Global incidence of serogroup B invasive meningococcal disease: a systematic review

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Use of recently licensed vaccines against *Neisseria meningitidis* serogroup B (NmB) will depend partly on disease burden estimates. We systematically reviewed NmB incidence and mortality worldwide between January, 2000, and March, 2015, incorporating data from 37 articles and 12 websites. Most countries had a yearly invasive NmB incidence of less than 2 per 100 000 people. Within these relatively low incidence rates (compared with common causes of invasive bacterial diseases), substantial variation was detected between countries, with a notably higher incidence in Australia, Europe, North America, and South America. China and India had reports only of sporadic cases, and except for South Africa, sub-Saharan Africa showed a near absence of disease. In countries with consistently collected data, NmB incidence has tended to decrease, even as the proportion of invasive meningococcal disease cases caused by serogroup B has increased. With few exceptions, case-fatality ratios were fairly consistent, ranging between 3% and 10%. In high-income countries, incidence rates of NmB were relatively low compared with other vaccine-preventable diseases and might be decreasing. High case-fatality ratios, substantial disease-related morbidity, and the threat of outbreaks could nevertheless make NmB an attractive target for preventive and reactive immunisation programmes. The low availability of data from low-income and middle-income countries suggests the need for improved surveillance before vaccination strategies are designed.

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Introduction

Six of 12 *Neisseria meningitidis* serogroups described (A, B, C, W, X, and Y) cause nearly all cases of invasive meningococcal disease.[1] Licensed vaccines have existed for many years for serogroups A, C, Y, and W, and since 1999 as protein–polysaccharide conjugate vaccines. The first meningococcal conjugate vaccine to be introduced was targeted to the serogroup C in the UK in 1999.[2] After this, quadrivalent (serogroups A, C, Y, and W) and monovalent (serogroup A) conjugate vaccines were licensed in 2000 and 2010, respectively. Monovalent serogroup A conjugate vaccines were licensed specifically for use in the African meningitis belt.[2]

Although *N meningitidis* belonging to serogroup B (NmB) is an important contributor to invasive meningococcal disease, the development of protein–polysaccharide conjugate vaccines against NmB has been impeded by low immunogenicity and potential crossreactivity between the serogroup B polysaccharide capsule and human tissue antigens.[3] To overcome this difficulty, vaccines were developed that used non-capsular antigenic components of serogroup B, such as outer membrane vesicles (OMV).[4] Vaccines based on OMV were used with success to control outbreaks caused by a specific strain. However, they did not offer broad protection against heterologous strains with different porin A (PorA) subtypes, particularly in young children and infants, which restricts the ability of these vaccines to protect against local clonal outbreaks. In January, 2013, Novartis received European Commission approval and subsequently licensure in Canada and Australia, for a multicomponent meningococcal B vaccine (4CMenB) marketed under the brand name Bexsero that contains four main immunogenic components: factor H binding protein, neisserial adhesion A, and neisserial heparin binding protein combined with the New Zealand NZ98/254 strain OMV (NZ OMV) expressing PorA serosubtype P1.4.[5,6]

In the USA, two NmB outbreaks took place in 2013 on the campuses of Princeton University (Princeton, NJ, USA) and the University of California, Santa Barbara (Santa Barbara, CA, USA).[7] Because no NmB vaccine was licensed in the USA at the time, the USA Food and Drug Administration (FDA) provided an Investigational New Drug designation that allowed for the use of nearly 30 000 doses of 4CMenB vaccine.[8] The FDA subsequently provided full licensure in 2015. In October, 2014, the FDA approved another protein-based serogroup B vaccine—marketed by Pfizer under the brand name Trumenba—containing subfamily A and B factor H binding protein variants.[9,10] Starting in February, 2015, Trumenba was used to control campus outbreaks at Providence College (Providence, RI, USA) and the University of Oregon (Eugene, OR, USA).[11,12]

A key question is how and where to use these new vaccines. The two major options are outbreak control and routine use in national immunisation programme schedules. The exact answer will depend partly on the incidence of disease, mortality, and sequelae; age and geographical distribution; coverage of the isolates by these vaccines; ability of the vaccine to provide cross-protection against other serogroups; and incompletely understood issues such as immunity duration and vaccine efficacy against carriage acquisition (and the consequent ability to provide indirect protection). A systematic review in 2010 described the distribution and heterogeneity of hypervirulent serogroup B meningococci causing invasive meningococcal disease.[13] Although serogroup B dominance in specific countries and the clonal complex distribution of NmB were described in that report, disease incidence was not quantified.[13] Our Review aims to describe the

worldwide NmB disease incidence and case-fatality ratio (CFR).

Methods

We undertook a systematic literature review according to PRISMA guidelines[14] to identify NmB invasive disease incidence and CFR by country. We searched PubMed, Cochrane, MEDLINE, the Global Health Library, and WHO regional databases. We searched for articles in English, French, Portuguese, and Spanish published from Jan, 1, 2000, to March 1, 2015. We did not search before the year 2000 because our goal was to provide data on NmB data that would inform decision-making rather than providing a historical perspective. In this context, several changes have taken place during the past few decades that could bias disease incidence and CFR estimates from earlier periods, including use of other *N meningitidis* vaccines, changes in antibiotic use, improvements in health-care access and clinical management, and better testing and diagnostic techniques.

