzae tipo B. 2016.

[21] Scheda Tecnica di Trumenba®. Available at: https://ec.europa.eu/health/documents/community-register/2017/20170524137650/anx_137650_it.pdf [Accessed 01/04/2019].

[22] Scheda Tecnica Bexsero(R). Available at: https://www.ema.europa.eu/en/documents/product-information/bexsero-epar-product-information_it.pdf [Accessed 01/04/2019].

[23] Trotter CL, Delea TE, Weycker D, Atwood M, Neame D, Alvarez FP, Forget E, Langley JM, Chit A. Cost-effectiveness of alternate strategies for childhood immunization against meningococcal disease with monovalent and quadrivalent conjugate vaccines in Canada. Plos One 2017;12(5). https://doi.org/10.1371/journal.pone.0175721

[24] Ortega-Sanchez IR, Meltzer MI, Shepard C, Zell E, Messonnier ML, Bilukha O, Zhang X, Stephens DS, Messonnier NE and Active Bacterial Core Surveillance T. Economics of an adolescent meningococcal conjugate vaccination catch-up campaign in the United States. Clin Infect Dis 2008;46(1):1-13. https://doi.org/10.1086/524041

[25] Shepard CW, Ortega-Sanchez IR, Scott RD 2nd, Rosenstein NE, Team AB. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. Pediatrics 2005;115(5):1220-32. https://doi.org/10.1542/peds.2004-2514

[26] Anonychuk A, Woo G, Vyse A, Demarteau N, Tricco AC. The cost and public health burden of invasive meningococcal disease outbreaks: a systematic review. Pharmacoeconomics 2013;31(7):563-76. https://doi.org/10.1007/s40273-013-0057-2

[27] Lecocq H, Parent du Châtelet I, Taha M-K, Lévy-Bruhl D, Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine 2016;34(19):2240-50. https://doi.org/10.1016/j.vaccine.2016.03.020

[28] Wang B, Santoreneos R, Afzali H, Giles L, Marshall H. Costs of invasive meningococcal disease: a global systematic review. Pharmacoeconomics 2018;36(10):1201-22. https://doi.org/10.1007/s40273-018-0679-5

[29] Wright C, Wordsworth R and Glennie L. Counting the cost of meningococcal disease. Pediatric Drugs 2013;15(1):49-58. https://doi.org/10.1007/s40272-012-0006-0

[30] De Wals P and Zhou Z. Cost-effectiveness comparison of monovalent C versus quadrivalent ACWY meningococcal conjugate vaccination in Canada. Pediatr Infect Dis J 2017;36(7):e203-7. https://doi.org/10.1097/INF.0000000000001512

[31] INPS - Istituto Nazionale Previdenza Sociale. Data available at: https://www.inps.it/nuovoportaleinps (Accessed 07/03/2019).

[32] Benard S, Wright C, Voisine J, Olivier CW, Gaudelus J. Lifetime cost of meningococcal disease in France: scenarios of severe meningitis and septicemia with purpura fulminans. J Infect Public Health 2016;9(3):339-47. https://doi.org/10.1016/j.jiph.2015.10.016

[33] Darba J, Kaskens L, Hark M, Wright C. Costs of surviving meningococcal disease in Spain: evaluation for two cases of severe meningitis and septicaemia. Vaccine 2014;32(39):5006-12. https://doi.org/10.1016/j.vaccine.2014.07.019

Immunogenicity and safety of the anti-meningococcal serogroup B vaccine Trumenba®

D. AMICIZIA[1], S. BOCCALINI[2], A. BECHINI[2], P. BONANNI[2], E. LECINI[1], P.L. LAI[1], D. PANATTO[1]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Department of Health Sciences, University of Florence, Italy

Introduction

The vaccine Trumenba® is indicated for the active immunization of subjects aged ≥ 10 years against invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B (Men B). It is a vaccine constituted by two lipidated recombinant variants of factor H-binding protein (fHbp). The protein fHbp is present on the surface of meningococcus and is essential to the microorganism in order to elude the host's immune defenses. The variants of fHbp are subdivided into two immunologically distinct subfamilies, A and B, and over 96% of the Men B strains isolated in Europe express variants of fHbp of both subfamilies on the bacterial surface [1].
The aim of vaccination with Trumenba® is to stimulate the production of bactericidal antibodies that recognize the fHbp expressed by meningococcus [1].

Challenges in the development of a vaccine against serogroup B meningococcus

The polysaccharides of the *Neisseria meningitidis* capsule are important virulence factors that inhibit the protective mechanisms of the host cell. Most of the available vaccines against meningococcus utilize a fragment derived from the capsular polysaccharides in order to trigger an immune response through the production of antibodies [2]. Although this strategy has been successful in the development of vaccines against serogroups A, C, W and Y, the same cannot be said of serogroup B, the capsule of which is composed of polymers of α 2-8 N-acetylneuraminic acid; as this is also found on the human neuron as a cellular adhesion molecule (NCAM), vaccines targeting the polysaccharides of serogroup B are not immunogenic in humans.
Since the polysaccharide vaccines are not efficacious against Men B, a new strategy has been adopted for the development of vaccines against this serogroup; a conserved protein antigen exposed on the bacterial surface has been identified with the aim of providing broad protection against the various strains of Men B [3].

Development of Trumenba®

The development of Trumenba® began with the identification of proteins exposed on the bacterial surface which were able to stimulate the production of bactericidal antibodies, thereby conferring immune protection against a broad range of Men B strains. Lipoprotein 2086 (LP2086), or fHbp, which is expressed on the bacterial surface, was identified as a major virulence factor. Indeed, during infection, fHbp is involved in the interaction of *N. meningitidis* with the immune system of the host organism, as it binds a negative complement regulator, factor H, to the bacterial surface and reduces complement-mediated bactericidal activity [4, 5]. The different variants of fHbp are subdivided into two immunologically distinct subfamilies, A and B, which display limited cross-reactivity [6].
The identification of fHbp led to the development of Trumenba®, the only vaccine against Men B that contains two fHbp antigens – one variant from each subfamily (A05 and B01) – thereby conferring broader protection against disease due to Men B [1, 7-9].
In order to assess the potential of Trumenba® to protect against Men B strains that cause invasive disease, numerous studies were conducted on thousands of Men B isolates collected between 2000 and 2006 by the reference laboratories for invasive diseases due to meningococcus in the United Kingdom, Norway, the Czech Republic, France, the United States, Germany and Spain. These studies revealed the distribution and sequence diversity of fHbp. Initially, 1263 isolates were collected in order to create a representative pool of invasive Men B strains, which was dubbed "pool of meningococcus B strains evaluated by means of the serum bactericidal activity (SBA) test". The pool was subsequently integrated with 551 strains from Spain and Germany [10]. A total of 198 different amino acid sequences of fHbp (called variants) were identified in the extended pool, and about 80% of the isolates from invasive disease expressed one of the 10 main variants of fHbp. The amino acid sequences of the different variants of fHbp were used to construct phylogenetic trees in order to describe the relationship of the sequences of the single variants. The fHbp variants segregate into two distinct subfamilies, named A and B; 30% of hypervirulent Men B strains were seen to express fHbp variants belonging to subfamily A, while 70% expressed variants belonging to subfamily B. Most (77%) of the isolates in the pool expressed one of the following fHbp variants: B24, B16, A22, B03, B44, B09, A19, A12, A05 and A07. Men B strains that had caused recent outbreaks in France and the United States mostly expressed similar fHbp variants, with the exception of two new variants (B153 and B228) [9, 11-13].

The level of expression of fHbp on the bacterial surface is a major factor in the susceptibility of Men B strains to the serum bactericidal antibodies induced by vaccination with Trumenba®. To evaluate the level of expression, the Meningococcal Antigen Surface Expression (*MEASURE*) assay was developed and validated; this utilizes an antibody that binds to all the fHbp variants belonging to both subfamilies, and accurately quantifies their level. This assay is able to correlate the level of surface expression of fHbp with the killing of Men B strains in tests of serum bactericidal activity with human complement (hSBA).
The results of a multi-center international study of over 2,150 Men B isolates collected in the period 2000-2014 in 7 European countries, the United States and Canada revealed that 91% of the isolates expressed levels of fHbp that were sufficient to determine susceptibility to the bactericidal action of the antibodies induced by the vaccine [1]. The hSBA test was used to measure the serum quantity of vaccine-elicited antibodies capable of triggering complement-dependent bactericidal activity [1].

Clinical development

During its clinical development program, Trumenba® proved able to stimulate the production of antibodies against various hypervirulent strains of Men B. Specifically, vaccination with Trumenba® stimulates the production of antibodies against fHbp that bind to the target protein expressed on the surface of *N. meningitidis*. Trumenba® is able to induce the production of antibodies against variants belonging to both the A and B subfamilies of fHbp.
As part of the clinical development program, Trumenba® was tested against several Men B strains identified during preclinical studies, and which expressed fHbp variants that were different from those contained in the vaccine, but which were representative (in terms of frequency of expression) of circulating hypervirulent strains; specifically, 4 primary strains (A22, A56, B24 and B44) and 10 additional strains (A06, A07, A12, A15, A19, A29, B03, B09, B15 and B16) were identified [1, 9, 14].
Owing to the low incidence of invasive meningococcal disease, it is not possible to evaluate the efficacy of anti-meningococcal vaccines directly by means of clinical trials. The efficacy of such vaccines is therefore deduced by demonstrating the induction of bactericidal antibodies (immunogenicity).

Immunogenicity

Immunogenicity is measured by means of a test which evaluates the capacity to induce serum bactericidal antibodies in the presence of human complement (hSBA test). The SBA test is a functional measure of the ability of vaccine-induced antibodies to kill *N. meningitidis*; hSBA titers ≥1:4 are considered indicative of a protective immune response against meningococcal disease [1,15-16].

In the main trials, the immunogenicity of Trumenba® was evaluated by measuring the antibody response against the four test strains defined as primary (A22, A56, B24 and B44). Each of these expressed fHbp variants that differed from those contained in the vaccine. These strains were chosen in order to have a panel that would be representative of Men B strains circulating in Europe and the United States (epidemiologically important in terms of frequency).
In the immunogenicity studies of Trumenba®, a response was defined as protective when an hSBA titer ≥ 1:8 or ≥1:16 was reached, according to the test strain used. The primary endpoint was a fourfold increase in the hSBA titer. In addition, the composite titer, which reflects a composite response to all 4 primary strains, was also evaluated [1].
The serum samples used for immunogenicity analysis were taken from subjects enrolled in controlled clinical studies; they were taken before the administration of the first dose of vaccine (baseline) and approximately one month after the second or third dose (according to the vaccination schedule used).
The ability of Trumenba® to induce a robust bactericidal immune response was demonstrated in phase I and II clinical studies [17-24].
Table I reports the controlled clinical studies conducted to evaluate the immunogenicity and safety of Trumenba®.

Phase III clinical studies

Two multicenter phase III controlled clinical studies were carried out in order to evaluate the immunogenicity and safety of Trumenba® in a population of adolescent subjects aged 10-18 years (ClinicalTrials.gov number NCT01830855) and young adults aged 18-25 years (ClinicalTrials.gov number NCT01352845) [16]. Both were phase III randomized, controlled studies versus the active substance (HAV vaccine/saline solution) or placebo (saline solution) [16]. In both studies, Trumenba® was tested against 4 test strains of Men B (representative of the diversity of circulating Men B strains) and was confirmed against 10 additional strains.
In both studies, the five primary endpoints were constituted by the proportion of subjects with at least a fourfold increase in their hSBA titer against each of the primary test strains (4) and the proportion of subjects with a composite response, defined as an hSBA titer ≥ the lower limit of quantification (1:8 [A56, B24 and B44] or 1:16 [A22]), to all four primary test strains, each assessed one month after the third vaccine dose.
The secondary endpoints included the immunogenic response to 10 additional strains, as indicated by hSBA titers above the predefined threshold.
In the study of adolescents after 3 doses of Trumenba®, the proportion of subjects achieving a ≥ 4-fold increase in their hSBA titers ranged from 78.8% to 90.2%. A composite response to the 4 test strains after 3 doses of Trumenba® was seen in 83.5% of subjects (Fig. 1) [1, 16].
A high percentage of subjects who had received 3 doses of Trumenba® reached an hSBA titer ≥ 1:8* towards the

Tab. I. Controlled clinical studies to evaluate the safety and immunogenicity of Trumenba®.

Study	Objective of the study	Subjects enrolled (N, age)	Country where conducted	Dosage and vaccination schedule
A phase 1, randomized, open-label, active-controlled trial to assess the safety of a meningococcal serogroup B bivalent rLP2086 vaccine in healthy adults [17]	Safety and immunogenicity in healthy adults	48: 18-40 years	USA	Group 1: 60 µg 0, 2, 6 months Group 2: 120 µg 0, 2, 6 months Group 3: 200 µg MenB-FHbp 0, 2, 6 months Group 4: Tdap, 0 months; Saline 2, 6 months
A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults [18]	Safety and immunogenicity in healthy adults	60: 18-40 years	Australia	Group 1: 120 µg MenB-FHbp 0, 1, 6 months
Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomized, single-blind, placebo-controlled, phase 2 study [19]	Safety and immunogenicity in adolescents	539: 11-18 years	Australia	Group 1: 60 µg MenB-FHbp 0, 2, 6 months Group 2: 120 µg MenB-FHbp 0, 2, 6 months; Group 3: 200 µg MenB-FHbp 0, 2, 6 months Group 4: saline solution
Meningococcal serogroup B-specific responses after vaccination with bivalent rLP2086: 4-year follow-up of a randomized, single-blind, placebo-controlled, phase 2 trial [20]	Antibody persistence 48 months after the 3rd dose	250: 11-18 year		No dose of vaccine
Meningococcal Serogroup B Bivalent rLP2086 Vaccine Elicits Broad and Robust Serum Bactericidal Responses in Healthy Adolescents [21]	Safety and immunogenicity	1713: 11-18 years	Czech Republic, Denmark, Finland, Germany, Poland, Spain, Sweden	All groups vaccinated with 120 µg Men-B-FHbp. Group 1: 0, 1, 6 months Group 2: 0, 2, 6 months Group 3: 0, 6 months Group 4: 0, 2 months Group 5: 0, 4 months
Immunogenicity, Safety, and Tolerability of Bivalent rLP2086 Meningococcal Group B Vaccine Administered Concomitantly With Diphtheria, Tetanus, and Acellular Pertussis and Inactivated Poliomyelitis Vaccines to Healthy Adolescents [22]	Safety and immunogenicity of Men-B-FHbp co-administered with dTaP/IPV	749: 11-18 years	Finland, Germany, Poland	Group 1: 0, 2, 6 months 120 µg Men-B-FHbp + dTaP/IPV 0 months; Group 2: dTaP/IPV 0 months, saline solution at 0, 2, 6 months
Immunogenicity, Tolerability and Safety in Adolescents of Bivalent rLP2086, a Meningococcal Serogroup B Vaccine, Coadministered with Quadrivalent Human Papilloma Virus Vaccine [23]	Immunogenicity of HPV4 in co-administration with Men-B-FHb; safety, tolerability and immunogenicity of Men-B-FHbp	2499: 11-17 years	USA	Group 1: 120 µg Men-B-FHbp+ HPV4 0, 2, 6 months; Group 2: 120 µg Men-B-FHbp + saline solution 0, 2, 6 months; Group 3: HPV4 + saline solution 0, 2, 6 months
A phase 2, randomized, active-controlled, observer-blinded study to assess the immunogenicity, tolerability, and safety of bivalent rLP2086, a meningococcal serogroup B vaccine, coadministered with tetanus, diphtheria and acellular pertussis vaccine and serogroup A, C, Y and W-135 meningococcal conjugate vaccine in healthy US adolescents [24]	Safety, tolerability and immunogenicity of Men-B-FHbp in co-administration with MCV4 and Tdap	2648: 10-12 years	USA	Group 1: 120 µg Men-B-FHbp 0, 2, 6 months, MCV4 and Tdap 0 months; Group 2: MCV4 0 months, Tdap 0 months, saline solution 0, 2, 6 months; Group 3: 120 µg Men-B-FHbp 0, 2, 6 months, MCV4 7 months, Tdap 7 months, saline solution 2 vaccinations 0 months

(continues)

Tab. I. Controlled clinical studies to evaluate the safety and immunogenicity of Trumenba® (*follows*).

Study	Objective of the study	Subjectsenrolled (N, age)	Country where conducted	Dosage and vaccination schedule
A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults [25]	Safety, tolerability and immunogenicity of Men-B-FHbp in healthy subjects	5712: 10-25 years	Australia, Chile, Czech Republic, Denmark, Estonia Finland, Germany, Lithuania, Poland, Sweden, USA	Group 1: 120 µg Men-B-FHbp 0, 2, 6 months; Group 2: hepatitis A/saline solution 0, 2, 6 months
A bivalent meningococcal B vaccine in adolescents and young adults [16]	Safety, tolerability and immunogenicity of Men-B-FHbp in healthy adolescents	3596: 10-18 years	Canada, Czech Republic, Finland, Germany, Italy, Poland, UK, USA	Group 1: 120 µg Men-B-FHbp 0, 2, 6 months; Group 2: saline solution + HAV 0, 2, 6 months
A bivalent meningococcal B vaccine in adolescents and young adults [16]	Safety, tolerability and immunogenicity of Men-B-FHbp in healthy young adults	3304: 18-25 yeaers	Canada, Denmark, Finland, Poland, Spain, USA	Group 1: 120 µg Men-B-FHbp 0, 2, 6 months; Group 2: saline solution 0, 2, 6 months

4 primary test strains and the 10 additional strains (≥1:16 for A06, A12, A19 and A22) (Fig. 2).

The clinical study conducted on young adults (18-25 years) revealed that, one month after the third vaccine dose, between 79.3% and 90.0% of subjects had reached a ≥ 4-fold increase in their hSBA antibody titers. A composite response to all four primary strains after 3 doses of Trumenba® was seen in 84.9% of subjects (Fig. 3) [1, 16].

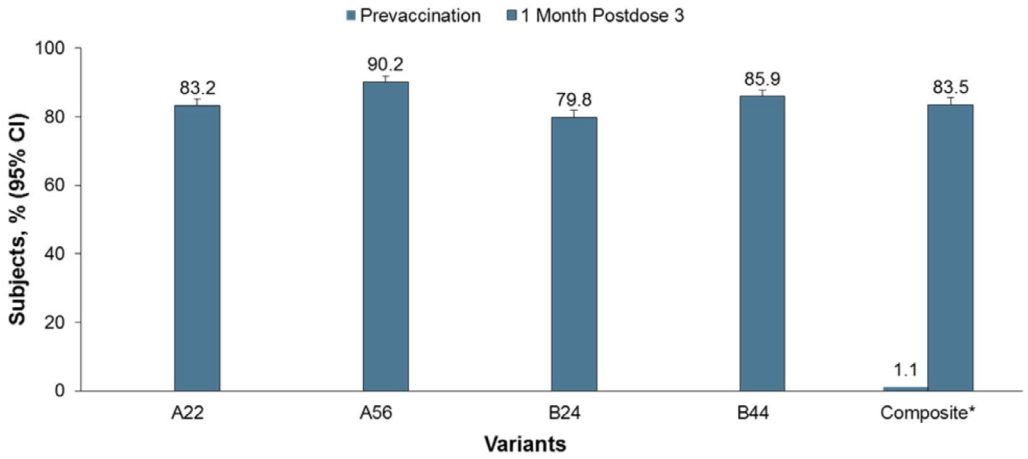
A high percentage of subjects who had received 3 doses of Trumenba® reached an hSBA titer ≥ 1:8* towards the 4 primary test strains and the 10 additional strains (≥ 1:16 for A06, A12, A19 and A22) (Fig. 4).

In both studies, the objectives were achieved; the ability of Trumenba® to provide a robust immunological response against antigenically and epidemiologically different Men B strains was demonstrated [16, 17].

Phase II clinical studies

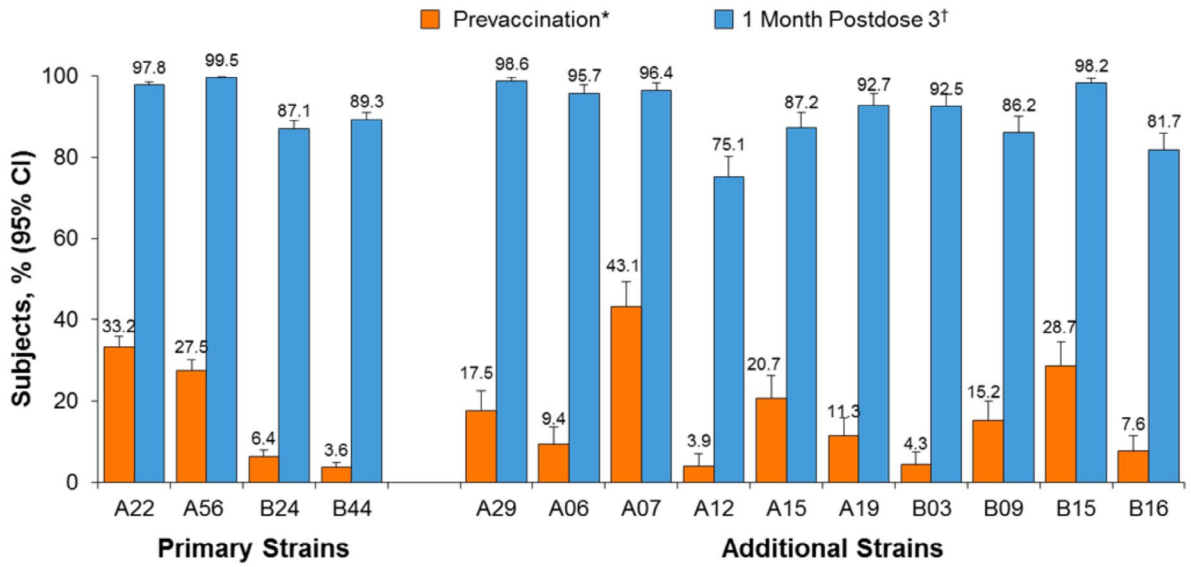
The immunogenicity of a 2- or 3-dose schedule of Trumenba® in adolescents aged 11-18 years was evaluated in a phase II, multicenter, randomized, controlled study [21]. The primary endpoint was the proportion of subjects who reached an hSBA titer ≥1:8 against each of the 4 primary test strains of Men B after 3 doses of Trumenba®. The secondary endpoints included the proportion of subjects with an hSBA titer ≥ 1:8 and the assessment of hSBA titers against each of the 4 primary test strains of Men B after 2 doses of Trumenba®.

Fig. 1. Percentage of adolescents achieving a ≥ 4-fold increase in their hSBA titers and a composite response to the primary test strains a month after 3 doses of Trumenba®.



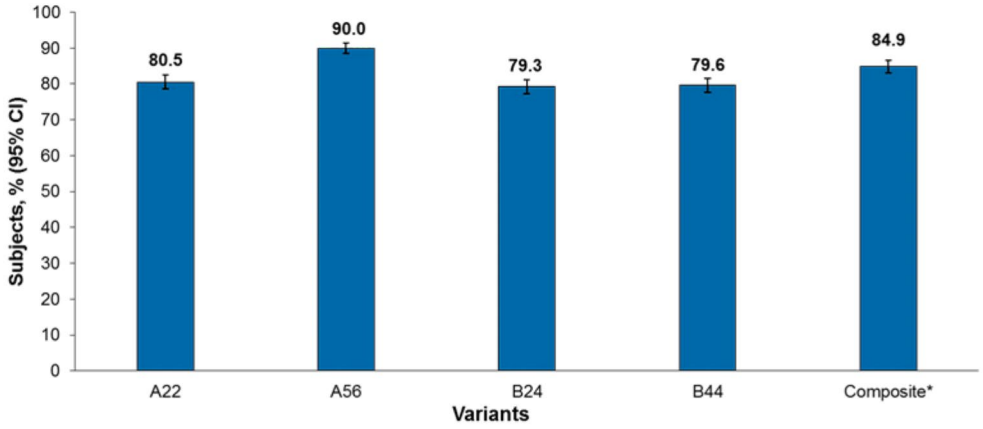
* hSBA titer ≥ the pre-specified threshold for all 4 primary strains (≥ 1:16 [A22] or ≥ 1:8 [A56, B24 and B44]) 1 month after vaccination. A 4-fold increase is defined as follows: (1) in subjects with a baseline hSBA titer < 1:4, a response is defined as an hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24, and B44); (2) in subjects with a baseline hSBA titer ≥ 1:4 and < 1:16 (A22) or <1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the pre-specified threshold (1:8 or 1:16); and (3) in subjects with a baseline hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the reference titer.

Fig. 2. Percentage of adolescents with hSBA titers ≥ 1:8 or ≥ 1:16 after vaccination with Trumenba®.



* hSBA titer ≥ the pre-specified threshold for all 4 primary strains (≥ 1:16 [A22] or ≥ 1:8 [A56, B24 and B44]) 1 month after vaccination. A 4-fold increase is defined as follows: (1) in subjects with a baseline hSBA titer < 1:4, a response is defined as an hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24, and B44); (2) in subjects with a baseline hSBA titer ≥ 1:4 and < 1:16 (A22) or < 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the pre-specified threshold (1:8 or 1:16); and (3) in subjects with a baseline hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the reference titer.

Fig. 3. Percentage of subjects who displayed a ≥ 4-fold increase in their hSBA titers and a composite response to the primary test strains one month after receiving the 3rd dose of Trumenba®.



* hSBA titer ≥ the pre-specified threshold for all 4 primary strains (≥ 1:16 [A22] or ≥ 1:8 [A56, B24 and B44]) 1 month after vaccination. A 4-fold increase is defined as follows: (1) in subjects with a baseline hSBA titer < 1:4, a response is defined as an hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24, and B44); (2) in subjects with a baseline hSBA titer ≥ 1:4 and < 1:16 (A22) or < 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the pre-specified threshold (1:8 or 1:16); and (3) in subjects with a baseline hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the reference titer.

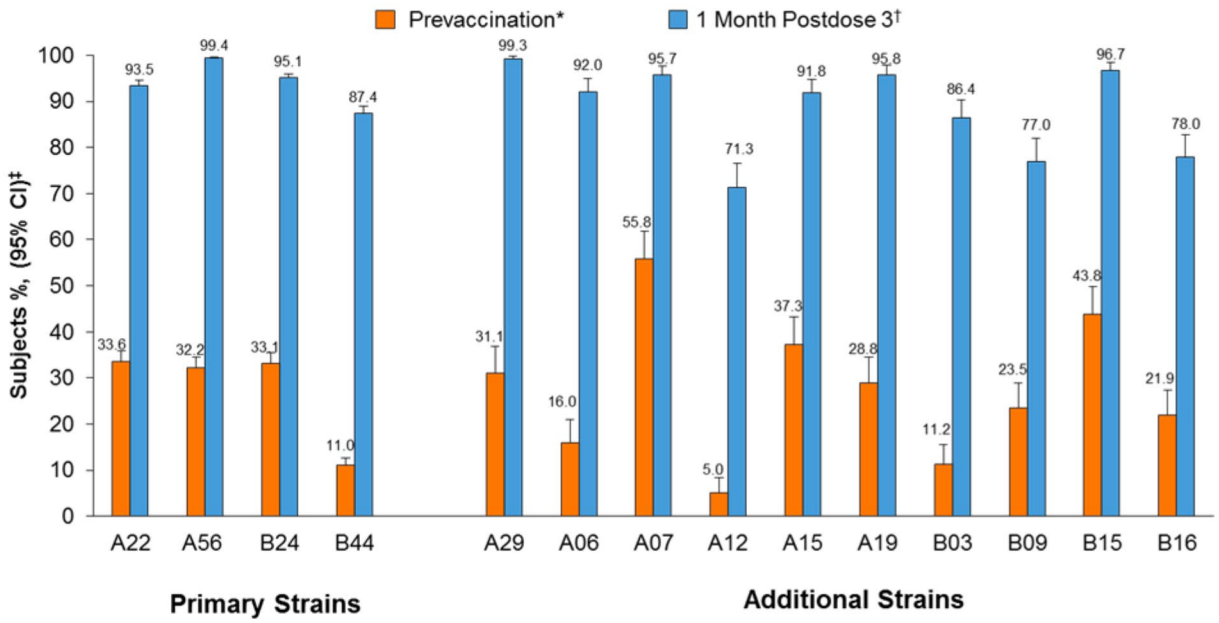
Figure 5 shows the proportion of subjects with hSBA titers ≥ 1:8 (≥ 1:16 for A22) after a primary course of Trumenba® administered in 3 doses at 0, 1 and 6 months or 0, 2 and 6 months and after a primary course of 2 doses (0 and 6 months).

In this study, vaccination with Trumenba® was able to stimulate a robust immune response against antigenically and epidemiologically different heterologous strains of Men B, both after 2 doses and after 3 doses [21]. Indeed, in subjects vaccinated according to the 2-dose schedule (0-6 months) the antibody response proved to be very similar to that elicited by the 3-dose schedule. Specifically, the proportions of subjects with antibody titers above the pre-established limits were: 93.2%, 98.4%, 81.1% and 77.5% against A22, A56, B24 and B44, respectively. Moreover, a composite response was seen in more than 73% of subjects [21].

The possibility to co-administer Trumenba® with the vaccines indicated in adolescence has been evaluated in two clinical trials. In the study by Senders et al. [23] co-administration with the anti-papilloma virus vaccine (HPV4) was evaluated, while the study by Muse et

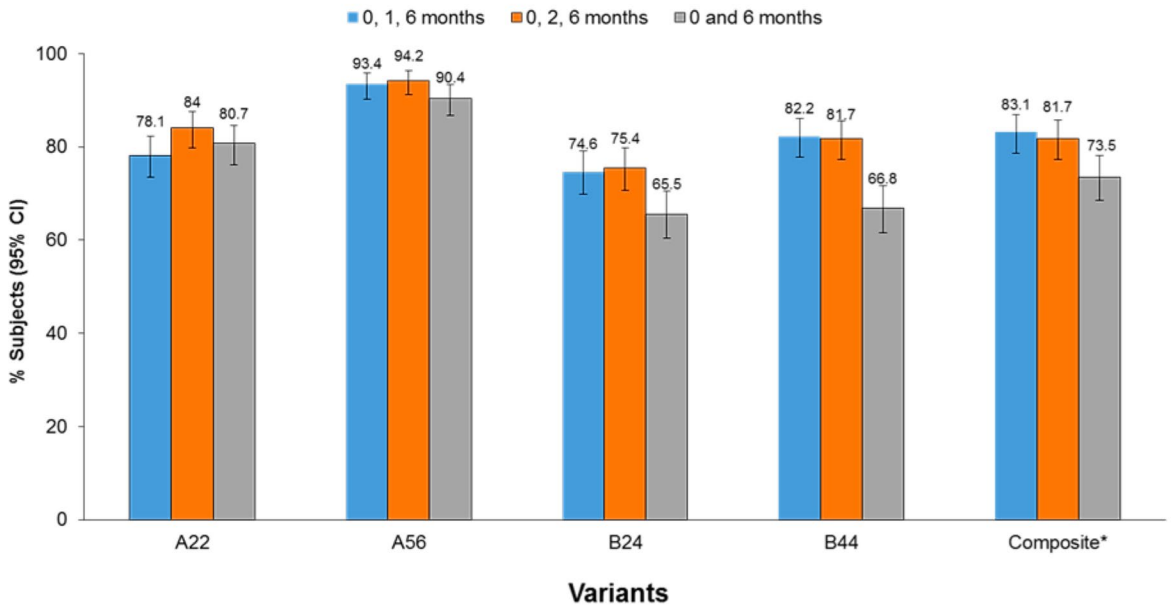
al. [24] investigated the possibility of co-administration with the anti-diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine (DTaP/IPV). Both studies demonstrated the non-inferiority of the immune response in the case of co-administration of the vaccines used. Moreover, the study by Muse et al. also evaluated

Fig. 4. Percentage of subjects with an hSBA titer ≥ 1:8 or ≥ 1:16 towards the primary test strains and additional strains of invasive serogroup B meningococcus one month after the 3rd dose of Trumenba®.



* hSBA titer ≥ the pre-specified threshold for all 4 primary strains (≥ 1:16 [A22] or ≥ 1:8 [A56, B24 and B44]) 1 month after vaccination. A 4-fold increase is defined as follows: (1) in subjects with a baseline hSBA titer < 1:4, a response is defined as an hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24, and B44); (2) in subjects with a baseline hSBA titer ≥ 1:4 and < 1:16 (A22) or < 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the pre-specified threshold (1:8 or 1:16); and (3) in subjects with a baseline hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the reference titer.

Fig. 5. Percentage of subjects who displayed a ≥ 4-fold increase in their hSBA titers and a composite response against the primary test strains after 2 or 3 doses of Trumenba®..



* hSBA titer ≥ the pre-specified threshold for all 4 primary strains (≥ 1:16 [A22] or ≥ 1:8 [A56, B24 and B44]) 1 month after vaccination. A 4-fold increase is defined as follows: (1) in subjects with a baseline hSBA titer < 1:4, a response is defined as an hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24, and B44); (2) in subjects with a baseline hSBA titer ≥ 1:4 and < 1:16 (A22) or < 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the pre-specified threshold (1:8 or 1:16); and (3) in subjects with a baseline hSBA titer ≥ 1:16 (A22) or ≥ 1:8 (A56, B24 and B44), a response is defined as an hSBA titer ≥ 4-fold higher than the reference titer.

the possibility of co-administering Trumenba® with the quadrivalent conjugated anti-meningococcal A, C, Y, W vaccine (MenACWY). In this case, too, the non-inferiority of the immune response was demonstrated [24].

Persistence of the immune response

A phase III study (study B1971033) was conducted in order to evaluate the persistence of hSBA responses up to 48 months after completion of a primary course of Trumenba®. In addition, the response to a single booster dose of Trumenba® administered 48 months after the primary course was also assessed [1].
The interim analysis revealed a reduction in the immune response a month after the last dose of Trumenba®, which had been administered up to the 12th month during the primary course. Subsequently, antibody titers stabilized, persisting up to 48 months both in subjects vaccinated in accordance with the 3-dose schedule and in those who had undergone the 2-dose schedule. Following a single booster dose of Trumenba®, administered about 4 years after the primary course of vaccination, the hSBA responses to the individual test strains ranged from 91.9% to 98.4% in subjects who had received 2 doses during the primary course, and from 94.9% to 100% in those who had received 3 doses. This study demonstrated that a single dose of Trumenba® administered about 4 years after the primary course elicited robust immune responses, thereby supporting the administration of a booster dose in order to re-establish adequate levels of protection [1, 9, 26].
Two phase II clinical studies also evaluated the persistence of antibody titers 48 months after the primary course [19, 20].
Generally speaking, the immunogenicity of a 2-dose regime (0, 6 months) seems to be similar to that of a 3-dose regime, in the light of the composite response, antibody persistence and the response to a booster dose administered 4 years after the primary course. The results obtained so far suggest that the 2-dose regime (0, 6 months) may be appropriate for routine vaccination programs [20, 26].

