Vaccinating Italian infants with a new multicomponent vaccine (Bexsero®) against meningococcal B disease: A cost-effectiveness analysis

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RESEARCH PAPER

Vaccinating Italian infants with a new multicomponent vaccine (Bexsero®) against meningococcal B disease: A cost-effectiveness analysis

Roberto Gasparini^a, Paolo Landab^c, Daniela Amicizia^a, Giancarlo Icardi^a, Walter Ricciardi^d, Chiara de Waure^d, Elena Tanfani^b, Paolo Bonanni^d, Carlo Lucioni^f, Angela Testi^b, and Donatella Panatto^a

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ABSTRACT

The European Medicines Agency has approved a multicomponent serogroup B meningococcal vaccine (Bexsero®) for use in individuals of 2 months of age and older. A cost-effectiveness analysis (CEA) from the societal and Italian National Health Service perspectives was performed in order to evaluate the impact of vaccinating Italian infants less than 1 year of age with Bexsero®, as opposed to non-vaccination. The analysis was carried out by means of Excel Version 2011 and the TreeAge Pro® software Version 2012. Two basal scenarios that differed in terms of disease incidence (official and estimated data to correct for underreporting) were considered. In the basal scenarios, we considered a primary vaccination cycle with 4 doses (at 2, 4, 6 and 12 months of age) and 1 booster dose at the age of 11 years, the societal perspective and no cost for death. Sensitivity analyses were carried out in which crucial variables were changed over probable ranges. In Italy, on the basis of official data on disease incidence, vaccination with Bexsero® could prevent 82.97 cases and 5.61 deaths in each birth cohort, while these figures proved to be three times higher on considering the estimated incidence. The results of the CEA showed that the Incremental Cost Effectiveness Ratio (ICER) per QALY was €109,762 in the basal scenario if official data on disease incidence are considered and €26,599 if estimated data are considered. The tornado diagram indicated that the most influential factor on ICER was the incidence of disease. The probability of sequelae, the cost of the vaccine and vaccine effectiveness also had an impact. Our results suggest that vaccinating infants in Italy with Bexsero® has the ability to significantly reduce meningococcal disease and, if the probable underestimation of disease incidence is considered, routine vaccination is advisable.

Introduction

Invasive disease caused by Neisseria meningitidis (Nm) is a serious public health problem and has a heavy economic impact.\(^6\) The incidence of invasive disease is highly variable according to geographical area.\(^7\) In Europe, since the introduction of massive meningococcal serogroup C vaccination, serogroup B has become the main causative agent of meningococcal disease, and is associated with high rates of mortality and disability; children under 1 year of age are mainly affected.\(^4,5\) In Italy, about 60% of typed cases of meningococcal invasive disease are now caused by Neisseria meningitidis B (NmB).\(^6–8\)

In the past, many attempts to produce an effective vaccine against NmB were made in various parts of the world. However, owing to the great similarity between NmB capsular polysaccharide and human neural components,\(^9\) preparation of an effective vaccine has proved very difficult.\(^4,5\) Consequently, research has focused on sub-capsular components, particularly on the antigens of the outer membrane vesicles (OMVs). Vaccines based on OMVs have been developed and have proved to be efficacious in Norway,\(^10\) Cuba,\(^11\) Brazil,\(^12\) Chile,\(^13\) and New Zealand.\(^14\) These experiences have shown that, because OMV vaccines are strictly strain-specific, they are useful in epidemics sustained by the same strain as that contained in the vaccine; this is logical, given the great variability of the outer membrane proteins.\(^15\)

A new multicomponent vaccine (Bexsero®), produced by means of reverse vaccinology, has now gained marketing authorisation in Europe,\(^16\) Canada,\(^17\) Australia\(^18\) and the US.\(^19\) We therefore felt that it would be useful to carry out a cost-effectiveness analysis (CEA) on the possible use of Bexsero® in the Italian epidemiological scenario.
Introducing vaccination with Bexsero® in Italian infants could prevent 82.97 cases and 5.61 deaths in each birth cohort, considering official data on disease incidence (0.23 per 100,000 subjects), and 248.91 cases and 16.83 deaths considering estimated data on disease incidence (0.69 per 100,000). The Incremental Cost Effectiveness Ratios (ICERs) per QALY were €109,762 for basal scenario 1 and €26,599 for basal scenario 5. The ICERs were €120,990 and €37,827 from the National Health Service (NHS) perspective, considering the official and estimated data on disease incidence, respectively.

With regard to the 8 scenarios developed, the 4 scenarios that considered estimated data on disease incidence proved cost-effective at a threshold value of €50,000 (Table 1).

The Incremental Cost-Effectiveness (ICE) ellipse scatterplots (Fig. 1) showed that, at a threshold value of €50,000 per QALY, the introduction of vaccination had 0.04% of probability of being cost-effective in scenario 1 and 97.08% of probability of being cost-effective in scenario 5. These findings were confirmed by the cost-effectiveness acceptability curves (Fig. 2).

One-way sensitivity analyses were developed on considering the influence of disease incidence on the ICER for the vaccination strategy (Fig. 3). Further one-way sensitivity analyses were developed on considering the influence of vaccine effectiveness on the ICER for the vaccination strategy (Fig. 4).

Figure 5 illustrates the results yielded by Tornado analyses on considering the ICER. The tornado diagrams indicate that the most influential factor is disease incidence. The probability of sequelae, the cost of the vaccine and vaccine effectiveness also have an impact.