See Online for appendix

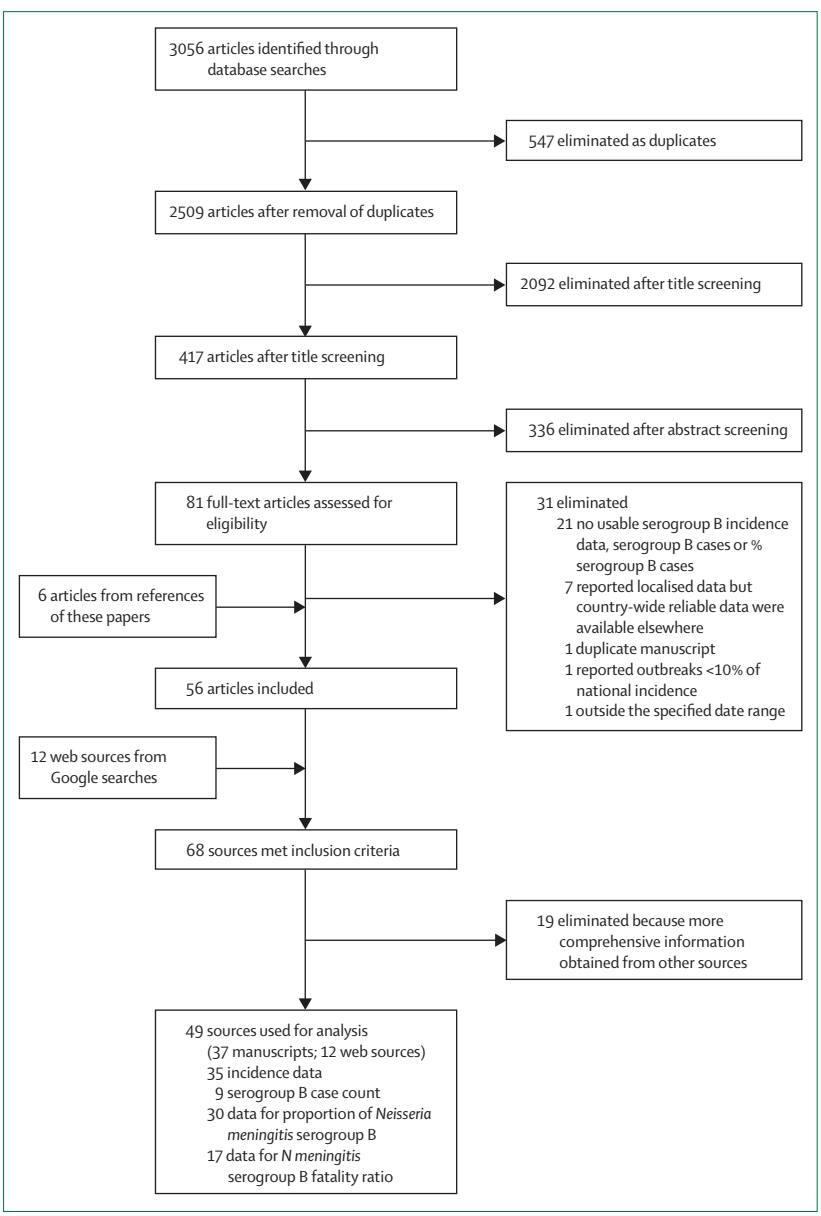

Figure 1: **Article selection**

Articles in languages other than English were translated with Google Translate. We developed search strategies using the Medical Subject Headings thesaurus and other keywords to identify articles that described NmB disease incidence. Search strategies were modified and adapted according to each database (appendix p 1). Additionally, we used Google to search for country-specific networks that reported meningococcal cases. We used data available on the internet and did not contact individuals to obtain additional data. After deleting duplicates, we systematically screened for the title, abstract, and the full-text according to our inclusion and exclusion criteria. Because of funding limitations, one investigator (SSr) did all title, abstract screening, and data collection. A second investigator (BDG) validated all steps of the search and screening process, including replication of the search on PubMed.

Inclusion and exclusion criteria

We included studies reporting observational (including routine surveillance reports), cross-sectional, retrospective, and prospective data for incidence rates of NmB or case counts. Systematic reviews, meta-analyses, and reviews on serogroup B incidence or prevalence were assessed for appropriate references, with only primary data sources used for data abstraction. Outbreak reports for serogroup B invasive meningococcal disease were included in the national estimates only if the outbreak persisted for more than a year and if the number of outbreak cases represented more than 10% of the total serogroup B cases reported for that year. This rule was implemented because we did not want to include the many reports that identified a small number of NmB cases, which did not contribute substantially to knowledge of overall disease burden. We included all appropriate studies irrespective of age or sex of study participants, geographical location of the study, or case definition used for the study.

We excluded articles not containing information on serogroup B meningitis, describing localised data (<10% of national incidence), vaccine efficacy studies, immunological studies, and studies on non-specific bacterial meningitis. If an article that met inclusion criteria provided subnational data, which was a complete subset of national data from another source, only the latter data were used for analysis (appendix).

Data abstraction and quality assessment

We abstracted incidence rates (number of cases per 100 000 per year) from relevant data sources. If incidence

rates were unavailable, we calculated the incidence rates using case counts and population of the region (according to statistics reported by World Bank).[15] If incidence data or case counts were unavailable, we abstracted data on the proportion of all invasive meningococcal disease caused by serogroup B. We reported CFRs if available.

Quality assessment scoring instruments do not exist for infectious disease incidence studies. To inform the reader about data quality deriving from different sources, we developed a method based on the notion that more accurate and representative incidence data generally result from studies that include more surveillance years, cover wide geographical areas, include all age groups, and use defined laboratory methods (appendix). Our method provided a maximum quality score of 15 for each individual article (appendix pp 2–5).

Data grouping and statistical analysis

In accordance with WHO recommendations on use of meningococcal vaccines,[2] we categorised NmB incidence as high (>10 cases per 100 000 per year), intermediate (2–10 cases per 100 000 per year), or low (<2 cases per 100 000 per year). Because almost all countries were assigned to the low category, we further subdivided this group into low (1–<2 cases per 100 000 per year), very low (0·01–0·99 cases per 100 000 per year), and negligible (<0·01 per 100 000 per year). We categorised separately countries that did not report NmB invasive disease, but accounted for more than 20% of all invasive meningococcal disease isolates obtained in the past.

Results

Search

Our search identified 3056 abstracts from PubMed, Global Health Library, and Cochrane (figure 1). After removal of 2975 manuscripts through title or abstract screening and elimination of duplicates, we selected 81 articles for full text assessment. Of these, 31 did not fulfil inclusion criteria and an additional six articles were identified through a review of references of included manuscripts.[16–21] The Google search for country-wide meningitis reporting networks led to inclusion of data from 12 networks including the USA,[22] Canada,[23] Japan,[24] Australia,[25] New Zealand,[26] the European Union,[27–30] South Africa (including two reports[31,32]), and Singapore.[33] Of the 68 sources that met inclusion criteria, 19 sources[34–52] replicated data that had been provided more comprehensively in another article (appendix) yielding 49 sources that were used for analysis including 37 manuscripts[16–21,53–83] and 12 website sources[22–33] (appendix).