Safety and tolerability

The safety profile of Trumenba® is based on the analysis of over 15,000 subjects (aged ≥ 10 years) vaccinated with at least one dose of Trumenba® within the framework of 11 clinical studies [27]. Specifically, the basic safety data on the vaccine were provided by 8 controlled clinical studies [16, 17, 19, 22-25]. The primary objective of these studies was to evaluate adverse events in a large study population [25].
In the clinical trials, the predefined adverse events elicited (local reactions at the injection site and systemic events) which occurred within 7 days after each vaccine dose were recorded in an electronic diary. In all the studies, Trumenba® proved to be well tolerated by adolescents and young adults, most adverse reactions being mild or moderate [27]. The most common adverse reactions recorded were: pain, reddening and swelling at the injection site, headache, tiredness, shivering, diarrhea, muscle pains, joint pains, and nausea [16, 17, 19, 22-25, 27]. The median duration of pain was 2-3 days [26].
Spontaneous reports of adverse events were collected from the day of administration of the first vaccine dose up to about one month after the third dose; most adverse effects were mild or moderate, and were reported in similar proportions in the vaccinated groups and the control groups [26]. Reports of serious adverse events (SAE) were collected up to about 6 months after the last dose administered; no difference in the frequency of SAE was observed between subjects vaccinated with Trumenba® and the control groups. Specifically, the largest study to evaluate the safety of Trumenba® revealed that the vaccine was safe and well tolerated in subjects aged between 10 and 26 years; indeed, only 1.6% of the subjects vaccinated reported SAE, as against 2.5% of control subjects (HAV/saline solution) [25]. Adverse reactions following the booster dose proved to be similar to those recorded during the primary course of vaccination with Trumenba® about 4 years earlier [1, 26, 27].
The good safety profile of the bivalent meningococcal vaccine also emerged from the study that evaluated its co-administration with the DTPa and the inactivated polio vaccines in healthy adolescents [22]. Moreover, in the study that investigated the co-administration of Trumenba® with the quadrivalent HPV vaccine, local reactions and systemic events were no more frequent after co-administration than after the administration of the meningococcal vaccine alone [23]. Finally, no safety concerns emerged from post-marketing studies conducted in the United States, where Trumenba® was authorized in 2014 for the vaccination of subjects aged between 10 and 25 years [26, 27].

Conclusions

The development of a vaccine against Men B proved to be an extremely difficult challenge, owing to the impossibility of utilizing capsular antigens and, consequently, the need to identify a protein antigen that would have the right characteristics for its inclusion in a vaccine. Lipoprotein 2086 (LP2086), or fHbp, which is expressed on the bacterial surface, was identified as a major virulence factor.
Controlled clinical trials have shown that a high percentage of subjects vaccinated develop a protective antibody response against the components of the vaccine. Moreover, it has been demonstrated that most of the Men B strains isolated in Europe, North America and Canada express sufficiently high levels of fHbp at the sub-capsular site to render them susceptible to killing mediated by the antibodies induced by the vaccine.
In conclusion, the available data show that Trumenba® is safe, able to induce a robust immune response and potentially capable of providing broad protection against

Men B strains circulating in Europe. Thus, it could constitute an effective weapon in the fight against meningococcal disease due to serogroup B.

References

[1] Agenzia Italiana del Farmaco (AIFA). Riassunto Caratteristiche del Prodotto. Trumenba®. Luglio 2019. Available at: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfwnloadServlet?pdfFileName=footer_004849_045429_RCP.pdf&retry=0&sys=m0b1l3

[2] Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med 2001;344(18):1378-88. https://doi.org/10.1056/NEJM200105033441807

[3] Tan LK, Carlone GM, Borrow R. Advances in the development of vaccines against Neisseria meningitidis. N Engl J Med 2010;362(16):1511-20. https://doi.org/10.1056/NEJMra0906357

[4] Schneider MC, Exley RM, Chan H, Feavers I, Kang YH, Sim RB, Tang CM. Functional significance of factor H binding to Neisseria meningitidis. J Immunol 2006;176(12):7566-75. https://doi.org/10.4049/jimmunol.176.12.7566

[5] Beernink PT, Leipus A, Granoff DM. Rapid genetic grouping of factor H-binding protein (genome-derived neisserial antigen 1870), a promising group B meningococcal vaccine candidate. Clin Vaccine Immunol 2006;13(7):758-63. https://doi.org/10.1128/CVI.00097-06

[6] Fletcher LD, Bernfield L, Barniak V, Farley JE, Howell A, Knauf M, Ooi P, Smith RP, Weise P, Wetherell M, Xie X, Zagursky R, Zhang Y, Zlotnick GW. Vaccine potential of the Neisseria meningitidis 2086 lipoprotein. Infect Immun 2004;72(4):2088-2100. https://doi.org/10.1128/iai.72.4.2088-2100.2004

[7] McNeil LK, Murphy E, Zhao XJ, Guttmann S, Harris SL, Scott AA, Tan C, Mack M, DaSilva I, Alexander K, Mason K, Jiang HQ, Zhu D, Mininni TL, Zlotnick GW, Hoiseth SK, Jones TR, Pride MW, Jansen KU, Anderson AS. Detection of LP2086 on the cell surface of Neisseria meningitidis and its accessibility in the presence of serogroup B capsular polysaccharide. Vaccine 2009;27(25-26):3417-21. https://doi.org/10.1016/j.vaccine.2009.01.075

[8] Anderson AS, Jansen KU, Eiden J. New frontiers in meningococcal vaccines. Expert Rev Vaccines 2011;10(5):617-34. https://doi.org/10.1586/erv.11.50

[9] Committee for Medicinal Products for Human Use. Assessment Report: Trumenba. London, United Kingdom: European Medicines Agency 2017. EMA/CHMP/232746/2017.

[10] Hoiseth SK, Murphy E, Andrew L, Vogel U, Frosch M, Hellenbrand W, Abad R, Vazquez JA, Borrow R, Findlow J, Taha MK, Deghmane AE, Caugant DA, Kriz P, Musilek M, Mayer LW, Wang X, Macneil JR, York L, Tan CY, Jansen KU, Anderson AS. A multi-country evaluation of Neisseria meningitidis serogroup B factor H-binding proteins and implications for vaccine coverage in different age groups. Pediatr Infect Dis J 2013;32(10):1096-101. https://doi.org/10.1097/INF.0b013e31829aa63b

[11] Madico G, Welsch JA, Lewis LA, McNaughton A, Perlman DH, Costello CE, Ngampasutadol J, Vogel U, Granoff DM, Ram S. The meningococcal vaccine candidate GNA1870 binds the complement regulatory protein factor H and enhances serum resistance. Immunol 2006;177(1):501-10. https://doi.org/10.4049/jimmunol.177.1.501

[12] Murphy E, Andrew L, Lee KL, Dilts DA, Nunez L, Fink PS, Ambrose K, Borrow R, Findlow J, Taha MK, Deghmane AE, Kriz P, Musilek M, Kalmusova J, Caugant DA, Alvestad T, Mayer LW, Sacchi CT, Wang X, Martin D, von Gottberg A, du Plessis M, Klugman KP, Anderson AS, Jansen KU, Zlotnick GW, Hoiseth SK. Sequence diversity of the factor H binding protein vaccine candidate in epidemiologically relevant strains of serogroup B Neisseria meningitidis. J Infect Dis 2009;200(3):379-89. https://doi.org/10.1086/600141

[13] Harris SL, Donald RG, Hawkins JC, Tan C, O'Neill R, McNeil LK, Perez JL, Anderson AS, Jansen KU, Jones TR. Neisseria meningitidis serogroup B vaccine, bivalent rLP2086, induces broad serum bactericidal activity against diverse invasive disease strains including outbreak strains. Pediatr Infect Dis J 2017;36(2):216-23. https://doi.org/10.1097/INF.0000000000001399

[14] Donald RG, Hawkins JC, Hao L, Liberator P, Jones TR, Harris SL, Perez JL, Eiden JJ, Jansen KU, Anderson AS. Meningococcal serogroup B vaccines: estimating breadth of coverage. Hum Vaccin Immunother 2017;13(2):255-65. https://doi.org/10.1080/21645515.2017.1264750

[15] Borrow R, Andrews N, Goldblatt D, Miller E. Serological basis for use of meningococcal serogroup C conjugate vaccines in the United Kingdom: reevaluation of correlates of protection. Infect Immun 2001;69(3):1568-73. https://doi.org/10.1128/IAI.69.3.1568-1573.2001

[16] Ostergaard L, Vesikari T, Absalon J, Beeslaar J, Ward BJ, Senders S, Eiden JJ, Jansen KU, Anderson AS, York LJ, Jones TR, Harris SL, O'Neill R, Radley D, Maansson R, Prégaldien JL, Ginis J, Staerke NB, Perez JL; B1971009 and B1971016 Trial Investigators. A bivalent meningococcal B vaccine in adolescents and young adults. N Engl J Med 2017;377(24):2349-62. https://doi.org/10.1056/NEJMoa1614474

[17] Sheldon EA, Schwartz H, Jiang Q, Giardina PC, Perez JL. A phase 1, randomized, open-label, active-controlled trial to assess the safety of a meningococcal serogroup B bivalent rLP2086 vaccine in healthy adults. Hum Vaccin Immunother 2012;8(7):888-95. https://doi.org/10.4161/hv.19983

[18] Marshall HS, Richmond PC, Nissen MD, Wouters A, Baber J, Jiang Q, Anderson AS, Jones TR, Harris SL, Jansen KU, Perez JL. A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults. Vaccine 2013;31(12):1569-75. https://doi.org/10.1016/j.vaccine.2013.01.021

[19] Richmond PC, Marshall HS, Nissen MD, Jiang Q, Jansen KU, Garcés-Sánchez M, Martinón-Torres F, Beeslaar J, Szenborn L, Wysocki J, Eiden J, Harris SL, Jones TR, Perez JL; 2001 Study Investigators. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis 2012;12(8):597-607.

[20] Marshall HS, Richmond PC, Beeslaar J, Jiang Q, Jansen KU, Garcés-Sánchez M, Martinón-Torres F, Szenborn L, Wysocki J, Eiden J, Harris SL, Jones TR, Lee SS, Perez JL; 6108A12001 Study Investigators. Meningococcal serogroup B-specific responses after vaccination with bivalent rLP2086: 4 year follow-up of a randomised, single-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis 2017;17(1):58-67. https://doi.org/10.1016/S1473-3099(16)30314-0

[21] Vesikari T, Østergaard L, Diez-Domingo J, Wysocki J, Flodmark CE, Beeslaar J, Eiden J, Jiang Q, Jansen KU, Jones TR, Harris SL, O'Neill RE, York LJ, Crowther G, Perez JL. Meningococcal serogroup B bivalent rLP2086 vaccine elicits broad and robust serum bactericidal responses in healthy adolescents. J Pediatric Infect Dis Soc 2016;5(2):152-60. https://doi.org/10.1093/jpids/piv039

[22] Vesikari T, Wysocki J, Beeslaar J, Eiden J, Jiang Q, Jansen KU, Jones TR, Harris SL, O'Neill RE, York LJ, Perez JL. Immunogenicity, safety, and tolerability of bivalent rLP2086 meningococcal group B Vaccine administered concomitantly with diphtheria, tetanus, and acellular pertussis and inactivated poliomyelitis vaccines to healthy adolescents. J Pediatric Infect Dis Soc 2016;5(2):180-7. https://doi.org/10.1093/jpids/piv064

[23] Senders S, Bhuyan P, Jiang Q, Absalon J, Eiden JJ, Jones TR, York LJ, Jansen KU, O'Neill RE, Harris SL, Ginis J, Perez JL. Immunogenicity, tolerability and safety in adolescents of bi-

valent rLP2086, a meningococcal serogroup B vaccine, coadministered with quadrivalent human papilloma virus vaccine. Pediatr Infect Dis J 2016;35(5):548-54. https://doi.org/10.1097/INF.0000000000001072

[24] Muse D, Christensen S, Bhuyan P, Absalon J, Eiden JJ, Jones TR, York LJ, Jansen KU, O'Neill RE, Harris SL, Perez JL. A phase 2, randomized, active-controlled, observer-blinded study to assess the immuno- genicity, tolerability, and safety of bivalent rLP2086, a meningococcal serogroup B vaccine, coadministered with tetanus, diphtheria and acellular pertussis vaccine and serogroup A, C, Y and W-135 meningococcal conjugate vaccine in healthy US adolescents. Pediatr Infect Dis J 2016;35(6):673-82. https://doi.org/10.1097/INF.0000000000001124

[25] Ostergaard L, Lucksinger GH, Absalon J, Beeslaar J, Eiden J, Jansen KU, York LJ, Quinn A, Graversen ME, Perez JL. A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults. Vaccine 2016;34:1465-71. https://doi.org/10.1016/j.vaccine.2016.01.044

[26] Shirley M, Taha MK. MenB-FHbp meningococcal group B vaccine (Trumenba®): a review in active immunization in individuals aged ≥ 10 years. Drugs 2018;78(2):257-68. https://doi.org/10.1007/s40265-018-086

[27] European Medicines Agency. Trumenba® (meningococcal group B vaccine): summary of product characteristics. 2017. Available at: http://www.ema.europa.eu [Accessed 22 December 2017].

Chapter 6

The clinical and economic impact of anti-meningococcal B vaccination with Trumenba® in adolescents

P. LANDA[1], S. BOCCALINI[2], P. BONANNI[2], A. BECHINI[2], F. ZANGRILLO[3], F. MARCHINI[3], E. LECINI[3], M. IOVINE[3], P.L. LAI[3], D. AMICIZIA[3], D. PANATTO[3]

[1] Department of Economics, University of Genoa, Italy; [2] Department of Health Sciences, University of Florence, Italy; [3] Department of Health Sciences, University of Genoa, Italy

Introduction

Invasive disease due to *Neisseria meningitidis* is a serious public health problem even in developed countries, owing to its high case fatality rate and the invalidating sequelae that are frequently suffered by survivors from the disease [1-5]. Indeed, it is estimated that about 60% of survivors, especially children, adolescents and young adults, suffer permanent sequelae which markedly impair the quality of life of both patients and their families [2, 6, 7] and generate a heavy clinical, social and economic impact. The percentage of survivors with complications varies according to their age [8], the severity of the acute phase of the disease and the serogroup involved. Infections by serogroups B and C are the most serious, as documented by numerous studies [8-10].

The incidence of meningococcal disease varies markedly according to the geographical area, period and age of the subjects involved [11]. In Europe, mean notification rates range from 0.5 to 0.7 cases per 100,000 inhabitants (data from the period 2011 – 2016) [4]. In Italy, the incidence is lower than the European average; the national Invasive Bacterial Diseases Surveillance System reported an overall incidence of 0.31 cases/100,000 inhabitants in 2015 and of 0.37 cases/100,000 inhabitants in 2016.

Serogroup distribution varies according to the geographical area. In Europe, serogroup B is the most common (> 50% of cases) [12]. This pattern can also be seen in Italy; indeed, in the period 2011-2017, about 36% of cases were due to serogroup B [13]. Serogroup distribution is also age-dependent; the highest percentage of cases due to meningococcus B is recorded in infants, though in children and adolescents, too, the proportion is considerable (25-32%) [12, 13].

It should, however, be pointed out that in Italy about 20% of cases are not typed [13] and that the number of cases is underestimated, chiefly as a result of the laboratory methods utilized for the detection of the microorganism in the various Italian regions. In this regard, a study published by Azzari et al. in 2016 reported a value of under-diagnosis of 3.28 [14].

As the microorganism is transmitted via the airborne route and the main source of contagion is healthy carriers [15, 16], the only weapon available in the fight against invasive disease due to *Neisseria meningitidis* is vaccination. Monovalent (MenC) and quadrivalent (ACWY) conjugate vaccines are currently available [17] as are two vaccines against invasive disease due to *Neisseria meningitidis* serogroup B (Bexsero® and Trumenba®) [18, 19].

Within the framework of the present HTA, we conducted a cost-utility analysis in order to evaluate the costs and benefits of anti-meningococcal B vaccination with Trumenba® (an adsorbed recombinant vaccine containing fHbp of *Neisseria meningitidis* serogroup B, subfamily A and subfamily B) in adolescents, and to compare the strategy of vaccination with that of no-vaccination in the Italian epidemiological scenario.

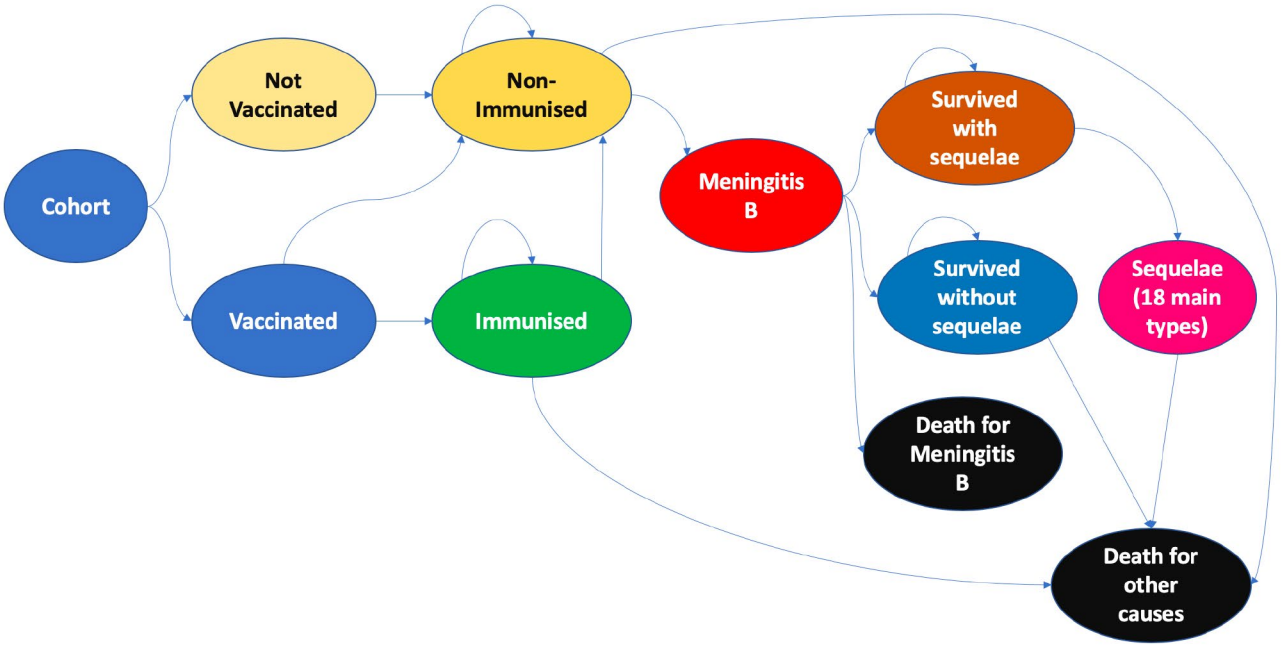
Materials and methods

Description of the model

In order to evaluate the cost-utility of anti-meningococcal B vaccination with Trumenba® in adolescents in Italy, a Markov model with mutually exclusive health states was developed in which two scenarios were considered: the first, in which vaccination is introduced, and the second, in which it is not (standard of care). Figure 1 shows the simplified model, with the related states of health and the flow of individuals in the cohort during simulation.

The cost-utility approach enables the efficacy of vaccination to be estimated in terms of Quality-Adjusted Life Years (QALYs). QALYs are able to quantify the benefits of the vaccination strategy by taking into account the various health outcomes that characterize meningococcal disease, in terms both of life years saved and of impact on quality of life. The benefits in terms of life years saved, weighted by quality of life, were evaluated for the entire life expectancy of the cohort under study. As the model has a "lifetime" horizon, it concludes with the extinction of the population of the cohort. In the model, two absorbing states were adopted: i) death caused by invasive disease due to serogroup B meningococcus, and ii) death due to other causes (derived from the mortality rate in each age-group) [20].

Fig. 1. Simplified model.



* see Table II.

The analysis is expressed in terms of the incremental cost-effectiveness ratio (ICER), in which the denominator consists of the difference between the QALYs, and the numerator consists of the difference between the cost of the vaccination strategy and the cost of the no-vaccination strategy. In the analysis, we adopted a threshold cost-effectiveness value of € 30,000/QALY; this value is utilized in economic analyses in the Italian setting [21, 22] and is in line with the average per capita income in Italy (€ 27,700 – year 2016) [23].

Vaccination with Trumenba® [19] (see chapter 5) was compared with the strategy of "no-vaccination", in that the 2017-2019 National Vaccine Prevention Plan does not include vaccination against meningococcus B in adolescents. The Markov model was used to analyze the cohort of adolescents aged 11 years who were resident in Italy on 1 January 2018, which consisted of 574,155 individuals [20]. The vaccination schedule considered was that of 2 doses (0-6 months) [19, 24] (Tab. I).

In the present model, a 70% coverage rate is considered for the base-case, and in the sensitivity analysis a range of 50%-90% is assumed (Tab. I).

In the model, the probability of vaccinated subjects' contracting invasive disease depends on the efficacy of the vaccine (see subsection on immunogenicity and duration of protection). It must be borne in mind that efficacy is only deduced from immunogenicity data, as the efficacy of anti-meningococcal vaccines cannot be directly evaluated through clinical trials, owing to the low incidence of invasive meningococcal disease. Moreover, as large-scale programs using Trumenba® are as yet lacking, no effectiveness data (efficacy in the field) are available.

Efficacy (deduced from immunogenicity data) is assumed to decline over time until the 10th year (minimum protection after 10 years: 25.29%). After the 10th year, protection is assumed to be absent.

In subjects who are not vaccinated or who are not immunized (vaccinated but not protected) the probability of contracting the disease is equal to the disease incidence in the various age-groups (see subsection on disease incidence and chapter 2). A subject who contracts the disease has two possible outcomes: survival or death. Survivors may: survive without sequelae or suffer short- and/or long-term sequelae (see chapter 3). The model envisions only the probability of developing single sequelae. In this model, the overall probability of developing sequelae is 61% [2]. Regarding this parameter, a sensitivity analysis was conducted in which a range between 30% and 70% was considered. Subjects who recover from invasive meningococcal disease are immune, since recurrence of the disease is very rare, being possible only in individuals with anatomical or immune deficiencies [25, 26].

In order to reflect the real-life setting more closely, the post-infection period is subdivided into three phases: the acute phase (one month starting from the time of hospitalization), the post-acute phase (up to 6 months following the acute phase) and the long-term phase (from the 6th month onwards) (see subsection on sequelae).

Two perspectives were considered: that of the National Health Service (NHS) (in which only direct costs are included) and that of society (which includes both the costs borne by the NHS and those borne by other sectors of the state and the community) (see chapter 4). All costs

Tab. I. General input data used in the model.

	Base-case	Range
Age of vaccination cohort Cohort: 574,155 subjects [20]	11 years	-
Vaccine doses	2 (0-6 months) [19, 24]	-
Coverage rate	70%	50-90%
Vaccine efficacy after 2 doses (hypothesized from available immunogenicity data)	73.5% [19]	68.5-78.1% [19]
Protection in the second year (hypothesized)	Reduced by 20%	-
Protection in the years following the second (hypothesized)	Annual decrease of 10% up to 10 year[a]	-
Mild/moderate adverse events [30]	29% after 1st dose[b] 22% after 2nd dose[b]	-
Serious adverse events [30]	1,9%[c]	
Incidence of meningococcal B disease per 100,000 subjects [13, 24]	10-14 years: 0.4084[d] 15-24 years: 0.6910[d] 25-64 years: 0.1645[d] > 64 years: 0.1594[d]	-/+ 20%
Acute-phase clinical presentation [13]	Meningitis: 45% Sepsis: 30% Meningitis/sepsis: 25%	-
Case fatality rate [4]	8%	6-10%
Overall probability of sequelae [2]	61%	30-70%

[a] in the model, it is hypothesized that protection is absent after 10 years. [b] refers to the mean value of the probabilities of mild or moderate adverse events recorded in phase III controlled clinical studies. [c] no difference was observed between the vaccinated group and the control group in phase III controlled clinical studies. [d] adjusted epidemiological datum (see subsection on disease incidence).

are referred to January 2018. In order to update costs and health outcomes, we applied a discount rate of 3.5%, as reported in the Italian and international guidelines [27-29]. Table 1 reports the general input data used as model parameters.

Economic analysis and sensitivity analysis

The analysis was conducted by means of Microsoft Excel 2010® (32-bit version 14.0.72325000).

Given the possible presence of variations in the input data, a sensitivity analysis was carried out in order to assess the variation in health outcomes and costs. Moreover, the strength of the association between the variables and the health outcomes was tested. A deterministic sensitivity analysis (DSA) was conducted to assess the impact of some model parameters on the ICER, and a probabilistic sensitivity analysis (PSA) was conducted in which the model parameters, the costs and the utilities were caused to vary according to probabilistic distributions. The aim of the PSA, which was made up of 5,000 simulations, was to ascertain the cost-effectiveness of the vaccination strategy on varying the epidemiological conditions, costs and healthcare policy.

Disease incidence

The estimates of the incidence of serogroup B meningococcal disease adopted in the present model are based on the data from the national Invasive Bacterial Diseases Surveillance System [13] (see chapter 2). For the purpose of this study, we calculated the mean annual number of confirmed cases of meningococcal B disease in the period 2011-2016. We used the mean incidence over a period of 6 years in order to reduce the impact of annual fluctuations on the results of the model. We did not consider the year 2017, as these data were not complete at the time of the analysis. The cases are subdivided into 7 age-groups: 0, 1-4, 5-9, 10-14, 15-24, 25-64 and >64 years. Since the model was designed to evaluate the cost-effectiveness of anti-meningococcus B vaccination in adolescents, we considered only the probability of disease in the following age-groups: 10-14, 15-24, 25-64 and > 64 years. In order to approximate these data as closely as possible to the real-life situation, we applied three correction parameters associated with the underestimation of disease incidence: the percentage of cases with non-typed meningococcus (period 2011-2016: annual mean 25.2%); the proportion of cases of meningococcus B among the non-typed cases, assuming that this would be equal to the proportion recorded among typed cases; and an underdiagnosis factor of 3.28 [14]. The incidence rates considered in the model are reported in Table I. The model does not consider the possible underestimation due to failure to notify cases to the national surveillance system.

Disease burden

In the present study, we considered three health outcomes subsequent to the acute phase of the disease: death, survival without sequelae, and survival with sequelae.

With regard to the acute phase, on the basis of the Italian and international literature data [3, 13, 31, 32], we hypothesized that 45% of patients would have meningitis, 30% sepsis and 25% both clinical presentations (Tab. I). A case fatality rate of 8% was assumed for all age-groups, as no Italian data subdivided by age are available in the literature [4, 33]. In the sensitivity analysis, a range between 6% and 10% was considered (Tab. I).

Regarding the general mortality rate of the Italian population by age-group, the ISTAT data were used [20].
The burden of invasive meningococcal disease is particularly heavy, chiefly as a result of the permanent sequelae that afflict a high percentage of survivors, especially children and adolescents. Indeed, many survivors have to live with single or multiple sequelae of a physical, neurological and/or psychological nature.
Given the objective of this HTA and the related economic analysis, we conducted a bibliographic search in order to identify articles published in international and national journals on the subject of the possible sequelae of invasive meningococcal B disease in adolescents. As few articles met the primary research criterion, the limits of the search were extended. The search modalities are described in chapter 3.
Having analyzed each of the articles deemed suitable for the present HTA, we took the value of 61% as the overall probability of suffering at least one sequela [2]. In the sensitivity analysis, a range of 30%-70% was considered (Tab. I). Table II reports the single sequelae considered in the study and their respective probabilities.
Although meningococcal disease generally causes multiple sequelae, the present study, like other pharmacoeconomic studies, considered the sequelae to be single, in order to simplify the model. Moreover, some minor sequelae, such as vasculitis, cardiovascular problems, cerebral abscesses, hydrocephalus, cranial nerve deficits/paralysis, psoriasis, and chronic pain, were not considered. These conditions were excluded on the grounds that the frequency of their occurrence is very low (few studies report them) and that they are difficult to quantify both in economic terms and in health terms. The model must therefore be regarded as conservative.

Quality of life

In this model, the reduction in the quality of life of patients affected by invasive meningococcal disease was considered. In this analysis, too, the post-infection period was subdivided into three phases: the acute phase, the post-acute phase and the long-term phase (see subsection on disease burden). This subdivision was necessary in order to better quantify the impact of the sequelae on the state of health. Few studies in the literature [40] have quantified the reduction in the quality of life of survivors from meningococcal disease and also subdivided the data according to the various sequelae. We therefore also utilized assessments regarding other similar pathologies; these assumptions have also been made in other pharmaco-economic studies [25, 26, 41].
Table III reports the residual health utilities during the acute phase, which is the most critical phase of the disease, when the patient is very often hospitalized in the intensive care unit.
Table IV reports the residual health utilities in the post-acute and long-term phases according to the type of sequela.

Immunogenicity of the vaccine and duration of protection

The vaccination strategy considered is that of the 2-dose schedule (0-6 months) [19, 24] (Tab. I), the immuno-

Tab. II. Probability of sequelae considered in the model.

Sequelae	Base-case	Range	Distribution
Amputation with substantial disability	8% [2]	(1% [33] - 33.3% [32])	Uniform (0.01; 0.3333)
Skin scars	18% [10]	(9.5% [34]-50% [35])	Uniform (0.095; 0.5)
Severe skin damage	12.5% [32]	(10%-15%)*	Uniform (0.1; 0.15)
Limb deformity	6% [2]	(3% [10]-6.9% [6])	Uniform (0.03; 0.069)
Bone and joint problems (arthritis)	2.8% [36]	(2.8% [36]-14.6% [7])	Uniform (0.028; 0.146)
Kidney damage	1.4% [3]	(1.4% [3]-13.3% [2])	Uniform (0.014; 0.133)
Kidney damage needing transplant	1.9% [36]	(1.52%-2.28%)*	Uniform (0.0152; 0.0228)
Deafness needing cochlear implant	2% [33]	(2% [33]-2.4% [37])	Uniform (0.02; 0.024)
Uni/bilateral deafness	10% [33]	(9.1% [37]-33.3% [32])	Uniform (0.091; 0.3333)
Severe visual disorders	0.4% [33]	(0.4% [33]-2.1% [3])	Uniform (0.004; 0.021)
Convulsions/epilepsy	2% [10, 33]	(2% [10, 33]-12.2% [7])	Uniform (0.02; 0.122)
Severe neurological damage	2.1% [25. 38]	(1.79% [37]-2.1% [25. 38])	Uniform (0.0179; 0.021)
Cognitive deficits/IQ < 85	17% [2]	(0.5% [37]-22.4% [36])	Uniform (0.005; 0.224)
Communication deficits	3.7% [33]	(3.7% [33]-22.4% [6])	Uniform (0.037; 0.224)
Motor deficits	4.1% [3]	(0.7% [37]-4.1% [3])	Uniform (0.007; 0.041)
Chronic headache/migraine	10% [36]	(10% [36]-12.2% [7])	Uniform (0.1; 0.122)
Depression	5.71% [36]	(4.57%-6.85%)*	Uniform (0.0457; 0.0685)
Anxiety	7.14% [36]	(5.71%-8.57%)*	Uniform (0.0571; 0.0857)

* in the absence of literature data, a 20% variation in the parameter was considered.

Tab. III. Residual health utilities associated with the clinical presentation of the disease in the acute phase.

Clinical presentation	Base-case	Range	Distribution
Meningitis	-0.40 [31] (45%) [41]	-0.48 - -0.32*	Beta (14.6; 21.9)
Sepsis	-0.51 [31] (30%) [41]	-0.41-0.61*	Beta (11.74; 11.28)
Meningitis/sepsis	-0.51 [31] (25%) [41]	-0.41 - -0.61*	Beta (11.74; 11.28)

* in the absence of literature data, a 20% variation in the parameter was considered.

Tab. IV. Residual health utilities in the post-acute and long-term phases according to the type of sequela [25].

Sequelae	Base-case	Distribution
Amputation with substantial disability	0.613	Beta (9.06; 5.72)
Skin scars	1	Beta (-1; 0)
Severe skin damage	0.900	Beta (1.6; 0.18)
Limb deformity	0.690	Beta (7.06; 3.17)
Bone and joint problems (arthritis)	0.690	Beta (7.06; 3.17)
Kidney damage	0.820	Beta (3.68; 0.81)
Deafness needing cochlear implant	0.810	Beta (4.2; 1.05)
Uni/bilateral deafness	0.910	Beta (1.34; 0.13)
Severe visual disorders	0.260	Beta (18.24; 51.91)
Convulsions/ epilepsy	0.830	Beta (3.42; 0.70)
Severe neurological damage	0.060	Beta (23.44; 367.23)
Cognitive deficits	0.541	Beta (10.93; 9.28)
Communication deficits	0.390	Beta (14.86; 23.24)
Motor deficits	0.830	Beta (3.42; 0.70)
Chronic headache/ migraine	0.814	Beta (3.84; 0.88)
Depression	0.729	Beta (6.05; 2.25)
Anxiety	0.687	Beta (7.14; 3.25)

Note: after the acute phase, the health utilities regarding a survivor without sequelae decrease according to age, as in a subject without disease. Reference values: death: 0; perfect health: 1.

genicity of which has been demonstrated in controlled clinical studies [30, 42-45]. On the basis of the analysis of immunogenicity results obtained in the various controlled clinical studies, we assumed an efficacy value of 73.5% [19, 42] in the first year after the course of vaccination. In the sensitivity analysis, a range of 68.5%-78.1% was considered [19]. As the vaccine has only recently been marketed, effectiveness data are not yet available and the data on the duration of protection are incomplete. Regarding the duration of protection, we can therefore only make hypotheses; in the present study, we hypothesized a 20% decline in protection in the second year (58.8%) and a subsequent annual decrease of 10% until the 10th year (Tab. I). After 10 years, protection was assumed to be nil. Moreover, controlled clinical studies have shown that the vaccine is able to confer immunological memory; indeed, one month after the administration of a booster dose, a very high value of bactericidal antibody titers is reached: 91.8% (81.9%-97.3%).