Discussion

When a new vaccine, such as Bexsero®, becomes available, decision-makers must decide whether to introduce it into the National Immunization Program (NIP) or to wait until more evidence has been obtained (cost–effectiveness, etc.) or until conditions change (price, financial resources, supply, program strength, etc.). World Health Organization (WHO) guidelines on this issue suggest considering: public health priorities (disease burden; other inventions; efficacy, quality and safety of the vaccine; and economic and financial issues), the available of the vaccine on the market, and the availability of supply. In this regard, cost-effectiveness studies are helpful to decision-makers.

Our study showed that vaccinating infants in Italy with Bexsero® has the ability to significantly reduce meningococcal disease, and that the vaccine program could be cost-effective if the possible underestimation of disease incidence is considered. It is important to highlight that the mathematical and economic models applied to the transmission and prevention of infectious diseases necessarily adopt a reductionist approach.

Table 1. Results of CEA analysis broken down by different scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Perspective</th>
<th>Cost of death</th>
<th>Number of vaccine doses</th>
<th>Disease incidence</th>
<th>ICER per QALY (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Social</td>
<td>0</td>
<td>5</td>
<td>official data</td>
<td>109,762</td>
</tr>
<tr>
<td>2</td>
<td>Social</td>
<td>SHC</td>
<td>5</td>
<td>official data</td>
<td>109,191</td>
</tr>
<tr>
<td>3</td>
<td>Social</td>
<td>WTP</td>
<td>5</td>
<td>official data</td>
<td>104,657</td>
</tr>
<tr>
<td>4</td>
<td>NHS</td>
<td>0</td>
<td>5</td>
<td>official data</td>
<td>120,990</td>
</tr>
<tr>
<td>5</td>
<td>Social</td>
<td>estimated data</td>
<td>5</td>
<td>estimated data</td>
<td>26,599</td>
</tr>
<tr>
<td>6</td>
<td>Social</td>
<td>SHC</td>
<td>5</td>
<td>estimated data</td>
<td>26,029</td>
</tr>
<tr>
<td>7</td>
<td>Social</td>
<td>WTP</td>
<td>5</td>
<td>estimated data</td>
<td>21,494</td>
</tr>
<tr>
<td>8</td>
<td>NHS</td>
<td>0</td>
<td>5</td>
<td>estimated data</td>
<td>37,827</td>
</tr>
</tbody>
</table>

Figure 1. Incremental Cost-Effectiveness (ICE) ellipse scatterplots showing the distribution of values of incremental costs and incremental effectiveness resulting from the Monte Carlo simulation. Points below the threshold value indicate cost-effectiveness.
In the case of meningococcal disease, this is particularly true with regard to the possible underestimation of disease incidence and the evaluation of possible sequelae and their costs.

Regarding the underestimation of disease incidence, although the Italian system of surveillance of invasive bacterial diseases is well established and well structured, it does have limitations. For instance, in most cases when the patient is taken to hospital, antibiotic therapy has already been started. Moreover, as the Regional Centers do not always promptly dispatch isolated strains to the National Institute of Health (ISS) for typing, a certain proportion of isolated strains cannot be typed. Finally, many fulminant cases are not recognizable as such according to the evidence requested by the WHO.23 Indeed, 2 recent Italian studies demonstrated that in Italy the real incidence of bacterial invasive diseases is greatly underestimated.20,24 Azzari et al.20 reported that culture has so far been the most frequently used technique for meningococcal surveillance in Italy. However, bacterial culture leads to considerable underestimation of the number of cases. In that study, the authors compared the culture method with the molecular method and found that the sensitivity of culture was less than one third of that of the molecular method. Furthermore, culture displayed lower sensitivity than the molecular method when patients had been treated with antibiotics.20 Therefore, on the basis of the results of the study by Azzari et al.20 and in order to limit the possible underestimation of disease incidence, we implemented option 2 considering an annual estimated disease incidence of 0.69 per 100,000 (scenarios 5, 6, 7 and 8). This issue is very important as disease incidence is the major factor influencing ICER, as highlighted by our results and also by previous economic evaluations.25-27

Another key issue that affects ICER is the estimation of sequelae. Indeed, many of the studies in the medical literature have not considered all relevant sequelae. Moreover, as it is not rare for survivors to suffer multiple sequelae, it is very difficult to evaluate their frequency and combinations. Therefore, we tried to limit this factor of underestimation (probability of long-term sequelae) as far as possible. We believe that this

Figure 2. Cost-effectiveness acceptability curves (“vaccinate” and “do not vaccinate”). The figures show the probability of being cost-effective on varying the threshold value.

Figure 3. Impact of average annual incidence (per 100,000) of serogroup B invasive disease on the ICER (one-way sensitivity analysis). The probability of disease is per person.
approach is one of the strengths of our study. Indeed, cost-effectiveness studies often neglect the issue of underestimation and tend to be very conservative.\textsuperscript{25-29} Our study indicated that the parameter “probability of sequelae” was one of the parameters impacting ICER.

An HTA analysis\textsuperscript{30} performed in Italy estimated that introducing Bexsero\textsuperscript{®} into the infant immunization program would be cost-effective from the social perspective under specific assumptions, in particular on considering discount rates lower than 3% (ICER = €44,872 considering discount rate 1.5% for outcomes and 3% for costs; ICER = €26,806 considering discount rate 1.5% both for outcomes and costs). Furthermore, a recent Italian cost-effectiveness analysis found that routine infant immunization with Bexsero\textsuperscript{®} would not be cost-effective with an ICER of > 350,000 €/QALY.\textsuperscript{25} In this latter study, Tirani et al.\textsuperscript{25} considered a 3-dose vaccine immunization schedule at 2, 3 and 4 months followed by 1 catch-up dose between 12 and 23 months, a cost per vaccine dose of €67, vaccine efficacy of 75% and 3-y duration of protection; however, their analysis only considered the direct costs associated with meningococcal invasive disease (NHS perspective). Notably, it is difficult to compare the results of these study\textsuperscript{25,30} with our findings, owing to the different values of the parameters used.