Of the 49 data sources (37 articles and 12 web sources), 35 had information on NmB incidence rates,[17,20,21,24–26,31,32,53–62,64,65,67,68,70–73,75–83] nine had data on case counts, which were used to calculate incidence rates using population data,[22,23,27–30,33,63,66] 30 articles had data on proportion of invasive meningococcal disease caused by NmB,[16–20,22,53,55–58,60–66,68–74,76,79–83] of which five had no incidence data or case counts,[16,18,19,69,74] and 17 had data on CFR.[22,53,55–57,59–62,65,67,75,77,79–81,83]

We identified data from seven world regions including eight from North America, five from Latin America, 14 from Europe, five from Asia, nine from north Africa and the Middle East, two from Oceania, and four from sub-Saharan Africa (only South Africa; tables 1, 2). On the basis of incidence rates, all countries except Ireland

	Years	Total cases	Mean annual serogroup B incidence per 100 000 population	Range
Africa				
South Africa[21,31,32,64]	2000–10	810	0·18	0·13–0·24
Asia				
Singapore[33]	2002–07; 2009–13	39	0·08	0·0–0·18
Taiwan[69]	2000–02	42	0·06	0·02–0·11
Thailand[68]	2007–08	45	0·04	0·02–0·05
Europe*				
Austria[27–30]	2000–11	337	0·37	0·18–0·70
Belgium[27–30]	2000–11	1203	1·20	0·70–1·67
Czech Republic[27–30]	2000–11	369	0·43	0·25–0·58
Denmark[27–30]	2000–11	513	0·99	0·48–1·83
Estonia[27–30]	2000–11	42	0·32	0·08–0·59
Finland[27–30]	2000–11	260	0·52	0·26–0·72
France[27–30]	2000–11	2844	0·53	0·34–0·67
Germany[27–30]	2000–11	4202	0·53	0·27–0·77
Greece[27–30]	2000–11	344	0·36	0·26–0·48
Hungary[27–30]	2003–11	150	0·24	0·16–0·37
Iceland[27–30]	2000–11	33	1·22	0·63–2·05
Ireland[27–30]	2000–11	698	2·08	1·65–3·27
Italy[27–30]	2000–11	615	0·12	0·09–0·15
Latvia[27–30]	2003–11	31	0·18	0·05–0·41
Lithuania[27–30]	2000–11	129	0·55	0·18–0·89
Malta[28–30,63]	2000–11	56	1·33	0·24–3·93
Netherlands[27–30]	2000–11	2283	1·40	0·40–2·63
Norway[27–30]	2000–11	249	0·64	0·40–1·18
Poland[27–30]	2000–11	772	0·25	0·06–0·39
Portugal[27–30]	2000–11	508	0·54	0·26–0·82
Slovakia[27–30]	2003–11	121	0·43	0·30–0·67
Slovenia[27–30]	2000–11	59	0·38	0·15–0·75
Sweden[27–30]	2000–11	207	0·25	0·16–0·36
Switzerland[19,79]	2000–11	275	0·54	0·43–0·72
Spain[27–30]	2000–03; 2008–11	2759	0·90	0·66–1·07
UK[27–30]	2000–11	7366	1·44	1·02–1·96
North America				
Canada[23,34]	2000–11	1173	0·3	0·22–0·40
USA[22]	2000–12	2155	0·16	0·06–0·24
Oceania				
Australia[25]	2000–12	2670	0·99	0·71–1·23
New Zealand[26]	2000–13	2401	4·26	0·67–12·5

(Table 1 continues on next page)

	Years	Total cases	Mean annual serogroup B incidence per 100 000 population	Range
(Continued from previous page)				
South America, Central America, Mexico, and the Caribbean				
Andean (Bolivia, Colombia, Ecuador, Peru and Venezuela)[66]	2006–10	103	0·01	0·01–0·02
Argentina[62]	2007	189	0·48	Only 1 year available
Brazil[66]	2006–10	814	0·09	0·06–0·14
Chile[62]	2006	103	0·62	Only 1 year available
Colombia[62]	2007	66	0·48	Only 1 year available
Cuba[67]	2000–03	..	0·53	0·30–0·70
Mexico, Central America, and Caribbean[66]†	2006–10	98	0·01	Individual year data not reported
Paraguay[62]	2005–06	19	0·16	0·15–0·17
Peru[62]	2005–06	14	0·03	0·01–0·04
Southern region (Argentina, Chile, Paraguay, and Uruguay)[66]	2006–10	754	0·23	0·17–0·30
Uruguay[62]	2006	41	1·24	Only 1 year available

*For total number of cases, data are missing from 2007 to 2009. †Anguilla, Antigua and Barbuda, Bahamas, Barbados, Belize, Bermuda, British Virgin Islands, Cayman Islands, Dominica, Grenada, Guyana, Jamaica, Montserrat, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, and Turks and Caicos.

Table 1: **Average incidence of serogroup B invasive meningococcal disease by country or region from Jan 1, 2000, to March 1, 2015**

	Years	Total number of meningococcal cases	Isolates belonging to serogroup B (%)
Asia			
Japan[74]	1974–2003	182	57%
Middle East and North Africa			
Egypt[72]	1999–2003	35	50%
Iran[18]	2004–06	12	17%
Israel[17]	1991–2001	133	62%
Israel[73]	1989–2010	650	77%
Kuwait[71]	Until 2003	86	43%
Kuwait[71]	2004–09	Not mentioned	19%
Morocco[70]	2000–10	Not mentioned	57%
Oman[71]	2001–08	45	2%
Qatar[71]	2008–10	47	13%
Saudi Arabia[76]	1995–2002	729	<1%
Tunisia[16]	1998–2004	23	83%
Turkey[20]	2005–06	243	31%

Table 2: **Meningococcal isolates attributed to serogroup B in selected countries with no incidence data available from Jan 1, 2000, to March 1, 2015**

and New Zealand were in the low category according to WHO classification for vaccine recommendations (figure 2). Within the low category, Australia, UK, Iceland, and Netherlands had incidence rates between 1 and less than 2 cases per 100 000 per year. The remainder of Europe, the Americas, and South Africa had incidence rates between 0·01 and 0·99 cases per 100 000 per year (table 1). Sub-Saharan Africa and southeastern Asia had the lowest incidence rates (<0·01 cases per 100 000 per year). For Japan, Taiwan, Egypt, Israel, Morocco, Tunisia, and Turkey, incidence rates were not available but the latest reports indicated that NmB accounted for more than 20% of total invasive meningococcal disease cases (table 2). The average data quality assessment score was 11·7 (range 9–14).