Disease-related costs

The aim of the present study is to provide decision-makers with a tool that will enable them to evaluate the possible impact of a vaccination strategy against meningococcus B in adolescents. It is therefore necessary to consider both the direct costs, i.e. those borne by the NHS, and the social costs generated by the disease (costs borne by other sectors of the state, patients' families and society in general). All these costs are expressed in € (converted to € if reported in other currencies) and accounted as of 1 January 2018.

In order to provide a more precise evaluation, each cost category (direct and indirect) has, in turn, been subdivided according to the three phases of disease: acute phase, post-acute phase, and long-term phase with sequelae.

Direct costs

Acute phase

The costs accruing to the acute phase include: hospitalization costs, the costs related to the public health response, and the costs of long-term rehabilitation in hospital. The first two direct costs are applicable to all cases of disease (100%) regardless of outcome; they are therefore also attributed to cases of death. The costs related to long-term hospitalization (maximum 20 days) are applicable only to those who survive and suffer sequelae (Tab. V).

The costs of hospitalization were evaluated by selecting hospital discharge forms (HDF) with the codes 036, 0360 and 0362, i.e. the codes most frequently associated to meningococcal disease, and calculating the mean value of the respective diagnosis-related groups (DRG), subdivided by age: < 18 years and > 18 years [46] (Tab. V).

The cost of the public health response was calculated per single case of disease by considering the mean number of contacts requiring chemoprophylaxis, the mean cost of a course of chemoprophylaxis and the mean working time that public health workers devote to avoiding secondary cases [25].

Post-acute phase

Table VI reports the costs related to the post-acute phase (up to 6 months after disease onset). In the model, 5 specialist outpatient examinations were estimated for each subject with sequelae.

Psychiatric/psychological support (undertaken in 62% of cases [48]) requires a mean of 20 sessions (one per week). With regard to the costs concerning subjects with amputations, limb deformities, bone and joint problems,

Tab. V. Acute phase: direct costs related to a single case and accounted as of 1 January 2018.

Direct costs		
Parameter	Base-case	Distribution
Hospitalization <18 years	HDF 036 [46]: € 4,952.64[a] HDF 0360 [46]: € 4,952.64[b] HDF 0362 [46]: € 4,529.00[c]	Gamma (25; 188.14)
Hospitalization >18 years	HDF 036 [46]: € 6,708.04[a] HDF 0360 [46]: € 6,542.06[b] HDF 0362 [46]: € 6,177.88[c]	Gamma (25; 259.04)
Public health response	€ 3,284 [25, 47]	Gamma (25; 131.36)
Hospitalization in long-term care (maximum 20 days)	€ 4,040.00 (€ 202.00/day [46])	Gamma (25; 161.6)

[a] mean of the principal DRGs associated to HDF cod. 036. [b] mean of the principal DRGs associated to HDF cod. 0360. [c] mean of the principal DRGs associated to HDF cod. 0362..

and motor deficits, we considered a mean of 40 sessions of rehabilitation: two sessions per week for 20 weeks. In some cases, we also included the mean cost of a manual wheelchair; latest-generation wheelchairs (e.g. electric) were not considered.
Regarding subjects with hearing deficits, the present economic evaluation considered the cost of providing a cochlear implant for patients suffering from severe deafness, and the cost of prosthetic hearing aids for those with moderate uni/bilateral deafness.
In patients with serious skin sequelae, the model considered three reconstructive plastic surgery operations; this figure, however, is a very conservative estimate, as a higher number of operations are required in the most severe cases. Finally, with regard to subjects with severe kidney damage, two weekly sessions of dialysis were considered.

Long-term phase

The annual costs connected with each sequela considered in the present study are reported in Table VII. These costs were calculated on the basis of the literature data and the DRG tariffs.
For what concerns the costs related to psychiatric/psychological support, after thorough analysis of the literature data, we concluded that subjects with sequelae would need this kind of support for 18 months at a frequency of one session per month.
The cost applicable to patients with limb deformities includes that of orthopedic surgery [46], which is normally performed within two years of the acute phase of the disease, and the costs of rehabilitation (one session per week).
With regard to the sequela "arthritis", medical costs were only considered for one year, as this complication generally resolves within a short period [25].
Severe neurological damage generates high direct costs, as hospitalization in specialized institutional facilities is often required [25].
High direct costs are also generated by kidney damage; indeed, some patients require long-term dialysis [37] and others require kidney transplantation [46].
In survivors who suffer severe deafness, the costs are also high, as cochlear implants require maintenance over time [49].
Regarding depression and anxiety, the costs chiefly depend on the prices of the pharmaceutical drugs used [25].

Indirect costs

Acute phase

The indirect costs related to the acute phase of disease are reported in Table VIII. The costs considered were: psychological support (for the family), applicable to 20% of patients up to the age of 25 years; psychiatric support (for the family), applicable to 59% [51] of patients up to the age of 25 years; the patient's loss of productivity, applicable to patients of working age (18-64 years) and the loss of productivity of one parent, applicable only to patients aged <18 years.
To calculate the patient's loss of productivity, we considered mean per capita income in Italy in 2016 (€ 27,700 [23]) corrected for the rate of employment (third quarter, 2017 [20]) in the various age-groups (15-24 years: 17.2%; 25-34 years: 61.2%; 35-44 years: 73.1%; 45-54 years: 72%; 55-64 years: 53.1%).
To calculate the loss of productivity of one parent, we considered mean per capita income in Italy in 2016

Tab. VI. Post-acute phase (up to 6 months after the acute phase): direct costs related to a single case and accounted as of 1 January 2018.

Direct costs			
Parameter	Base case		Distribution
	Cost per single parameter	Total cost in the post-acute phase	
Specialist outpatient examinations	€ 20.66 [46] (1 visit) [a]	€ 103.30 (5 visits) [a]	Gamma (25; 4.13)
Psychiatric/psychological support	€ 19.37 [46] (1 session) [b]	€ 387.40 (20 sessions) [b]	Gamma (25; 15.50)
Cochlear prosthesis and implantation [c]	Pre-implantation € 6,113.97 [49]; Bilateral deafness € 36,025.01 [49]; Unilateral deafness € 18,012.51 [49];	Pre-implantation € 6,113.97 [49]; Bilateral deafness € 36,025.01 [49]; Unilateral deafness € 18,012.51 [49];	Gamma (25; 244.56) Gamma (25; 1441) Gamma (25; 720.50)
Moderate bi/unilateral deafness	€ 30,848.71 [37]	€ 30,848.71[37]	Gamma (25;1233.95)
Hearing aids [d]	€ 19.52 [46]	€ 97.5 (5 visits)	Gamma (25; 3.90)
Sustantial amputations	€ 13,296.48 [37]	€ 13,296.48 [37]	Gamma (25; 531.86)
Rehabilitation [e]	€ 20.66 [46] (1 session)	€ 826.4 (40 sessions)	Gamma (25; 33.06)
Wheelchair [e]	€ 563 [49]	€ 563 [49]	Gamma (25; 22.52)
Reconstructive plastic surgery [f]	€ 5,680.50 [46] (1 operation)	€ 17,041.5 (3 operations) (expert opinion)	Gamma (25; 681.66)
Ordinary day-hospitalization for kidney dialysis	€ 204 [46] (1 session)	€ 8,160 (40 sessions) (expert opinion)	Gamma (25; 326.40)

[a] applicable to subjects with sequelae. [b] applicable to 62% of cases. [c] applicable to subjects who require a cochlear implant. [d] applicable to subjects with bi/unilateral deafness. [e] applicable to subjects with amputations, limb deformities, bone and joint problems, and motor deficit. [f] applicable to patients with severe skin sequelae.

Tab. VII. Long-term phase: direct costs related to a single case and accounted as of 1 January 2018.

Annual direct costs (one case)		
Sequelae	**Base-case cost**	**Distribution**
Psychiatric/psychological support	€ 232.44 [46][a]	Gamma (25; 12.94)
Specialist outpatient visits	€ 20.66 [46]	Gamma (25; 0.83)
Amputation with substantial disability	€ 2,463.67 [37]	Gamma (25; 98.55)
Limb deformities	€ 1,074.32 [46][b] (rehabilitation); € 13,244 [46][b] orthopedic surgery within 2 years	Gamma (25; 42.97) Gamma (25; 529.76)
Skin scars	€ 2,068.55 [37] (first year); € 543 [25] (subsequent yearsi)	Gamma (25; 82.74) Gamma (25; 21.72)
Severe skin damage	€ 2,068.55 [37] (first year); € 1,086.25 [25] (subsequent years)	Gamma (25; 82.74) Gamma (25; 43.45)
Arthritis	1,206.50 [25]	Gamma (25;48.26)
Kidney damage	€ 10,394.80 [37] (first year); € 4,345.38 [37] (subsequent years)	Gamma (25; 415.79) Gamma (25; 173.82)
Kidney transplantation	€ 33,162 [46][c]	Gamma (25;1326.48)
Cochlear implant	€ 19,308.92 [49]: (first year); € 9,420.51 [49]: (second year); € 6,425.90 [49]: (third year); € 6,113.97 [49]: every year until 18th year; € 5,677.26 [49]: every year ≥ 18th year	Gamma (25;772.36) Gamma (25; 376.82) Gamma (25; 257.04) Gamma (25; 244.56) Gamma (25; 227.09)
Uni/bilateral deafness	€ 1,371.20 [37]	Gamma (25; 54.85)
Visual disorders	€ 757.58 [37]	Gamma (25; 30.30)
Convulsions/epilepsy	€ 2,315.17 [25]	Gamma (25; 92.61)
Severe neurological damage	€ 96,682.72 [25]	Gamma (25; 3867.31)
Cognitive deficits	€ 2,045.06 [37] (first year); € 1,206.84 (subsequent years) [50]	Gamma (25; 81.80) Gamma (25; 48.27)
Communication deficits	€ 1,961 [37] (first year); € 880.5 (subsequent years) [37]	Gamma (25; 78.44) Gamma (25; 35.22)
Motor deficits	€ 1,074.32 [46][d]	Gamma (25; 42.97)
Chronic headache/migraine	€ 908.95 [25]	Gamma (25; 36.36)
Depression	€ 3,252.65 [25]	Gamma (25; 130.11)
Anxiety	€ 1,167.77 [25]	Gamma (25; 46.71)

[a] cost of 12 sessions (expert opinion) (cost of one session: € 19.37 [46]). [b] annual cost (cost of one session: € 20.66 [46]; one session/week). [c] once-in-a-lifetime cost. [d] rehabilitation (one session/week for one year). Cost of € 20.66 [46] per session..

Tab. VIII. Acute phase: indirect costs related to a single case and accounted as of 1 January 2018.

Indirect costs (one case)		
Parameter	**Base-case cost**	**Distribution**
Psychological support (for the family)	€ 400 [52][a]	Gamma (25; 16)
Psychiatric support (for the family)	€ 500[b]	Gamma (25; 6.25)
Loss of productivity of patient	€ 2,308	Gamma (25; 92.32)
Loss of productivity of one parent	€ 2,308	Gamma (25; 92.32)

[a] one session (min. € 45 – max. € 115); mean € 80.00 [52]; 5 sessions considered. [b] one session (min. € 50 – max. € 150); mean € 100.00; 5 sessions considered

(€ 27,700 [23]) corrected for the rate of female employment in the various age-groups [20] (25-34 years: 53.2%; 35-44 years: 62.5%; 45-54 years: 60.8%; 55-64 years: 43.2%), as the literature data indicate that, in the majority of cases, it is the mother who cares for the child in the event of illness [25]. We hypothesized that all patients were born to mothers aged 30.5 years (mean age at the time of first childbirth – 2006) [20].

Post-acute phase

Table IX reports indirect costs in the post-acute.

Psychiatric/psychological support (for the family), applicable to 69% [53] of patients aged less than 25 years with sequelae, is assumed to require a mean of 10 sessions.

To calculate the patient's loss of productivity, applicable to patients of working age (18-64 years), we considered mean per capita income in Italy in 2016 (€ 27,700 [23]) corrected for the rate of employment (third quarter, 2017 [20]) in the various age-groups (15-24 years: 17.2%; 25-34 years: 61.2%; 35-44 years: 73.1%; 45-54 years: 72%; 55-64 years: 53.1%).

We calculated the loss of productivity of one parent, applicable in the case of patients aged up to 18 years, by considering that the patient would be cared for by the mother (rate of female employment [20]) and that she would maintain a part-time (50%) work contract.

Tab. IX. Post-acute phase (up to 6 months after the acute phase): indirect costs related to a single case and accounted as of 1 January 2018.

Indirect costs (one case)		
Parameter	Base-case cost	Distribution
Psychiatric/psychological support (for the family)	€ 800 [52][a]	Gamma (25; 3.2)
Loss of productivity of patient	€ 11,542 [23]	Gamma (25; 461.68)
Loss of productivity of one parent	€ 5,771 [23]	Gamma (25; 230.84)

[a] one session (min. € 45 – max. € 115); mean € 80.00 [52]; 10 sessions considered.

Long-term phase

Table X summarizes the indirect costs related to a single case and updated to 1 January 2018. With regard to psychiatric/psychological support (for the family), we considered the cost of one monthly session, applicable to 39% of patients up to one year, to 33% up to two years and to 31% up to three years [53].

The cost of psychiatric/psychological support for patients with sequelae was applied from the 18th month to the 36th month after the acute phase, on considering a mean of 1 session per month.

The patient's loss of productivity (which varies according to the sequela) is expressed as the annual cost (applicable to patients of working age: 18-64 years) and corresponds to the mean per capita income in Italy in 2016, corrected for the rate of employment [20] and the percentage of disability caused by each sequela (Tab. XI).

In the present model, we considered the loss of productivity of one parent in the case of subjects aged < 18 years with permanent severe disabilities (motor deficits, severe visual damage, epilepsy, severe neurological disability, mental retardation, deafness, impairment of communication). The value was calculated on the basis of the mean per capita income in Italy in 2016, corrected for the rate of female employment [20] and on hypothesizing a part-time (50%) work contract.

The cost of special education for subjects aged < 18 years with serious sequelae (mental retardation, severe neurological disability, severe impairment of communication, epilepsy, severe visual damage, motor deficits, amputations with substantial disability, and deafness) was also calculated. This is an annual cost and is borne by the Ministry of Education.

Social cost of death

Two approaches are generally used to estimate the social cost of death: those of "willingness to pay" and "human standard capital" [25]. In the present (conservative) model, the cost of death was not included.

Tab. X. Long-term phase: indirect costs related to a single case with sequelae and accounted as of 1 January 2018.

Indirect costs (one case)		
Parameter	Base-case cost	Distribution
Psychiatric/psychological support (for the family)	€ 80.00 [52][a]	Gamma (25; 3.2)
Psychiatric/psychological support (for the patient)	€ 80.00 [52][a]	Gamma (25; 3.2)
Loss of productivity of patient	27,700 [23][b]	Gamma (25; 1108)
Loss of productivity of one parent	13,850 [23][c]	Gamma (25; 554)
Special education	14,842.75 [25][d]	Gamma (25; 593.71)

[a] cost of one session. [b] annual cost - per capita income, Italy 2016. [c] annual cost, corresponding to half of the per capita income in Italy in 2016. [d] annual cost.

Tab. XI. Percentage of disability, subdivided by type of sequela.

Sequelae	Disability values [54]	Range [54]
Amputations with substantial disability	77.5%	55-100%
Limb deformities	45.5%	11-80%
Kidney damage	65.5%	31-100%
Severe deafness	65%	-
Moderate deafness	30%	1-59%
Bilateral blindness	100%	-
Epilepsy	70.5%	41-100%
Severe neurological damage	100%	-
Cognitive deficits	70.5%	41-100%
Moderate-severe communication deficits	80.5%	61-100%
Motor deficits	45.5%	11-80%
Depression	45%	10-80%
Anxiety	15%	-

Other indirect costs related to permanent sequelae

As permanent sequelae result in disabilities that differ in type and severity, the costs accruing to the state social security institutions (see chapter 4) are very variable. It is therefore very difficult to generalize and to assign to them an unequivocal mean value. We therefore decided not to consider the indirect social security costs in our calculation of the general costs of meningococcal disease (conservative model).

Costs related to vaccination

The costs related to vaccination are reported in Table XII. The discounted price of each single dose of vaccine is borne by the NHS. The cost of administration (€ 5.91) is applicable to each vaccine dose.

Possible severe or mild/moderate adverse events following administration of the vaccine have been considered. The probabilities of adverse events are based on the data from controlled clinical trials; the mean value of the probabilities recorded in phase III controlled clinical trials has been adopted. The probabilities of mild/moderate adverse events have been reported to be 29% after the first dose and 22% after the second dose [30].

For what concerns severe adverse events, the controlled clinical trials have not registered any safety problems. Indeed, the probability of severe adverse events in vaccinated subjects is reported to be similar to that observed in control subjects (1.9% – no difference between the vaccinated group and the control group) [30].

Results

The results of our study indicate that vaccinating adolescents (11th year of life) with Trumenba® is cost-effective. Indeed, the ICER proved to be € 7,911.98/QALY from the NHS perspective and € 7,757.73/QALY from the perspective of society. Both of these values are well below the threshold of € 30,000/QALY, which is the reference value of cost-effectiveness.

Vaccinating adolescents reduces the number of cases of disease due to meningococcus B in one of the periods of highest incidence of the disease (adolescents/young adults). Specifically, on considering the parameters of the base-case – i.e. 70% vaccination coverage and hypothesized efficacy of 73.5%, with protection declining over time (hypothesized) (Tab. I) – the vaccination program would achieve a 9% reduction in the number of cases in the 11-21-year age-group. Moreover, these parameters should be regarded as conservative.

The present model enabled us to calculate the mean cost of a case of an individual affected by meningococcal disease at the age of 11 years. Given the gravity of the disease and its consequences, the total cost of one case would amount to € 503,223.79 (costs not discounted) and to € 268,865.48 (costs discounted). The non-discounted cost of a case is made up of: € 13,952.93 in the acute phase, € 11,145.09 in the post-acute phase and € 478,125.76 in the long-term phase. If we apply the discount rate to these costs, the cost of cases made up of: € 13,952.93 in the acute phase, € 11,145.09 in the post-acute phase and € 243,767.46 in the long-term phase.

Table XIII reports the costs of the "vaccination" strategy versus the "no vaccination" strategy.

Tab. XII. Costs related to vaccination and cost of a possible adverse event.

Parameter	Price	Distribution
Cost of one vaccine dose	€ 50 (regional supply cost)	Gamma (25; 2)
Cost of administering each vaccine dose	5.91 [25, 47]	Gamma (25; 0.24)
Cost of a severe adverse event	€ 951 (< 18 years) [46] € 1.404 (> 17 years) [46]	Gamma (25; 38.04) Gamma (25; 56.16)
Cost of a mild/moderate adverse event	3.46 [25]	Gamma (25; 0.14)

Tab. XIII. Costs related to the "vaccination" strategy and those related to the "no vaccination" strategy.

Costs (€)	Not discounted			Discounted		
	Vaccination	No Vaccination	Difference	Vaccination	No Vaccination	Difference
NHS perspective						
Vaccination costs	46,332,012	0	**46,332,012**	46,332,012	€ 0	**46,332,012**
Costs: acute phase	1,138,803	1,195,964	**-57,161**	737,994	792,776	**-54,782**
Costs: post-acute phase	352,536	366,137	**-13,601**	212,392	225,511	**-13,119**
Costs: long-term phase	5,419,891	5,724,391	**-304,500**	2,111,452	2,260,267	**-148,815**
Total	**53,243,242**	**7,286,492**	**45,956,750**	**49,393,850**	**3,278,554**	**46,115,296**
Society perspective						
Vaccination costs	46,332,012	0	**46,332,012**	46,332,012		**46,332,012**
Costs: acute phase	1,293,283	1,371,136	**-77,853**	€ 839,222	905,000	**-65,778**
Costs: post-acute phase	901,985	929,000	**-27,015**	€ 534,733	560,822	**-26,089**
Costs: long-term phase	14,638,501	15,486,499	**-847,998**	€ 5,916,967	6,339,139	**-422,172**
Total	**63,165,781**	**17,786,635**	**45,379,146**	**53,622,934**	**7,804,961**	**45,817,973**

In Table XIII, the costs refer to the entire cohort for the entire period of time of the simulation, and are subdivided by the three phases: acute, post-acute and long-term. The benefits yielded by the vaccination strategy are evident. Indeed, vaccination leads to a reduction in expenditure in all the phases of disease from the perspectives of both the NHS and society, its impact being especially great in the long-term phase.

With regard to QALYs, the vaccination strategy generates a saving of 5,906 QALYs for the entire cohort considered.

In order to evaluate the impact of the uncertainty of the input data at the level of costs, health utilities and the probability of transition between the various states in the model, we carried out a deterministic sensitivity analysis and a probabilistic analysis. These analyses were conducted from the NHS perspective.

The deterministic analysis assessed the impact on the ICER of some parameters considered individually: disease incidence (-/+ 20% variation in the mean incidence – Tab. I); hypothesized vaccine efficacy (variation from 50% to 90%); vaccination coverage among the population (variation from 50% to 90%); the probability of suffering sequelae (variation from 30% to 80%); the case fatality rate of the disease (variation from 6% to 10%), and the costs related to the disease (-/+ 20% variation in base-case costs).

Table XIV reports the ICER values yielded by the analysis of deterministic probability on considering the hypothesized vaccine efficacy, vaccination coverage, disease incidence, probability of sequelae, and case fatality rate.

The analysis revealed a slight variation in all the ICER values for all the parameters considered, with the exception of vaccine efficacy, the ICER of which varies from € 11,640.54 (corresponding to the minimum value of the range of variation) to € 6,450.87 (corresponding to the maximum value of the range of variation) though still remains below the threshold value of cost-effectiveness. The parameter that displays the least influence is case fatality rate, owing to the absence of costs related to death (conservative approach).

Figure 2 reports the variations in the ICER on varying vaccine efficacy.

The deterministic sensitivity analysis of the costs of the disease (-/+ 20%) reveals that only the long-term costs related to sequelae influence the ICER, though not greatly. This low correlation is due to the low incidence of the disease and to the hypothetical decline in vaccine efficacy over time.

Tab. XIV. Results of the deterministic analysis.

Efficacy of the vaccine	ICER (€)	Vaccination coverage	ICER (€)	Incidence	ICER (€)	Overall probability of sequelae	ICER (€)	Disease case fatality rate	ICER (€)
50%	11,640	50%	7,906	-20%	7,913	40%	7,911	6%	7,909
60%	9,694	60%	7,907	-10%	7,909	50%	7,909	7%	7,908
70%	8,304	70%	7,907	No variazione	7,907	60%	7,907	8%	7,907
80%	7,262	80%	7,907	+10%	7,904	70%	7,905	9%	7,906
90%	6,451	90%	7,908	+20%	7,901	80%	7,903	10%	7,905

Fig. 2. Deterministic sensitivity analysis of the parameter vaccine efficacy.

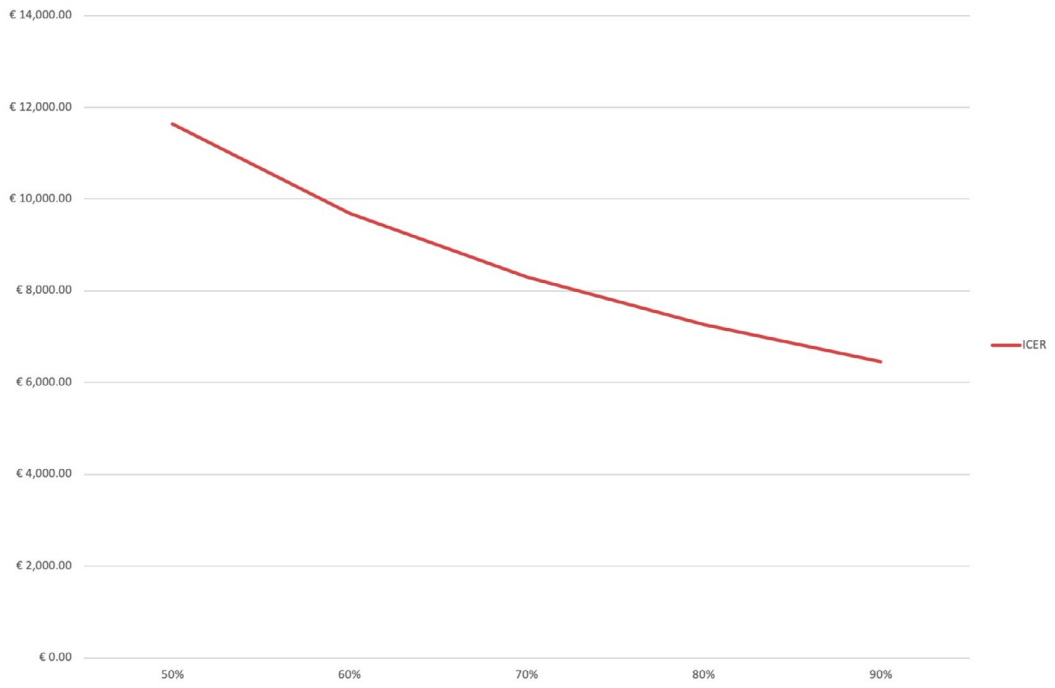


Fig. 3. Distribution of cost-effectiveness values yielded by the probabilistic sensitivity analysis.

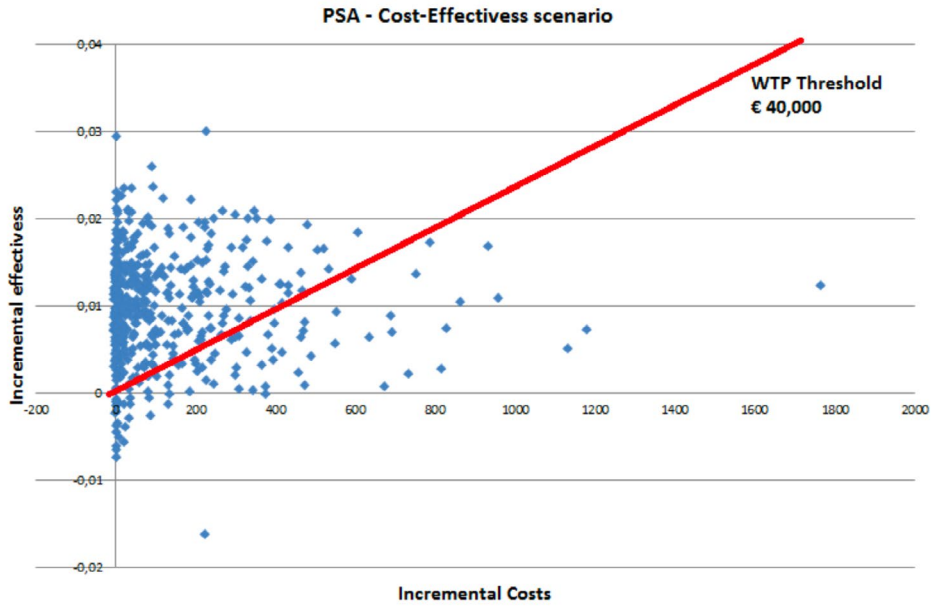
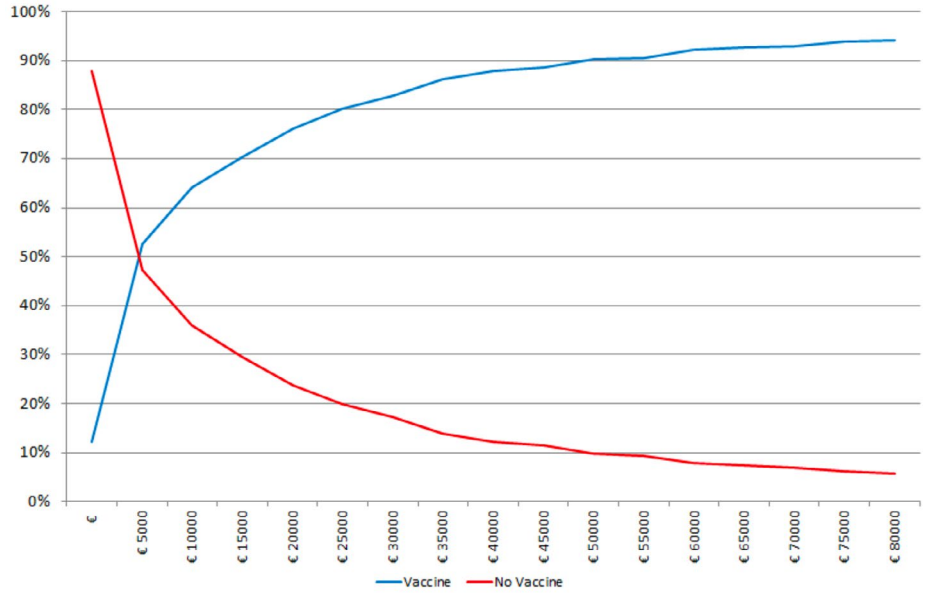


Fig. 4. Acceptability curve of cost-effectiveness of the "vaccination" and "no-vaccination" strategies.



The probabilistic sensitivity analysis is depicted by a Monte Carlo simulation in which the simultaneous variation of all the values in the model is shown by means of 5,000 simulations. Figure 3 shows the points of incremental cost and incremental effectiveness yielded by each simulation. The cluster of points to the left of the red line (cost-effectiveness threshold value) comprises about 80% of the simulated scenarios, indicating a high percentage of cost-effective scenarios if the threshold is set at € 30,000. Figure 4 depicts the acceptability curve of cost-effectiveness; the percentages of cost-effective simulations are shown for the "vaccination" and "no-vaccination" strategies. The uncertainty of the values of the input parameters displays a modest impact on the model; indeed, more than three quarters of the scenarios are found below the threshold value of € 30,000.

Discussion

This is the first study to evaluate the cost-effectiveness of vaccination with Trumenba® in adolescents not only in Italy but also in the international setting.

The model demonstrated the cost-effectiveness of vaccinating adolescents with Trumenba®, which was confirmed by the probabilistic sensitivity analysis. Vaccination was seen to determine not only a reduction in the number of cases of disease, but also savings in the

direct and indirect costs related to the permanent and invalidating sequelae that afflict a considerable number of survivors [2, 3, 10, 32, 33, 36, 38]. Indeed, the sensitivity analysis revealed that the long-term costs are those which have the greatest impact on the level of cost-effectiveness.

The cost-effectiveness of the vaccine is chiefly related to a set of factors: the incidence and the high costs of the disease (particularly long-term costs); the efficacy of the vaccine; the duration of the protection elicited, and the price of the vaccine.

It should, however, be borne in mind that the mathematical and pharmaco-economic models applied to prevention necessarily adopt a reductionist approach. In the case of meningococcal disease, this is particularly true, especially with regard to the underestimation of the incidence of the disease in Italy [5, 14, 55] and to the assessment of its possible sequelae (single and multiple) and their costs.

Although the Italian Invasive Bacterial Diseases Surveillance System [13], which is coordinated by the *Istituto Superiore di Sanità* (ISS), is well structured, it does have certain limitations, owing to a few important factors: 1) the under-utilization of molecular methods for the detection of *N. meningitidis* in some Italian laboratories; 2) failure to send isolates to the ISS for typing, and 3) the under-notification of cases, as revealed by comparing the data from the surveillance system with those reported on hospital discharge forms (HDF) [56]. With regard to underestimation of laboratory detection, a study by Azzari et al. [24] found that, for the detection of *N. meningitidis*, many laboratories in Italy utilized culture methods, which are less sensitive than molecular methods, resulting in a value of underestimation of 3.28. This finding was further confirmed by a recent study conducted by the same research group [57]. Moreover, culture methods have been seen to display lower sensitivity than molecular methods when patients are treated with antibiotics [58]. For what concerns the lack of typing of cases, the mean annual value was 25.2% in the period 2011-2016 [13]. Another factor leading to the underestimation of cases in Italy was highlighted by a recent study, which found that the number of cases of *N. meningitidis* reported by the national surveillance system was lower than that indicated by the HDF [period 2007-2016: 0.29/100,000 (surveillance data) *vs* 0.42/100,000 (adjusted rate of incidence)] [56]. Finally, according to the evidence reported by the WHO, many fulminant cases are not registered [59]. In this context, the correction factors applied to the incidence of the disease constitute one of the strong points of this study, and enabled us to obtain results that were closer to the true situation; indeed, this parameter is one of the principal factors that influence the ICER, as has also been pointed out by previous economic assessments [25, 26, 60].

With regard to the assessment of the probability of suffering sequelae, one of the strengths of the study lies in the fact that we conducted an in-depth literature review (see chapter 3) in order to reduce the possibility of underestimating the impact of short- and long-term sequelae on both the health of the patient and the quality of life of patients and their caregivers. Many of the studies published to date have underestimated this parameter by considering only the most frequent sequelae; consequently, they have tended to be very conservative and not to reflect the actual situation closely [26, 60, 61, 62]. A further strength of the study is that the disease was analyzed in its various phases: acute, post-acute and long-term. This enabled us to describe the disease itself more accurately, to match the model as closely as possible to reality, and to rigorously relate the sequelae to their costs and health utilities. Moreover, this study is one of the few in which the psychological and psychiatric impact of the disease on both patients and their caregivers has been included in the analysis. This is certainly an innovative aspect which should not be overlooked, as is highlighted in chapter 3 and supported by numerous studies [9, 10, 51, 63].

Although the sequelae of meningococcal disease are generally multiple [2, 3, 39], the present study evaluated them singly; this was because, on analyzing the data available in the literature, their possible combinations and frequency could not be precisely assessed. Indeed, the models published to date have also adopted this reductionist approach [25, 26, 61], and the few studies that have considered multiple sequelae have not evaluated them in detail [62, 64]. In this regard, given the heavy impact of multiple sequelae, the model must be regarded as conservative. It is, however, supported by numerous literature data. For example, the study by Sadarangani et al. reported that 37% of all patients who suffered complications had multiple sequelae: 33% of children and 42% of adults [3]. Bettinger et al. found that 23.3% of subjects had multiple sequelae [39], while Buysse et al. reported a 35% probability of suffering multiple sequelae [2].