So far, some economic analyses of the introduction of vaccination against NmB have been published in developed countries.\textsuperscript{26-29} Pouwels et al. concluded that: at the current low level of disease incidence, the introduction of routine infant vaccination (4-dose schedule) is unlikely to be cost-effective in the Netherlands\textsuperscript{28}; Tu et al. also reported the same conclusions with regard to the Canadian setting.\textsuperscript{26} Christensen et al. claimed that the new MenB vaccine could substantially reduce the disease in England and be cost-effective if competitively priced, particularly if the vaccine can prevent carriage as well as disease.\textsuperscript{27,29}

It is important to consider that some economic studies on vaccinations are performed only from the perspective of the third-party payer (usually the NHS).\textsuperscript{25,26} However, meningococcal disease generates very high indirect costs, such as, for instance, the loss of productivity of patients and their parents, and the need for special education for the subjects affected by severe complications (for example mental retardation, cognitive
problems, hearing loss and severe speech or communication problems, etc.). We therefore considered the societal perspective as the basal scenario, precisely in order to provide a complete picture of the general costs of the disease. Indeed, WHO recommends to evaluating the widest perspective.\textsuperscript{31}

The cost and effectiveness of the vaccine and the duration of protection may also play an important role in influencing ICER. With regard to vaccine effectiveness, we considered the results of clinical trials on vaccine efficacy and the results of the study by Vogel et al.\textsuperscript{32} on predicted strain coverage. Their study assessed the predicted strain coverage by using the Meningococcal Antigen Typing System (MATS) method, which a very recent study considered to be a conservative predictor of strain coverage by Bexsero\textsuperscript{®} in infants. Indeed, the authors demonstrated that, although MATS and hSBA yielded significantly associated results, hSBA more often also revealed protection against strains which did not prove positive on MATS.\textsuperscript{33} Strain coverage could therefore be higher.

With regard to the duration of protection, complete information is not yet available, as the vaccine is recent; the duration of protection can therefore only be hypothesized. We assumed a 10-y duration of full vaccine protection\textsuperscript{26} and subsequent waning of protection, whereby vaccination would only directly prevent one-quarter of cases over the lifetime of a vaccinated birth cohort.\textsuperscript{34} It must be noted that the majority of cases occur in the first years of life,\textsuperscript{4,5,20} followed by a secondary lower peak in adolescents and young adults.\textsuperscript{35} Given the epidemiological trend of meningococcal disease, an adolescent booster dose may be useful in order to prevent the cases that occur during this period of life. This strategy has also been advocated by other researchers.\textsuperscript{34} Our model therefore considered a booster dose at 11 y of age.

Like all pharmaco-economic analyses, the present study has limitations because the models are a simplification of the real world setting. Firstly, as only limited data are available on some parameters, we had to make certain assumptions, particularly with regard to the duration of protection conferred by the vaccine. For what concerns sequelae-related costs, we had to use data from studies conducted outside Italy, as no Italian study reports the data needed in order to carry out a pharmaco-economic analysis. We assumed that the life expectancy of subjects affected by disease who survive with sequelae was the same as that of unaffected subjects (except for the sequela “renal failure”). This is not completely true, though the differences seem to be small.\textsuperscript{29,36} The whole cohort (531,372 individuals) experienced a naturally occurring, age-related decline in quality of life.

We implemented a static model and did not consider herd immunity. However, it is probable that Bexsero\textsuperscript{®} would have an impact on carriage; this issue was investigated in a very recent study.\textsuperscript{37} Nevertheless, herd protection is more likely to occur if a booster dose is administered in adolescence, as carriage is particularly high in teenagers.\textsuperscript{28,38,39}

In conclusion, our results suggest that vaccinating infants in Italy with Bexsero\textsuperscript{®} has the ability to significantly reduce meningococcal disease and, if the probable underestimation of disease incidence is considered, routine vaccination is advisable.

Surveillance after vaccine implementation will be crucial in order to evaluate some parameters, as the true effectiveness of the vaccine and the duration of protection are not yet fully known. Furthermore, potential benefits due to cross-protection against non-B serogroups\textsuperscript{40-42} and the vaccine ability to induce herd protection will need to be assessed.

### Materials and methods

#### Design

A static cohort-simulation model was developed. In order to evaluate the vaccination strategy, a decisional-tree model was created by means of TreeAge Pro\textsuperscript{®} software (Microsoft Inc., Redmond, WA; 1988–2012 TreeAge Software, Inc.). Figure 6 shows a simplified version of the decisional tree; the complete decisional tree is reported in Electronic Supplementary Material A1. Our decisional tree defined two strategies: vaccinating or not vaccinating infants less than 1 y of age. A cohort of 531,372 individuals was used, corresponding to the number of children less than 1 y of age who were resident in Italy at the 2012 census.\textsuperscript{43}

The cost-effectiveness study was modeled on routine immunization with 4 doses (at 2, 4, 6 and 12 months of age) of Bexsero\textsuperscript{®} (primary cycle) and 1 booster dose at the age of 11 y (Table 2).

The “Vaccination” branch of the tree (Fig. 6) was divided into two branches, according to whether or not parents chose to have their children vaccinated (compliance node). Compliance influences the coverage rate. We considered a coverage rate of 90% as the base case. In the sensitivity analysis, a range of 50–100% was considered.