Variations in case definitions

Case definitions varied substantially (appendix). In the USA, the Active Bacterial Core surveillance network confirmed a case of invasive meningococcal disease only if bacteria were isolated from a usually sterile site (such as cerebrospinal fluid, serum, blood, synovial fluid, bone, surgical aspirate, or an internal body site).[84] The surveillance networks in Australia and Canada confirmed invasive meningococcal disease on the basis of *N meningitidis* isolation or identification of *N meningitidis* nucleic acid from a usually sterile site.[25,85] The South African surveillance network confirmed invasive meningococcal disease on the basis of isolation of *N meningitidis* from a usually sterile site.[64,86] In the European Union, the surveillance network of the European Centre for Disease Prevention and Control confirmed invasive meningococcal disease on the basis of any of three criteria: isolation of *N meningitidis* or detection of *N meningitidis* nucleic acid in a usually sterile site (including purpuric skin lesions), *N meningitidis* detection in cerebrospinal fluid by antigen detection test, or identification by Gram stain of Gram-negative diplococci in cerebrospinal fluid.[87] *N meningitidis* genotyping relies on multilocus sequence typing, with clustering of isolates into sequence types (ST), which are further clustered into clonal complexes. Genotyping is completed by sequencing the fragment encoding the variable regions (VR1 and VR2) of the *PorA* gene and the variable region of *FetA*.[88] Second-generation sequencing has enabled whole-genome sequencing to be increasingly used for epidemiological surveillance.[89]

North America

The population-based Active Bacterial Core surveillance network and the Public Health Agency of Canada reported meningococcal disease incidence in the USA and Canada, respectively.[22,23] Since 2000, incidence of NmB invasive meningococcal diseases has declined in the USA, with some minor fluctuations, while remaining relatively stable in Canada (figure 3). The average NmB incidence rate in Canada (0·30 per 100 000) was almost double that in the USA (0·16 per 100 000) between 2000 and 2012.[23,53]

As of January, 2014, the Active Bacterial Core surveillance network includes sites in ten states covering a population of 42·8 million people.[84] It is based on data collected from all microbiological laboratories within the surveillance zones and includes audits. Race and age-adjustment enable the yearly projection of incidence rates, cases, and deaths for the whole USA.[90]

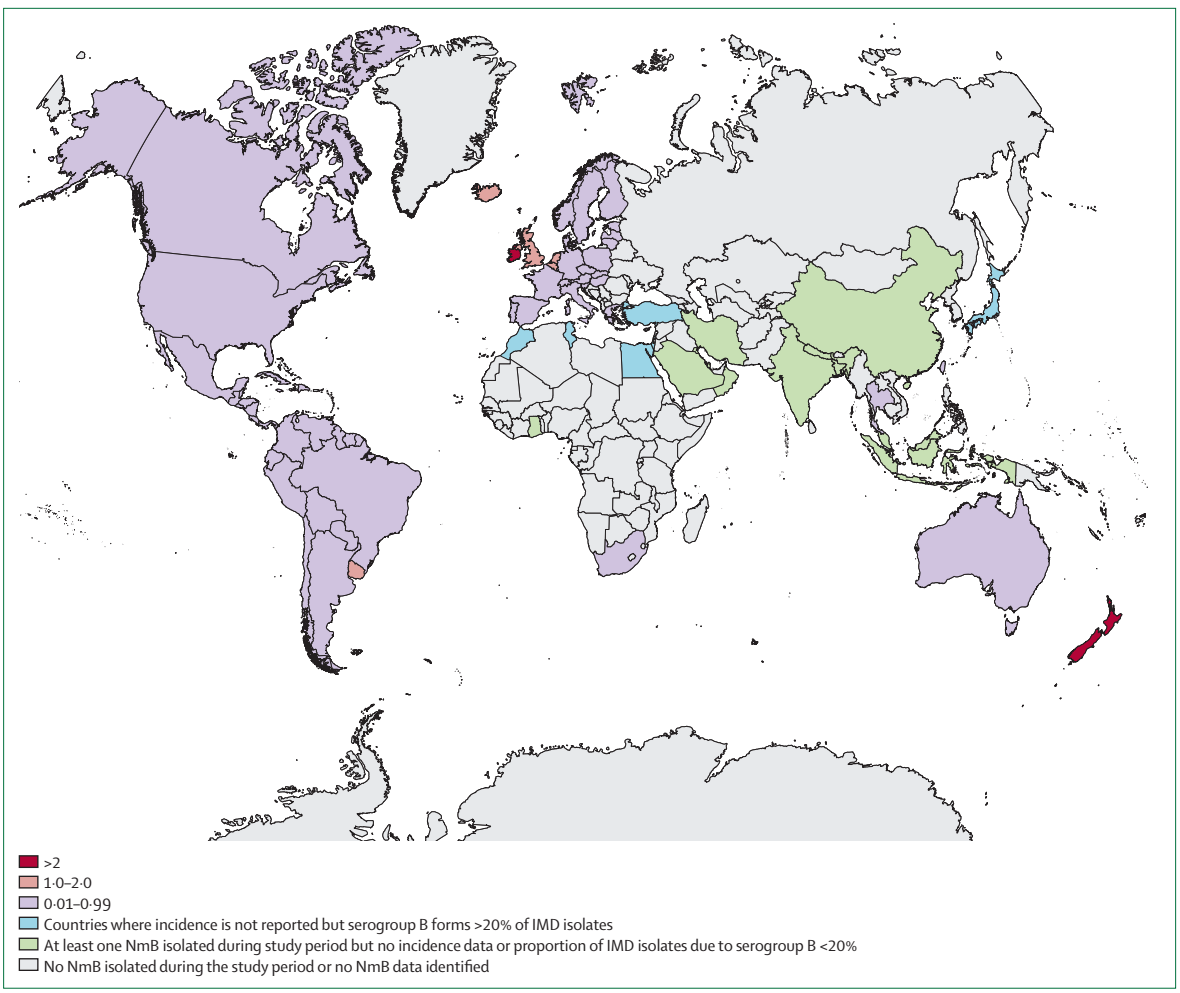

Figure 2: **yearly incidence per 100 000 people of serogroup B invasive meningococcal disease worldwide from Jan 1, 2000, to March 1, 2015**
Where multiple data sources existed, we used the most recent one. For South America, Central America, Mexico and the Caribbean, data from individual countries were used preferentially over regional data from the SIREVA network. IMD=invasive meningococcal disease. NmB=*Neisseria meningitidis* serogroup B.