Another important aspect to consider is that the present study analyzed the impact of vaccination not only from the NHS perspective, but also from that of society. This feature is of considerable relevance, in that meningococcal disease gives rise to high indirect costs, chiefly owing to the fact that severe invalidating sequelae cause loss of productivity on the part of both patients and caregivers and necessitate special education for patients with serious complications (mental retardation, deafness, communication problems, etc.). Our approach is in line with the WHO recommendation to consider the broadest possible perspective in economic assessments, in order to obtain a complete description of the impact of the disease under examination [65].

A final strength of the present study is that the model was parameterized with data drawn from published studies, even if these did not always focus on the vaccination target under examination or were not conducted in Italy. Only in a few cases was use made of "expert opinion", which constitutes routine practice in pharmaco-economic modeling studies [65].

Like all pharmaco-economic analyses, the present study has limitations, since models are simplifications of the real world. The modeling techniques commonly utilized in studies aimed at determining benefits and costs

include decision trees and Markov models. One of the main limitations of decision trees, however, is their lack of flexibility in modeling events in the long term (e.g. sequelae) [64]. For this reason, we developed a Markov model, which enabled us to make a long-term assessment, especially of sequelae and their costs.
One of the limits of the study is that it utilized international data on the probability of sequelae and on their costs. This choice was dictated by the fact that exhaustive studies on the sequelae of meningococcal disease and their related costs in the Italian context are not yet available. Moreover, in the case of some parameters, we used estimates that referred to different populations (children or adults) from the population under study (adolescents). In addition, the residual health utility values used for each type of sequela did not always refer to the consequences of meningococcal disease [25], and utility estimates of psychiatric/psychological sequelae (which have a long-term impact on quality of life) were taken from studies that followed up patients for a limited period of time; consequently, these parameters could have been underestimated. Finally, the life expectancy of survivors with sequelae was assumed to be equal to that of the age-matched general population. This is not completely true, though the differences are minimal [66, 67, 68].
A further limit lies in the fact that the study did not consider the cost of death. Indeed, the deterministic sensitivity analyses revealed that the ICER decreased as case fatality rate increased, in that, in the case of death, no disease costs are sustained and the social costs of the death itself are not considered (conservative approach).
Furthermore, as no data on some parameters were available, assumptions were made. Specifically, vaccine efficacy and the duration and decline of protection were hypothesized on the basis of the available data from controlled clinical studies of immunogenicity. Trumenba® is a recently authorized vaccine. Therefore, to gauge its efficacy, we used the results of controlled clinical studies [19, see chapter 5] and of studies aimed at correlating the level of surface expression of fHbp with the killing of Men B strains in assays of serum bactericidal activity with human complement (hSBA) [19]. In the future, once new data have become available, it will be necessary to confirm the results of the present study and to include the new scientific evidence. In this regard, it will be essential to implement effective surveillance systems, in order to obtain data on some parameters that are still uncertain, such as vaccine effectiveness and the duration of protection.
Finally, as the model is static, it did not consider herd immunity, nor did it assess the possible impact of Trumenba® on carriage. It must, however, be pointed out that few studies have been aimed at evaluating the impact of anti-meningococcal B vaccines on carrier status and that the data are not exhaustive [69].

Conclusions

In conclusion, this model demonstrated the cost-effectiveness of anti-meningococcal B vaccination with Trumenba® in adolescents in their 11th year of life.
Not only does this vaccination reduce the number of cases of disease, it also yields economic and social benefits as a result of the lower costs of treating the disease and managing medium- and long-term sequelae.
Although cases of invasive disease due to meningococcus B are few, if the overall impact of the disease is adequately considered, it becomes clear that inserting anti-meningococcal B vaccination into the immunization program for adolescents is strongly recommended from the economic standpoint.

References

[1] CDC - Centre for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. The Pink Book, 13th Edition, 2015, Chapter 14: Meningococcal Disease. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/mening.html [Accessed 28/02/2019].

[2] Buysse CM, Vermunt LC, Raat H, Hazelzet JA, Hop WC, Utens EM, Joosten KF. Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care 2010;14(3):R124. https://doi.org/10.1186/cc9087.

[3] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program A. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028

[4] ECDC - European Centre for Disease Prevention and Control. Invasive meningococcal disease - Annual epidemiological report for 2015. 2015. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-meningococcal-disease.pdf [Accessed 28/02/2019].

[5] Bosis S, Esposito S. Meningococcal disease in childhood: epidemiology, clinical features and prevention. J Prev Med Hyg 2015;56:E121-4.

[6] Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics 2009;123(3):e502-9. https://doi.org/10.1542/peds.2008-0581

[7] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. Vaccine 2014;32(37):4791-8. https://doi.org/10.1016/j.vaccine.2014.05.069

[8] Erickson L, De Wals P. Complication and sequelae of meningococcal disease in Quebec, Canada 1990-1994. Clin Infect Dis 1998;26(5):1159-64. https://doi.org/10.1086/520303

[9] Vyse A, Anonychuk A, Jakel A, Wieffer H, Nadel S. The burden and impact of severe and long-term sequelae of meningococcal disease. Expert Rev Anti Infect Ther 2013;11(6):597-604. https://doi.org/10.1586/eri.13.42

[10] Olbrich KJ, Muller D, Schumacher S, Beck E, Meszaros K and Koerber F. Systematic review of invasive meningococcal disease: sequelae and quality of life impact on patients and their caregivers. Infect Dis Ther 2018;7(4):421-38. https://doi.org/10.1007/s40121-018-0213-2

[11] Harrison LH, Trotter CL, Ramsay M. Global epidemiology of meningococcal disease. Vaccine 2009;27(2):B51-63. https://doi.org/10.1016/j.vaccine.2009.04.063

[12] ECDC - European Centre for Disease Prevention and Control. Invasive meningococcal disease - Annual epidemiological report for 2016. 2016. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2016-invasive-meningococcal-disease_1.pdf [Accessed 24/04/2019].

[13] Dipartimento Malattie Infettive, Istituto Superiore di Sanità.

Sorveglianza delle malattie batteriche invasive. Rapporto "Interim" 2017. Roma, aprile 2018. Available at: http://old.iss.it/binary/mabi/cont/InterimReport2017.pdf [Accessed 24/04/2019].

[14] Azzari C, Nieddu F, Moriondo M, Indolfi G, Canessa C, Ricci S, Bianchi L, Serranti D, Poggi GM, Resti M. Underestimation of invasive meningococcal disease in Italy. Emerg Infect Dis 2016;22(3):469-75.https://doi.org/10.3201/eid2203.150928

[15] McNamara LA TJ, MacNeil J, Chang HY, Day M, Fisher E, Martin S, Poissant T, Schmink SE, Steward-Clark E, Jenkins LT, Wang X, Acosta A. Oregon meningococcal carriage team meningococcal carriage following a vaccination campaign with menB-4C and menB-FHbp in response to a university serogroup B meningococcal disease outbreak-Oregon, 2015-2016. J Infect Dis 2017;216(9):1130-40. https://doi.org/10.1093/infdis/jix446

[16] Gasparini R CM, Amicizia D, Ansaldi F, Canepa P, Orsi A, Icardi G, Rizzitelli E, De Angelis G, Bambini S, Moschioni M, Comandi S, Simmini I, Boccadifuoco G, Brunelli B, Giuliani MM, Pizza M, Panatto D. Molecular and serological diversity of Neisseria meningitidis carrier strains isolated from Italian students aged 14 to 22 years. J Clin Microbiol 2014;52(6):1901-10. https://doi.org/10.1128/JCM.03584-13

[17] Agenzia Italiana del Farmaco. Vaccini obbligatori e a offerta gratuita e attiva (Legge 119/2017). 2018. Availabel at: http://www.aifa.gov.it/content/vaccini-obbligatori-e-offerta-gratuita-e-attiva-legge-1192017 [Accessed 24/04/2019].

[18] Scheda Tecnica Bexsero(R). Available at: https://www.ema.europa.eu/en/documents/product-information/bexsero-epar-product-information_it.pdf [Accessed 24/04/2019].

[19] Scheda Tecnica di Trumenba®. Available at: https://ec.europa.eu/health/documents/community-register/2017/20170524137650/anx_137650_it.pdf [Accessed 24/04/2019].

[20] Istituto Nazionale di Statistica ISTAT 2017. Available at: https://www.istat.it [Accessed 15/02/2019].

[21] Di Pietro ML, Poscia A, Specchia ML, De waure C, Zace D; al. GRe. Valutazione di Health Technology Assessment (HTA) del vaccino antinfluenzale adiuvato nella popolazione anziana italiana. QIJPH 2017;6(8). Available at: https://www.ijph.it/pdf/2017-v6-n9.pdf

[22] Boccalini S, Innocenti M, Sartor G, Manzi F, Bonanni P, Panatto D, Lai PL, Zangrillo F, Rizzitelli E, Iovine M, Amicizia D, Bini C, Marcellusi A, Mennini FS, Rinaldi A, Trippi F, Ferriero AM, Lisi GC. La vaccinazione universale dei bambini contro l'influenza con il vaccino Vaxigrip Tetra® in Italia: risultati di una valutazione di Health Technology Assessment (HTA). J Prev Med Hyg 2018;59(Suppl 1):E1-E86.

[23] Eurostat 2016. Available at: https://ec.europa.eu/eurostat/data/database [Accessed 10 febbraio 2019].

[24] Azzari C, Bonanni P. A new meningococcal B vaccine for adolescents and adults: characteristics and methods of use. J Prev Med Hyg 2018;59(4):E257-60. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1096

[25] Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, Tanfani E, Bonanni P, Lucioni C, Testi A, Panatto D. Vaccinating Italian infants with a new multicomponent vaccine (Bexseroâ) against meningococcal B disease: a cost-effectiveness analysis. Hum Vaccin Immunother 2016;12(8):2148-61. https://doi.org/10.1080/21645515.2016.1160177.

[26] Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. Vaccine 2013;31(23):2638-46. https://doi.org/10.1016/j.vaccine.2013.03.034

[27] AIES. Proposta di line guida per la valutazione economica degli interventi sanitari in Italia PharmacoEconomics. Italian Research Articles 2009;11(2):83-93.

[28] Capri S, Ceci A, Terranova L, Merlo F, Mantovani L. Guidelines for economic evaluations in Italy: recommendations from the Italian Group of Pharmacoeconomic Studies. Drug Information J 2001;35:189-201.

[29] Drummond MF SM, Torrance GW, O'Brien B, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd Edition. Oxford: Oxford University Press 2005.

[30] Ostergaard L, Vesikari T, Absalon J, Beeslaar J, Ward BJ, Senders S, Eiden JJ, Jansen KU, Anderson AS, York LJ, Jones TR, Harris SL, O'Neill R, Radley D, Maansson R, Pregaldien JL, Ginis J, Staerke NB, Perez JL; Investigators BT. A bivalent meningococcal B vaccine in adolescents and young adults. N Engl J Med 2017;377(24):2349-62. https://doi.org/10.1056/NEJMoa1614474

[31] Lecocq H, Parent du Châtelet I, Taha M-K, Lévy-Bruhl D; Dervaux B. Epidemiological impact and cost-effectiveness of introducing vaccination against serogroup B meningococcal disease in France. Vaccine 2016;34(19):2240-50. https://doi.org/10.1016/j.vaccine.2016.03.020

[32] Rivero-Calle I, Vilanova-Trillo L, Pardo-Seco J, Salvado LB, Quinteiro LI, Martinon-Torres F, Network MR. The burden of pediatric invasive meningococcal disease in Spain (2008-2013). Pediatr Infect Dis J 2016;35(4):407-13. https://doi.org/10.1097/INF.0000000000001048

[33] Viner RM, Booy R, Johnson H, Edmunds WJ, Hudson L, Bedford H, Kaczmarski E, Rajput K, Ramsay M, Christie D. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. The Lancet Neurology 2012;11(9):774-83. https://doi.org/10.1016/s1474-4422(12)70180-1

[34] Kaplan SL, Schutze GE, Leake JA, Barson WJ, Halasa NB, Byington CL, Woods CR, Tan TQ, Hoffman JA, Wald ER, Edwards KM, Mason EO, Jr. Multicenter surveillance of invasive meningococcal infections in children. Pediatrics 2006;118(4):e979-84. https://doi.org/10.1542/peds.2006-0281

[35] Vermunt LC, Buysse CM, Joosten KF, Oranje AP, Hazelzet JA, Verhulst FC, Utens EM. Self-esteem in children and adolescents after septic shock caused by Neisseria meningitidis: scars do matter. J Adolesc Health 2008;42(4):386-93. https://doi.org/10.1016/j.jadohealth.2007.09.026

[36] Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, Schneerson R, Robbins JB, Miller MA. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis 2011;53(9):e117-24. https://doi.org/10.1093/cid/cir500

[37] Scholz S, Koerber F, Meszaros K, Fassbender RM, Ultsch B, Welte RR, Greiner W. The cost-of-illness for invasive meningococcal disease caused by serogroup B Neisseria meningitidis (MenB) in Germany. Vaccine 2019. https://doi.org/10.1016/j.vaccine.2019.01.013

[38] Shepard CW, Ortega-Sanchez IR, Scott RD, 2nd, Rosenstein NE, Team AB. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. Pediatrics 2005;115(5):1220-32. https://doi.org/10.1542/peds.2004-2514

[39] Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R; Members of Canadian Immunization Monitoring Program A. The disease burden of invasive meningococcal serogroup B disease in Canada. Pediatr Infect Dis J 2013;32(1):e20-5. https://doi.org/10.1097/INF.0b013e3182706b89

[40] Oostenbrink R, Henriette AM, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. J Clin Epidemiol 2002;55:791-9. https://doi.org/10.1016/S0895-4356(02)00448-1

[41] Dipartimento Malattie Infettive ISdS. Sorveglianza delle malattie batteriche invasive. Rapporto consolidato 2017. Roma, aprile 2018. Available at: http://old.iss.it/binary/mabi/cont/InterimReport2017.pdf [Accessed 26 February 2019].

[42] Shirley M, Kheir TM. MenB-FHbp meningococcal group B vaccine (Trumenba®): a review in active immunization in individuals aged ≥ 10 years. Drugs 2018;78:257-68. https://doi.org/10.1007/s40265-018-0869-7

[43] Vesikari T, Ostergaard L, Diez-Domingo J, Wysocki J, Flodmark CE, Beeslaar J, Eiden J, Jiang Q, Jansen KU, Jones TR, Harris SL,

O'Neill RE, York LJ, Crowther G, Perez JL. Meningococcal serogroup B bivalent rLP2086 vaccine elicits broad and robust serum bactericidal responses in healthy adolescents. J Pediatric Infect Dis Soc 2016;5(2):152-60. https://doi.org/10.1093/jpids/piv039

[44] Vesikari T, Wysocki J, Beeslaar J, Eiden J, Jiang Q, Jansen KU, Jones TR, Harris SL, O'Neill RE, York LJ, Perez JL. Immunogenicity, safety, and tolerability of bivalent rLP2086 meningococcal group B vaccine administered concomitantly with diphtheria, tetanus, and acellular pertussis and inactivated poliomyelitis vaccines to healthy adolescents. J Pediatric Infect Dis Soc 2016;5(2):180-7. https://doi.org/10.1093/jpids/piv064

[45] Perez JL, Absalon J, Beeslaar J, Balmer P, Jansen KU, Jones TR, Harris S, York LJ, Jiang Q, Radley D, Anderson AS, Crowther G, Eiden JJ. From research to licensure and beyond: clinical development of MenB-FHbp, a broadly protective meningococcal B vaccine. Expert Rev Vaccines 2018;17(6):461-77. https://doi.org/10.1080/14760584.2018.1483726

[46] Ministero della Salute. Decreto del 18 ottobre 2012. "Remunerazione delle prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale". Available at: http://www.gazzettaufficiale.it/eli/gu/2013/01/28/23/so/8/sg/pdf [Accessed 19/04/2019].

[47] Di Pietro ML, Capri S, Kheiraoui F, de Waure C, Quaranta G, Poscia A, Specchia ML, Veneziano MA, Di Nardo F, Cadeddu C, Lovato E, Ferriero AM, Mancuso A, Miglietta A, Delon M, Mufida Alicevjc Health Technology Assessment della vaccinazione contro meningococco B. QIJPH 2013;2:1-113.

[48] Judge D, Nadel S, Vergnaud S, Garralda ME. Psychiatric adjustment following meningococcal disease treated on a PICU. Intensive Care Med 2002;28(5):648-50. https://doi.org/10.1007/s00134-002-1237-2

[49] Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. Paediatr Drugs 2013;15(1):49-58. https://doi.org/10.1007/s40272-012-0006-0

[50] Panca M, Buszewicz M, Strydom A, Hassiotis A, Welch CA, Hunter RM. Resource use and cost of annual health checks in primary care for people with intellectual disabilities. J Intellect Disabil Res 2019;63(3):233-43. https://doi.org/10.1111/jir.12569

[51] Shears D, Nadel S, Gledhill J, Garralda ME. Short-term psychiatric adjustment of children and their parents following meningococcal disease. Pediatr Crit Care Med 2005;6(1):39-43. https://doi.org/10.1097/01.PCC.0000144705.81825.EE.

[52] Tariffario. Ordine degli Psicologi. Available at: http://www.ordinepsicologi-liguria.it/wp-content/uploads/2017/03/Nomenclatore.pdf [Accessed 10/02/2019].

[53] Ehrlich TR, Von Rosenstiel IA, Grootenhuis MA, Gerrits AI, Bos AP. Long-term psychological distress in parents of child survivors of severe meningococcal disease. Pediatr Rehabil 2005;8(3):220-4. https://doi.org/10.1080/13638490400022246

[54] Decreto Ministeriale - Ministero della Sanità - 5 febbraio 1992. "Approvazione della nuova tabella indicativa delle percentuali d'invalidità per le minorazioni e malattie invalidanti." Gazz. Uff. 26 febbraio 1992, n. 47, S.O. Availabe at: http://www.gazzettaufficiale.it [Accessed 15 February 2019].

[55] Baldovin T, Lazzari R, Cocchio S, Furlan P, Bertoncello C, Saia M, Russo F, Baldo V. Invasive meningococcal disease in the Veneto region of Italy: a capture-recapture analysis for assessing the effectiveness of an integrated sur.veillance system. BMJ Open 2017;7(4):e012478. https://doi.org/10.1136/bmjopen-2016-012478

[56] Pezzotti P, Bellino S, Riccardo F, Lucaroni F, Cerquetti M, Pantosti A, Rezza G, Stefanelli P. Vaccine preventable invasive bacterial diseases in Italy: a comparison between the national surveillance system and recorded hospitalizations, 2007-2016. Vaccine 2019;37(1):41-8. https://doi.org/10.1016/j.vaccine.2018.11.047

[57] Guiducci S, Moriondo M, Nieddu F, Ricci S, De Vitis E, Casini A, Poggi GM, Indolfi G, Resti M, Azzari C. Culture and real-time polymerase chain reaction sensitivity in the diagnosis of invasive meningococcal disease: does culture miss less severe cases? PLoS One 2019;14(3):e0212922. https://doi.org/10.1371/journal.pone.0212922

[58] Azzari C, Canessa C, Lippi F, Moriondo M, Indolfi G, Nieddu F, Martini M, de Martino M, Castiglia P, Baldo V, Resti M; Italian Group for the Study of Invasive Bacterial Disease. Distribution of invasive meningococcal B disease in Italian pediatric population: implications for vaccination timing. Vaccine 2014;32(10):1187-91. https://doi.org/10.1016/j.vaccine.2013.09.055

[59] WHO. Laboratory methods for the diagnosis of meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae. http://www.who.int/cst/resources/publications/meningitis/WHO_CDS_CSR_EDC_99_7_EN/en/

[60] Tu HA, Deeks SL, Morris SK, Strifler L, Crowcroft N, Jamieson FB, Kwong JC, Coyte PC, Krahn M, Sander B. Economic evaluation of meningococcal serogroup B childhood vaccination in Ontario, Canada. Vaccine 2014;32(42):5436-46. https://doi.org/10.1016/j.vaccine.2014.07.096

[61] Pouwels KB, Hak E, van der Ende A, Christensen H, van den Dobbelsteen GP, Postma MJ. Cost-effectiveness of vaccination against meningococcal B among Dutch infants: crucial impact of changes in incidence. Hum Vaccin Immunother 2013;9(5):1129-38. https://doi.org/10.4161/hv.23888

[62] Si S, Zomer E, Fletcher S, Lee J, Liew D. Cost-effectiveness of meningococcal polysaccharide serogroups A, C, W-135 and Y conjugate vaccine in Australian adolescents. Vaccine 2019;37(35):5009-15. https://doi.org/10.1016/j.vaccine.2019.07.008

[63] Martinón-Torres F. Deciphering the burden of meningococcal disease: conventional and under-recognized elements. J Adolesc Health 2016;59(2 Suppl):S12-20. https://doi.org/10.1016/j.jadohealth.2016.03.041

[64] Wang B, Haji Ali Afzali H, Giles L, Marshall H. Lifetime costs of invasive meningococcal disease: a Markov model approach. Vaccine 2019;37(46):6885-93. https://doi.org/10.1016/j.vaccine.2019.09.060

[65] WHO. Guide to cost-effectiveness analysis. Available at: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf

[66] Tirani M, Meregaglia M, Melegaro A. Health and economic outcomes of introducing the new menB vaccine (Bexsero) into the Italian routine infant immunisation programme. Plos One 2015;10(4):e0123383. https://doi.org/10.1371/journal.pone.0123383

[67] Christensen H, Trotter CL, Hickman M, Edmuds WJ. Re-evaluanting cost effectiveness of universal meningitis vaccination (Bexsero) in England: modeling study. BMJ 2014;349:g5725. https://doi.org/10.1136/bmj.g5725

[68] Roed C, Omland LH, Engsig FN, Skinhoj P, Obel N. Long-term mortality in patients diagnosed with meningococcal disease: a Danish nationwide cohort study. PloS One 2012;5:e9662. doi: https://doi.org/10.1371/journal.pone.0009662

[69] Soeters HM, McNamara LA, Whaley M, Wang X, Alexander-Scott N, Kanadanian KV, Kelleher CM, MacNeil J, Martin SW, Raines N, Sears S, Vanner C, Vuong J, Bandy U, Sicard K, Patel M; Centers for Disease Control (CDC). Serogroup B meningococcal disease outbreak and carriage evaluation at a college - Rhode Island, 2015. MMWR Morb Mortal Wkly Rep 2015;64(22):606-7.

Chapter 7

The role of communication in adolescents' acceptance of anti-meningococcal vaccination

M. INNOCENTI[1], A. BECHINI[2], P. BONANNI[2], S. BOCCALINI[2]
[1] Medical School of Specialization in Hygiene and Public Health, University of Florence, Italy; [2] Department of Health Sciences, University of Florence, Italy

Introduction

The present chapter looks at the role of communication in the acceptability of anti-meningococcal vaccination among adolescents. The data available in the literature will be used in order to examine the following aspects:

1. current communication in the sphere of vaccinations, with particular regard to meningococcal diseases;
2. attitudes towards vaccination in the general population and among adolescents;
3. vaccine literacy and vaccine hesitancy;
4. the use of new means of communication and information in order to increase the acceptability of vaccinations.

In the area of health care, information and prevention are inseparably linked. Indeed, proper communication is a key factor in ensuring the efficacy of healthcare interventions, such as preventive measures. However, while access to information is simpler today than ever before, thanks to the widespread use of new means of communication (i.e. Internet and social media), the quality of this information is sometimes doubtful. Indeed, in recent years, together with the growing use of new means of communication, such as social networks, we have seen a marked increase in the spread of fake news; that is to say, news containing information that is invented, misleading or distorted, which is made public with the deliberate intention to disinform or to spread hoaxes through these means of information [1].

This phenomenon is becoming increasingly widespread with regard to news concerning vaccinations. For example, a recent study conducted from June 2014 to September 2017, and published in the *American Journal of Public Health*, analyzed the activity of a group of "trolls" on Twitter. These are individuals, usually anonymous, who interact with others by means of messages that are provocative, irritating, irrelevant or simply senseless and/or completely erroneous, their sole aim being to disrupt communication. The study revealed the existence of an organized network which, over the years, has stirred up and "poisoned" the debate regarding vaccinations by propagating the hoax that there is a link between vaccines and autism [2].

Thus, the communication of correct information on vaccine-preventable infectious diseases is becoming an increasingly important issue for Public Health, in that it plays a vital role in increasing vaccination coverage rates up to the target levels set in the 2017-2019 National Vaccine Prevention Plan (NVPP) [3]. Today, such communication is assuming even greater relevance in view of the declining vaccination coverage rates recorded in Italy in recent years. Indeed, in 2016, none of the obligatory or recommended vaccinations met the 95% coverage target set by the NVPP in force at the time. In particular, coverage rates of hexavalent vaccines and vaccination against measles-mumps-rubella (MMR) had diminished over the previous years, and in 2016 they were seen to have fallen by 2.8% in comparison with 2012 and by 3.6% in comparison with 2010 [4].

This reduced vaccination coverage in Italy may be related to the fact that infectious diseases no longer arouse as much fear as they used to in the past; consequently, it is no longer considered necessary or particularly important to vaccinate against them. Indeed, it is noteworthy that, according to a survey conducted in 2014 by the Italian Center for Social Investment Studies (Censis), among the most feared diseases in future life, infectious diseases accounted for only 3.9%. Specifically, these diseases were ranked fifth after cancers, diseases impairing physical self-sufficiency, cardiovascular diseases, progressive neurological diseases and dementia. According to the same survey, among the prevention strategies adopted by Italian parents, vaccination ranked lower than a healthy diet, physical activity, refraining from the use of tobacco and alcohol, and the use of vitamins/dietary supplements [5].

According to another survey conducted by the Censis in 2014, the supply of and demand for scientific information in Italy are very high (biomedicine alone accounted for 55% of the information appearing in newspapers and 64% of that broadcast on television). However, it should be pointed out that health communication often takes the form of information regarding knowledge and skills, rather than of education, information on risks, or the promotion of correct behaviors [6].

In this context, however, it is advisable to adopt a critical attitude toward the information available in the health sphere; the reliability of sources needs to be checked, and the scientific evidence on which claims are based should be verified. On the other hand, however, not everyone is currently able to carry out this sort of evaluation, not least because it requires a certain level of education. Thus, there is an ever greater need for proper health information and education, in order to raise the awareness of citizens, to make them responsible for the protection of their own health and, in particular, to make them understand the importance of preventive interven-

tions, such as vaccination. Efficacious, targeted communication strategies would have enabled us to achieve the same coverage objectives as those achieved through Law N° 119/17. Indeed, a marked increase in coverage rates has been seen in the 2015 cohort, with hexavalent vaccination reaching the 95% threshold in 13 Italian regions, and MMR coverage in the same cohort reaching 94% [7].

Meningococcal disease and communication

As suggested above, the perception of the risk of contracting a given disease and of suffering its consequences is a key factor in the population's acceptance of an immunization program, especially if the disease is particularly severe. In a period when the disease is endemic, and when the risk is medium-low, the population's perception of the disease risk is practically nil. During an epidemic, by contrast, this perception is much higher; it may therefore be necessary to adequately manage a possible panic reaction [8, 9]. In this latter situation, when the perceived disease risk is high, compliance with vaccination increases markedly.

Thus, in the event of an epidemic, communication plays a determining role. Indeed, in such situations, if institutional communication is not prompt, unfounded or incorrect information tends to spread rapidly; this may give rise to anxiety in the population. For example, following the hospitalization of two 12-year-old pupils attending a school in the north-west of England, who were diagnosed as having meningitis due to *Neisseria meningitidis*, a questionnaire was administered to the students of the same school in order to evaluate the methods of communication used by the Health Protection Agency (HPA). The information provided by the HPA through the school was generally deemed to be useful, but late. Many respondents stated that, while awaiting precise communications from official sources, the unofficial news that circulated caused confusion and anxiety. This news was spread through chats, messages and the web. The timely provision of accurate information would have helped to allay the potentially unfounded fears of the population [10].

Anxiety regarding meningococcal disease was recently observed in the population in Tuscany (Italy). Indeed, in 2015-2016, an unexpected rise in the number of cases of invasive meningococcal disease was documented; a total of 43 cases, 10 of which were fatal, were caused by a hypervirulent strain of meningococcus C. On the advice of the European Centre for Disease Control (ECDC), the standard operative procedures for the public health management of meningococcal disease were implemented; these included tracing the patients' contacts and administering chemoprophylaxis in order to avoid further transmission of the disease. Moreover, vaccination was recommended for non-immunized persons [11]. Specifically, to curb the rising incidence of cases of meningitis in the region, a dose of quadrivalent anti-meningococcus ACWY vaccine was offered free of charge to subjects aged between 11 and 18 years. Subsequently, this offer was extended to persons aged between 18 and 20 years and between 21 and 45 years who lived in areas where at least one case of disease had occurred. Owing to the high number of cases among persons aged more than 45 years, in February 2016 free vaccination against meningococcus was extended to all subjects over the age of 11 years in the areas where cases had been recorded. For citizens over the age of 45 years who lived in other areas of Tuscany, anti-meningococcal vaccination was made available on payment of a reduced charge. This extended campaign of immunization was chiefly driven by the population's great demand for vaccination, which was also sustained by the media. Indeed, a public communication campaign was also implemented, which included various strategies aimed at achieving the objectives set by the regional health authorities (a toll-free telephone number for information on vaccination, communications by means of newspapers, radio, television and websites, information letters for mayors, schools, local education institutions and sporting associations, and vaccine-promotion days). The population's response to the campaign was satisfactory; anti-meningococcal C vaccination coverage reached 47.1% in the primary target. Moreover, the population's request for vaccination proved to be strongly correlated with the appearance of the news of new cases in the media. A heightened perception of the risk of meningitis therefore favored compliance with vaccination, which was recognized by the population as an important means of preventing a "frightening" disease [12].

Thus, it is evident that clear and efficacious communication in epidemic periods is fundamental to the proper management of the population's anxiety, even though the acceptance of vaccination is easier to achieve when the perception of risk is more tangible. Nevertheless, it should be remembered that suitable communication should also be implemented during endemic periods, in order to inform citizens of the possible consequences of a vaccine-preventable disease and to promote good compliance with vaccination campaigns. However, it should be borne in mind that the perception of the risk and severity of meningococcal disease, in comparison with other vaccine-preventable infections, is already high even in non-epidemic periods; this should, in itself, favor the implementation of preventive interventions.

Meningococcus B infection: the public's perception of the risk of disease and attitude to vaccination

In 2012, an Australian survey involving 3055 individuals aged between 15 and 97 years was conducted in order to assess the population's knowledge of type B meningococcal disease and attitude toward vaccination. Some 23.5% (n = 717) of respondents had no knowledge of this disease, 36.6% (n = 1,114) had only a vague knowledge, and 9.1% (n = 278) erroneously believed that it was

due to a viral infection. The level of general knowledge of the disease was seen to be lower among adolescents ($p < 0.050$) and those who had a low level of education ($p = 0.019$), low family income ($p = 0.011$) or low/medium socio-economic status ($p < 0.050$). Moreover, the level of concern regarding meningococcal disease proved to be lower among males ($p < 0.001$), single people ($p < 0.001$), those who were not parents ($p < 0.001$), the highly educated ($p = 0.022$) and those with a high family income ($p = 0.015$). Of the 3055 individuals interviewed, 966 were parents; 82.5% (95% CI: 79.7-85.4) of parents (797/966) were in favor of having their children vaccinated against meningococcus B, while 12.2% (95% CI: 9.7-14.7) (118/966) stated that they were unsure. The main worry expressed by parents with regard to vaccination concerned potential side effects (41.3%; 95% CI: 26.7-46.0) [13, 14].

In a study conducted between 1 May and 31 December 2013 in various general medicine and pediatric outpatient clinics and nurseries in France, a questionnaire was administered to 1,270 parents who had at least one child aged between 2 months and 16 years. Of these, 671 (52.8%) stated that they were in favor of anti-meningococcal B vaccination. This choice was principally motivated by the gravity of the disease (63.8%) and the desire to protect their children (51.7%). On multivariate analysis, acceptance of vaccination proved to be correlated with: younger age of the parents (OR 0.949 for each additional year, $p < 10^{-3}$), a history of vaccination against serogroup C invasive meningococcal diseases (OR 6.755; $p < 10^{-3}$), and previous knowledge of the vaccine (OR 2.081; $p = 0.001$). One of the main reasons for refusal was the fear of possible side effects caused by the vaccine (45.5%) [15].

A similar survey was conducted in 2015 in the areas of Naples and Salerno in Italy. The sample consisted of 910 parents, and the response rate was 59.7%. Almost all the parents (95.8%) had heard of meningitis; 79.8% were aware of its mode of transmission, and 62.5% knew which population groups were at highest risk (infants, children and adolescents). Moreover, 86% of respondents knew that vaccination was a preventive measure. Married parents who had children, and who required further information on vaccination, as they had not been informed by their doctors about vaccination against meningococcus B, were more likely to be aware of the importance of vaccination as a preventive measure against meningitis. With regard to attitudes toward anti-meningococcus B vaccination, about two thirds (67.2%) of parents considered vaccination to be useful and stated that they would have their children vaccinated (64.1%). A greater probability of having a positive attitude toward the vaccination of their children was recorded among: parents whose children had already had at least one recommended vaccination; those who considered vaccination useful; those who wished to receive further information on vaccination, and those who knew that vaccination was a preventive measure against meningitis [16].

In another Italian study, conducted in Milan in the period May-July 2013, 2,050 questionnaires regarding the acceptability of anti-meningococcal B vaccination were distributed to parents of children who attended vaccination clinics to receive the hexavalent vaccine. A total of 1,842 parents (89.1%) completed the questionnaire; 64.4% of these parents were in favor of anti-meningococcal B vaccination. On multivariate analysis, a strong correlation was observed between the acceptance of vaccination and: awareness of the gravity of meningitis (OR: 2.3; CI: 1.4-3.6), awareness that vaccination was a beneficial preventive measure (very beneficial *vs* no benefits: OR = 6.4; CI: 3.0-13.7) and prior knowledge of the anti-meningococcal C vaccine (OR = 1.4; CI: 1.1-1.8). By contrast, a higher level of education was associated with the refusal to vaccinate (university level *vs* lower than middle-school level: OR = 0.68; CI:0.47-0.97) [17]. Thus, unlike other vaccinations, vaccination against meningococcus is accepted by the population, and especially by parents, on account of perceived gravity of the disease. Nevertheless, its acceptance remains closely correlated with the diffusion of proper information regarding its safety and efficacy as a preventive measure.