Vaccinated children may or may not be protected, depending on the predicted effectiveness of the vaccine (see sub-section

### Table 2. Scenarios evaluated.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Perspective</th>
<th>Cost of death</th>
<th>Number of vaccine doses</th>
<th>Disease incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Social</td>
<td>0</td>
<td>5</td>
<td>official data</td>
</tr>
<tr>
<td>2</td>
<td>Social</td>
<td>SHC</td>
<td>5</td>
<td>official data</td>
</tr>
<tr>
<td>3</td>
<td>Social</td>
<td>WTP</td>
<td>5</td>
<td>official data</td>
</tr>
<tr>
<td>4</td>
<td>NHS</td>
<td>0</td>
<td>5</td>
<td>official data</td>
</tr>
<tr>
<td>5*</td>
<td>Social</td>
<td>0</td>
<td>5</td>
<td>Estimated data</td>
</tr>
<tr>
<td>6</td>
<td>Social</td>
<td>SHC</td>
<td>5</td>
<td>Estimated data</td>
</tr>
<tr>
<td>7</td>
<td>Social</td>
<td>WTP</td>
<td>5</td>
<td>Estimated data</td>
</tr>
<tr>
<td>8</td>
<td>NHS</td>
<td>0</td>
<td>5</td>
<td>Estimated data</td>
</tr>
</tbody>
</table>

*Basal scenarios.
Vaccine efficacy, predicted effectiveness and duration of protection

Unprotected infants were considered to be susceptible; their probability of acquiring meningococcal disease was therefore deemed to be the same as that of unvaccinated subjects ("Not Vaccinated" branch).

We assumed that protection would wane over time (see subsection "Vaccine efficacy, predicted effectiveness and duration of protection"). Protection began after 2 doses of the vaccine.27,44

Unvaccinated infants ("Not Vaccinated" branch) were regarded as having the possibility to live their whole lives without contracting the disease. If, however, they contracted the disease, 2 outcomes were possible: death or survival. Survivors were then divided into 2 different categories: without or with sequelae. We assumed that any subjects who had had the disease would no longer be susceptible (as repeat invasive disease is rare and is associated with individuals with immune deficiencies and anatomical defects27).

We considered the acute-phase and lifetime consequences of invasive disease caused by NmB (direct and indirect costs). For each case, the burden of meningococcal disease was assessed on the basis of age-adjusted life expectancy on disease acquisition. We considered an average life expectancy of 82.03 y as reported by the Italian National Statistics Institute (ISTAT).43

We calculated the costs of the vaccination strategy, including the costs due to the treatment of adverse events caused by vaccination. On the basis of the difference between the costs of both strategies (vaccination and no vaccination), the potential benefits of the new vaccine were evaluated. The study was conducted from the perspectives of both the third-party payer [National Health Service (NHS)] and society. In the societal perspective, two options were considered: no cost for death and cost for death.

All costs were adjusted to the value of € in 2013,45 and were discounted as indicated by Italian guidelines (discount rate of 3% both for costs and utilities).46,47 In the sensitivity analysis, a range of 0 – 8% was considered.

Our model considered 2 options on the basis of 2 different probabilities of disease, as reported in the subsection "Disease incidence."7,20

Eight scenarios were evaluated (Table 2), the basal scenarios being scenarios 1 and 5. Scenario 1 considered the following parameters: social perspective, no cost of death, primary vaccination cycle with 4 doses (2, 4, 6 and 12 months of age) and booster dose at the age of 11 y and official data on disease incidence. Scenario 5 considered the following parameters: social perspective, no cost of death, primary vaccination cycle with 4 doses (2, 4, 6 and 12 months of age) and booster dose at the age of 11 y and estimated data on disease incidence.

Disease incidence

Disease-incidence estimates were based on the special Invasive Diseases Surveillance System (MIB) of the Italian Ministry of Health.48

In Italy, it is mandatory to notify the MIB of laboratory-confirmed cases of invasive disease caused by Nm. Cases are reported to the Local Health Unit (LHU), which communicates the data to the Regional and National Authorities. Concurrently, all hospitals should report any confirmed or suspected cases of bacterial invasive disease to the LHU. Cases are described on individual case-report forms, which include information on the clinical status, microbiological results and vaccination status.49

All labs that isolate a strain of Nm are requested to send the isolate to the National Reference labs, based at the National Institute of Health (ISS), for confirmation, serotyping and molecular typing. In the reports of the ISS, cases are subdivided into 7 age-classes: 0, 1–4, 5–9, 10–14, 15–24, 25–64, and >64 y and by Nm serogroup.7,8

Our model considered 2 options on the basis of 2 different probabilities of disease: option 1 considered the average
number of confirmed NmB cases that occurred annually in Italy from 2007 to 2012 (133 cases/y) (official data); option 2 considered a number of cases (399 cases/y) 3 times higher than in option 1, on the basis of 2 recent Italian studies which demonstrated that the real incidence of bacterial invasive disease in Italy is greatly underestimated (estimated data).

In option 1, we assumed an annual disease incidence of 0.23 per 100,000 subjects. In option 2, we assumed an annual disease incidence of 0.69 per 100,000. In the sensitivity analysis, a range of 0.1–0.7 per 100,000 was considered.

The annual distribution of cases broken down by age is reported in Supplementary Material (Electronic Supplementary Material A2).

### Disease consequences

Death, survival without sequelae, and survival with long-term sequelae were the 3 outcomes considered in our model.