In 2000–12, NmB represented on average 31% of all invasive meningococcal disease cases, similar to results from an earlier study.[38] 30% of all NmB cases in the USA reported during this time period were from Oregon, where a serogroup B epidemic caused by strain ST-32 began in 1993.[72] NmB incidence peaked in 1994 (3·4 cases per 100 000 people) and declined steadily since then. In 2012, 40% of cases in Oregon were attributed to NmB with an estimated incidence of 0·06 cases per 100 000 people.[82] In 2005–12, NmB incidence was highest among infants younger than 1 year (1·61 cases per 100 000 infants *vs* 0·12 cases per 100 000 for older individuals). The NmB CFR was about 11% from 1999 to 2007 (table 3) and was consistently higher for infants younger than 1 year during that period.[56] Isolates of cc32 predominated throughout the USA, whereas cc41/44 and cc162 were less represented.[91,92]

In Canada, the province of Quebec had an average NmB incidence of 0·62 cases per 100 000 individuals per year in 2000–11. This incidence was more than double that in the country as a whole and Quebec contributed more than 50% of the total number of NmB cases in Canada.[65] From 2000 to 2004, 35% of all cases were in people younger than 5 years and 20% were in those aged 25–64 years. The average NmB CFR (6%) from 1995 through 2006 was lower than that for serogroup C (13%) during the same time period.[53]

Latin America

In 1993, the Pan American Health Organization and WHO implemented a Latin American laboratory-based passive surveillance programme, named SIREVA (Sistema de Redes de Vigilancia de los Agentes Responsables de Neumonías y Meningitis Bacterianas), which was initially used to assess cases of invasive *Streptococcus pneumoniae* infection. In 1999, this network was extended to cases of *Haemophilus influenzae* and in 2000 to cases of *N meningitidis*. The SIREVA II network includes 19 national reference laboratories from an

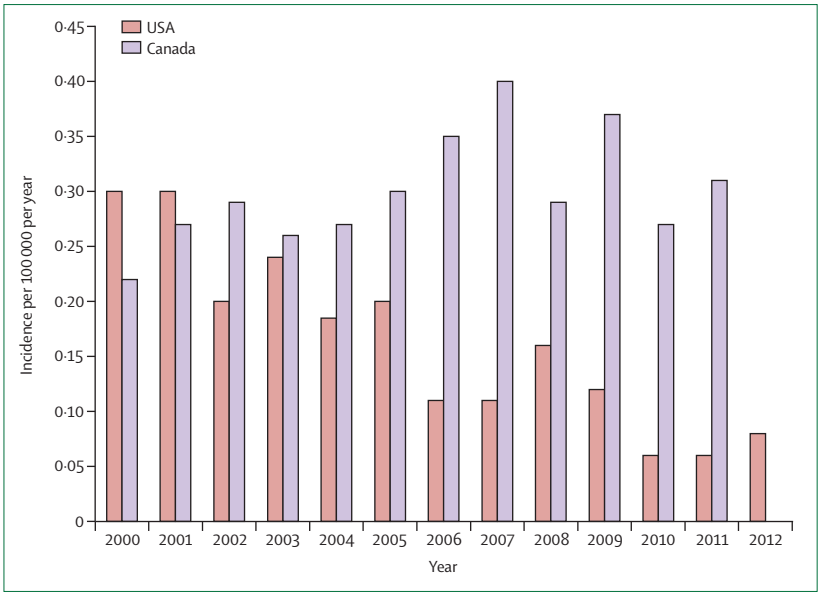

Figure 3: **Yearly incidence of serogroup B invasive meningococcal disease in the USA and Canada between 2000 and 2012**

	Year	Case-fatality ratio
Australia[25]	2000–12	6%
Australia[56]	1990s	6·4%
Brazil (southern)[60,62]	2000–03	7%
Brazil (Campinas)[83]	1993–98	22·2%
Canada[23,34]	2000–15	6%
Canada[65]	1999–2011	5·7%
Canada (Quebec)[79]	1990–94	7%
Cuba[67]	2000–03	3%
England and Wales[58]	2000–04	5%
Europe[55]	2008–09	7·4%
France[80]	2001–09	6%
France (outbreak)[77]	2003–05	16%
New Zealand (epidemic strain)[59]	1991–2000	5%
Spain (Catalonia)[57,81]	2000–07	7%
South Africa[61,64]	2002–06	10%
Thailand[68]	2007–08	23%
USA[22,56]	2000–12	10%
Overall	..	9%

Table 3: **Case fatality ratio for serogroup B invasive meningococcal disease recorded in different countries from Jan 1, 2000, to March 1, 2015**

equivalent number of countries from the Latin American and Caribbean regions.[93]

From 1996 to 2002, almost 80% of reported invasive meningococcal disease cases in northern and northeastern Brazil were caused by NmB.[62] In the early 2000s, on the basis of information reported by SIREVA on the number of meningococcal serogroup isolates across Latin America and the Caribbean, serogroup B was the most prevalent cause of invasive meningococcal disease in Argentina, Brazil, Chile, Colombia, Cuba, Uruguay, and Venezuela, although a decreasing trend in the incidence rates of serogroup B was reported in Latin America since 2000. In Brazil, strain B:4:P1.15,19 clonal complex ST-32 (cc32) predominated throughout the country.[94] Since 2002, a substantial increase in the proportion of cases attributed to serogroup C, associated with the ST-103 complex, was recorded, and serogroup C is the most frequent cause of invasive meningococcal disease in Brazil. From 1993 to 1998, a study in the Campinas region of Brazil reported an average NmB CFR of 22·2%.[83] Serogroup Y was predominant in Colombia and Venezuela in 2006. Serogroup W has recently emerged in the region: in Argentina, the proportion of invasive meningococcal disease caused by serogroup W increased from 2% in 2000 to 50% in 2010, and in Chile from no cases in 2001 to 55% in 2010.[95] In Mexico, Central America, and the Caribbean, 54% of all invasive meningococcal disease cases in children aged less than 1 year were caused by serogroup B.

The southern countries of South America (Argentina, Chile, Paraguay and Uruguay) reported the highest NmB incidence (table 1) followed by Colombia.[66] However, this result, and changes with time in the same location, might have taken place because of an ascertainment bias within the network resulting from differences in biological specimen collection, processing delays, and variation in diagnostic tests used, including the addition of PCR for routine aetiologic ascertainment. The percentage of *N meningitidis* isolates received by a laboratory undertaking serogrouping has differed between these countries. Although the central laboratory in Uruguay received most *N meningitidis* isolates obtained in the country, the percentage dropped to 50–60% in Argentina, Brazil, and Chile, and even less in Mexico, Central America, and the Caribbean and Andean regions.[66]

After an NmB outbreak in Cuba in 1980, a vaccination programme was implemented in 1987, initially in high-risk groups and subsequently involving infants, children, and young adults up to 24 years of age using a locally-produced serogroup B OMV presented with a serogroup C polysaccharide vaccine.[96] Since 1991, this vaccine has been introduced into the routine immunisation programme at 3 months and 5 months of age.[97] From 2000 to 2003, the average yearly incidence rate of NmB was 0·53 cases (range 0·3–0·7) per 100 000 individuals, which is about 3% of the incidence of the prevaccination period.[67] Yearly incidence was consistently highest among children aged 1–5 years (0·83 cases per 100 000 individuals). The CFR reported in these years was 3%.