Meningococcus B: adolescents' perception of the risk of disease and their attitude to vaccination

In the literature, few studies have analyzed the attitude of adolescents toward anti-meningococcal vaccination.

In 2017, a cross-sectional study in Italy was carried out on a sample of 771 adolescents aged between 11 and 18 years, who had been selected from a random sample of 5 state schools in Naples. A questionnaire was administered in order to investigate their knowledge of and attitude toward vaccinations. Some 57.2% of respondents claimed to have a good/satisfactory knowledge of vaccine-preventable diseases. The level of knowledge was significantly higher among those who had at least one parent with a university degree, who had received information on vaccinations from doctors, and who wanted to know more about vaccinations. Moreover, 41.3% of respondents stated that vaccines were very useful tools for preventing disease. With regard to decisions concerning vaccinations, 47.2% believed that adolescents themselves should be allowed to decide autonomously [18].

In Australia in May 2014, a telephone survey was conducted in order to assess the opinions of parents and adolescents regarding the acceptability of the multicomponent vaccine against meningococcus B. Most of the interviewees considered meningitis to be a dangerous disease, and 75% of the adolescents interviewed (n=138) stated either that they had been vaccinated or that they intended to be vaccinated. The main reasons for not undergoing vaccination cited by adolescents were the lack of interest, time or information, and scant perception of the gravity of the disease [19].

In a study conducted by Pelullo et al. on a sample of 771 Italian adolescents, 85.2% of participants had heard about meningitis and 57.2% were aware that adolescents were at high risk of meningococcal disease, but only

30.3% knew that meningitis was transmitted via the respiratory route. Moreover, 40.5% knew that meningitis was a vaccine-preventable disease and that adolescents were a target group for vaccination. The level of knowledge was significantly higher among the following subgroups: females; those who spoke about vaccinations with their parents; those who had received information on vaccinations from doctors; those who had a positive opinion of the utility of the information received on vaccination, and those who felt that they did not need further information on meningitis. In addition, 25.7% of respondents deemed vaccination very useful. The probability of regarding vaccination as useful was higher among males, subjects aged 11-13 years, those who had a positive view of the utility of the information received, and those who had received at least one vaccination in the last year [20].

These studies indicate that, among adolescents who have knowledge of meningitis, attitudes toward anti-meningococcal vaccination are positive, as a result of the correct information that they have received and their high awareness of the risk of disease.

Thus, the provision of correct information and the health education of the population, and especially of adolescents, play a fundamental role in increasing the acceptance of anti-meningococcal vaccination, especially among those subjects whose knowledge of meningococcal disease may be inadequate.

Vaccine literacy and vaccine hesitancy

Proper information and approp riate education regarding vaccinations are of fundamental importance. However, in order to be effective, the messages provided must be calibrated to people's ability to grasp and to understand them.

Health Literacy (HL) is defined as the knowledge, motivation and competence needed in order to acquire, understand, evaluate and utilize information on health. Individuals who are "literate" in this sense will be able to express opinions and take decisions regarding health care, disease prevention and health promotion, thereby maintaining or improving their quality of life [21].

Health literacy influences people's behavior and their use of healthcare services, resulting in improvements in health outcomes and reductions in the costs accruing to both the individual and society. Indeed, an inadequate level of health literacy is associated with a scant ability to understand healthcare information, unsatisfactory compliance with therapy, insufficient attention to prevention, more frequent hospitalization, a worse state of health, and a higher mortality rate [22]. In particular, limited or insufficient health literacy is associated with a lower propensity to adopt protective behaviors, such as vaccination [23, 24].

The concept of "vaccine literacy" concerns health literacy from the point of view of attitudes and hesitancy toward vaccination, and its evaluation is geared to achieving a better understanding of the main determinants of the acceptance of vaccination. Vaccine literacy does not simply mean a knowledge of vaccines; it also involves developing an uncomplicated system for communicating information and offering vaccination, which can be seen as an indispensable feature of an efficient healthcare system [25].

In a recent literature review conducted by Lorini et al. in 2018, the relationship between health literacy and adherence to vaccination was investigated. This relationship seems to be influenced by the population's perception of disease-related risks. Indeed, if the risk of disease is perceived as probable and carries possible short-term consequences, health literacy impacts positively on adherence to vaccination. By contrast, if the perception of risk is low, health literacy either has a negative effect on adherence to vaccination or no effect at all [26]. This aspect is of particular importance with regard to infections such as meningitis, which are perceived as carrying a serious health risk.

In 2016 in Italy, a survey was conducted among the parents of children aged between 16 and 36 months, the aim being to assess their hesitancy toward having their children vaccinated and to investigate the possible determinants of this phenomenon. A total of 3,130 questionnaires were administered: 83.7% of parents were in favor of vaccination; 15.6% expressed hesitancy, and 0.7% were against vaccination. Doubts regarding the safety of vaccines were the main reason for refusing (38.1%) or interrupting (42.4%) vaccination. Although safety issues were a cause for concern to all the parents, those who opposed vaccination and those who were hesitant were much more afraid of possible adverse reactions than parents who were in favor of vaccinations. Nevertheless, both the parents in favor of vaccinations and those who manifested hesitancy considered vaccine to be an important means of prevention and deemed adequate communication to be necessary [27].

Vaccine hesitancy could be partly overcome by improving education and health literacy, especially if interventions target not only parents and the general adult population, but also primary and secondary school students [28].

With regard to improving the acceptance of vaccinations, some considerations concerning healthcare workers need to be made. In Italy's Veneto region, a study was conducted from June 2009 to May 2011 in order to investigate the factors underlying the refusal to vaccinate. This revealed that the level of education had a significant influence on the acceptance of vaccination, in that parents who did not have their children vaccinated had a significantly higher level of education; indeed, almost half of the mothers who did not have their children vaccinated stated that they had a university degree. The results also revealed that many of these were healthcare workers, a finding which is in line with the low rates of vaccination coverage recorded among these professionals [29].

Thus, the training of future healthcare workers with regard to this issue is extremely important, in order to tackle any doubts and to promote the active immunization of the general population. This aspect is particularly

important in the case of pathologies such as meningococcal disease.
In this regard, a study conducted at the University of Palermo (Italy) assessed the knowledge of vaccinations of 118 students of medicine and biology. Questionnaires were administered to the students before and after a seminar on vaccinations and the pre- and post-seminar results were compared. The post-test results revealed a significant improvement in the students' knowledge, with the overall percentage of correct answers increasing from 38.8% to 77.6% ($p<0.001$). This study highlighted the importance of providing students of medicine and biology with proper education/training, in order to improve their knowledge of and attitudes toward vaccinations, and to prepare them to promote vaccination among the general public [30].
Training healthcare professionals to provide homogeneous information that is in line with national recommendations is essential, in order to respond to the concerns of the population with regard to an important means of prevention, as is vaccination.

Information today: adults and social networks

In the past, the main source of information on health (and also on vaccinations) was the family doctor or the Public Health Service doctor. Today, however, new means of communication are being increasingly used. This change must be taken into account if we are to increase the acceptance of vaccination, especially when adolescents are targeted for vaccination.
Today, more than half of the world's population is connected to the Internet. Indeed, according to the 2018 Global Digital Report, which was based on data from 239 countries, the current number of Internet users in the world exceeds 4 billion. In Italy, the use of social media is growing in parallel with the number of people connected to the Internet, with 73% of the population (43 million people) being online and 34 million actively using social media. Indeed, Italians spend about 6 hours per day online (almost twice as much time as they spend watching television). Of these 6 hours, almost two are spent using a social media platform, the most commonly used apps (applications) being Facebook, Whatsapp and Instagram [31].
In recent years the number of health-related apps has increased. In 2013, there were about 31,000 health-related apps in the world, and their number is rapidly increasing [32].
According to the report mHealth App Developer Economics 2014, which categorized 808 health-related apps available from the main app stores, almost one third of these concerned the monitoring of physical activity, 16.6% provided medical information (on diseases, symptoms and drugs) and 15.5% were devoted to well-being (yoga, meditation, etc.). Apps aimed at improving compliance with treatment accounted for only 1.6% [33]. A critical point that needs to be addressed, however, is that there is no form of control or regulation of health-related apps; the information provided is therefore often inaccurate or not up to date [34].
A survey conducted in June 2015 in the United States, which involved 1,604 smartphone users, investigated the use of health-related apps. Slightly over half (934/1,604, 58.23%) of the respondents stated that they had downloaded a health-related mobile app; the most commonly utilized concerned fitness and diet. The most frequent reasons cited for not downloading apps were: lack of interest, cost and concerns that personal data might be collected. Younger and more highly educated people tended to be more likely to use health-related apps. Cost proved to be a significant concern, with 41.3% of subjects indicating that they were unwilling to pay for a health-related app. Interestingly, most of those who had downloaded health-related apps claimed that these had improved their health. About half of those who had downloaded health-related apps (427/934, 45.7%) reported having stopped using some apps, mainly because of the burden of having to input data, loss of interest and hidden costs. What emerges from these results is that, while many people use health-related apps, a considerable portion of the population does not, and that, even among those who do use health-related apps, many stop using them. These data suggest that app designers should be more sensitive to consumers' needs with regard to cost and data load. Moreover, the efficacy of health-related apps needs to be tested in order to broaden their appeal and increase their adoption [35].
This expanding world of social networks and apps could become a useful channel for promoting vaccinations by informing and educating the public. Indeed, according to a survey conducted by the *Censis* in 2017, 17% of parents in Italy seek information on vaccinations on the Internet and social networks. Specifically, 42.8% do so before deciding whether or not to have their children vaccinated [36].
However, people need to be able to judge the reliability and quality of the information that they find on these new means of communication. First of all, as reported in a recent study, it is important to know who posts news about vaccines on social media such as Facebook and Twitter. Indeed, posts by specialists and institutions each account for only 1% of the total, while 31% of posts are made by members of the anti-vaccination lobby. This means that there is a shortage of correct information on the safety and efficacy of vaccinations [37].
Careful evaluation of the sources of information posted on social networks becomes even more important when these posts concern diseases that attract particular attention, such as meningococcal diseases. On the other hand, this latter aspect could be exploited in order to transform social networks from a misleading or deleterious means of communication into a highly effective tool for health promotion through prevention.

Information today: adolescents and social networks

Today, these new technologies, particularly the social networks, are an important part of adolescents' lives. The ever-growing diffusion of smartphones among adolescents makes it difficult for parents to quantify the actual amount of time spent by their children on social networks. From the periodic survey *Abitudini e stili di vita degli adolescenti italiani* (Habits and lifestyles of Italian adolescents), promoted by the Italian Society of Pediatrics (ISP), on a representative sample of the national population, it emerges that, while in 2000 only 5% of adolescents reported having used the Internet at least once, this percentage had risen to 57% in 2004 and had reached 100% by the time the results of the most recent survey were published (2013-2014). Moreover, while 42% of adolescents in 2008 used the Internet every day, by 2014 this percentage had doubled (81%). Today, almost all adolescents are able to access the Internet whenever they want, at any time of the day. In this age-group, access to the Internet usually means using social networks. This great familiarity with the world of the web has resulted in a growth of socialization within digital platforms and through apps that enable individuals to make simultaneous contact with a practically limitless number of people. Again according to the research of the ISP, 81% of adolescents in 2014 had their own Whatsapp account, 42% were active members of Instagram, and 30% of males and 37% of females subscribed to Ask, a social network that enables users to communicate while maintaining their anonymity [38].

How much do adolescents use these means of communication to search for information regarding their own health? To answer this question, a 2017 study was conducted in Boston through the administration of an anonymous questionnaire. The questionnaire was completed by 204 young people, with a rate of participation of 83.6%. Almost all (98%) of the respondents had utilized social media in the previous month, while only 51.5% had shared health information online. Those who reported having health problems were more likely to share health information. Only 25% of respondents believed that social media could provide them with useful health information. Not considering social media to be a useful source of information on health could therefore limit the efficacy of online public health messages in this age-group [39].

Thus, on the one hand, the Internet and social networks could constitute a useful means of conveying health information, in view of their widespread use by young people. On the other hand, however, it is important to foster the conviction among adolescents that the web is a useful channel through which to obtain information on health, including vaccine prevention. At the same time, young people need to receive adequate education on how to acquire the skill to seek out reliable information.

Conclusions

According to a systematic review of the literature conducted by Yonker et al., social media, if used properly, can be regarded as new efficacious means of communication that are able to involve, inform and educate adolescents and young adults with regard to health. Indeed, social media have already been successfully used in order to involve young people in health-related issues, to identify risk behaviors, and to provide adequate intervention and education [40].

Using the new means of communication to increase knowledge of meningococcal disease and how it can be prevented could improve adolescents' acceptance of vaccination. Indeed, social networks, which in some cases purvey fake news that undermines this acceptance, could become a useful tool for the promotion of health. In this regard, health-related apps, particularly those dealing with the prevention of meningococcal disease, could play an important role in fostering the acceptance of vaccination. One such app is "Liberi da meningite" ("Free from Meningitis"), the aim of which is to inform parents about the disease and to teach them how to recognize and prevent it [41].

In order to implement successful immunization programs, it is essential to identify the factors that influence – whether positively or negatively – adolescents' acceptance of vaccination. Indeed, a major challenge currently facing immunization programs in developed countries is how to improve the compliance of adolescents in order to reach and maintain high vaccination coverage rates in this age-group. It is therefore necessary to implement interventions aimed at improving adolescents' knowledge of meningitis and how it can be prevented through vaccination. A final relevant aspect concerns the importance of directly involving adolescents, and not only their parents, in decisions regarding their health [42].

Thus, in order to improve vaccination coverage against meningococcus B among adolescents, we should consider the possibility of implementing suitable campaigns of information/communication that include the use of social media and target both adolescents and their parents.

Bibliografia

[1] Stella R. Sociologia delle comunicazioni di massa. UTET Università 2012.

[2] Broniatowski DA, Jamison AM, Qi S, AlKulaib L, Chen T, Benton A, Quinn SC, Dredze M. Weaponized health communication: twitter bots and russian trolls amplify the vaccine debate. Am J Public Health 2018;108(10):1378-84. https://doi.org/10.2105/AJPH.2018.304567

[3] Ministero della Salute. Piano Nazionale della Prevenzione Vaccinale (PNPV) 2017-2019. Availabe at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf

[4] Signorelli C, Odone A, Cella P, Iannazzo S, D'Ancona F, Guerra R. Infant immunization coverage in Italy (2000-2016). Ann Ist Super Sanita 2017;53(3):231-7. https://doi.org/10.4415/ANN_17_03_09

[5] Centro Studi Investimenti Sociali (Censis). Monitor Biomedico 2014. Available at: http://www.censis.it/

[6] Centro Studi Investimenti Sociali (Censis). 48° Rapporto sulla situazione sociale del Paese 2014. Available at: http://www.censis.it/

[7] Vaccinazioni dell'età pediatrica e dell'adolescente - Coperture vaccinali. Available at: http://www.salute.gov.it/portale/documentazione/p6_2_8_3_1.jsp?lingua=italiano&id=20 [Accessed 18/09/2019].

[8] Hooker C, Capon A, Leask J. Communicating about risk: strategies for situations where public concern is high but the risk is low. Public Health Res Pract 2017;27(1).pii:2711709. https://doi.org/10.17061/phrp2711709

[9] Dickmann P, Biedenkopf N, Keeping S, Eickmann M, Becker S. Risk communication and crisis communication in infectious disease outbreaks in Germany: what is being done, and what needs to be done. Disaster Med Public Health Prep 2014;8(3):206-11. https://doi.org/10.1017/dmp.2014.36

[10] Taylor-Robinson D, Elders K, Milton B, Thurston H. Students' attitudes to the communications employed during an outbreak of meningococcal disease in a UK school: a qualitative study. J Public Health (Oxf) 2010;32(1):32-7. https://doi.org/10.1093/pubmed/fdp080.

[11] Stefanelli P, Miglietta A, Pezzotti P, Fazio C, Neri A, Vacca P, Voller F, D'Ancona FP, Guerra R, Iannazzo S, Pompa MG, Rezza G. Increased incidence of invasive meningococcal disease of serogroup C / clonal complex 11, Tuscany, Italy, 2015 to 2016. Euro Surveill 2016;21(12). https://doi.org/10.2807/1560-7917.ES.2016.21.12.30176

[12] Bechini A, Paolini D, Pieralli F, Baggiani L, Mereu G, Santini MG, Brocca T, Gostinicchi S, Gori E, Boccalini S, Bonanni P, Bonaccorsi G. Do Tuscan people adhere to meningococcal C vaccination during an emergency campaign? J Prev Med Hyg 2018;59(3):E187-93. https://doi.org/10.15167/2421-4248/jpmh2018.59.3.952

[13] Marshall H, Clarke M, Sullivan T. Parental and community acceptance of the benefits and risks associated with meningococcal B vaccines. Vaccine 2014;32(3):338-44. https://doi.org/10.1016/j.vaccine.2013.11.042

[14] Wang B, Clarke M, Afzali HH, Marshall H. Community, parental and adolescent awareness and knowledge of meningococcal disease. Vaccine 2014;32(18):2042-9. https://doi.org/10.1016/j.vaccine.2014.02.054

[15] Le Ngoc Tho S, Ader F, Ferry T, Floret D, Arnal M, Fargeas S, Chidiac C, Valour F. Vaccination against serogroup B Neisseria meningitidis: perceptions and attitudes of parents. Vaccine 2015;33(30):3463-70. https://doi.org/10.1016/j.vaccine.2015.05.073

[16] Morrone T, Napolitano F, Albano L, Di Giuseppe G. Meningococcal serogroup B vaccine: knowledge and acceptability among parents in Italy. Hum Vaccin Immunother 2017;13(8):1921-7. https://doi.org/10.1080/21645515.2017.1313940

[17] Mameli C, Faccini M, Mazzali C, Picca M, Colella G, Duca PG, Zuccotti GV. Acceptability of meningococcal serogroup B vaccine among parents and health care workers in Italy: a survey. Hum Vaccin Immunother 2014;10(10):3004-10. https://doi.org/10.4161/21645515.2014.971602

[18] Pelullo CP, Di Giuseppe G. Vaccinations among Italian adolescents: knowledge, attitude and behavior. Hum Vaccin Immunother 2018;14(7):1566-72. https://doi.org/10.1080/21645515.2017.1421877

[19] Dubé E, Gagnon D, Hamel D, Belley S, Gagné H, Boulianne N, Landry M, Bettinger JA. Parents' and adolescents' willingness to be vaccinated against serogroup B meningococcal disease during a mass vaccination in Saguenay-Lac-St-Jean (Quebec). Can J Infect Dis Med Microbiol 2015;26(3):163-7. https://doi.org/10.1155/2015/732464

[20] Pelullo CP, Napolitano F, Di Giuseppe G. Meningococcal disease and vaccination: knowledge and acceptability among adolescents in Italy. Hum Vaccin Immunother 2018;14(5):1197-202. https://doi.org/10.1080/21645515.2018.1436918

[21] Sørensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, Brand H; (HLS-EU) Consortium Health Literacy Project European. Health literacy and public health: a systematic review and integration of definitions and models. BMC Public Health 2012;12:80. https://doi.org/10.1186/1471-2458-12-80

[22] Berkman ND, Sheridan SL, Donahue KE, Halpern DJ, Crotty K. Low health literacy and health outcomes: an updated systematic review. Ann Intern Med 2011;155(2):97-107. https://doi.org/10.7326/0003-4819-155-2-201107190-00005

[23] Heijmans M, Uiters E, Rose T, Hofstede J, Devillé W, van der Heide I, Boshuisen H, Rademakers J. Study on sound evidence for a better understanding of health literacy in the European Union. Final report. RfS Chafea/2014/health/01, June 2015. Available at: https://ec.europa.eu/health/sites/health/files/health_policies/docs/2015_health_literacy_en.pdf

[24] Biasio LR. Vaccine hesitancy and health literacy. Hum Vaccin Immunother 2017;13(3):701-2. https://doi.org/10.1080/21645515.2016.1243633

[25] Ratzan SC. Vaccine literacy: a new shot for advancing health. J Health Commun 2011;16(3):227-9. https://doi.org/10.1080/10810730.2011.561726.

[26] Lorini C, Santomauro F, Donzellini M, Capecchi L, Bechini A, Boccalini S, Bonanni P, Bonaccorsi G. Health literacy and vaccination: a systematic review. Hum Vaccin Immunother 2018;14(2):478-88. https://doi.org/10.1080/21645515.2017.1392423.

[27] Giambi C, Fabiani M, D'Ancona F, Ferrara L, Fiacchini D, Gallo T, Martinelli D, Pascucci MG, Prato R, Filia A, Bella A, Del Manso M, Rizzo C, Rota MC. Parental vaccine hesitancy in Italy - Results from a national survey. Vaccine 2018;36(6):779-87. https://doi.org/10.1016/j.vaccine.2017.12.074

[28] Biasio LR, Corsello G, Costantino C, Fara GM, Giammanco G, Signorelli C, Vecchio D, Vitale F. Communication about vaccination: a shared responsibility. Hum Vaccin Immunother 2016;12(11):2984-2987. https://doi.org/10.1080/21645515.2016.1198456

[29] Valsecchi M, Speri L, Simeoni L, Campara P, Brunelli M. Progetto "Indagine sui determinanti del rifiuto dell'offerta vaccinale nella Regione Veneto", report di ricerca, analisi dei dati e indicazioni operative. Availabe at: http://www.epicentro.iss.it/temi/vaccinazioni/pdf/Ulss20Verona_04-2012ReportDeterminantiRifiutoVaccinale.pdf

[30] Marotta C, Raia DD, Ventura G, Casuccio N, Dieli F, D'Angelo C, Restivo V, Costantino C, Vitale F, Casuccio A. Improvement in vaccination knowledge among health students following an integrated extra curricular intervention, an explorative study in the University of Palermo. J Prev Med Hyg 2017;58(2):E93-8. https://doi.org/10.15167/2421-4248/jpmh2017.58.2.720

[31] We Are Social, HootSuite. Report Global Digital 2018. Available at: https://wearesocial.com/it/blog/2018/01/global-digital-report-2018.

[32] Payne HE, Lister C, West JH, Bernhardt JM. Behavioral functionality of mobile apps in health interventions: a systematic review of the literature. JMIR Mhealth Uhealth 2015;3(1):e20. https://doi.org/10.2196/mhealth.3335

[33] Research2Guidance. The app market specialists. mHealth App Developer Economics 2014. The State of the Art of mHealth App Publishing. Fourth annual study on mHealth app publishing. Available at: http://www.research2guidance.com/r2g/mHealth-App-Developer-Economics-2014.pdf

[34] Ozdalga E, Ozdalga A, Ahuja N. The smartphone in medicine: a review of current and potential use among physicians and students. J Med Internet Res 2012;14(5):e128. https://doi.org/10.2196/jmir.1994

[35] Krebs P, Duncan DT. Health app use among US mobile phone owners: a national survey. JMIR Mhealth Uhealth 2015;3(4):e101. https://doi.org/10.2196/mhealth.4924

[36] Centro Studi Investimenti Sociali (Censis). 51° Rapporto sulla situazione sociale del Paese 2014. Available at: http://www.censis.it/

[37] Health Web Observatory. I vaccini per l'infanzia sul web. 2017. Available at: http://www.healthwebobservatory.org/

[38] Società Italiana di Pediatria (SIP). Abitudini e stili di vita degli adolescenti italiani. Indagine 2013-2014. 2014. Available at: http://sip.it/wp-content/uploads/2010/05/Risultati-indagine-2013-2014-completi.pdf

[39] Hausmann JS, Touloumtzis C, White MT, Colbert JA, Gooding HC. Adolescent and young adult use of social media for health and its implications. J Adolesc Health 2017;60(6):714-9. https://doi.org/10.1016/j.jadohealth.2016.12.025

[40] Yonker LM, Zan S, Scirica CV, Jethwani K, Kinane TB. "Friending" teens: systematic review of social media in adolescent and young adult health care. J Med Internet Res 2015;17(1):e4. https://doi.org/10.2196/jmir.3692

[41] Comitato Nazionale contro la meningite. Liberi dalla meningite. Scarica l'app "Liberi dalla meningite". Available at: http://www.liberidallameningite.it/sidebar-scarica-lapp/

[42] World Health Organization, Global Accelerated Action for the Health of Adolescents (AA-HA!) Guidance to Support Country Implementation. 2017. Available at: http://apps.who.int/iris/bitstream/handle/10665/255415/9789241512343-eng.pdf;jsessionid=4E6F49E3F50D6AAEE4007838BB97273A?sequence=1

Chapter 8

Strategies for anti-meningococcal vaccination for adolescents in Italy

D. PAOLINI, A. BECHINI, P. BONANNI, S. BOCCALINI
Department of Health Sciences, University of Florence, Italy

The 2017-2019 National Vaccine Prevention Plan (NVPP)

Although adolescence is a particularly important stage of life for what concerns vaccinations, it is often neglected or inadequately considered. Indeed, not only is it the elective period in which some vaccines, such as anti-HPV, should be administered, it is also the time when childhood vaccinations (e.g. against diphtheria, tetanus, whooping cough and poliomyelitis) should be checked and booster doses administered. Moreover, in this phase of life, it is essential to check the vaccination status with regard to measles, mumps, rubella, and chickenpox, and to undertake or complete any incomplete courses of vaccination.

For what concerns anti-meningococcus (anti-Men) vaccination, the strategies currently implemented respond to various criteria of analysis. In some cases, these have prompted the direct offer of vaccination, mainly in childhood; in other cases, they have identified adolescence as a fundamental period for this vaccination, both with regard to the administration of booster doses in order to maintain high antibody titers, and as a further possible population target for vaccination.

In Italy, the 2017-2019 National Vaccine Prevention Plan (NVPP) [1] recommended that adolescents receive a dose of the quadrivalent anti-meningococcical vaccine ACYW135 (anti-Men ACYW135), either if they did not undergo vaccination in childhood (anti-Men C or ACYW135), or if they did, in that the bactericidal antibody titer tends to diminish over time, thereby reducing protection against the disease.

With regard to the anti-meningococcus B vaccine (anti-Men B), in view of its recent introduction, the 2017-2019 NVPP assigns its priority use to early childhood, the age at which the impact of the disease is greatest. Nevertheless, given the epidemiology of meningococcal infections, this vaccination will also need to be actively offered to adolescents in the future [1].

Evaluation of the possible introduction of vaccination with anti-Men B in adolescence stems from the fact that adolescents and young adults constitute risk categories, as revealed by the epidemiological trend of invasive meningococcal diseases. Indeed, they account for a significant percentage of all cases, and among non-elderly persons (<65 years old) the case fatality rate is highest in subjects aged between 15 and 24 years [2]. In 2017, 17.3% of cases of invasive meningococcal disease in Europe occurred in the 15-24-year age-group [3]. Moreover, in adolescence, the symptoms are often recognized late, which means that hospitalization is prolonged and that physical and psychological outcomes are more frequent and more severe [4, 5].

Anti-Men B vaccination in regional vaccination schedules

In Italy, the Regions and the Autonomous Provinces have followed the indications of the 2017-2019 NVPP. Specifically, for what concerns anti-Men B, vaccination is currently provided for children in all Regions, while in older age-groups, it is only offered to subjects at risk. In 2017, the regional government of Sicily approved free anti-Men B vaccination for at-risk subjects and, in general, on request by the family pediatrician, for subjects aged from 5 to 10 years with two doses being administered at least 30 days apart; it was also offered free of charge to previously un-vaccinated subjects in the 12th year of life (11 years and one day), starting from the 2006 cohort [6].

Since 2018, the new regional calendar in Puglia has provided for free active vaccination with anti-Men B for subjects aged 11-12 years in concomitance with anti-Men ACWY vaccination (number of doses according to age and to the data sheet) [7].

In 2019, the Campania Region established that anti-Men B vaccination should be ensured through active call and free of charge for newborns, and also for adolescents during the 13th year of life (12 years and one day) in concomitance with anti-Men ACWY vaccination [8].

The 2019 "Lifetime Immunization Schedule" (LIS)

The fourth and latest edition of the Lifetime Immunization Schedule (2019) [9] – the vaccination schedule compiled by the Italian Society of Hygiene, Preventive Medicine and Public Health (SitI), by the Italian Society of Pediatrics (ISP), by the Italian Federation of Pediatricians (IFP) and by the Italian Federation of General Physicians (IFGP) – recommends the introduction of a booster dose of anti-Men ACWY vaccine for subjects aged 6-9 years, especially in the event of the diffusion of hypervirulent strains and in view of the fact that a considerable portion of vaccinees prove to be unprotected 5 years after vaccination. In addition, a booster dose in the 12th year of life is strongly recommended for those

who have not received a booster at the age of 6-9 years. The indication for vaccination during adolescence also remains valid for adolescents who have been vaccinated during childhood and for those who have received a booster at 6-9 years of age, given the need to maintain a high antibody titer in order to combat the rapid invasion of hypervirulent strains of meningococcus.
With regard to the anti-Men B vaccine, the LIS recommends maintaining the free active offer for all newborns and the active offer for subjects of all ages who are at risk on account of concomitant diseases, professional exposure, or, in the event of outbreaks, close contact with affected subjects. Given the epidemiology of invasive meningococcal diseases, it also urges that the possibility of introducing the vaccine extensively among adolescents be promptly evaluated. Indeed, vaccination has already been undertaken in this population in cases of community outbreaks or to reduce the disease risk in highly endemic regions, and has proved efficacious, safe and tolerable. Moreover, those Regions that are already able to introduce vaccination for this age-group into pilot projects are urged to carry out a detailed assessment of this strategy.

Vaccination coverage among adolescents in Italy

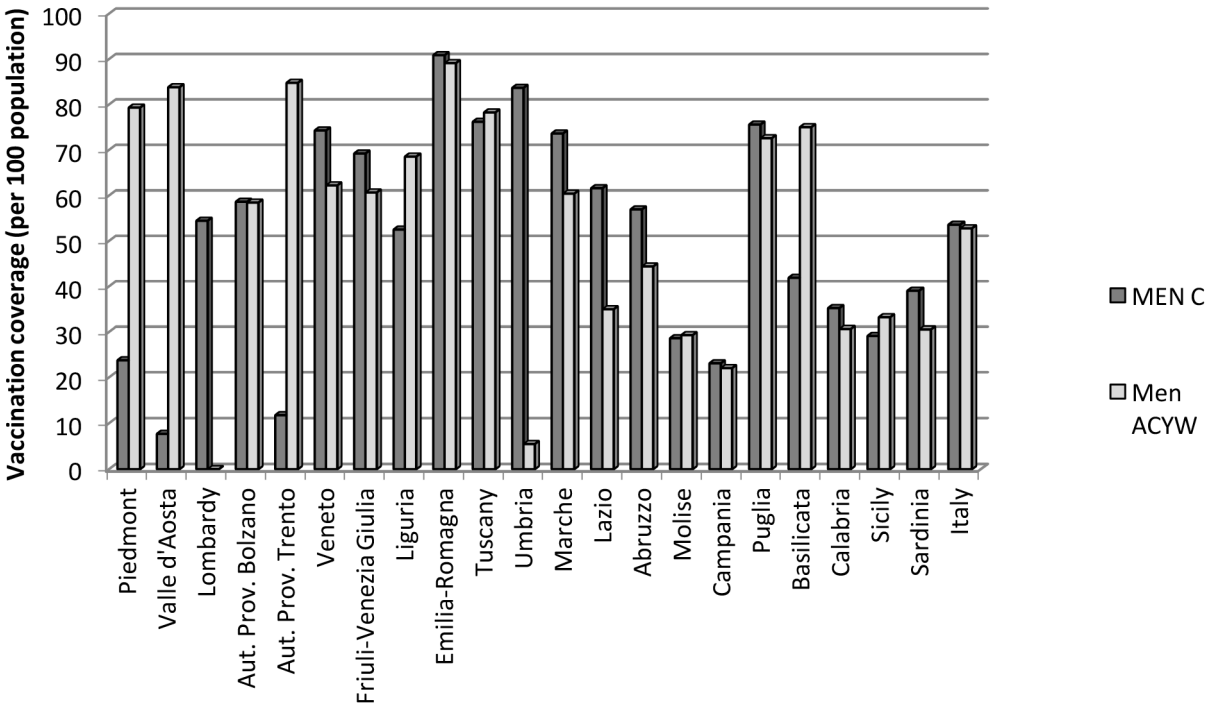
Given the current recommendations, the possible levels of vaccination coverage that can be achieved by means of the new immunization strategy need to be estimated, with a view to the possible introduction of vaccination with anti-Men B in adolescence.
Figures 1 and 2 show the coverage rates for adolescent vaccination with anti-Men C and anti-Men ACWY among 16-year-olds (2002 cohort) and 18-year-olds (2000 cohort) in Italy in 2018 [10].
These data reveal marked heterogeneity among the various regions, both with regard to vaccination with anti-Men C as a single antigen and in terms of anti-Men ACYW135 vaccination [10].
Following the publication of the 2017-2019 NVPP, and in order to ensure provision of all the vaccinations defined as "Essential Levels of Care" (ELC) throughout the country by the end of 2018, in 2017 the Italian Ministry of Health established both the timing of the introduction of the active offer of the new vaccinations and their target coverage rates. Specifically, it was established that vaccination with anti-Men ACYW135 (1 dose) for adolescents be introduced in 2017, the coverage target being ≥ 60% and gradually increasing over the following years (≥75% in 2018, ≥ 95% in 2019 and 2020) [11]. Thus, in the 2000 and 2002 cohorts, the 2017-2019 NVPP target of ≥ 95% coverage by anti-Men ACYW135 vaccination among adolescents (range: 11-18 years) was not achieved. It must be pointed out, however, that a precise evaluation of these data cannot be made, as the various regions adopted different anti-meningococcal vaccination strategies at different times.