The case-fatality rate, broken down by age, was applied according to the 2006 EU-IBIS report. In our model, we assumed a global probability of death of 6.73%. In the sensitivity analysis, a range of 0–10% was considered.

While it is fairly easy to find papers on the sequelae from invasive bacterial disease, it is difficult to obtain accurate measurements of the long-term consequences of serogroup B disease. We assumed that 40.2% of survivors would have at least 1 sequela, as reported by a recent study. In the sensitivity analysis, a variation of 20% was considered. The single sequelae considered in our study and their frequency, are reported in Table 3. Additionally, a personal communication by Magnus Gottfredsson allowed us to evaluate the incidence of some sequelae in the cohort study performed by this author. Although meningococcal disease can cause multiple sequelae, in our study, as in other health economics studies, we assumed that each survivor would have only 1 sequela. Other sequelae, such as brain abscess, cranial nerve palsy, obstructive hydrocephalus, ataxia, chronic organ damage, etc, as defined by Woods and by Brandtzaeg were not considered.

### Table 3. Probability of sequelae.

<table>
<thead>
<tr>
<th>Sequele</th>
<th>Base case</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation with substantial disability</td>
<td>0.01</td>
<td>Uniform (0.008; 0.012)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.068</td>
<td>Uniform (0.0544; 0.0816)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.025</td>
<td>Uniform (0.02; 0.03)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.05</td>
<td>Uniform (0.04; 0.06)</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>0.019</td>
<td>Uniform (0.0152; 0.0228)</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.004</td>
<td>Uniform (0.0032; 0.0048)</td>
</tr>
<tr>
<td>Epilepsy or Seizure</td>
<td>0.02</td>
<td>Uniform (0.016; 0.024)</td>
</tr>
<tr>
<td>Severe Neurological disability</td>
<td>0.021</td>
<td>Uniform (0.0168; 0.0252)</td>
</tr>
<tr>
<td>Mental retardation (cognitive problems)</td>
<td>0.254</td>
<td>Uniform (0.196; 0.312)</td>
</tr>
<tr>
<td>Hearing loss requiring cochlear implantation</td>
<td>0.02</td>
<td>Uniform (0.016–0.024)</td>
</tr>
<tr>
<td>Moderate/severe unilateral hearing loss</td>
<td>0.05</td>
<td>Uniform (0.04; 0.06)</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>0.015</td>
<td>Uniform (0.012; 0.018)</td>
</tr>
<tr>
<td>Scars</td>
<td>0.03</td>
<td>Uniform (0.024; 0.036)</td>
</tr>
<tr>
<td>Severe speech or communication problems</td>
<td>0.037</td>
<td>Uniform (0.0296; 0.0444)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.019</td>
<td>Uniform (0.0152; 0.0228)</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>0.10</td>
<td>Uniform (0.08; 0.12)</td>
</tr>
</tbody>
</table>

*According to [56]; † According to [55]; ‡ According to [28]; ‡‡ According to [53]; ‡‡‡ According to [57]; ‡§ According to [54].

### Table 4. Health utilities of single sequelae.

<table>
<thead>
<tr>
<th>Sequele</th>
<th>Base case</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation with substantial disability</td>
<td>0.613</td>
<td>Uniform (0.490; 0.7356)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.687</td>
<td>Uniform (0.5496; 0.8244)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.690</td>
<td>Uniform (0.552; 0.828)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.729</td>
<td>Uniform (0.583; 0.875)</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>0.830</td>
<td>Uniform (0.664; 0.996)</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.260</td>
<td>Uniform (0.208; 0.312)</td>
</tr>
<tr>
<td>Epilepsy or Seizure</td>
<td>0.830</td>
<td>Uniform (0.664; 0.996)</td>
</tr>
<tr>
<td>Severe Neurological disability</td>
<td>0.060</td>
<td>Uniform (0.048; 0.072)</td>
</tr>
<tr>
<td>Mental retardation (cognitive problems)</td>
<td>0.541</td>
<td>Uniform (0.4328; 0.6492)</td>
</tr>
<tr>
<td>Hearing loss requiring cochlear implantation</td>
<td>0.810</td>
<td>Uniform (0.648; 0.972)</td>
</tr>
<tr>
<td>Moderate/severe bilateral hearing loss</td>
<td>0.910</td>
<td>Uniform (0.728; 1)</td>
</tr>
<tr>
<td>Moderate unilateral hearing loss</td>
<td>0.910</td>
<td>Uniform (0.728; 1)</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>0.900</td>
<td>Uniform (0.720; 1)</td>
</tr>
<tr>
<td>Scars</td>
<td>1.000</td>
<td>Uniform (0.8; 1)</td>
</tr>
<tr>
<td>Severe speech or communication problems</td>
<td>0.390</td>
<td>Uniform (0.312; 0.468)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.820</td>
<td>Uniform (0.656; 0.984)</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>0.814</td>
<td>Uniform (0.6512; 0.9768)</td>
</tr>
</tbody>
</table>

*According to [53]; † According to [62]; ‡ According to [63]; ‡‡ According to [64]; ‡‡‡ According to [65]; ‡‡‡‡ According to [60]; ‡‡‡‡‡ According to [66]; ‡‡‡‡‡‡ According to [67]; ‡‡‡‡‡‡‡ According to [68]; ‡‡‡‡‡‡‡‡ According to [69]; ‡‡‡‡‡‡‡‡‡ According to [61].
Quality of life