Isolates of cc32 harbouring the PorA P1.19,15 were prevalent in Cuba in the 1980s, which stimulated the implementation of the Cuban OMV-based vaccine.[96] In addition to isolates with variable PorA, the same variant circulated in Brazil.[98] In Argentina, most NmB isolates detected in 2010 belonged to cc865, which is consistent with earlier reports from 2006. Isolates of the three major clonal complexes (cc41/44, cc32, and cc269) from Europe

and the USA were rare or even absent (cc269), whereas isolates of cc35 were present.[99]

Australia and New Zealand

In 2000–12, the Australian meningococcal surveillance programme reported an average yearly NmB incidence of 1 case per 100 000 individuals (range 0·71–1·23),[25] with 70% of meningococcal meningitis cases caused by serogroup B. The peak incidence happened in 2005 (figure 4). 37% of NmB cases arose in children younger than 5 years. Within Australia, 30% of NmB cases were reported from New South Wales, consistent with this state having 32% of the total population.[75,100] The NmB CFR was 6% in 2000–10. The highest CFR took place in 2002 at 11%.[25] Australia introduced the serogroup C conjugate vaccine in 2003, but has not introduced the NmB vaccine developed for New Zealand, in part because the strains in Australia differed genotypically and phenotypically from the epidemic strain in New Zealand.[75,101]

In New Zealand, meningococcal disease is a notifiable disorder.[26] Major fluctuations in the NmB incidence rates happened in the 2000s (figure 4), with an epidemic of NmB in 1996.[59] After an average NmB incidence of 9·7 cases per 100 000 individuals that was seen in 2000–03, a tailor-made OMV-based NmB vaccine was introduced in 2004, which was followed by an incidence decrease to 1·75 cases per 100 000 individuals in 2007. The vaccination programme was discontinued in 2008 because of the large decrease of epidemic strains nationally. The yearly NmB incidence was 0·97 cases per 100 000 individuals in 2012 and 0·67 cases per 100 000 individuals in 2013. The NmB CFR was about 4% in 2009, similar to the CFR before 2000 (4·5%; table 3).[59]

Middle East and north Africa

Data were not identified for most Middle Eastern and north African countries because most did not have routine meningococcal surveillance programmes.[70] NmB incidence rates were not available for any of the countries, but the percentage of total invasive meningococcal disease cases caused by NmB was occasionally reported (table 1). In Egypt and Morocco, during 1992 to 1995, a decrease in serogroup A cases but an increase in NmB cases was reported after the introduction of bivalent meningococcal A–C polysaccharide vaccine immunisation programmes.[72,102]

Sub-Saharan Africa

In the meningitis belt of Africa, the WHO Multi-Disease Surveillance Center has reported only outbreaks of serogroups A, X, W, and during the 2014–15 epidemic season, C. In the sub-Saharan region, only South Africa and Ghana have reported NmB cases during the past 15 years.[44,55,103,104] The South African National Institute for Communicable Diseases has reported a consistent predominance of NmB in the Western Cape region in the 2000s, in which almost 50% of invasive meningococcal disease cases were caused by serogroup B in 2009 and 2010.[31,32] The Western Cape accounted for 40% and 33% of all NmB cases in South Africa in 2009 and 2010, respectively, despite having only about 11% of the total South African population. The highest NmB incidence was reported among infants younger than 1 year.[64]

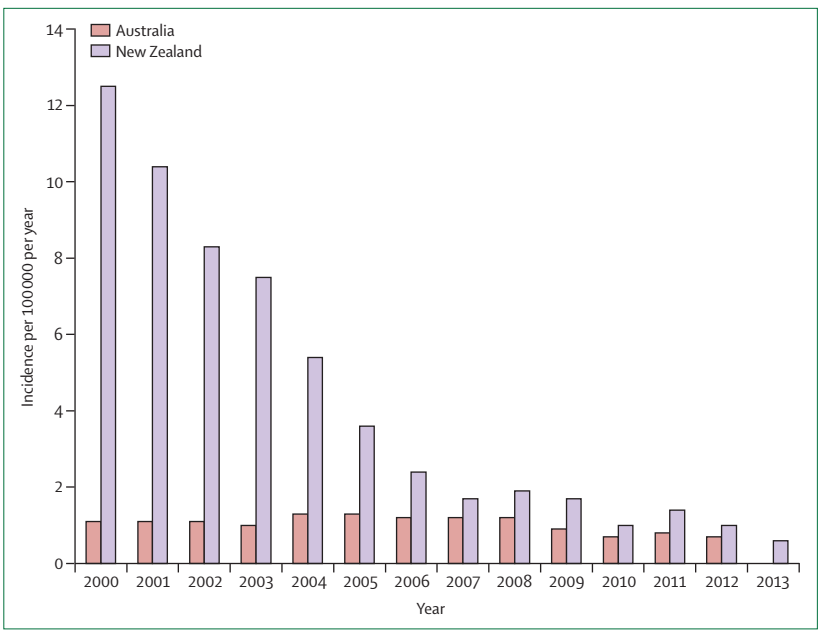

Figure 4: **Yearly incidence of serogroup B invasive meningococcal disease in Australia and New Zealand between 2000 and 2013**

Europe

A new system for invasive bacterial surveillance that represented all European Union countries was established in 1999.[27] The *N meningitidis* surveillance network was built on existing frameworks of the European Monitoring Group on Meningococci (established in 1995) and the European Bacterial Meningitis Surveillance Project (established in 1988). Since the successful implementation of serogroup C vaccines in the European Union in the 1990s and 2000s, a general decline in invasive meningococcal disease cases has been reported with a shift in the relative predominance of different serogroups.[44] Since 2000, serogroup B accounts for 60–72% of meningitis cases in the European Economic Area.[27–30] Incidences of NmB within individual European countries have varied substantially (table 1). Similarly, the percentage of meningococcal meningitis cases attributed to serogroup B varied from 100% in Latvia and Iceland to 38% in Slovenia in 2006. Almost 50% of the total NmB cases between 2008 and 2011 occurred in children younger than 5 years. The CFR for serogroup B in Europe was 7·4%, which was the lowest for any serogroup.[55] All countries except Belgium, Iceland, Ireland, Malta, Netherlands, and the UK had a yearly incidence of less than 1 case per 100 000 individuals from 2000 to 2011 (table 1, figure 2).