The anti-Men B vaccine may be administered together with anti-HPV vaccination during the 12th year of life, as proposed in the Sicilian Regional Schedule [6]. However, compliance with the complete course of anti-HPV vaccination is suboptimal in Italy (Fig. 3), and the data show wide variability among the various Regions and Autonomous Provinces in all the female cohorts from 1997 to 2005 [12]. Specifically, no Region or Autonomous Province achieved the 95% coverage target [1] in any of the cohorts considered. With regard to females, in the last three cohorts considered, coverage ranged from 35.7% to 79.9% in the 2003 cohort, from 35.4% to 78.9% in the 2004 cohort, and from 30.5% to 75.5% in the 2005 cohort; the mean coverage values were 64.71%, 63.46% and 49.92%, respectively. In the case of the male cohorts from 2003 to 2005, coverage was also far below the incremental objective set: 60% in 2018 [11]. Nevertheless, better coverage rates among boys (2004 cohort, complete course: Veneto 60.0%; Friuli Venezia Giulia 52.7%; Puglia 53.2%) were achieved in those Regions and Autonomous Provinces where the free active offer had already been extended to males before the approval of the 2017-2019 NVPP [12].
To increase compliance with vaccination among adolescents, targeted strategies can be implemented (e.g. making vaccination a requirement for access to school, sending reminders) [13].
For instance, in Tuscany, an extraordinary anti-Men C vaccination campaign was initiated in April 2015, following a rise in the number of notified cases of meningococcal disease. The anti-Men ACYW135 vaccine was actively offered free of charge to a priority target population of subjects aged 11-20 years [14]. In the ex-ASL (Local Health Agency) area in Florence, the campaign was implemented in 19 vaccination stations (14 districts and 5 hospitals). In addition, general practitioners (68%) and family pediatricians (80.7%) were invited to participate on a voluntary basis. A large-scale information campaign was launched through the main means of communication, and involved schools and sports clubs. A dedicated telephone service, run by healthcare assistants, was also instituted in order to provide information, and text messages containing information were sent out to subjects aged 18-20 years. The campaign was promoted via newspapers, TV, radio and websites, and during waiting times on telephone connections for the booking of appointments for healthcare services. Moreover, information letters were also sent to schools and sports clubs. As a result, by February 2016, 47.1% of the population in the target age-group in the ex-ASL area in Florence and 46.3% in the Region had been vaccinated [15].

Anti-meningococcal vaccination strategies in Europe

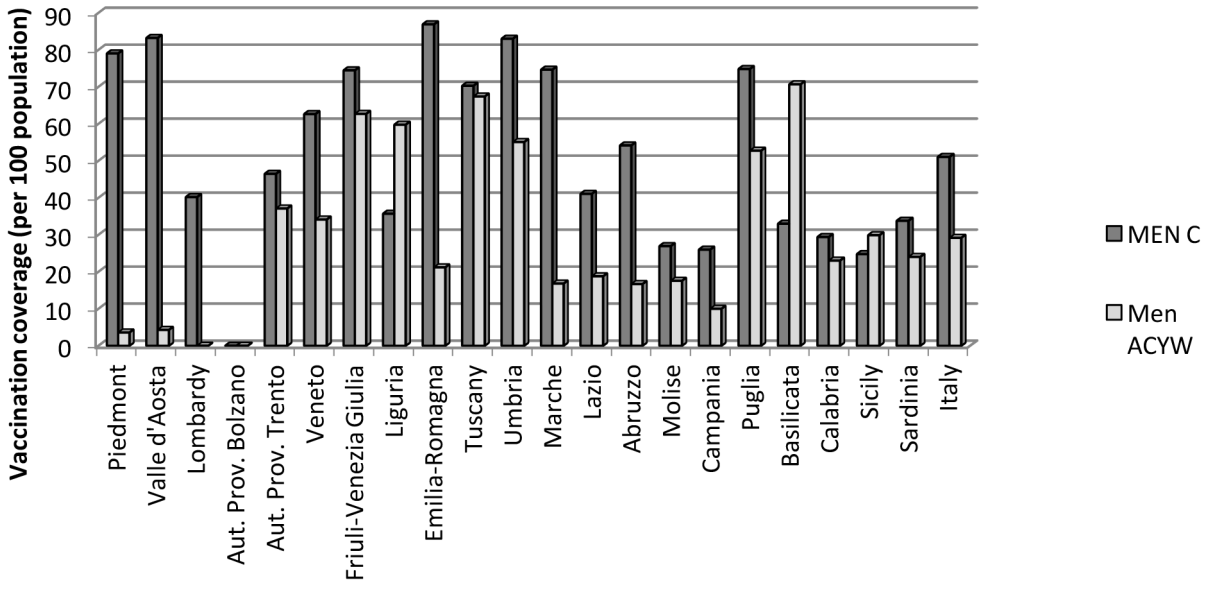
In European countries, anti-Men C vaccination with the monovalent or quadrivalent vaccine is undertaken either as part of the general recommendations or within the framework of catch-up strategies. Regarding anti-Men B

Fig. 1. Adolescent vaccinations: year 2018 (2002 cohort: aged 16 years). Vaccination coverage rates (per 100 population), calculated on data from Regions and Autonomous Provinces (per single antigen) (Ministry of Health). Sources: Data from regions. Elaboration: Office 5, Prevention of transmissible diseases and international prophylaxis. DG Health Prevention, Ministry of Health. Updated 18th April 2019.



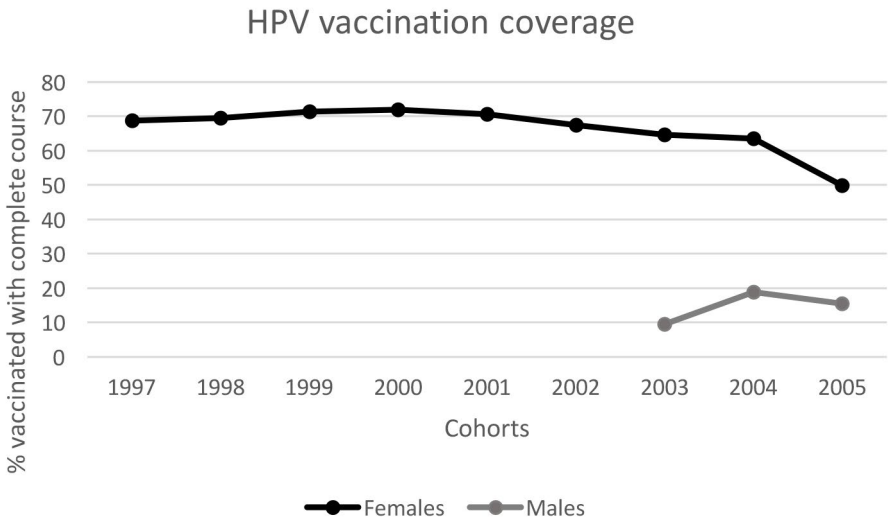
MEN C: Meningococcus C conjugate vaccine (complete 1-dose course, as per 2012-2014 NVPP); Men ACYW: Meningococcus ACYW conjugate vaccine.

Fig. 2. Adolescent vaccinations: year 2018 (2000 cohort: aged 18 years). Vaccination coverage rates (per 100 population), calculated on data from Regions and Autonomous Provinces (per single antigen) (Ministry of Health). Sources: Data from regions. Elaboration: Office 5, Prevention of transmissible diseases and international prophylaxis. DG Health Prevention, Ministry of Health. Updated 18th April 2019.



MEN C: Meningococcus C conjugate vaccine (complete 1-dose course, as per 2012-2014 NVPP); Men ACYW: Meningococcus ACYW conjugate vaccine.

Fig. 3. Percentage of adolescents undergoing a complete course of anti-HPV vaccination in the 1997-2005 cohorts (females) and the 2003-2005 cohorts (males) in Italy (Ministry of Health).



vaccination, however, there are, as yet, no general recommendations for its administration in adolescence [16].

Anti-meningoccoccal B vaccination in the United States

The US Advisory Committee on Immunization Practices (ACIP) recommends anti-Men C vaccination in adolescents by means of the quadrivalent vaccine, administered according to a 2-dose schedule: the first dose at 11-12 years of age; the second at 16 years. Indications are also provided for catch-up strategies: one dose for subjects aged 13-15 years, followed by a booster dose at the age of 16-18 years. In subjects already aged 16-18 years, one vaccine dose is administered.

For what concerns vaccination against meningococcus B, the ACIP reports that either of the two available vaccines – MenB-FHbp (Trumenba®) or MenB-4C (Bexsero®) – can be used. However, as they are not interchangeable, the same vaccine must be used in order to complete the course of immunization. Specifically, if the subject is not in a condition of increased risk, and according to the clinical judgment of the individual case, anti-Men B vaccination is recommended for adolescents and young adults aged between 16 and 23 years; it should preferably be administered at the age of 16-18 years, by means of the 2-dose schedule (Men4BC: 0-1 month, MenBF-Hbp: 0-6 months). In subjects with risk conditions that determine greater susceptibility to infection, or in the event of an epidemic, vaccination with MenB-FHbp is recommended according to the 3-dose schedule (0, 1-2, 6 months) and with MenB-4C according to the 2-dose schedule (1 month apart) in subjects aged 10 years and upwards [17, 18].

The utilization of anti-Men B vaccination in young people in the event of an epidemic has already been adopted in the United States. Indeed, the MenB-FHbp vaccine was first used as a preventive measure during an epidemic involving a college in Rhode Island (USA) in 2015. A total of 3,745 persons were eligible for vaccination, and less than 48 hours after the beginning of the vaccination sessions, 3,061 subjects had been vaccinated. A further 464 individuals were vaccinated in the following week. Overall, 94% of eligible individuals received the first dose of vaccine. This prompt intervention prevented the occurrence of further cases of meningococcal B disease in the college [19]. Following the immunization campaign, vaccine-related adverse events were retrospectively recorded 2-4 months after each vaccine dose. The most commonly reported reaction was pain at the injection site. The rates of reports of pain at the injection site, fatigue, myalgia, fever and shivering proved to be similar to those recorded in clinical studies, while reports of headache were fewer [20]. The same vaccine was used in other outbreaks that occurred in colleges, one in Oregon in 2015 [21] and one in New Jersey in 2016 [22]. On these occasions, too, no further cases of meningococcal B disease occurred after the vaccination campaign.

Anti-meningococcal B vaccination and carrier status

Vaccinating adolescents with the anti-Men B vaccine enables us not only to protect a group of subjects who are at high risk of contracting meningococcal disease, but also to maximize community protection by potentially interrupting carriage. From the epidemiological point of view, a particularly important consideration is that adolescents and young adults display the highest rates of *N. meningitidis* carrier status, owing to their typical behaviors [23-26].

On the basis of current knowledge, the impact of anti-Men B vaccination on carriage is not yet clear [27]. The studies conducted so far have not revealed a reduction in carriage nor prevention of the acquisition of carrier status, either when the MenB-FHbp vaccine has been used alone [28] or when both MenB-FHbp and MenB-4C have been used [29]. This type of analysis, howev-

er, is particularly difficult to conduct, as it necessitates sampling numerous subjects several times over a long period. The ability of the anti-Men B vaccine to prevent carriage will therefore need to be investigated further in future large-scale studies.

Conclusions

Anti-meningococcal vaccination in childhood enables the disease to be prevented in the age-group with the highest incidence. However, it requires the administration of several vaccine doses and of booster doses in order to maintain a long-standing high response in the case of infection.
Vaccinating adolescents, as is already recommended in the United States, enables us to protect one of the main groups at risk of contracting meningococcal disease [30]. Moreover, this strategy involves administering fewer doses. On the other hand, it presents greater difficulty in reaching the subjects to be vaccinated; indeed, unlike children, adolescents have less frequent contact with healthcare services and, in general, display less compliance with vaccination, as is demonstrated by current vaccination coverage rates in the adolescent age-group [31-33]. Meningococcal diseases have a heavy impact on society, owing to the gravity of their outcomes and sequelae. In this context, strategies aimed at increasing adolescents' adherence to vaccination [13] could lead to a substantial improvement in this critical area. Finally, the implementation of a strategy of vaccination with anti-Men B in adolescents should also include interventions aimed at improving information, education and health literacy (see chapter 7).

Bibliografia

[1] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-2019. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf

[2] Edge C, Waight P, Ribeiro S, Borrow R, Ramsay M, Ladhani S. Clinical diagnoses and outcomes of 4619 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: Linkage analysis of multiple national databases. J Infect 2016;73(5):427-36. https://doi.org/10.1016/j.jinf.2016.07.016

[3] European Centre for Disease Prevention and Control (ECDC). ECDC surveillance atlas of infectious diseases. Available at: http://atlas.ecdc.europa.eu/public/index.aspx [Accessed: 30 July 2019].

[4] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program, ACTive (IMPACT). Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028.

[5] Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, Harnden A, Mant D, Levin M. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367(9508):397-403. https://doi.org/10.1016/S0140-6736(06)67932-4.

[6] Regione Sicilia. Adeguamento del Calendario Vaccinale Regionale al "Piano Nazionale di Prevenzione Vaccinale 2017-2019", recepito dalla Regione Sicilia con il D.A. n. 1004 del 22 Maggio 2017. Available at: http://pti.regione.sicilia.it/portal/page/portal/PIR_PORTALE/PIR_LaStrutturaRegionale/PIR_AssessoratoSalute/PIR_DecretiAssessratoSalute/PIR_Decreti-Assessoriali/PIR_DecretiAssessorialianno2017

[7] Regione Puglia. Deliberazione della Giunta Regionale 31 gennaio 2018, n. 113. DGR n.2279/2017 – Calendario Vaccinale per la Vita nella Regione Puglia e Calendario operativo per le vaccinazioni dell'adulto. Modifica per mero errore materiale. Bollettino Ufficiale della Regione Puglia, n 26 del 19-2-2018. Available at: https://www.sanita.puglia.it/documents/20182/1897678/DELIBERAZIONE+DELLA+GIUNTA+REGIONALE+31+gennaio+2018%2C+n.+113/ee434cc4-e3c5-4b86-b8fd-1ef-008e5c8a9, Legge Regionale n. 67 del 29 dicembre 2017, art. 60, Bollettino Ufficiale della Regione Puglia, n. 149 del 30-12-2017.

[8] Regione Campania. Decreto C.A. n. 28 del 25 marzo 2019 "Ulteriori misure per la prevenzione della malattia meningococcica nella fascia di età adolescenziale".

[9] Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica (SItI), Società Italiana di Pediatria (SIP), Federazione Italiana Medici Pediatri (FIMP), Federazione Italiana Medici di Medicina Generale (FIMMG). Calendario Vaccinale per la Vita - 4° edizione 2019. Available at: https://www.vaccinarsi.org/notizie/2019/07/%E2%80%8Bcalendario-vaccinale-per-la-vita-2019

[10] Ministero della Salute. Vaccinazioni dell'età pediatrica e dell'adolescente - Coperture vaccinali. Anno 2018. Available at: http://www.salute.gov.it/portale/documentazione/p6_2_8_3_1.jsp?lingua=italiano&id=20

[11] Ministero della Salute. Circolare ministeriale "Aspetti operativi per la piena e uniforme implementazione del nuovo PNPV 2017-2019 e del relativo Calendario vaccinale", 9 marzo 2017. Available at: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2017&codLeg=58583&parte=1%20&serie=null

[12] Ministero della Salute. Vaccinazione contro il papilloma virus (HPV) - Coperture vaccinali al 31/12/2017. Available at: http://www.salute.gov.it/imgs/C_17_tavole_27_allegati_iitemAllegati_0_fileAllegati_itemFile_1_file.pdf

[13] Das JK, Salam RA, Arshad A, Lassi ZS, Bhutta ZA. Systematic review and meta-analysis of interventions to improve access and coverage of adolescent immunizations. J Adolesc Health 2016;59(4S):S40-8. https://doi.org/10.1016/j.jadohealth.2016.07.005

[14] Regione Toscana. DGRT n. 571 del 27/04/2015 Prevenzione della diffusione del meningococco C in Toscana. Aggiornamento calendario e direttive aprile 2015. Available at: https://www.ars.toscana.it/files/aree_intervento/malattie_infettive/notifica_obbligatoria/Delibera_n.571_del_27-04-2015.pdf

[15] Bechini A, Paolini D, Pieralli F, Baggiani L, Mereu G, Santini MG, Brocca T, Gostinicchi S, Gori E, Boccalini S, Bonanni P, Bonaccorsi G. Do Tuscan people adhere to meningococcal C vaccination during an emergency campaign? J Prev Med Hyg 2018;59(3):E187-93. https://doi.org/10.15167/2421-4248/jpmh2018.59.3.952

[16] European Centre for Disease prevention and Control (ECDC). Vaccine scheduler. Meningococcal disease: recommended vaccinations. Available at: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=48&SelectedCountryIdByDisease=-1 [Accessed: 30 luglio 2019].

[17] Center of Disease Control and Prevention (CDC). Recommended immunization schedule for children and adolescents aged 18 years or younger, United States, 2019. Available at: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

[18] Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for use of MenB-FHbp serogroup B meningococcal Vaccine - advisory committee on immunization practices,

2016. Morb Mortal Wkly Rep 2017;66(19):509-13. https://doi.org/10.15585/mmwr.mm6619a6

[19] Fiorito TM, Bornschein S, Mihalakos A, Kelleher CM, Alexander-Scott N, Kanadanian KV, Raymond P, Sicard K, Dennehy PH. Rapid response to a college outbreak of meningococcal serogroup B disease: nation's first widespread use of bivalent rLP2086 vaccine. J Am Coll Health 2017;65(4):294-6. https://doi.org/10.1080/07448481.2017.1285772

[20] Fiorito TM, Baird GL, Alexander-Scott N, Bornschein S, Kelleher C, Du N, Dennehy PH. Adverse Events following vaccination with bivalent rLP2086 (Trumenba®): an observational, longitudinal study during a college outbreak and a systematic review. Pediatr Infect Dis J 2018 Jan;37(1): e13-9. https://doi.org/10.1097/INF.0000000000001742

[21] Fisher EA, Poissant T, Luedtke P, Leman R, Young C, Cieslak P. Evaluation of mass vaccination clinics in response to a serogroup b meningococcal disease outbreak at a large, public university-Oregon, 2015. J Adolesc Health 2018;63(2):151-6. https://doi.org/10.1016/j.jadohealth.2018.03.018

[22] Soeters HM, Dinitz-Sklar J, Kulkarni PA, MacNeil JR, McNamara LA, Zaremski E, Chang HY, Lujan E, Granoff D, Lasky M, Montana B. Serogroup B meningococcal disease vaccine recommendations at a university, New Jersey, USA, 2016. Emerg Infect Dis 2017;23(5):867-9. https://doi.org/10.3201/eid2305.161870

[23] Vetter V, Baxter R, Denizer G, Sáfadi MA, Silfverdal SA, Vyse A, Borrow R. Routinely vaccinating adolescents against meningococcus: targeting transmission & disease. Expert Rev Vaccines 2016;15(5):641-58. https://doi.org/10.1586/14760584.2016.1130628

[24] Tully J, Viner RM, Coen PG, Stuart JM, Zambon M, Peckham C, Booth C, Klein N, Kaczmarski E, Booy R. Risk and protective factors for meningococcal disease in adolescents: matched cohort study. BMJ 2006;332(7539):445-50. https://doi.org/10.1136/bmj.38725.728472.BE

[25] Bruce MG, Rosenstein NE, Capparella JM, Shutt KA, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. JAMA 2001;286(6):688-93. https://doi.org/10.1001/jama.286.6.688

[26] MacLennan J, Kafatos G, Neal K, Andrews N, Cameron JC, Roberts R, Evans MR, Cann K, Baxter DN, Maiden MC, Stuart JM; United Kingdom Meningococcal Carriage Group. Social behavior and meningococcal carriage in British teenagers. Emerg Infect Dis 2006;12(6):950-7. https://doi.org/10.3201/eid1206.051297

[27] Perez JL, Absalon J, Beeslaar J, Balmer P, Jansen KU, Jones TR, Harris S, York LJ, Jiang Q, Radley D, Anderson AS, Crowther G, Eiden JJ. From research to licensure and beyond: clinical development of MenB-FHbp, a broadly protective meningococcal B vaccine. Expert Rev Vaccines 2018;17(6):461-77. https://doi.org/10.1080/14760584.2018

[28] Soeters HM, Whaley M, Alexander-Scott N, Kanadanian KV, MacNeil JR, Martin SW, McNamara LA, Sicard K, Vanner C, Vuong J, Wang X, Bandy U, Patel M; Rhode Island Meningococcal Carriage Evaluation Team. Meningococcal carriage evaluation in response to a serogroup B meningococcal disease outbreak and mass vaccination campaign at a College-Rhode Island, 2015-2016. Clin Infect Dis 2017;64(8):1115-22. https://doi.org/10.1093/cid/cix091

[29] McNamara LA, Thomas JD, MacNeil J, Chang HY, Day M, Fisher E, Martin S, Poissant T, Schmink SE, Steward-Clark E, Jenkins LT, Wang X, Acosta A; Oregon Meningococcal Carriage Team. Meningococcal carriage following a vaccination campaign with MenB-4C and MenB-FHbp in response to a university serogroup B meningococcal disease outbreak-Oregon, 2015-2016. J Infect Dis 2017;216(9):1130-40. https://doi.org/10.1093/infdis/jix446

[30] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(12):853-61. https://doi.org/10.1016/S1473-3099(10)70251-6

[31] Bernstein HH, Bocchini JA Jr; committee on infectious diseases. The need to optimize adolescent immunization. Pediatrics 2017;139(3).pii:e20164186. https://doi.org/10.1542/peds.2016-4186

[32] Wong CA, Taylor JA, Wright JA, Opel DJ, Katzenellenbogen RA. Missed opportunities for adolescent vaccination, 2006-2011. J Adolesc Health 2013;53(4):492-7. https://doi.org/10.1016/j.jadohealth.2013.05.009

[33] Reagan-Steiner S, Yankey D, Jeyarajah J, Elam-Evans LD, Singleton JA, Curtis CR, MacNeil J, Markowitz LE, Stokley S. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years - United States, 2014. Morb Mortal Wkly Rep 2015;64(29):784-92. https://doi.org/10.15585/mmwr.mm6533a4

Chapter 9

Organizational aspects of anti-meningococcal B vaccination for adolescents in Italy

M. IOVINE, E. LECINI, P.L. LAI, F. ZANGRILLO, D. PANATTO
Department of Health Sciences, University of Genoa, Italy

Introduction

The most effective means of defeating some infectious diseases is vaccination, which is one of the most efficacious, cost-effective and safe public health interventions. However, in order to implement a primary prevention plan correctly, it is necessary not only to have safe, efficacious vaccines, but also to adopt strategies that can yield the greatest benefit in terms of health and economics. Careful epidemiological evaluation and thorough knowledge of the spread of pathogens enable us to choose the best vaccination strategies [1], the objectives of which are to reduce the individual's risk of disease and death, to curb transmission, and to reduce the direct and indirect costs of the disease.
In recent years, research has led to the development of new safe and efficacious vaccines and provided evidence to support new vaccination strategies. As the opportunities for prevention continue to increase, when planning to introduce a new vaccination into the vaccination calendar, we must necessarily consider the organizational impact involved. In this context, various organizational modalities have to be hypothesized, in order to respond adequately to the needs of the population and of the territorial facilities of the National Health Service; this means adhering to the concept of "organizational appropriateness". The Italian Ministry of Health defines this concept in terms of "a health intervention (preventive, diagnostic, therapeutic, rehabilitative) that is geared to the needs of the patient (or the community), which is provided in a suitable manner and within an appropriate time, is based on recognized standards, and achieves a positive balance among benefits, risks and costs. Appropriateness involves performing the correct procedure on the right patient at the right time and in the most suitable setting" [2]. Thus, it is necessary to design flexible organizational models that can be adapted efficaciously and efficiently to local settings and to foster active cooperation with family pediatricians and general practitioners, in order to promote vaccination and to achieve adequate vaccination coverage rates.
Invasive meningococcal disease can have extremely serious outcomes; not only can it be fatal, its long-term consequences (physical, neurological and psychological/behavioural sequelae) impair the quality of life of both patients and their families [3, 4] (see chapter 3).
The disease mainly affects children, adolescents and young adults, the highest lethality rates being recorded in these latter two age-classes [5]. Moreover, adolescents and young adults (15-24 years of age) are the main reservoir of the microorganism; in Europe, the prevalence rates of carriage vary enormously – from 5.3% to 61.9% [6] – and serogroup B is the most frequent in this age-group [7].
The rationale behind introducing anti-meningococcal vaccination in adolescence is supported by epidemiological and clinical data. In Italy, the 2017-2019 National Vaccine Prevention Plan (2017-2019 NVPP) [8] currently recommends anti-meningococcal vaccination with the quadrivalent ACWY conjugate vaccine. Anti-meningococcal B vaccination is recommended only for children. However, the epidemiological, clinical and economic data available in the literature suggest that the possibility of extending this strategy to adolescents should be considered. Indeed, the fourth edition of the "Calendario per la Vita" ["Calendar for Life"] (2019) [9] recommends its introduction.

Organizational impact of anti-meningococcal B vaccination in adolescents

The success of any vaccination strategy depends on the achievement of adequate coverage rates. These are influenced by many factors, such as the efficient organization of vaccination centers, the implementation of suitable interventions to raise awareness by providing users with appropriate information, and the creation of innovative, integrated pathways (by strengthening cooperation among public health authorities, family paediatricians and general practitioners, and by carrying out vaccination in schools).

Organization of vaccination centers

In an optimal organizational perspective, a new vaccination program needs to be supported by the allocation of suitable resources: financial, structural (e.g. number of vaccination clinics in the territory) and human.
In a policy of immunizing adolescents, anti-meningococcal B vaccination could be added to other vaccinations that are already provided for in the 2017-2019 NVPP (tetanus, diphtheria, whooping cough and polio boosters; anti-meningococcal vaccination with the quadrivalent ACWY conjugate vaccine, and anti-HPV vaccination) [8]. This, however, could create a work overload for the Departments of Prevention of the Local Health Agencies (LHA), which have been called upon in the

last two years to cope with the increased workload resulting from the promulgation of Law 119/17 on mandatory vaccination [10].
A possible solution could be co-administration. Indeed, the vaccine Trumenba®, which is indicated for the active vaccination of subjects aged ≥ 10 years, could be co-administered with the following vaccines: tetanus/diphtheria/pertussis/polio (Tdap-IPV), quadrivalent anti-HPV vaccine, anti-meningococcus ACWY vaccine, tetanus toxoid/reduced diphtheria toxoid/adsorbed acellular pertussis (Tdap) [11]. As the nonavalent vaccine against human papillomavirus has only recently been authorized, no co-administration studies are as yet available. Nevertheless, it is reasonable to hypothesize that Trumenba® could be co-administered with this vaccine, as the development process of the nonavalent vaccine is similar to that of the quadrivalent vaccine [12, 13]. Hopefully, studies that support this strategy will soon be published.
With regard to the organization of vaccination centers, the allocation of adequate resources could enable opening hours to be extended and vaccination sessions to be organized at "strategic" locations (e.g. youth clubs and schools) [14, 15]; this would not only improve accessibility, but also make it easier to involve subjects who are "hard-to-reach" (adolescents) or "hesitant" (parents) [16].
Moreover, in order to overcome the obstacles related to the communication of information on the offer of vaccination, email and text messages should be used in addition to ordinary letters [17-19]. Indeed, this approach has already been adopted in international studies, in which users have been asked to indicate the mode of communication that they prefer, and has proved to be effective in reaching a larger number of subjects [20].

National vaccination registry and disease surveillance systems

A further organizational obstacle is the lack of a computerized national vaccination registry [15, 16] accessible not only to healthcare workers in LHA clinics, but also to family pediatricians and general practitioners. The 2017-2019 NVPP has already urged that such a registry be instituted, in order to monitor the implementation of vaccination programs and to eliminate the discrepancies in statistical measurements and certification throughout the country [8, 10]. Construction of the national vaccination registry and the regional registries is currently underway [21]. Moreover, the national vaccination registry would enable the surveillance of adverse events to be improved and support the system of monitoring of pharmaceutical drugs [22], in that real-time registration of the date of administration of the vaccine and, especially, of the commercial name of the product would ensure accurate matching between the vaccine used and the adverse event reported, thereby reducing errors and false correlations.
Further economic resources should be invested in the system of surveillance of invasive bacterial diseases, in order to enable the effectiveness of vaccination programs and the related vaccination coverage rates to be monitored over time [23, 24].

Vaccination counseling

Another fundamental aspect concerns vaccination counseling for both adolescents (target population of the vaccination program) and their parents. In order to foster a trusting relationship with the public, healthcare workers must be constantly kept up to date and trained in communication strategies, which must be appropriate to each population group [15]. Indeed, in all EU countries, healthcare workers are still identified by the population as "the most important and trusted source of information" [25-28]. Given the central role that they play, healthcare professionals have to carefully prepare their interviews with subjects who are the target of the vaccination strategy (adolescents) and their caregivers, in order to achieve the best possible results. This involves devoting sufficient time to the interview and leaving room for dialogue and, especially, listening. In this context, moreover, visual, non-verbal and para-verbal communication should not be underestimated.
The continuous evolution of preventive medicine and the consequent modifications to the vaccination calendar have given rise to confusion in the population; efficacious counseling should also be able to anticipate and tackle these difficulties.

Innovative and integrated organizational approaches

The role of family pediatricians and general practitioners in promoting vaccination among adolescents

In order to raise public awareness of the importance of vaccination, innovative and integrated organizational approaches are required. This clearly means strengthening efforts to consolidate continuous close cooperation among public health operatives, family pediatricians and general practitioners.
Within the framework of an immunization strategy aimed at adolescents, a fundamental role is played by the family pediatrician. Indeed, as family pediatricians know their patients, they are in a position to adopt a proactive approach and to propose vaccination for the subjects targeted.
A survey involving 903 Italian pediatricians, which was conducted in 2016 and published in Eurosurveillance in 2019, found that most pediatricians in Italy were in favor of vaccinations. However, it also revealed gaps between their generally positive attitude and their knowledge, aptitude and practice. It emerged from the survey that 95.3% of the pediatricians interviewed were completely in favor of vaccinations and that 66% considered themselves to be sufficiently informed about vaccinations and vaccine-preventable diseases to be able to discuss these issues competently with parents. Nevertheless, one third of respondents admitted that they did not systematically check whether their patients had received all the vaccinations scheduled in the vaccination calendar, and only 5.4% were able to correctly

distinguish all the true contraindications from the false ones. According to the authors of the study, it is clear that targeted interventions are required in order to increase pediatricians' confidence in dealing with parents' concerns and to strengthen parents' trust in healthcare institutions with regard to vaccinations [29, 30].
In order to increase vaccination coverage rates, it is essential for public health services and pediatricians to share the same objectives and activities. As stated in the Italian report by Boccalini et al., the family pediatrician plays a fundamental role in vaccination counseling, has frequent opportunities to meet and discuss with parents, and can carry out vaccination (and registration of the same). Family pediatricians and public health personnel should form part of a single network; this would enable them to share the same objectives, operating protocols and tools for vaccination promotion, and to adopt a common approach to the management of reluctance to vaccinate. In addition, they should be involved in efficacious joint training and in meetings for the monitoring, analysis and critical evaluation of their activities and the results achieved in terms of vaccination coverage. For their part, public health operatives should have a fundamental role in guaranteeing the governance of the network through the organization of vaccination campaigns and ongoing training programs and, finally, the collection of data on vaccination coverage and their computerised elaboration in aggregate form [31].
General practitioners also play an essential role in raising public awareness with regard to vaccinations. Indeed, as they know their patients well, they can implement vaccination campaigns in a proactive manner, thereby not only tailoring prevention to their own patients, but also favoring prevention in the population at large. Reasoning in terms of population-based medicine, while actively participating in the health choices of their own patients, places new responsibilities on doctors; these include maximising value by achieving the right outcomes, for the right patients, in the right place and with the least consumption of resources. This means stepping beyond the traditional boundaries of care and prevention and moving toward a kind of medicine that produces "value" in all of its manifestations [1].

Vaccination strategies in the school setting

According to the literature, implementing information campaigns or setting up vaccination centers in schools can effectively improve compliance with vaccinations. In the school setting, various strategies can be undertaken in order to increase adherence to vaccination, such as setting up vaccination centres in school facilities or implementing awareness-raising programs during school activities.
School-based programs are aimed at providing teachers, students and parents with correct information, clarifying doubts and allaying concerns, especially those aroused by the fake news that circulates on the web. They could therefore constitute a valid means of reaching "difficult" targets, such as adolescents and, especially, the underprivileged. Moreover, it should be stressed that adolescents are the members of society who have least contact with their doctors.
Interestingly, the investigation "Habits and lifestyles of adolescents", conducted by the Italian Society of Pediatrics on students in the third year of middle school, revealed that the majority of Italian teenagers had reasonably good knowledge and a positive opinion of vaccinations; and yet did not know their own vaccination history [32]. Investing in knowledge, starting from a very early age, may turn out to be a winning move. Indeed, these youngsters have a positive view of vaccinations, with only 2% claiming that they are useless [32]. Making students "ambassadors" for the cause of vaccinations may therefore help to raise the awareness of parents.
Numerous Italian and international studies have demonstrated that such awareness-raising initiatives are feasible and effective and can yield direct benefits for vaccinees and indirect benefits for the community. Future research should address this issue through prospective studies aimed at establishing the effectiveness of such strategies [33-36].
Active intervention in schools also involves setting up vaccination centers. In addition to providing vaccinations, these can conduct information campaigns that target teachers, parents and students. In this regard, the literature contains data from international studies that confirm the positive results of such interventions in terms of compliance. Indeed, all of these studies have reached the same conclusion: i.e. that integrated strategies which involve local schools and public health departments determine a marked increase in adherence to vaccinations [33-35].
In a new organizational perspective, it is essential to consider the results yielded by experiences of vaccinating adolescents in the school setting, in order to evaluate the feasibility of this approach in the Italian context. The issue of "school vaccinations" is not new in Italy; in the past, information and/or vaccination campaigns have been undertaken in school facilities on designated days. The aim of these campaigns was to achieve adequate levels of coverage in susceptible subjects as rapidly as possible, while assuring families that vaccination would be carried out by trained personnel, in a suitable environment where any possible, albeit rare, emergency could be managed [36].
An active strategy implemented in the school setting, accompanied by the solicitation of absentees, is a useful means of reaching coverage targets. At the same time, it provides feedback for operators (and therefore institutions) with regard to the degree of vaccine hesitancy of families [31, 36]. Moreover, a solid, integrated organization (vaccination clinics in the departments of preventive medicine and school vaccination centers) would enable vaccinations to be systematically provided at the right age and would favor the co-administration of vaccines, thereby optimizing vaccination sessions, maximizing adherence and generating resource savings. Finally, this opportunity could also be used as a bridgehead for the introduction of other campaigns of health prevention/promotion among adolescents.

Conclusions

In order to reduce cases of invasive disease due to type B *Neisseria meningitidis*, it is strongly advisable to offer free active vaccination for adolescents, who are one of the main targets of the disease [8, 9].