Our model also considered the impairment of the quality of life (QoL) of survivors with long-term sequelae. This assessment was necessary in order to evaluate the permanent consequences for health status. Furthermore, because few data are available on the QoL of survivors of meningococcal disease, we sometimes used QoL evaluations for sequelae or pathologies similar to those caused by meningitis; for instance, for chronic migraine, the results reported by Xu et al. were used.61

Table 4 shows the health utilities broken down by sequelae.53,60-69

Vaccine efficacy, predicted effectiveness and duration of protection

In clinical trials conducted with rMenB+OMV (Bexsero®), vaccine efficacy has been studied by means of the serum bactericidal antibody assay by human complement (hSBA).44,70-72

In studies involving infants, adolescents and young adults, the 4CMenB vaccine has been shown to induce robust bactericidal antibodies against strains expressing the vaccine antigens.73 Therefore, on the basis of the results of clinical trials,74,75 and considering another economic evaluation,29 we assumed that vaccinated subjects would have 95% protection against disease. Furthermore, a study estimating the strain coverage of Bexsero® predicted strain coverage in Italy to be 87%.32 Therefore, we used this estimate in our model. In the sensitivity analysis, a variation of 20% was considered both for vaccine efficacy and for predicted strain coverage.

Data on the duration of protection conferred by Bexsero® are incomplete. Considering the basic assumptions of immunology,76 the results obtained in clinical trials of Bexsero® and an economic evaluation conducted in Canada,26 we assumed 10-y duration of full vaccine protection and subsequent waning of protection, whereby vaccination would only directly prevent one-quarter of cases over the lifetime of a vaccinated birth cohort.34 Furthermore, clinical trials have demonstrated the ability of Bexsero® to induce immunological memory.35,74,77 If immunological memory is induced by the vaccine, the natural MenB infection could act as booster and help to maintain long-term protection.

Given the epidemiological trend of meningococcal disease, an adolescent booster dose may be useful in order to prevent the cases that occur during this period of life. Our model therefore considered a booster dose at 11 y of age.

Costs associated with the disease

The study was conducted from the perspective of both the Italian NHS and society. All costs were measured in € at January 2013 values, with previous years being adjusted to January 2013 levels.45 To determine the total cost of meningococcal

Table 5. Acute phase of disease: costs (no discount rate) were measured in € at January 2013 values and were referred to 1 case.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical care: cost of hospitalization per case</td>
<td>7,900</td>
<td>Gamma (25; 316)</td>
</tr>
<tr>
<td>Public Health Response</td>
<td>3,223</td>
<td>Gamma (25; 128)</td>
</tr>
<tr>
<td>Lost productivity of parent or relatives</td>
<td>870</td>
<td>Gamma (25; 35)</td>
</tr>
<tr>
<td>Lost productivity of patient</td>
<td>1,426</td>
<td>Gamma (25; 57)</td>
</tr>
</tbody>
</table>

*According to [78]; †Assumed based upon [53]; ‡According to [8,79].

Table 6. Meningococcal sequelae. Costs (no discount rate) were measured in € at January 2013 values.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Base Case</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual direct costs (1 case)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation with substantial disability</td>
<td>7,339</td>
<td>Gamma (25; 293.6)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1,146</td>
<td>Gamma (25; 45.8)</td>
</tr>
<tr>
<td>Arthritis (1-y cost)</td>
<td>1,184</td>
<td>Gamma (25; 47.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>3,192</td>
<td>Gamma (25; 127.7)</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>7,682</td>
<td>Gamma (25; 307.3)</td>
</tr>
<tr>
<td>Blindness</td>
<td>4,076</td>
<td>Gamma (25; 163.0)</td>
</tr>
<tr>
<td>Epilepsy or seizure</td>
<td>2,272</td>
<td>Gamma (25; 90.9)</td>
</tr>
<tr>
<td>Severe neurological disability</td>
<td>94,880</td>
<td>Gamma (25; 3795.0)</td>
</tr>
<tr>
<td>Mental retardation (cognitive problems)</td>
<td>7,307</td>
<td>Gamma (25; 300.3)</td>
</tr>
<tr>
<td>Hearing loss requiring cochlear implantation</td>
<td>6,327</td>
<td>Gamma (25; 253.1)</td>
</tr>
<tr>
<td>Moderate/severe bilateral/unilateral hearing loss</td>
<td>3,163</td>
<td>Gamma (25; 126.5)</td>
</tr>
<tr>
<td>Skin necrosis</td>
<td>1,066</td>
<td>Gamma (25; 42.6)</td>
</tr>
<tr>
<td>Scars</td>
<td>533</td>
<td>Gamma (25; 21.3)</td>
</tr>
<tr>
<td>Severe speech or communication problems</td>
<td>9,796</td>
<td>Gamma (25; 391.8)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>56,126</td>
<td>Gamma (25; 2245.0)</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>892</td>
<td>Gamma (25; 35.7)</td>
</tr>
</tbody>
</table>

| Annual indirect costs (1 case)                |           |              |
| Special case education                        | 14,566    | Gamma (25; 582.2) |
| Lost productivity of parent                  | 24,500    | Gamma (25; 980.0) |
| Lost productivity of patient                 | 24,500    | Gamma (25; 980.0) |

*According to [53]; †According to [80]; ‡According to [81]; ††According to [82]; †‡According to [83]; †§According to [84]; †¶According to [85,86]; †‖According to [87]; †¶¶According to [30]; †¶¶¶According to [88]; †¶¶¶¶According to [89]; †¶¶¶¶¶According to [90,91,92]; †¶¶¶¶¶¶According to [90,92,93].

Applied to: mental retardation (cognitive problems), severe neurological disability, severe speech or communication problems, epilepsy, blindness, motor deficit, severe amputations and hearing loss.