An NmB outbreak took place in the Seine-Maritime department in France between 2003 and 2005 with 50% of isolates belonging to the B:14:P1.7,16 strain.[77] The French Ministry of Health responded by introducing the Norwegian MenBvac in 2006 targeting 1–5 year old children residing in the Dieppe area, which was the epicentre for the outbreak. The yearly NmB incidence rate subsequently decreased from 4·9 cases per 100 000 individuals (95% CI 2·2–9·2) in 2003–06 to 1·5 cases per 100 000 individuals (0·3–4·4) in 2008–10 in this region.[54] Another outbreak happened in 2008–09 in the Landes department in France, with a yearly incidence of 3 cases per 100 000 individuals, which was five-times greater than the national average at that time.[78]

The GPIP/ACTIV (Groupe de Pathologie Infectieuse Pédiatrique et Association Clinique et Thérapeutique Infantile du Val de Marne) network in France reported that between 2001 and 2009, 62% of all *N meningitidis* cases in patients younger than 18 years were caused by serogroup B.[80] The CFR reported for serogroup B (5·9%) was substantially lower than that for serogroup C (9·2%). Between 2003 and 2005, Switzerland reported that 57% of *N meningitidis* cases across all age groups were caused by serogroup B.[79] A study in Spain reported that the highest incidence of NmB happened in children younger than 6 years in 2001–07 (11·1 cases per 100 000 people); in the same period, the average NmB CFR was 7·7% (maximum 13·1% in 2002 and minimum 3% in 2007).[57]

Compared with other European countries, Malta had a relatively high incidence of invasive NmB disease from 2000 to 2011, averaging 1·33 cases per 100 000 people per year (95% CI 0·24–3·93).[29,63] At the end of this period, however, incidence declined, and for the period of 2008 to 2011, the average yearly NmB incidence was 0·36 cases per 100 000 people, almost ten-times lower than the incidence in 2000. No national immunisation programme-directed mass vaccination took place; instead the public health response emphasised chemoprophylaxis of household contacts and registration of quadrivalent *N meningitidis* (serogroups A, C, Y, and W) polysaccharide vaccine.

Data from Europe showed the temporal and geographical variation of serogroup B isolates, with a predominance of three major hyperinvasive genotypes (cc32, cc41/44, and cc269).[104] Other clonal complexes are present with local predominance in some countries, such as the prevalence of cc162 isolates in Greece.[105] Age-specific analysis showed a higher prevalence of hyperinvasive genotypes in adolescents and young adults, a feature that influenced the design and implementation of recently licensed vaccines.[106,107] For example, Belgium, Cyprus, Germany, France, Greece, Iceland, Italy, Ireland, Luxembourg, Netherlands, Portugal, Spain, and the UK use serogroup C conjugate vaccine as a part of routine childhood immunisation.

Asia

No identified online reporting systems for *N meningitidis* exist in many Asian countries including Bangladesh, China, India, Myanmar, Pakistan, and Sri Lanka. Indonesia, Mongolia, Nepal, Philippines, South Korea, and Vietnam have reported endemic and outbreak-related cases with yearly NmB incidences of less than 0·01 cases per 100 000 individuals.[33,68]

Meningitis is a notifiable disorder in Japan and Singapore. Japan reported about 7–15 NmB cases per year.[24] A previous study from Japan reported that, in 1974–2003, 103 (57%) of 182 meningococcal isolates were serogroup B (table 2).[74] In China, few recent outbreaks of *N meningitidis* have been reported, and those that took place were mainly caused by serogroups A and C.[44,68,108] The mean annual NmB incidence reported in Singapore during 2002–13 (except 2008, which was not available) was 0·08 per 100 000 individuals per year (table 1) with annual peaks during 2002 (0·14 per 100 000), 2006 (0·18 per 100 000), and 2010 (0·12 per 100 000); the 39 NmB identified during 2002–13 represented 57% of all invasive meningococcal disease cases.[33] NmB incidence in Thailand was less than 0·06 cases per 100 000 per year (table 1).[68]

Few sequence type data from Asia exist. NmB isolates from Taiwan in 1996–2002 derived from several distinct lineages including ccST-41/44, ST-3439, and ST-3200.[69]

Discussion

Our systematic review emphasises several aspects of NmB epidemiology. The overall burden is low, with a decreasing trend in incidence rates and only few countries having a yearly incidence greater than 2 cases per 100 000 people. Within these relatively low overall incidence rates, substantial variation exists, with NmB being a major cause of meningococcal disease in North America, South America, Australia, and Europe, infrequent in China and India, and—with the exception of South Africa—almost absent in sub-Saharan Africa. Where consistently collected data were available, NmB incidence has decreased, even as the proportion of invasive meningococcal disease cases caused by serogroup B has increased (table 2). With a few exceptions, CFRs were fairly consistent ranging between 3% and 10%.

Reasons for the substantial variation in NmB incidence remain unknown. Possibilities include relatively slow changes in population immunity, a natural cyclical pattern of meningococcal serogroup distribution with waxing and waning based on features such as population immunity and bacterial virulence, differences in risk factors for infection either for NmB directly or for other organisms that compete with NmB for nasopharyngeal colonisation, differences in risk factors for progression of NmB infection to disease, or broad differences in risk factors for invasive *N meningitidis* disease or invasive bacterial disease as a whole.[109,110]

A speculative hypothesis is that use of conjugate vaccines that have the ability to reduce vaccine serogroup carriage will create a niche for other meningococcal serogroups including NmB. Data to lend support to this hypothesis

are sparse. In Netherlands, despite a predominance of serogroup B, no evidence of serogroup replacement has been recorded after introduction of conjugate serogroup C vaccine;[111] Canada and Scotland have shown similar results.[58,112,113] Limited caspsular switching but with no clonal expansion has been reported in Spain.[114] In 2010, Ghana introduced MenAfriVac, a conjugate serogroup A vaccine, and in 2013, two cases of NmB were reported; these were the first known NmB cases in the country that usually has a predominance of serogroup A with some disease caused by serogroups C, W, and Y.[104] Since 2008, epidemics in the African meningitis belt have been mild and a decreasing trend has been reported generally in meningococcal cases. However, longer term future follow-ups should be able to better define whether widespread use of non-serogroup B vaccines will influence NmB incidence rates.