When a new vaccine is to be introduced, the organizational aspects must be considered; particular attention must be paid to the age at which vaccination is to be undertaken, so as not to overload healthcare facilities and, if possible, to enable co-administration in a single session. In the case of the vaccine against meningococcus B in adolescents, there are several possibilities of co-administration [11]. An aspect that needs to be borne in mind is that adolescents are a difficult target to reach, in that they generally have little contact with healthcare facilities. Nevertheless, as demonstrated by a survey conducted in Italy, they attach great importance to vaccinations.

With regard to the establishment of innovative and integrated organizational approaches, efforts must be made to consolidate continuous close cooperation among public health operatives, family pediatricians and general practitioners. Indeed, it is necessary to foster the active and proactive involvement of all the parties concerned in order to create an organizational model that can integrate the various points of view and the different possibilities of action at all levels. An important contribution to achieving the objective of adequate vaccination coverage would be made by the establishment of a computerized vaccination registry. This would enable public health agencies, general practitioners and family pediatricians to exchange information on vaccinated/eligible subjects in real time [1, 10, 21, 30, 31].

An integrated and coordinated system would be fully in line with the principles of population-based medicine and would go beyond the traditional confines of care, thereby increasing the "value" of prevention. When we speak of "value" in prevention, we mean both the health outcomes obtained through the implementation of optimal vaccination strategies and the framework for improving the organizational system.

Finally, administering vaccines directly in school facilities would not only improve adherence to vaccination [33-36] but also raise awareness, which, over time, may also exert a positive influence on the entire population.

References

[1] Specchia ML, Ferriero AM. Aspetti organizzativi della vaccinazione antinfluenzale in Italia: nuove sfide per una strategia preventiva efficace nell'ottica della medicina di popolazione orientata al valore. Valutazione di Health Technology Assessment (HTA) del vaccino antinfluenzale quadrivalente da coltura cellulare: Flucelvax Tetra. Quaderni dell'Ital J Public Health 2019;8(5):144-57.

[2] Dipartimento della programmazione e dell'ordinamento del Servizio Sanitario Nazionale - Direzione Generale della Programmazione Sanitaria Ufficio III ex D.G. PROGS. Manuale di formazione per il Governo Clinico: appropriatezza. Luglio 2012. Available at: http://www.salute.gov.it/ imgs/C_17_pubblicazioni_1826_allegato.pdf [Accessed: 05.03.2019].

[3] Bénard S, Wright C, Voisine J, Olivier C W, Gaudelus J. Lifetime cost of meningococcal disease in France: scenarios of severe meningitis and septicemia with purpura fulminans. J Infect Public Health 2016;9(3):339-47. https://doi.org/10.1016/j.jiph.2015.10.016

[4] Buysse CMP, Vermunt LCAC, Raat H, Hazelzet1 JA, Hop WCJ, Utens EMWJ, Joosten KFM. Research Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care 2010;14:R124. https://doi.org/10.1186/cc9087

[5] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program A. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028

[6] Peterson ME, Li Y, Shanks H, Mile R, Nair H, Kyaw MH; Meningococcal Carriage Group: Amicizia D, Bayliss CD, Campos LC, Cleary PR, Delbos V, Esposito S, Kristiansen PA, Mbaeyi SA, Oldfield NJ, Panatto D, Rodrigues F, Soeters HM, Turner DP, Xu A. Serogroup-specific meningococcal carriage by age group: a systematic review and meta-analysis. BMJ Open 2019;9(4):e024343. https://doi.org/10.1136/bmjopen-2018-024343

[7] Gasparini R, Comanducci M, Amicizia D, Ansaldi F, Canepa P, Orsi A, Icardi G, Rizzitelli E, De Angelis G, Bambini S, Moschioni M, Comandi S, Simmini I, Boccadifuoco G, Brunelli B, Giuliani MM, Pizza M, Panatto D. Molecular and serological diversity of Neisseria meningitidis carrier strains isolated from Italian students aged 14 to 22 years. J Clin Microbiol 2014;52(6):1901-10. https://doi.org/10.1128/JCM.03584-13

[8] Piano Nazionale Prevenzione Vaccinale 2017-2019(PNPV). Available at: http://www.salute.gov.it/portale/vaccinazioni/dettaglioContenutiVaccinazioni.jsp?lingua=italiano&id=4824&area=vaccinazioni&menu=vuoto [Accessed 10/07/19].

[9] Calendario Vaccinale Per La Vita. 4° Edizione 2019. Available: http://www.quotidianosanita.it/allegati/allegato690018.pdf [Accessed 6/07/2019].

[10] Testo del decreto-legge 7 giugno 2017, n. 73, (in Gazzetta Ufficiale - Serie generale - n. 130 del 7 giugno 2017), coordinato con la legge di conversione 31 luglio 2017, n. 119, recante: "Disposizioni urgenti in materia di prevenzione vaccinale, di malattie infettive e di controversie relative alla somministrazione di farmaci". Available at: https://www.gazzettaufficiale.it/eli/id/2017/08/05/17A05515/sg [Accessed 01/08/2019].

[11] Scheda Tecnica di Trumenba®. Available at: https://ec.europa.eu/health/documents/community-register/2017/20170524137650/anx_137650_it.pdf [Accessed 24/04/2019].

[12] Scheda Tecnica Gardasil - human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed). Available at: https://www.ema.europa.eu/en/documents/product-information/gardasil-epar-product-information_it.pdf [Accessed 11/07/2019].

[13] Scheda Tecnica Gardasil 9 - human papillomavirus 9-valent vaccine (recombinant, adsorbed). Available at: https://www.ema.europa.eu/en/documents/product-information/gardasil-9-epar-product-information_it.pdf [Accessed 11/07/2019].

[14] Regione Veneto, Indagine sui determinanti del rifiuto dell'offerta vaccinale in Regione Veneto, 2011. 3. CENSIS, La cultura della vaccinazione in Italia: un'indagine sui genitori. Roma: 2014.

[15] European Centre for Disease Prevention and Control (ECDC). Let's talk about hesitancy. 2016. Available at: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/lets-talk-about-hesitancy-vaccination-guide.pdf [Accessed 6/07/2019].

[16] Giambi C, Del Manso M, De Mei B, D'Ancona F, Giovannelli I, Cattaneo C, Possenti V, Declich S; gruppo di lavoro

VALORE. Progetto VALORE (VAlutazione LOcale e REgionale delle campagne di vaccinazione contro l'HPV): favorire l'adesione consapevole alla vaccinazione. Rapporti ISTISAN 2013;7(157):13-47.

[17] Amicizia D, Domnich A, Gasparini R, Bragazzi NL, Lai PL, Panatto D. An overview of current and potential use of information and communication technologies for immunization promotion among adolescents. Hum Vaccin Immunother 2013;9(12):2634-42. https://doi.org/10.4161/hv.26010

[18] Panatto D, Domnich A, Gasparini R, Bonanni P, Icardi G, Amicizia D, Arata L, Bragazzi NL, Signori A, Landa P, Bechini A, Boccalini S. Development and preliminary data on the use of a mobile app specifically designed to increase community awareness of invasive pneumococcal disease and its prevention. Hum Vaccin Immunother 2016;12(4):1080-4. https://doi.org/10.1080/21645515.2015.1114196

[19] Amicizia, D, Iovine, M. HTA e comunicazione in ambito vaccinale, cap. 7 in Health Technology Assessment e Sanità Pubblica. J Prev Med Hyg 2017; 58(Suppl 1): E42-E45.

[20] Dombkowski KJ, Cowan AE, Reeves SL, Foley MR, Dempsey AF. The impacts of email reminder/recall on adolescent influenza vaccination. Vaccine 2017;35(23):3089-95. https://doi.org/10.1016/j.vaccine.2017.04.033

[21] Decreto 17 settembre 2018. Istituzione dell'Anagrafe nazionale vaccini. (G.U. Serie Generale, n. 257 del 05 novembre 2018). Available at: http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=66388 [Accessed 01/08/2019].

[22] Rapporto Vaccini 2018: la sorveglianza postmarketing in italia. Available at: https://www.aifa.gov.it/documents/20142/241056/Rapporto+Vaccini+2018.pdf/62975a0e-a836-da32-f7b9-1e39196374dd [Accessed 01/08/2019].

[23] Hardt K, Bonanni P, King S, Santos JI, El-Hodhod M, Zimet GD, Preiss S. Vaccine strategies: optimising outcomes. Vaccine 2016;34(52):6691-9. https://doi.org/10.1016/j.vaccine.2016.10.078.

[24] World Health Organization. Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation. Geneva, Switzerland: WHO 2005.

[25] European Centre for Disease Prevention and Control (ECDC). Let's talk about protection. 2016. Available at: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/lets-talk-about-protection-vaccination-guide.pdf [Accessed 7/08/2019].

[26] Stefanoff P, Mamelundb S, Robinsonc M, Netterlidd E, Tuellse J, Riise Bergsakerb M, Heijbel H, Yarwood J; VACSATC working group on standardization of attitudinal studies in Europe. Tracking parental attitudes on vaccination across European countries: the Vaccine Safety, Attitudes, Training and Communication Project (VACSATC). Vaccine 2010;28:5731-7. https://doi.org/10.1016/j.vaccine.2010.06.009

[27] Heininger U. An internet-based survey on parental attitudes towards immunization, Vaccine 2006;24:6351-5. https://doi.org/10.1016/j.vaccine.2006.05.029

[28] Schmitt H, Booy R, Aston R, Van Damme P, Schumacher R, Campins M, Rodrigo C, Heikkinen T, Weil-Olivier C, Finn A, Olcén P, Fedson D, Peltola H. How to optimise the coverage rate of infant and adult immunisations in Europe. BMC Med 2007;5:11. https://doi.org/10.1186/1741-7015-5-11

[29] Filia A, Bella A, D'Ancona F, Fabiani M, Giambi C, Rizzo C, Ferrara L, Pascucci MG, Rota MC. Childhood vaccinations: knowledge, attitudes and practices of paediatricians and factors associated with their confidence in addressing parental concerns, Italy, 2016. Euro Surveill 2019;24(6).pii:1800275. https://doi.org/10.2807/1560-7917.ES.2019.24.6.1800275

[30] Istituto Superiore di Sanità. Vaccini e vaccinazioni. Ultimi aggiornamenti. Available at: https://www.epicentro.iss.it/vaccini/aggiornamenti [Accessed 01/08/2019].

[31] Boccalini S, Bechini A, Innocenti M, Sartor G, Manzi F, Bonanni P, Panatto D, Lai PL, Zangrillo F, Rizzitelli E, Iovine M, Amicizia D, Bini C, Marcellusi A, Mennini FS, Rinaldi A, Trippi F, Ferriero AM, Lisi GC. La vaccinazione universale dei bambini contro l'influenza con il vaccino Vaxigrip Tetra® in Italia: risultati di una valutazione di Health Technology Assessment (HTA). J Prev Med Hyg 2018;59(Suppl 1):E1-E86.

[32] Società Italiana di Pediatria. "Abitudini e stili di vita degli adolescenti". Available at: https://www.sip.it/2017/08/30/grande-successo-per-a-scuola-di-vaccini [Accessed 6/07/2019].

[33] Cawley J, Hull HF, Rousculp MD. Strategies for implementing schoollocated influenza vaccination of children: a systematic literature review. J Sch Health 2010;80(4):167-75. https://doi.org/10.1111/j.1746-1561.2009. 00482.x

[34] Humiston SG, Rosenthal SL. Challenges to vaccinating adolescents: vaccine implementation issues. Pediatr Infect Dis J 2005;24(6 Suppl):S134-S140. Pmid: 15931141. https://doi.org/10.1097/01.inf.0000166161.12087.94

[35] Lindley MC, Boyer-Chu L, Fishbein DB, Kolasa M, Middleman AB, Wilson T, Wolicki J, Wooley S; working group on the role of schools in delivery of adolescent vaccinations. The role of schools in strengthening delivery of new adolescent vaccinations. Pediatrics 2008;121(Suppl 1):S46-S54. https://doi.org/10.1542/ peds.2007-1115F

[36] Desiante F, Russo C, Giorgino A, Caputi G, Battista T, Cipriani R, Conversano M. Universal proposal strategies of anti-HPV vaccination for adolescents: comparative analysis between school-based and clinic immunization programs. J Prev Med Hyg 2017;58(3):E225-30.

Chapter 10

Ethical and social aspects of anti-meningococcal vaccination for adolescents

S. BOCCALINI, P. BONANNI, A. BECHINI
Department of Health Sciences, University of Florence, Italy

Ethical evaluations and HTA of vaccinations

Today more than ever, no HTA can dispense with the ethical and social evaluation of the possible impact of adopting a healthcare technology, as is envisioned in the domains indicated by EUnetHTA [1]. This is particularly important with regard to the evaluation of vaccinations. Indeed, unlike pharmaceutical drugs, vaccines are preventive tools that are administered to healthy persons, whose health must, first and foremost, be safeguarded. Safeguarding the health of the population, however, is a task which today is jeopardized by the current suboptimal vaccination coverage rates recorded in Italy in recent years and the widespread diffusion of fake news via new means of communication [2, 3].
The ethical domain must therefore take into account the prevailing moral and social norms and the important values related to the vaccination under examination. Specifically, ethical evaluation must examine the possible consequences of adopting or not adopting the vaccination in relation to the prevalent social values and to the norms and values that the vaccination itself determines. Moreover, ethical evaluation must also consider moral and ethical questions related to the consequences of performing the HTA: for example, questions concerning the ethical consequences of the choice of specific objectives and parameters and the possible existence of ethical problems related to the economic evaluation carried out [1].
In this ethical evaluation of anti-meningococcal B vaccination with the vaccine Trumenba® in adolescents, the "triangular model" [4] was used.

The "triangular model" of ethical evaluation based on the person-centered approach

The "triangular model", which is utilized in ethical evaluations of healthcare technologies, is centered on the fundamental concept of the human being, which is the reference value around which all ethical judgments are coordinated [4].
The triangular model is subdivided into three phases of analysis:

1. data collection (the "scientific" phase, with in-depth analysis of data, including qualitative and relational data);
2. anthropological aspects (anthropological understanding of the facts, with analysis of values related to human life, integrity and dignity of the person);
3. ethical-normative evaluation (evaluation of the practical choices to be made).

In accordance with this model, the explanation of a given subject (descriptive step) is followed by a normative phase, from which it is possible to draw conclusions within a biomedical, anthropological and ethical debate. Specifically, in the phase of anthropological analysis, we should identify the values to protect and promote and the norms that should guide human action at both the individual and social levels.
The normative evaluation in this model [4-6] is based on the following principles:

1. physical human life must be defended in its entirety and in its integrity;
2. the principles of freedom (capacity of the human will) and responsibility (with intra- and inter-subject evaluations of the acts and will of the individual) must be followed and guaranteed;
3. the therapeutic principle (the person must be treated as mind-body whole) must be followed;
4. the principles of sociality and subsidiarity (public or private authority must intervene and help the person only if she is unable to fend for herself) must be evaluated [4].

Exploratory biomedical phase

According to the "triangular model" of the ethical evaluation of healthcare technologies, in the exploratory phase we need to gather data and scientific evidence on the disease that we wish to treat/prevent and on the technology under examination. The main scientific evidence available to date, as described in the previous chapters of the present report, is summarized below.
The bacterium *Neisseria meningitidis* is hosted in the upper airways of healthy carriers. In some cases, it can cause invasive disease. Invasive disease has a high case fatality rate and may result in severe complications and permanent sequelae. In Italy, the etiological diagnosis is made by means of two main methods (culture testing and real-time PCR); as these display different degrees of sensitivity, diagnosis rates may differ. Meningococcal disease manifests itself in both endemic and epidemic forms. Italy has one of the lowest notification rates in Europe (0.35 cases per 100,000 population, with a mean

of 200 cases per year being notified) [7, 8]. Moreover, the reported incidence of the disease differs markedly from one region of the country to another (owing to the different diagnostic methods used). Together with meningococcus C, meningococcus B is the most frequently detected serogroup in Italy (36% of cases of invasive disease due to *N. meningitidis* in 2011-2017). In recent years, however, cases attributed to other serogroups have been reported. Meningococcus B is responsible for about 62 cases per year in the general population, 3 of which occur in the 10-14-year age-group and 11 in subjects aged 15-24 years. The mean rate of incidence of invasive meningococcal B disease in the period 2011-2017 was 0.11 cases per 100,000 in subjects aged 10-14 years and 0.18 cases per 100,000 in those aged 15-24 years [7].
However, considering the percentage of samples that are not typed by the Italian system of invasive bacterial disease surveillance [8] and the under-diagnosis rate (correction factor 3.28) of cell culture (the most frequently used diagnostic test) in comparison with real-time PCR [9], we can estimate a more realistic incidence of 0.41 cases per 100,000 in subjects aged 10-14 years and 0.69 cases per 100,000 in those aged 15-24 years (see chapter 2).
Although invasive meningococcal disease does not have a particularly high incidence in the general population, in adolescents it has a heavy clinical impact. Indeed, the case fatality rate in this age-group is particularly high (8-15%) and, in cases of sepsis, can reach 40% [10-13]. The onset of specific symptoms of meningitis is extremely rapid (12-15 hours) [14], which often makes antibiotic therapies ineffective. Sepsis occurs in 5-20% of cases [10]. Moreover, up to 60% of survivors suffer at least one sequela, and many have multiple sequelae [11]; these may be transient or permanent and of variable severity, and determine a significant clinical and economic impact. The main physical sequelae are skin scars (6.4-48%), amputations (0.8-14%), kidney dysfunction (2-8.7%) and arthritis/vasculitis (4.7%) [15]. In addition to physical sequelae, major neurological sequelae may occur. Finally, many survivors suffer post-traumatic stress disorders (significant psychiatric and psychological damage) which impair their quality of life (fatigue, anxiety, reduced ability to work or engage in recreational activities) to a variable degree, depending on the severity of the symptoms and sequelae. Sequelae also have a heavy indirect psychological and psychiatric impact on family members and caregivers, whose productivity is reduced (see chapter 3).
Invasive meningococcal disease, owing to its severe acute phase and its possible multiple sequelae, generates significant direct and indirect costs both for the NHS and for society (see chapter 4).
In addition to the risk of invasive disease, however, it must also be borne in mind that the highest rates of carriage (up to 20%) are recorded in young adults [16]. These subjects are therefore a major source of contagion, especially in situations of social aggregation, as evidenced by epidemics that have occurred both nationally and internationally [17, 18].
To prevent invasive disease caused by *N. meningitidis* serogroup B in subjects aged 10 years or more, the vaccine Trumenba® is now available in Italy. This vaccine contains two recombinant lipidated variants of the factor H-binding protein (fHbp), which is essential in enabling the bacteria to elude the host's immune defenses. Indeed, over 96% of meningococci B isolated in Europe express fHbp variants belonging to the two subfamilies, A and B, on the bacterial surface. As Trumenba® contains a variant of each of these subfamilies, it stimulates the production of bactericidal antibodies that recognize the fHbp expressed by the meningococci [19]. In clinical trials, Trumenba® has been seen to elicit a broadly protective response against antigenically and epidemiologically different strains of meningococcus B in both adolescents (10-18 years) and young adults (19-25 years) [20] following a 2- or 3-dose schedule [21] (see chapter 5).
From the economic standpoint, introducing anti-meningococcal B vaccination for adolescents is advantageous. Indeed, its incremental cost-effectiveness (ICER) has proved to be € 7,907.08 from the NHS perspective and € 7,757.73 from the perspective of society, in comparison with no-vaccination confirming the cost-effectiveness of the implementation of this immunization program. Given the severity of the disease and its consequences, the total cost of one case of disease is estimated to amount to € 503,223.79 (costs not discounted) and to € 268,865.48 (discounted costs). Thus, economic evaluation has shown that vaccinating adolescents against meningococcus B can reduce the clinical impact of the disease, thereby reducing both direct and indirect costs and, consequently, yielding an overall benefit for the community (see chapter 6).

Anthropological phase of evaluation

According to the triangular model, the facts have to be evaluated from an anthropological standpoint; this means analyzing the values related to human life and to the integrity and dignity of the person.
In accordance with the topics and issues proposed by the ethical domain of the HTA Core Model of EUnetHTA [1], the anthropological evaluation of anti-meningococcal B vaccination for adolescents is reported below.

Risk-benefit analysis

1. *What are the symptoms and the disease burden for the patient?*

Epidemiological data indicate that meningococcal infections have a low incidence in the general population. However, this rare disease particularly strikes adolescents. While this is true of all *N. meningitids* serotypes, it is even more so in the case of serotype B. The course of invasive meningococcal B disease is particularly rapid and severe and carries a high risk of death or serious permanent sequelae (see chapters 2 and 3). Adopting

specific preventive measures would therefore avoid this devastating clinical impact.

2. *What are the known and estimated benefits and harm resulting from vaccination or non-vaccination against meningococcus B?*

Vaccinating adolescents against meningococcus B would, first of all, safeguard their life and health. Indeed, meningococcal disease is particularly severe, as it has a low incidence rate but often causes permanent serious sequelae that undermine the quality of life of both survivors and their family members. Moreover, avoiding this disease is particularly advantageous when the subjects involved are young and have the prospect of a long life in front of them, that could be heavy compromise by disease. At the cost of causing mild and transitory adverse reactions (injection site pain, reddening and swelling, headache, fatigue, shivering, diarrhea, muscle and joint pains, and nausea), Trumenba® elicits a robust immune response to the invasive disease caused by *N. meningitidis* serogroup B [19]. In addition to this clinical benefit, vaccination avoids the psychological and psychiatric (post-traumatic stress) and social effects (inability to work and reduced recreational activity) of invasive meningococcal disease (see chapter 3). Moreover, it also saves the indirect healthcare costs generated by the disease (see chapter 4).

3. *What benefit or harm does anti-meningococcal vaccination bring to parents, other patients, organizations, commercial bodies, society, etc.?*

As invasive meningococcal disease is particularly severe, its therapy is very demanding both during the acute phase and during the phases of recovery and rehabilitation (post-acute and long-term phases). In addition to the treatment provided by the NHS, the clinical, rehabilitative, educational, psychological/psychiatric assistance provided for survivors by their family members and caregivers is also burdensome. Indeed, as care may be required for a very long time (even months or years), family members are sometimes forced to give up working, in order to devote themselves full-time to this task. This aspect is particularly important when the patient affected is a young person with a long life expectancy, as is typically the case of meningococcal diseases. Moreover, in some cases, the heavy emotional burden caused by the disease necessitates post-traumatic psychological support for both patients and family members, both in the acute phase and subsequently (see chapter 3).
In sum, hospitalization, therapy, rehabilitation, special education and sociological/psychiatric support generate high costs (in money and personnel) both for the NHS and from the societal respective (especially for family members and education authorities).
Vaccination could avoid all these deleterious consequences, while causing only rare, mild and transitory adverse reactions [19].

4. *Do meningococcal B vaccination and its applications have any hidden or unintentional consequences for vaccinees, parents, other patients, organizations, commercial bodies, society, etc.?*

Vaccinating adolescents against meningococcus B directly protects one of the groups of subjects at highest risk of disease. Moreover, as this age-group also presents the highest rates of carriage, vaccinating adolescents with Trumenba® could maximize the protection of the community by potentially interrupting carrier status and, therefore, the transmission of meningococcus. To date, however, the impact of anti-meningococcal B vaccination on carriage is not yet clear [22]. Indeed, studies have not demonstrated that either the MenB-FHbp vaccine [23] or the MenB-4C vaccine [24] reduces the probability of becoming a carrier. Thus, the possible impact of anti-meningococcal B vaccination on carrier status in adolescents and its consequent effect on the transmission of the bacterium will need to be further investigated in the future. If the impact of vaccination on carrier status should been demonstrated, this would enhance the value of this vaccination with regard not only to the single individual, but also the whole community.
Clinical trials have shown that Trumenba® has a good safety and tolerability profile, with only mild and temporary adverse reactions being recorded [19]. Nevertheless, as in the case of any new vaccine, thorough post-marketing pharmaco-vigilance will need to be undertaken in order to identify any rare reactions following large-scale vaccination. This is particularly important in the case of Trumenba®, which, like every new vaccine, is classified as a "medicinal product subject to additional monitoring", precisely in order to rapidly identify any new safety issues, other than those recorded in the clinical trials [19]. Thus, it is important that all healthcare workers should report any suspected adverse reaction that may come to their knowledge. Moreover, the vaccinees themselves and/or their carers must be informed as to the possibility of reporting any adverse events to their doctors, in order to ensure optimal post-marketing surveillance. Careful pharmaco-vigilance should therefore enable any hidden or unintentional consequences to be detected and, if necessary, allow prompt intervention in order to safeguard the health of vaccinees.

5. *Are there any ethical obstacles to generating evidence of the benefits or harm of this vaccination?*

At the moment there are no ethical obstacles to generating evidence of the benefits or harm resulting from anti-meningococcal B vaccination in adolescents. Indeed, the authorizing clinical trials conducted so far have shown that Trumenba® is immunogenic and safe [19-21] (see chapter 5). Moreover, in order to ensure the ethical nature of the vaccination, as previously mentioned, Trumenba® is subject to careful, in-depth post-marketing pharmaco-vigilance [19].
Finally, in the United States, vaccination with Trumenba® is already provided for subjects aged 10 years and above [25, 26]; in Italy, the Puglia, Sicily and Campania

Regions have already recommended this vaccination for adolescents [27-29].
Evaluation of experiences in the field, in addition to those collected during clinical experimentation, should provide further information concerning the benefits and tolerability levels of this vaccine.

Self-determination

1. *Is anti-meningococcal B vaccination administered to particularly vulnerable persons?*

In the present case, anti-meningococcal B vaccination would be administered to adolescents (aged 11 years). As they are minors who do not have the complete capacity to decide, the approval of their parents or legal guardians is required. Legal guardians have the right/duty to evaluate the benefits of vaccination in relation to its possible risks, provided that they receive adequate information from healthcare workers, in order to be able to decide and to provide their informed consent.
Moreover, the aim of vaccination is precisely to safeguard adolescents at the time of their lives in which they are at increased risk of disease and, therefore, of vulnerability; thus, their future self-determination is not compromised.

2. *Does the adoption or use of anti-meningococcal B vaccination influence the capability of vaccinees and their capacity to exercise self-determination?*

Vaccinating adolescents does not require that vaccinees modify their behavior or undergo restrictions on their autonomy. However, in order to be completely autonomous, even in their choices, these adolescents should understand not only the direct risks of treatment, but also all the alternatives, if side effects should occur, and how these may influence quality of life or life choices. Therefore, the adolescents themselves, in addition to their legal guardians, should be suitably informed as to the risks and benefits of vaccination, and should provide their consent (see chapter 8).
On the other hand, vaccinating adolescents against meningococcus B will positively influence the future autonomy of vaccinees. Indeed, vaccination will be able to prevent cases of disease due to *N. meningitidis*, which could be fatal or give rise to permanent severe sequelae. Thus, vaccination can be viewed as an intervention to safeguard the long-term future autonomy of the adolescents vaccinated, who would otherwise be seriously at risk of meningococcal disease and its sequelae.

3. *Are specific supportive interventions or actions regarding information necessary in order to respect the adolescent's self-determination when the anti-meningococcus B vaccine is administered?*

It should be common, and obligatory, professional practice to inform subjects who are to be vaccinated and to adequately discuss the vaccine with them or, in the case of minors, with their parents or legal guardians. In the case of new vaccines or vaccination strategies, as is that of anti-meningococcal B vaccination in adolescents, the information phase requires particular attention, in order to ensure that the subjects involved are given all the information that they need in order to decide.
Specifically, both the adolescents and their parents or legal guardians must be explicitly informed about, for example, the possibility of adverse reactions and their frequency and gravity, as indicated by the results of clinical trials and post-marketing pharmaco-vigilance. Furthermore, healthcare workers should inform these individuals as to the level of immunogenicity of Trumenba® and the possible loss of immune protection over time, according to the scientific evidence available. In addition, information on the clinical benefits of vaccination should be provided; that is to say, the prevention of a serious disease which, though not particularly frequent in the general population, more often strikes adolescents and carries a high risk of severe, and often permanent, sequelae. Thus, it is important that healthcare personnel properly communicate both benefits and risks through the channels that are most suited to the subjects targeted by vaccination (see chapter 8).

4. *Does the adoption of anti-meningococcal B vaccination for adolescents challenge or modify professional values, ethics or traditional roles?*

Health technologies can sometimes change the doctor-patient relationship, challenge professional autonomy and interfere with professional ethics and values. In general, the doctor-patient relationship is traditionally based on mutual trust, confidentiality and professional autonomy, in such a way that decisions may be taken by the healthcare worker in the interests of the patient. However, in the sphere of vaccinations (and not only) this relationship is being increasingly undermined by the diffusion of fake news on social networks [3]. When anti-meningococcus B vaccination for adolescents is introduced, all healthcare workers will need to be prepared and able to provide consistent answers to all the questions asked by the subjects involved, in order to maintain a proper doctor-patient relationship and to stave off false information (see chapter 8).
Health technologies that are in line with professional ethics generally have a better chance of being successfully implemented. By contrast, those technologies which interfere with the fundamental values and principles of medical and professional ethics call into question the professional integrity of doctors and other healthcare workers, and are less likely utilized. Anti-meningococcus B vaccination for adolescents, like all vaccinations against meningococcus, could well be amply requested by the population, on account of the high perception of the gravity of the disease. Nevertheless, healthcare professionals might erroneously consider this vaccination to be unnecessary, on account of the low incidence of the disease and the high cost of immunization. Moreover, they might consider it more ethical to devote the limited resources of the NHS to other healthcare priorities. It is therefore essential that all the healthcare professionals

involved receive adequate information and training on the basis of all the scientific evidence regarding the disease and vaccination.

Respect for the person

1. *Does the adoption or use of anti-meningococcal B vaccination in adolescents affect human dignity?*

Some health technologies that target subjects with limited autonomy (such as children or adolescents) may violate the dignity of the person (i.e. the idea that all human beings have an intrinsic value and should not therefore be as means of achieving other end). Labeling people as the result of the use of a health technology may also threaten their dignity. In the case of anti-meningococcal B vaccination for adolescents, vaccination does not threaten the dignity of this vulnerable population group; on the contrary, it safeguards these subjects by preventing invasive meningococcal disease.

2. *Does the adoption or use of the anti-meningococcus B vaccine affect the moral, religious or cultural integrity of the vaccinee?*

There is no evidence to suggest that vaccinating adolescents with the anti-meningococcus B vaccine affects the moral, religious or cultural integrity of the subjects vaccinated, their parents or legal guardians.

3. *Does vaccination with the anti-meningococcus B vaccine affect the privacy of the vaccinee?*

As in the case of all vaccinations, the vaccination of adolescents with the anti-meningococcus B vaccine will be recorded in the databases of the vaccination registry. Information on the vaccination will be allowed to be divulged only in aggregate form and only for the purposes of research or epidemiological impact and safety of the vaccination.
From the physical point of view, vaccination is non-invasive, consisting of the administration of two doses of the Trumenba® vaccine.

Justice and equity

1. *In what way does the introduction of vaccination with the anti-meningococcus B vaccine in adolescents impact on the distribution of health care resources?*

Vaccinating a cohort of adolescents with the anti-meningococcus B vaccine will involve considerable costs for the NHS; some of these will be recovered through the avoidance of cases of invasive meningococcal disease, and hence of the high costs of treating such cases. If a specific *ad hoc* budget is not provided, these costs could/should be covered by resources diverted from other areas, following an assessment of the possible redistribution of the available resources. The study of the reallocation of NHS resources may prove somewhat difficult and raise ethical dilemmas regarding choices among various population groups and patients with different priorities. However, it must be stressed that, on evaluating the costs of invasive meningococcal disease in its various phases (acute, post-acute and long-term), and especially of its sequelae, vaccinating adolescents against meningococcus B is highly cost-effective, and therefore acceptable to the NHS. Moreover, the ICER values yielded by the present economic evaluation can provide useful indications of the level of priority of this vaccination in comparison with other health interventions (see chapter 6). In addition, it should be borne in mind that vaccinating adolescents against meningococcus B will avoid deaths and irreversible sequelae (which severely impair quality of life) among young subjects, the value of which, though not morally quantifiable, impacts heavily on both patients and their families.
For what concerns the human resources of the NHS, the impact of vaccination will be modest. Indeed, Trumenba® can be co-administered with the vaccines already available and recommended in adolescence, such as, for example, the anti-HPV vaccine, the anti-tetanus/diphtheria/pertussis/polio vaccine (DTaP/IPV) and the anti-meningococcus ACYW135 conjugate vaccine.

2. *How are vaccinations with similar ethical problems treated by the health system?*

In the past, there was a great deal of debate in Italy about the adoption of anti-meningococcal B vaccination in the pediatric age. Indeed, like the vaccination of adolescents, the universal vaccination of newborns, which places a considerable economic burden on the NHS, did not seem to be justified, in that it was aimed at preventing a relatively infrequent, albeit very severe, disease. Several studies were therefore conducted in order to assess the impact of its introduction [30, 31]. Despite the disadvantages highlighted by these studies (high cost of vaccination versus low incidence of disease), this vaccination was included among those recommended for newborns by the 2017-2019 NVPP [32]. The present economic evaluation, which focuses on adolescents, reveals that vaccination against meningococcus B has a favorable economic profile from the perspectives of both the NHS and society (see chapter 6). One of the reasons for this is that the vaccination schedule in adolescents involves the administration of only 2 doses; this means that the costs of purchasing vaccines and organizing vaccination services are lower than those of pediatric vaccination, which involves a primary course of 4 or 3 doses. Moreover, as mentioned above, the possibility of co-administering Trumenba® with the other vaccines recommended for adolescents enables savings in terms of organization. In addition, the 2017-2019 NVPP also recommends administering a dose of the quadrivalent anti-meningococcus ACYW135 conjugate vaccine to adolescents [32].
Given the importance of deploying this new preventive weapon, some Italian Regions (Puglia, Sicily and Campania) have already begun to provide anti-meningococcal B vaccination for adolescents, having overcome every ethical problem (see chapter 7) [27-29].

3. *Are there any factors that might preclude any group or person from access to vaccination?*

Introducing the vaccination of adolescents against meningococcus B into the new national vaccination schedule would make this vaccination equally available to all adolescents residing in Italy. This would overcome the current inequality inherent in the fact that some Italian Regions (Puglia, Sicily and Campania) offer this vaccination, while others do not (see chapter 7) [27-29]. Moreover, it should be borne in mind that investing in the reduction of health inequalities is one of the objectives set by the European Commission in order to promote social cohesion by reducing the poor health that contributes to poverty and exclusion.
Finally, if this vaccination is not offered free of charge at the national level, it could be carried out on the request of the adolescents or their parents/legal guardians on payment of a fee; this would hinder the equal access to the safeguard of health on an economic and social basis.