Applied to: severe amputations, anxiety, depression, motor deficit, blindness, epilepsy or seizure, severe neurological disability, mental retardation (cognitive problems), Hearing loss requiring cochlear implantation, Moderate/severe bilateral/unilateral hearing loss, renal failure, severe speech or communication problems.
The direct costs related to the acute phase of meningococcal disease were applied to all cases and are shown in Table 5. The direct costs related to the acute phase of meningococcal disease were those of medical care, i.e. hospitalization and public health response. In evaluating the costs of hospitalization, we used the cost of the Diagnosis Related Group (DRG) associated to meningococcal disease. \cite{96} We calculated the cost of the public health response to a case of meningococcal disease by considering the average number of contacts that required chemoprophylaxis treatment, the average cost of a course of chemoprophylaxis treatment, and the average working time devoted by public health departments to a single reported case of meningococcal disease. \cite{53}

The indirect costs were those associated with lost productivity of the patient and lost productivity of the parents or relatives. With regard to costs of lost productivity of the patient, we only considered the cases which occurred during working age (18–64 y). We considered an average cost of €16.2 per working hour \cite{79} for 8 hours/day (€129.6) and an average length of stay in hospital of 11 d (€1,426). \cite{8} The costs of lost productivity of parents or relatives were applied to all cases. \cite{8,79}

### Costs related to meningococcal sequelae

Survivors with sequelae constituted a subset of nonfatal cases; these incurred sequela-specific direct medical costs. For some complications, in addition to direct medical costs, other indirect costs (special education, lost productivity of parents and lost productivity of patients) were also considered. The annual direct and indirect costs of meningococcal sequelae are shown in Table 5.

#### Table 7. The social costs (no discount rate) of death were measured in € at January 2013 values.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Willingness to pay (WTP)*</th>
<th>Distribution</th>
<th>Human Standard Capital (HSC)*</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>1,513,985</td>
<td>Gamma (25; 60559.4)</td>
<td>81,434</td>
<td>Gamma (25; 3257.1)</td>
</tr>
<tr>
<td>1–4</td>
<td>1,594,678</td>
<td>Gamma (25; 63787.2)</td>
<td>101,143</td>
<td>Gamma (25; 4045.7)</td>
</tr>
<tr>
<td>5–9</td>
<td>1,743,967</td>
<td>Gamma (25; 69738.5)</td>
<td>148,817</td>
<td>Gamma (25; 5941.9)</td>
</tr>
<tr>
<td>10–14</td>
<td>1,924,832</td>
<td>Gamma (25; 76993.1)</td>
<td>228,391</td>
<td>Gamma (25; 9135.6)</td>
</tr>
<tr>
<td>15–24</td>
<td>2,122,126</td>
<td>Gamma (25; 84887.8)</td>
<td>368,015</td>
<td>Gamma (25; 14720.6)</td>
</tr>
<tr>
<td>25–64</td>
<td>1,260,459</td>
<td>Gamma (25; 50418.1)</td>
<td>336,674</td>
<td>Gamma (25; 13466.9)</td>
</tr>
<tr>
<td>&gt;64</td>
<td>96,178</td>
<td>Gamma (25; 3847.2)</td>
<td>40,377</td>
<td>Gamma (25; 1615.1)</td>
</tr>
</tbody>
</table>

*According to [94].

The social costs (no discount rate) of death were measured in € at January 2013 values.

#### Table 8. Costs associated with vaccination (€).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Case</th>
<th>Min</th>
<th>Max</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of the primary cycle of vaccination (4 doses)*</td>
<td>200.00</td>
<td>100.00</td>
<td>300.00</td>
<td>Fixed</td>
</tr>
<tr>
<td>Cost of vaccine administration per dose*</td>
<td>5.80</td>
<td>–</td>
<td>–</td>
<td>Fixed</td>
</tr>
<tr>
<td>Cost of hospitalization for 1 anaphylactic reaction*</td>
<td>1,175</td>
<td>–</td>
<td>–</td>
<td>Fixed</td>
</tr>
<tr>
<td>Cost of 1 mild or moderate adverse event*</td>
<td>3.40</td>
<td>–</td>
<td>–</td>
<td>Fixed</td>
</tr>
</tbody>
</table>

*According to [96]; **According to [97]; ***According to [78]; ****According to [98].

The direct costs of the sequela "amputation with substantial disability" included both the costs of acute treatment (e.g. cost of the amputation procedure) and lifetime medical costs (e.g., maintenance of prosthetics, rehabilitation etc). \cite{53} The direct costs of the sequela "hearing loss requiring cochlear implantation" included not only the costs of the cochlear implant, but also that of its implantation and lifetime maintenance. \cite{53} With regard to severe neurological disability, our estimate of the direct costs also considered the costs of long-term institutional care, \cite{87} while for the sequela "arthritis," we only considered the medical costs for 1 y, as this complication is usually resolved by short-term therapy. \cite{81,95} Finally, our estimate of the costs of the sequela "renal failure" took into account the permanent organ damage that can lead to kidney transplantation or dialysis, assuming a life expectancy of 5 y. \cite{88}