Some of the variation in incidence rates almost certainly shows differences in surveillance procedures including differences in the aforementioned case definitions we documented, health-care access, indications and their implementation for conducting lumbar puncture and blood culture, laboratory capacity including availability of tests for aetiological confirmation, and reporting of results from peripheral to central levels. These issues might occur differentially with time, by location, and by risk group (eg, age groups), thereby affecting the ability to interpret differences between cohorts.[115,116] Nevertheless, these issues probably do not account for a large part of the reported variation. For example, most of these issues will affect incidence estimates of all meningococcal disease serogroups and yet substantial variations in the proportion of invasive meningococcal disease caused by serogroup B were shown. Moreover, resource-poor settings such as the African meningitis belt have a long history of documenting meningococcal serogroups but not serogroup B, which suggests that diagnostic bias alone cannot explain all of the identified variation.[117]

Since NmB strains are highly varied, not all of them will express components of 4CMenB, and the subcapsular antigens used in 4CMenB can vary with time and place. A Meningococcal Antigen Typing System has been developed to predict the level of protection against a particular strain. Using ELISA, the Meningococcal Antigen Typing System attempts to establish if the concentration of antigens included in the 4CMenB vaccine for a particular strain is sufficient for postvaccination antibodies to provide immunity. A strain is covered when a vaccine component is at a defined threshold or higher than this threshold.[118]

A WHO position report suggests that routine vaccination might be an inefficient strategy when the invasive meningococcal disease yearly incidence is less than 2 cases per 100 000 people.[2] However, this recommendation might not hold true in developed countries, which bear the highest burden of NmB disease. Specifically, vaccination efficiency may be increased in these settings because of the high health-care costs for treatment and potentially lifelong management of sequelae, and the social and political effect of meningococcal outbreaks.[119] Even in developed countries, however, the major modifiable determinant of cost-effectiveness is probably vaccine cost, the populations that are targeted, and discounting rates.[120] With the notable exception of MenAfriVac, meningococcal vaccines are among the most expensive vaccines included in national immunisation programmes.[121] For example, the UK's National Health Service reports a list price per dose of £75 for 4CMenB.[122] A 2014 study in England concluded that this vaccine would be cost effective as part of routine infant immunisation only when it is priced less than £4 per dose in the short-term.[123] A study in Dutch infants reported that at a disease incidence of 5·7 cases per 100 000 person-years or an NmB vaccine price of €10 per dose including administrative costs, the incremental cost-effective ratio becomes more acceptable.[124]

If NmB vaccines provide protection or immunogenicity against non-B isolates by targeting common subcapsular antigens, this should improve vaccine cost-effectiveness. Additionally, vaccine characteristics, operational issues, and changes in NmB epidemiology might affect the decision-making process for vaccine use. For example, meningococcal conjugate vaccines achieve much of their high population effectiveness by a reduction of carriage and indirect protection. However, the ability of NmB vaccines to achieve this remains unknown.[125] Preliminary investigation of the effect of 4CMenB on carriage in university students during a 1 year follow-up study showed that two vaccine doses led to an overall reduction in *N meningitidis* carriage regardless of serogroup and with no significant influence on NmB carriage.[126] In theory, this finding suggests the possibility for substantial indirect protection by reduction in transmission if the vaccine is implemented in large catch-up campaigns that include the age groups (such as adolescents) most responsible for transmission. However, 4CMenB reduced carriage by only 30%, a level that, depending on the reproductive number, might or might not be sufficient to affect transmission.[127] Moreover, data do not exist on carriage reduction duration. Operationally, although evidence of good short-term protection after two primary doses exists, long-term protection might decline, necessitating one or more booster doses.[125] The age group indication for 4CMenB vaccine is 10–25 years of age, which might not correspond with local epidemiology. Additionally, because this age range falls outside of the routine infant immunisation age group, vaccination might be programmatically complex in some regions of the world.[128] Finally, epidemiological changes could alter disease burden and potentially vaccine usefulness. For example, bacterial meningitis might be associated with second-hand smoke exposure.[129] To the extent that this

Search strategy and selection criteria

These are described in detail in the Methods section.

exposure declines (eg, with higher taxes or laws prohibiting smoking in public places), invasive meningococcal disease might decrease in the absence of vaccine use.

Our study had several limitations. We did not review scientific literature in all languages and did not have access to all potential sources of unpublished data, including public health reports not posted on the internet. Variations in surveillance methods, including diagnostic instruments, limit comparison of results across countries. Finally, many areas of the world, specifically south Asia, lack adequate surveillance capacity of any kind, such that NmB disease might occur and go unreported.

We have noted a general decrease in invasive NmB incidence rates even as the proportion of invasive meningococcal disease caused by NmB has increased. The data presented in this Review could assist in informing decisions regarding vaccine policy. However, additional data are needed in many low-income and middle-income countries to better define disease burden, an issue that is more urgent in view of the availability of a serogroup B vaccine. Future efforts should more fully define vaccine characteristics including strain coverage and efficacy, duration of immunity, carriage reduction, marginal cost-effectiveness across different settings and vaccine prices, and optimum schedules.

Contributors

SSr and BDG jointly generated the idea for the study, developed the methods, and wrote the first version of the Review. BG, CH, SP, MAS, SSa, MKT, and OT contributed equally to data interpretation, reviewing the text, and providing input to the final version of the Review. All authors read and approved the final submitted Review.

Declaration of interests

SSr and BDG work for Agence de Médecine Preventive, which receives or has received during the previous 2 years grant support from Crucell, GlaxoSmithKline, Merck, Novartis, Pfizer, and Sanofi-Pasteur. CH works for the UK Meningitis Research Foundation, an independent charity, which has received during the previous 2 years some grant support from GlaxoSmithKline, Novartis, and Pfizer. SP is a consultant to vaccine manufacturers, including those who manufacture meningococcal vaccines, but declares no financial conflict related to this Review. MAS has received grants to support research projects and speaker's honoraria from Novartis, GlaxoSmithKline, Pfizer, and Sanofi Pasteur. SSa receives or has received grants from Novartis and GlaxoSmithKline to work on group B streptococcus and *Streptococcus pneumoniae*. M-KT has consulted for or received grants from Novartis, Pfizer, GlaxoSmithKline, and Sanofi Pasteur. BG and OT declare no competing interests.

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