Legislation

1. *Does the introduction of anti-meningococcal B vaccination affect the realization of basic human rights?*

The United Nations Declaration of Human Rights (http://www.un.org/en/documents/udhr/) sets out the basic human rights. With regard to the vaccination of adolescents against meningococcus B, the most relevant rights are: the rights to equality, non-discrimination, security, adequate standards of living and health care. Anti-meningococcal B vaccination in adolescents guarantees all these rights.

2. *Can the use of the anti-meningococcal B vaccine in adolescents raise ethical challenges that have not been considered in current legislation and regulations?*

On the basis of current legislation, vaccinating adolescents against meningococcus B appears to be fair and appropriate. Indeed, according to the indications provided in the Summary of Product Characteristics, Trumenba® is indicated for the active immunization of subjects aged 10 years or more in order to prevent invasive meningococcal disease caused by *N. meningitidis* serogroup B [19]. At the moment, therefore, this vaccination does not give rise to ethical challenges that have not been considered at the regulatory level.
Moreover, if this vaccination will be included in the next National Vaccine Prevention Plan (NVPP 2020-2022), its use would be officially recognized throughout the country and it would be actively provided free of charge.

Ethical consequences of the HTA

1. *What are the ethical consequences of the choice of endpoints, threshold values and comparators/controls in the evaluation?*

This HTA on anti-meningococcal B vaccination in adolescents is based on scientific evidence currently available at the national and international levels.
Previous evaluations of anti-meningococcal vaccination have focused on the low incidence of the disease and the high cost of vaccination, while scant attention has been paid to the high number and impact of sequelae. Only a thorough examination of these data (see chapter 3), as carried out in this report, can fully reveal the true impact of the disease and the benefits yielded by vaccination. These data, however, are not always available in detailed form at the international level and, especially, at the national level. This fact may have determined, in our analysis as well as in others, a partial description of the impact of vaccination on the disease and its complications. However, even though the available data are not always complete and exhaustive, they are, to our knowledge, the only ones we have. The results of the present HTA may be reassessed in the future when new scientific evidence become available.

2. *Are there any ethical problems related to the data used or the hypotheses advanced in the economic evaluation?*

A possible ethical problem regarding the data utilized in the economic evaluation is related to the hypotheses of efficacy and duration of the immunity conferred by Trumenba®. As this vaccine has only recently become available, the true data are not actually known. Thus, our assumptions regarding the efficacy and duration of protection in the economic evaluation were based on the available scientific data and on expert opinion; they will therefore need to be reconsidered when new scientific evidence becomes available (see chapter 6).

3. *What are the ethical consequences of conducting the HTA at the present time?*

The present HTA of anti-meningococcal B vaccination in adolescents in Italy will constitute a useful tool, based on currently available scientific evidence, which can be used by decision-makers in drawing up the new 2020-2022 NVPP in the near future. In particular, this evaluation will help decision-makers to determine the level of priority of anti-meningococcal B vaccination in adolescents in relation to other health interventions. Introducing this vaccination into the 2020-2022 NVPP would ensure its equal provision throughout the country. Current knowledge is not always complete and generalizable. Nevertheless, it is sufficient to support the introduction of this vaccination.

Ethical and normative evaluation (evaluation of the practical choices to be made)

The epidemiological data evaluated show that invasive meningococcal diseases have a low incidence but a particularly severe course and high case fatality rate. After children aged less than 5 years, adolescents constitute

one of the age-groups hardest hit by this terrible disease. Vaccinating adolescents with Trumenba® against meningococcus B would therefore enable us to safeguard the life and health of these vulnerable subjects and to avoid irreversible sequelae that gravely and permanently impair their quality of life.

Moreover, anti-meningococcal B vaccination would also have a major social impact. Indeed, it would not only reduce the direct and indirect health costs of the disease and its consequences; it would also alleviate the heavy burden of social assistance for patients and their families (special education and disability invalidity pensions).

Anti-meningococcal B, C/ACYW135 vaccinations are already recommended in the pediatric age, and anti-meningococcal ACYW135 vaccination in adolescents. Moreover, anti-meningococcal B vaccination for adolescents is already provided in some Italian Regions (Puglia, Sicily and Campania). In order to achieve equality of treatment and access to healthcare services, this latter vaccination should be provided throughout the country.

A fundamental prerequisite to the introduction of anti-meningococcal B vaccination for adolescents is that vaccination should stem from a conscious informed choice on the part of the parent or legal guardian of the adolescent, following proper communication of correct information on the benefits and possible risks of vaccination. This informed choice must also involve the adolescents themselves, who, though minors, should be adequately informed and should be able to express any doubts that they may have, which should then be clarified by healthcare personnel in a manner that is appropriate to the subject's age.

In sum, on the basis of the data available, of the risk/benefit and cost/benefit analyses and, finally, of the social value of vaccination, the ethical judgment of anti-meningococcal B vaccination for adolescents is, on the whole, positive, on condition that adequate information is provided, informed consent is given, and the vaccination is equally available throughout the country. Finally, it is essential that, in accordance with the law, careful surveillance be carried out in order to detect possible side-effects of the new vaccination that have not come to light during clinical trials.

In conclusion, vaccinating adolescents against meningococcus B would protect human life and its integrity while guaranteeing the principles of liberty (capacity of human will), responsibility and mind-body integrity, yielding benefits for society by reducing both the economic and social costs generated by the severe sequelae of invasive meningococcal B disease.

References

[1] EUnetHTA Joint Action 2, Work Package 8. HTA Core Model® version 3.0 (Pdf); 2016. Available at: www.htacoremodel.info/BrowseModel.aspx

[2] Ministero della Salute. Dati coperture vaccinali. Availabe at: http://www.salute.gov.it/portale/temi/p2_6.jsp?id=811&area=Malattie%20infettive&menu=vaccinazioni

[3] Broniatowski DA, Jamison AM, Qi S, AlKulaib L, Chen T, Benton A, Quinn SC, Dredze M. Weaponized health communication: twitter bots and russian trolls amplify the vaccine debate. Am J Public Health 2018;108(10):1378-84. https://doi.org/10.2105/AJPH.2018.304567

[4] Sgreccia E. Manuale di Bioetica. Volume I. Fondamenti ed etica biomedica. 4th Edition Milano: Vita e Pensiero 2007.

[5] Sacchini D, Spagnolo AG, Minacori R, Carrasco de Paula I. HTA and ethics: the framework of ethical positions and the proposal of a person-centred model. Italian J Public Health 2005;2(2):304.

[6] Sacchini D, Refolo P. L'Health Technology Assessment (HTA) e i suoi aspetti etici. Medicina e Morale 2007;1:101-39.

[7] Istituto Superiore di Sanità (ISS). Dati di sorveglianza delle malattie batteriche invasive aggiornati al 19 marzo 2018. Available at: http://old.iss.it/binary/mabi/cont/InterimReport2017.pdf [Accessed 24/10/2019].

[8] Commissione Europea. European Core Health Indicators (ECHI). Available at: https://ec.europa.eu/health/communicable_diseases/indicators_it

[9] Azzari C, Nieddu F, Moriondo M, Indolfi G, Canessa C, Ricci S, Bianchi L, Serranti D, Poggi GM, Resti M. Underestimation of invasive meningococcal disease in Italy. Emerg Infect Dis 2016;22(3):469-75. https://doi.org/10.3201/eid2203.150928

[10] Center for Disease Control and Prevention (CDC). Epidemiology and prevention of vaccine-preventable diseases. The Pink Book, 13th Edition (2015), Chapter 14: Meningococcal disease. Available at: https://www.cdc.gov/vaccines/pubs/pinkbook/index.html [Accessed 31 December 2018].

[11] Buysse CM, Vermunt LC, Raat H, Hazelzet JA, Hop WC, Utens EM, Joosten KF. Surviving meningococcal septic shock in childhood: long-term overall outcome and the effect on health-related quality of life. Crit Care. 2010;14(3):R124. https://doi.org/10.1186/cc9087

[12] Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, Bettinger JA; investigators of the Canadian Immunization Monitoring Program, ACTive (IMPACT). Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis 2015;60(8):e27-35. https://doi.org/10.1093/cid/civ028

[13] European Centre for Disease Prevention and Control (ECDC). Invasive meningococcal disease - Annual Epidemiological Report for 2015. Available at: https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-meningococcal-disease.pdf [Accessed 31 December 2018].

[14] Thompson MJ, Ninis N, Perera R, Mayon-White R, Phillips C, Bailey L, Harnden A, Mant D, Levin M. Clinical recognition of meningococcal disease in children and adolescents. Lancet 2006;367(9508):397-403. https://doi.org/10.1016/s0140-6736(06)67932-4.

[15] Martinón-Torres F. Deciphering the burden of meningococcal disease: conventional and under-recognized elements. J Adolesc Health 2016;59(2 Suppl):S12-20. https://doi.org/10.1016/j.jadohealth.2016.03.041

[16] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(12):853-61. https://doi.org/10.1016/S1473-3099(10)70251-6

[17] Stefanelli P, Fazio C, Vacca P, Palmieri A, Ambrosio L, Neri A, Piana A, Castiglia P, Argiolas F, Santus S, Masala L, Steri G, Riccardo F, Iannazzo S, Maraglino FP, D'Amario C, Rezza G. An outbreak of severe invasive meningococcal disease due to a capsular switched Neisseria meningitidis hypervirulent strain B:cc11. Clin Microbiol Infect 2018. pii: S1198-743X(18)30532-9. https://doi.org/10.1016/j.cmi.2018.07.014

[18] National Foundation for Infectious Diseases. Meningococcal serogroup B cases and outbreaks on US college campuses. Available at: http://www.nfid.org/idinfo/meningococcal/meningococcal-b-college-outbreaks.html.

[19] Agenzia Italiana del Farmaco (AIFA). Riassunto Caratteristiche del Prodotto. Trumenba®. Luglio 2019. Available at: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004849_045429_RCP.pdf&retry=0&sys=m0b1l3

[20] Ostergaard L, Vesikari T, Absalon J, Beeslaar J, Ward BJ, Senders S, Eiden JJ, Jansen KU, Anderson AS, York LJ, Jones TR, Harris SL, O'Neill R, Radley D, Maansson R, Prégaldien JL, Ginis J, Staerke NB, Perez JL; B1971009 and B1971016 Trial Investigators. A bivalent meningococcal B vaccine in adolescents and young adults. N Engl J Med 2017;377(24):2349-62. https://doi.org/10.1056/NEJMoa1614474.

[21] Vesikari T, Østergaard L, Diez-Domingo J, Wysocki J, Flodmark CE, Beeslaar J, Eiden J, Jiang Q, Jansen KU, Jones TR, Harris SL, O'Neill RE, York LJ, Crowther G, Perez JL. Meningococcal serogroup B bivalent rLP2086 vaccine elicits broad and robust serum bactericidal responses in healthy adolescents. J Pediatric Infect Dis Soc 2016;5(2):152-60. https://doi.org/10.1093/jpids/piv039

[22] Perez JL, Absalon J, Beeslaar J, Balmer P, Jansen KU, Jones TR, Harris S, York LJ, Jiang Q, Radley D, Anderson AS, Crowther G, Eiden JJ. From research to licensure and beyond: clinical development of MenB-FHbp, a broadly protective meningococcal B vaccine. Expert Rev Vaccines 2018;17(6):461-77. https://doi.org/10.1080/14760584.2018.1483726

[23] Soeters HM, Whaley M, Alexander-Scott N, Kanadanian KV, MacNeil JR, Martin SW, McNamara LA, Sicard K, Vanner C, Vuong J, Wang X, Bandy U, Patel M; Rhode Island Meningococcal Carriage Evaluation Team. Meningococcal carriage evaluation in response to a serogroup B meningococcal disease outbreak and mass vaccination campaign at a College-Rhode Island, 2015-2016. Clin Infect Dis 2017;64(8):1115-22. https://doi.org/10.1093/cid/cix091

[24] McNamara LA, Thomas JD, MacNeil J, Chang HY, Day M, Fisher E, Martin S, Poissant T, Schmink SE, Steward-Clark E, Jenkins LT, Wang X, Acosta A; Oregon Meningococcal Carriage Team. Meningococcal carriage following a vaccination campaign with MenB-4C and MenB-FHbp in response to a university serogroup B meningococcal disease Outbreak-Oregon, 2015-2016. J Infect Dis 2017;216(9):1130-40. https://doi.org/10.1093/infdis/jix446

[25] Center of Disease Control and Prevention (CDC). Recommended immunization schedule for children and adolescents aged 18 years or younger, United States, 2018. Available at: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf

[26] Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for use of MenB-FHbp serogroup B meningococcal vaccine - advisory committee on immunization practices, 2016. Morb Mortal Wkly Rep 2017;66(19):509-13. https://doi.org/10.15585/mmwr.mm6619a6

[27] Regione Sicilia. Adeguamento del Calendario Vaccinale Regionale al "Piano Nazionale di Prevenzione Vaccinale 2017-2019", recepito dalla Regione Sicilia con il D.A. n. 1004 del 22 Maggio 2017. Available at: http://pti.regione.sicilia.it/portal/page/portal/PIR_PORTALE/PIR_LaStrutturaRegionale/PIR_AssessoratoSalute/PIR_Infoedocumenti/PIR_DecretiAssessratoSalute/PIR_DecretiAssessoriali/PIR_DecretiAssessorialianno2017/D.A._n%B0_1965%5B1%5D%20-%20serv.4.pdf

[28] Regione Puglia. Deliberazione della Giunta Regionale 31 gennaio 2018, n. 113. DGR n. 2279/2017 - Calendario Vaccinale per la Vita nella Regione Puglia e Calendario operativo per le vaccinazioni dell'adulto. Modifica per mero errore materiale. Bollettino Ufficiale della Regione Puglia, n. 26 del 19-2-2018. Available at: https://www.sanita.puglia.it/documents/20182/1897678/DELIBERAZIONE+DELLA+GIUNTA+REGIONALE+31+gennaio+2018%2C+n.+113/ee434cc4-e3c5-4b86-b8fd-1ef008e-5c8a9

[29] Regione Campania. Decreto n. 28 del 25.03.2019. Ulteriori misure per la prevenzione della malattia meningococcica nella fascia di età adolescenziale. Available at: http://www.aiopcampania.it/public/normativa/4b06bd76312d445d85b9f8caa6082a8b.pdf

[30] Gasparini R, Landa P, Amicizia D, Icardi G, Ricciardi W, de Waure C, Tanfani E, Bonanni P, Lucioni C, Testi A, Panatto D. Vaccinating Italian infants with a new multicomponent vaccine (Bexsero®) against meningococcal B disease: a cost-effectiveness analysis. Hum Vaccin Immunother 2016;12(8):2148-61. https://doi.org/10.1080/21645515.2016.1160177

[31] di Pietro ML, Capri S, Kheiraoui F, de Waure C, Quaranta G, Poscia A, Specchia ML, Veneziano MA, Di Nardo F, Cadeddu C, Lovato E, Ferriero AM, Mancuso A, Miglietta A, Delon M, Alicevjc M, La Torre G, Fantoni S, Bianchi A. Health Technology Assessment della vaccinazione contro meningococco B. QIJPH - 2013, Volume 2, Number 13. Available at: https://www.ijph.it/pdf/2013-v2-n13.pdf

[32] Ministero della Salute. Piano Nazionale Prevenzione Vaccinale 2017-2019. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2571_allegato.pdf

Chapter 11

Key points for decision-makers

S. BOCCALINI[1], P. LANDA[2], D. AMICIZIA[3], A. BECHINI[1], P. BONANNI[1], M. INNOCENTI[4], P.L. LAI[3], F. MARCHINI[3], D. PAOLINI[1], G. SARTOR[4], F. ZANGRILLO[3], E. LECINI[3], M. IOVINE[3], D. PANATTO[3]
[1] Department of Health Sciences, University of Florence, Italy; [2] Department of Economics, University of Genoa, Italy; [3] Department of Health Sciences, University of Genoa, Italy; [4] Medical School of Specialization in Hygiene and Public Health, University of Florence, Italy

Epidemiology of meningococcal disease in Italy

Neisseria meningitidis, a bacterium found in the upper airways of healthy carriers, can, in some cases, cause invasive disease; this disease, which is not easy to diagnose, has a high lethality rate and can cause severe complications and sequelae. The etiological diagnosis is made mainly by means of two methods (culture and real-time PCR), which display different degrees of sensitivity and can yield different diagnosis rates.
In Italy, the surveillance of invasive bacterial diseases is coordinated by the *Istituto Superiore di Sanità* and requires that all cases of invasive bacterial diseases, including invasive meningococcal disease, be reported. These data are also uploaded to the European Surveillance System.
Meningococcal disease occurs in endemic and epidemic forms. Italy has one of the lowest notification rates in Europe, and in terms of incidence, major differences are observed among the various Regions; this is due especially to the diagnostic techniques used.
In Italy, the most frequently detected serogroup is meningococcus B (in about 36% of cases of invasive disease due to *N. meningitidis* in 2011-2017), despite an upsurge of meningococcus C in 2015-2016 and a rise in the percentages of cases attributed to other serogroups. Meningococcus B is responsible for a mean of about 62 cases per year in the general population, 3 of which in subjects aged 10-14 years (28%) and 11 of which in those aged 15-24 years (32%).
It must also be borne in mind that many adolescents are healthy carriers; these are a source of contagion, especially in settings of intense social aggregation, which are typical of this age-group, as revealed by outbreaks that have occurred both in Italy and internationally.

The disease burden and sequelae of meningococcal disease

In industrialized countries, meningococcal disease mainly strikes children, adolescents and young adults. Its lethality rate is high (8-15%) and, in the event of sepsis, can reach 40%.
Invasive meningococcal disease may manifest itself in different forms, the most common being meningitis. Specific symptoms generally appear about 12-15 hours after the onset of the disease; later symptoms, such as loss of consciousness, convulsions and delirium, occur after about 15 hours in infants and 24 hours in older children. The clinical presentation of meningococcal meningitis is: rapid-onset fever, headache, stiffness of the neck, nausea, vomiting, photophobia and alteration of the mental state. Sepsis occurs in 10-30% of cases and is characterized by rapid-onset fever, petechiae, purpuric rash, often associated to the typical signs of shock, with hypotension, acute adrenal hemorrhage and multiorgan failure. Less frequent acute manifestations are pneumonia (5-15%), arthritis (2%), otitis media (1%) and epiglottitis (< 1%).
The risk factors associated with the development of meningococcal disease are related both to the host and to the environment. The principal host-related factors are immunological defects and the presence of chronic diseases. The main environmental risk factor is frequenting crowded enclosed spaces.
The heavy impact of the disease is chiefly associated with the transitory and/or permanent sequelae, of variable severity, which afflict survivors. Up to 60% of patients suffer at least one sequela, and many have multiple sequelae. However, most of the studies that have estimated the probability of suffering complications have not evaluated their association with the various serogroups or their distribution by age-group. The most frequently reported physical sequelae are: skin scars (6.4-48%), amputations (0.8-14%), renal dysfunction (2-8.7%) and arthritis/vasculitis (4.7%). The main neurological sequelae are: bilateral/unilateral deafness (2-5%), cognitive impairment (up to 24%), visual disorders (up to 23%), convulsions/epilepsy (up to 40%) and problems of communication (up to 25%).
Meningococcal disease may also give rise to significant psychiatric problems (anxiety 5.71%, depression 7.14%). As these arise after hospitalization, they are frequently underestimated in the medium and long term. Moreover, many survivors suffer from post-traumatic stress disorders (up to 62% of patients). Another important aspect to consider is that, during the acute and post-acute phases of their child's disease, about 60% of mothers and 40% of fathers suffer psychological/psychiatric disorders that require specialist support.

The costs of invasive disease due to *Neisseria meningitidis*

Invasive meningococcal disease generates high direct and indirect costs.

The direct costs are those borne by the National Health Service (NHS), and can be subdivided into: acute-phase costs (hospitalization, rehabilitation and public health response), post-acute-phase costs (up to 6 months after the acute phase), and the long-term costs associated with temporary or permanent sequelae. These costs are updated to 1/1/2018.
The direct cost of hospitalization is calculated on the basis of the SDO codes (ICD-9) assigned to meningococcal meningitis, septicemia and both of these clinical conditions, and the related DRG codes. The mean cost ranges from a minimum of € 4,529 to a maximum of € 6,708 according to the clinical presentation and the patient's age.
The direct costs related to the public health response refer to: the antibiotic therapy administered to close contacts; any vaccination campaign undertaken, and the mean time devoted by the staff of the Local Health Agency to avoiding secondary cases. As complete data are not yet available in Italy, international data were utilized in the present HTA and were contextualized, as far as possible, to fit the Italian setting.
The direct costs attributable to the post-acute phase comprise the costs incurred up to 6 months after the acute phase; these include the costs of managing sequelae, of rehabilitation and of providing psychiatric and psychological support for the patient. In this phase, the costs vary according to the type of sequela. The direct cost of each outpatient examination is € 20.66, and of each session of psychological support € 19.37.
Long-term direct costs include all the costs of managing temporary or permanent sequelae. As no Italian data on the direct costs related to possible sequelae are as yet available, data from international studies were considered and were contextualized, as far as possible, to fit the Italian setting.
Indirect costs comprise: the cost of death, the costs related to the loss of productivity of patients and their family members and psychiatric/psychological support for family members suffering from post-traumatic stress during the acute phase of the disease; the costs of managing the patient in the post-acute phase (including loss of productivity of patients and caregivers and of psychiatric/psychological support for the family); the costs of managing patients with sequelae (special education, disability pension, invalidity benefits and accompaniment allowances) and the costs of long-term psychiatric/psychological support for patients and their families.
Although cases of invasive meningococcal disease are relatively rare, each case generates high costs for both the NHS and society, if all the direct and indirect costs of the disease and its sequelae are appropriately considered. In the acute phase alone, the mean overall cost of a case of disease amounts to about € 13,952. The overall costs incurred during the post-acute and long-term phases are very variable and depend on the type of sequela.

Immunogenicity and safety of the anti-meningococcus B vaccine Trumenba®

Trumenba® is indicated for the active immunization of subjects aged ≥ 10 years against invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B (Men B).
This vaccine is constituted by two recombinant lipidated variants of factor H-binding protein (fHbp), which is present on the surface of meningococcus and is essential to the microorganism in order to elude the host's immune defenses.
The variants of fHbp are subdivided into two immunologically distinct subfamilies, A and B, and over 96% of the Men B strains isolated in Europe express variants of fHbp of both subfamilies on the bacterial surface.
The aim of vaccination with Trumenba® is to stimulate the production of bactericidal antibodies that recognize the fHbp expressed by meningococcus.
Clinical trials (phase II and phase III) have shown that Trumenba® is able to elicit a broad immune response against antigenically different strains of Men B in adolescents (10-18 years) and healthy young adults (19-25 years) following either a 3-dose or 2-dose schedule.
In a phase III clinical study involving adolescents, the proportion of subjects with a ≥ 4-fold increase in their hSBA titers after 3 doses of Trumenba® ranged from 78.8% to 90.2%. A composite response to the 4 test strains after 3 doses of Trumenba® was seen in 83.5% of subjects.
A clinical study aimed at evaluating the immunogenicity of Trumenba® when administered according to the 2-dose schedule showed that the antibody response in subjects who had received 2 doses (0-6 months) was very similar to that yielded by the 3-dose schedule. Specifically, one month after the second dose, the proportions of subjects with antibody titers above the pre-established limits were: 93.2%, 98.4%, 81.1% and 77.5% against the primary strains A22, A56, B24 and B44, respectively. Moreover, a composite response was seen in 73.5% of subjects.
Following the primary course of vaccination according to both schedules (2- or 3-dose), the immune response has been seen to persist 4 years after vaccination. Moreover, a single dose of Trumenba® administered about 4 years after the primary course elicits robust immune responses.
Clinical trials have also shown that, in the event of co-administration with the anti-papilloma virus vaccine (HPV4) or the anti-diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine (DTaP/IPV), the immune response is not blunted. Trumenba® can also be co-administered with the conjugated vaccine against meningococcal serogroups A, C, Y, W.
The most common adverse reactions observed after at least one dose of Trumenba® are: pain, reddening and swelling at the injection site, headache, tiredness, shivering, diarrhea, muscle pains, joint pains and nausea. Adverse reactions following a booster dose in subjects aged

15-23 years are reported to be similar to those recorded during the primary course of vaccination.
For what concerns severe adverse events, controlled clinical trials have not revealed any safety issues; indeed, the probability of severe adverse events in vaccinated subjects (adolescents) is reported to be similar to that observed in control subjects (1.9% *vs* 2.5%).

Clinical and economic impact of anti-meningococcal B vaccination with Trumenba® in adolescents

In order to evaluate the impact of vaccinating adolescents with Trumemba® in terms of cost-utility in the Italian context, a Markov mathematical cohort simulation model was constructed. Vaccination with Trumenba® was compared with a "non-vaccination" strategy, as the 2017-2019 National Vaccine Prevention Plan does not envision vaccinating adolescents against meningococcus B. The Markov model was used to analyze an Italian cohort of male and female adolescents aged 11 years (ISTAT data as of 1 January, 2018) over a lifetime follow-up.
The economic assessment was conducted in accordance with the indications provided by the Italian Health Technology Assessment (HTA) guidelines.
Two perspectives were considered: that of the National Health Service (NHS) (direct costs) and that of society (which included both the costs borne by the NHS and those borne by the community).
The health outcome considered was the QALY (Quality Adjusted Life Year), which represents the measure of one year of life weighted by the state of health. Secondary or surrogate health outcomes were not included in the study.
The results are reported in terms of the incremental cost-effectiveness ratio (ICER), expressed in € per annual QALY. In the analysis, a threshold cost-effectiveness value of € 30,000 was adopted.
The data on disease incidence and lethality were those recorded in the Italian population, while the probabilities of suffering sequelae were taken from international studies, as data on the Italian population are not available.
The values of the health outcomes (utilities) associated with the various health conditions were extrapolated from international studies, as no Italian data have yet been published.
All costs are reported in € and updated to 2018. Some costs were taken from Italian sources, while others were extrapolated from international sources and adapted to the Italian context.
Costs and health outcomes were actualized by applying a discount rate of 3.5%.
Given the possibility of variations in the input data, a sensitivity analysis was conducted. We carried out a deterministic sensitivity analysis (DSA) to assess the impact of some model parameters on the ICER, and a probabilistic sensitivity analysis (PSA) in which the model parameters, costs and utilities were caused to vary according to probabilistic distributions. The aim of the PSA was to verify the cost-effectiveness of the vaccination strategy on varying the epidemiological, market and health policy conditions.
The results of the study revealed that vaccinating adolescents (11th year of life) with Trumenba® was cost-effective. Indeed, the ICER proved to be € 7,911.98/QALY from the NHS perspective and € 7,757.73/QALY from the perspective of society. Both values are far below the threshold value of cost-effective.
It emerged that vaccination yielded not only a reduction in cases of disease, but also savings in direct and indirect costs, which are chiefly related to the permanent and invalidating sequelae that afflict a considerable percentage of survivors from invasive meningococcal disease.

The role of communication in adolescents' acceptance of anti-meningococcal vaccination

Today, as a result of the widespread diffusion of the web and social networks, access to information has become far easier. However, the information available is sometimes of poor quality, incomplete or incorrect (fake news).
It is increasingly necessary to provide appropriate health information and education, in order to raise citizen's awareness and sense of responsibility with regard to their own health, and to make people understand the importance of vaccinations by fostering their ability to critically analyse the information available.
One of the factors underlying the public's adherence to a vaccination program is their perception of the risk of contracting a given disease and of suffering its consequences. The acceptability of anti-meningococcal vaccination, unlike other vaccinations, is high, on account of the high perceived risk of disease. Nevertheless, adherence is strongly conditioned by the diffusion of adequate information on this vaccination as a safe and effective preventive measure.
A low level of health literacy is associated with scant adoption of preventive behaviours, such as vaccination.
Vaccine hesitancy could, at least in part, be overcome by improving health education and literacy, especially if interventions are aimed not only parents and the adult population, but also at students, starting from the primary and secondary school levels. Moreover, improving the training of healthcare professionals may reduce hesitancy.
While the Internet and social networks are useful channels for the transmission of health information, owing to their widespread use among young people, it is important to make adolescents aware of the risks and unreliability of some websites.
Thus, in order to increase anti-meningococcal B vaccination in adolescents, suitable information/communication campaigns should be implemented. These should

target adolescents and their parents and also involve the use of social media.

Strategies for anti-meningococcal vaccination for adolescents

The 2017-2019 National Vaccine Prevention Plan (NVPP 2017-2019) makes no recommendation for anti-Men B vaccination in adolescents. However, it emphasizes the importance of evaluating its introduction for this age-group, as suggested by the indications provided by the scientific societies (Calendario per la Vita 2019) and as already adopted in three Italian regions (Sicily, Puglia and Campania).
Coverage rates among subjects aged 16 years (2002 cohort) and 18 years (2000 cohort) in Italy in 2018 displayed broad variability from one Region to another, with regard to both the anti-Men C and the anti-Men ACWY135 vaccines. In both cohorts, vaccination coverage rates in most Regions fell far short of the targets set. In order to increase the level of adherence to vaccination among adolescents, tailor-made strategies could be implemented.
In European countries, there are no recommendations regarding administration of the anti-Men B vaccine in adolescence.
In the United States, anti-Men B vaccination with either of the two vaccines available – MenB-FHbp (Trumenba®) or MenB-4C (Bexsero®) – is recommended for adolescents and young adults aged 16-23 years, provided that they have no increased risk conditions and that individual clinical judgment is favorable. MenB-FHbp was used in outbreaks that occurred in colleges in the states of Rhode Island (2015), Oregon (2015) and New Jersey (2016). In these instances, no further cases of meningococcal B disease occurred after the vaccination campaigns.

Organizational aspects of anti-meningococcal B vaccination for adolescents in Italy

In the fight against invasive disease due to type-B *Neisseria meningitidis*, it is advisable to actively provide vaccination free of charge for adolescents, as these subjects are a principal target of the disease.
When planning to introduce a new vaccination into the vaccination calendar, we must necessarily consider the organizational impact involved. As various vaccinations are already scheduled for adolescents, the addition of another could create a work overload for the Departments of Prevention of the Local Health Agencies (LHA). To overcome this problem, Trumenba® could be co-administered with other vaccines already scheduled in the vaccination calendar.
When a new vaccination strategy is implemented, problems of compliance may arise. In order to reach coverage targets, it is therefore necessary to set up innovative and integrated organizational systems that can promote ongoing constructive collaboration among public health workers, family pediatricians and general practitioners, in order to share objectives and strategies and to raise public awareness.
In order to optimize the entire organizational process, the possibility of performing vaccination in the school setting should be considered. Both national and international studies have shown that integrated strategies are the most effective in fighting vaccine-preventable diseases.

Ethical and social aspects of anti-meningococcal vaccination for adolescents

Today more than ever, no HTA can dispense with ethical and social evaluation. This is particularly important with regard to the evaluation of vaccinations. Indeed, unlike pharmaceutical drugs, vaccines are preventive tools that are administered to healthy persons, whose health must be safeguarded.
The data gathered in the exploratory phase of the "triangular model" of the ethical evaluation of anti-meningococcal vaccination indicate that invasive meningococcal diseases have a low incidence but a particularly severe course and high lethality. Moreover, these diseases frequently strike adolescents. The physical, neurological and psychological/psychiatric sequelae have a heavy impact on both patients and caregivers (with significant social consequences). The direct and indirect costs of each case are very high both for the NHS and for society.
The anti-meningococcal B vaccine Trumenba®, which is authorized for use in subjects aged ≥ 10 years, is safe, well-tolerated and immunogenic against invasive meningococcal B diseases.
As transpires from the evaluation phase, vaccinating adolescents against meningococcus B would safeguard the life and health of these vulnerable subjects, avoiding the occurrence of severe lifelong sequelae.
Other anti-meningococcal vaccinations are already actively offered in childhood and adolescence, and anti-meningococcal B vaccination for adolescents is already provided in some Italian Regions (Puglia, Sicily and Campania). In order to achieve equality of treatment and access to health care resources, this latter vaccination should be offered nationwide.
A fundamental prerequisite to the introduction of anti-meningococcal B vaccination for adolescents is that vaccination should stem from a conscious informed choice on the part of the parent or legal guardian of the adolescent, once adequate information has been provided in a proper manner. This informed choice must also involve the adolescents themselves.
Furthermore, in accordance with the law, careful post-marketing surveillance must be implemented in order to detect possible side-effects of the new vaccination.
With regard to ethical-normative evaluation, vaccinating adolescents against meningococcus B would protect hu-

man life and its integrity while guaranteeing the principles of liberty (capacity of human will), responsibility and mind-body integrity, thereby yielding benefits for society by reducing both the economic and social costs generated by the severe sequelae of invasive meningococcal B disease.

Chapter 12

Conclusions

S. BOCCALINI[1], P. BONANNI[1], D. PANATTO[2]
[1] Department of Health Sciences, University of Florence, Italy; [2] Department of Health Sciences, University of Genoa, Italy

As new vaccines have become available, it is of the utmost importance to evaluate new vaccination strategies in order to maximize health benefits. In this regard, health technology assessments (HTA) that include pharmaco-economic models have become an indispensable tool for decision-makers and a point of reference for healthcare professionals.

Our HTA of the scientific evidence currently available at the national and international levels revealed that vaccinating adolescents in Italy against meningococcus B should be recommended, as it would prevent many cases of invasive meningococcal disease. Although disease due to *N. meningitidis* B is not particularly frequent, it has a severe course, a high lethality rate and a high probability of causing invalidating sequelae until 60%. Moreover, each case generates considerable direct costs for the NHS and indirect costs for society as a whole. In addition, the heavy intangible costs related to the premature death of young subjects and the impaired quality of life of survivors and their caregivers must also be considered. In this context, the strategy of vaccinating an entire cohort of adolescents, when weighed against the heavy clinical and economic impact of invasive meningococcal disease, proves cost-effective.

The results of this HTA provide decision-makers with a precious tool in their evaluation of extending anti-meningococcal B vaccination to adolescents, in order to strengthen the global fight against invasive meningococcal disease and to ensure equality of treatment, access and allocation of healthcare resources nationwide.