With regard to indirect costs, we considered the costs of special education \cite{87} for the following sequelae: motor deficits, blindness, epilepsy or seizure, mental retardation (cognitive problems), hearing loss and severe speech or communication problems. These costs were calculated by determining the age-specific additional costs per child per year in comparison with regular education, and were applied to subjects younger than 17 y of age, as education is compulsory up to that age in Italy. Moreover, some severe sequelae require a parent to give up work in order to assist her child. We therefore evaluated the additional cost of lost productivity of a parent for the following severe complications: mental retardation (cognitive problems), severe neurological disability, severe speech or communication problems, epilepsy, blindness, motor deficit, severe amputations and hearing loss. This additional cost was considered up to the age of 17 y. In our calculations, we
supposed that it would be the mother who gave up her job. The calculation of lost productivity of the mother consid-
ered the following parameters: the mean age at which women in Italy have their first child, the mean number of
potential working years lost by these women, the percentage
of women employed and their per capita income.90–92

To evaluate the lost productivity of patients, we estimated
the residual earning capacity of patients affected by each
sequela; this calculation was based on the disability percentages
defined by Italian law93 and considered the year of disease
onset, income per capita, residual working years and unem-
ployment rate in Italy.90,92 We evaluated the additional cost of
lost productivity of a patient for the following severe complica-
tions: severe amputations, anxiety, depression, motor deficit,
blindness, epilepsy or seizure, severe neurological disability,
mental retardation (cognitive problems), hearing loss requiring
cochlear implantation, moderate/severe bilateral/unilateral
hearing loss, renal failure, severe speech or communication
problems.

Social cost of death (indirect cost)

To evaluate the social cost of death, 2 approaches are usually
used: the “willingness to pay” and the “human standard capital”
methods. In our model, we calculated the social cost of death by
means of each method separately.94 The cost was computed on
considering the age of death. These values are reported in
Table 7.

Costs associated with vaccination

The costs associated with vaccination are reported in
Table 8.78,96–98

Costs of vaccine

We considered a cost of €200,00 for the primary cycle of vacci-
nation (4 doses) from the NHS and societal perspectives.96 The
cost of the booster dose at 11 y was set at €36.12 (discount rate
of 3% applied). Private sector prices were not considered. In
the sensitivity analysis, a range of costs for the primary cycle of
vaccination of €100–300 was considered.

A cost of €5.80 was attributed to the administration of each
dose of vaccine.97

Costs of vaccine-associated adverse events

Our assessment of the costs determined by mild and moderate
adverse events after vaccine administration was based on the
study by Gossger et al.99 These authors estimated a total fre-
quency of local and systemic adverse events of 30%, 26%, 28%
and 28% after the first, second, third and fourth doses, respec-
tively.99 We considered a frequency of local and systemic
adverse events of 28% for the booster dose. As fever is the most
frequent adverse event, our evaluation considered the cost of
the most widely used antipyretic in Italy (1 box of paracetam-
ol)98 as the cost of 1 mild or moderate adverse event. In the
case of moderate adverse events, we did not consider the cost
of consultation of the pediatrician or general practitioner, as

house calls and outpatient visits are free of charge in Italy.
Regarding severe adverse events, we considered the frequency
(1 case per 719,790 doses) and costs of anaphylactic reactions
on the basis of evaluations by Christensen et al. and
AGENAS.27,78

Economic analysis

In order to evaluate the effect of introducing the meningococcal
B vaccine into the Italian immunization program, we con-
ducted a cost–effectiveness analysis (CEA). The analysis was
carried out by means of Excel Version 2011 and the TreeAge
Pro® software Version 2012 (Build 12.2.3.0).

The analysis is expressed in terms of Incremental Cost Effec-
tiveness Ratio (ICER), where the denominator is the health gain
in quality-adjusted life years (QALYs) and the numerator is the
difference between the costs of the vaccination strategy and
those of a no-vaccination strategy.

Sensitivity analysis

One-way sensitivity analyses were performed in order to evalu-
ate how the uncertainty of disease incidence and vaccine effec-
tiveness can influence the ICER.

Furthermore, to obtain the best set of parameters for the
Monte Carlo simulation, a multivariate sensitivity analysis was
performed. In this analysis, we varied: disease incidence, the
probability of sequelae, the probability of death, vaccine effec-
tiveness, the probability of coverage, the cost of the vaccine,
and the cost and QALY discount rate.

The sensitivity analysis was performed for the 2 basal sce-
narios (Table 2, scenarios 1 and 5).

Monte Carlo simulation

We developed a second-order Monte Carlo simulation, which
is a 2-dimensional simulation used to propagate variability and
uncertainty separately. This procedure consists of multiple real-
izations of model parameters and iterations of input variables.
The outcome is a collection of cumulative distribution func-
tions that simultaneously display the uncertainty and variability
in the results.100 This simulation was developed by using 10,000
samples.

We then performed a CEA in which incremental costs and
health outcomes were computed and plotted on an X-Y scatter
plot. Furthermore, we drew cost-effectiveness acceptability
curves, whereby “threshold value” was plotted against the pro-
portion of runs (samples) that resulted in incremental cost-
effectiveness ratios below this threshold value.101

The Monte Carlo simulation was performed for the 2 basal
scenarios (Table 2, scenarios 1 and 5).

Tables 4, 5, 6, 7 and 8 report the range of values used in the
sensitivity analysis and Monte Carlo simulation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.
Acknowledgments
The authors thank Dr Bernard Patrick for his linguistic review of the manuscript.

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Author contributions
RG designed, coordinated and supervised the research. PL, ET, AT developed the economic model and carried out the economic analysis. RG, DP, DA, GDW, WR, GI, PB collected and analyzed epidemiological data. RG, DP, DA, GI, Gir collected and analyzed economic parameters. RG, DP, DA, PB, WR, GI carried out the epidemiological data-quality control. AT, PL, carried out the economic data-quality control. RG, DA, DP wrote the manuscript. All authors revised the manuscript and contributed to improving the paper; all authors read and approved the final manuscript.

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