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Review

Case fatality rates of invasive meningococcal disease by serogroup and age: A systematic review and meta-analysis

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ABSTRACT

Introduction: Invasive meningococcal disease (IMD) is uncommon but still causes considerable public health burden due to its high mortality and morbidity. This review aims to quantitatively synthesise all published evidence pertinent to mortality caused by IMD and assess the effect of age and serogroup on case fatality rates (CFRs).

Methods: The PubMed and Embase databases, and the Cochrane Library were searched. Articles reporting national CFRs and published in English between January 2000 and May 2018 were eligible. The studies reporting mortality resulting from a specific symptom of IMD (e.g. meningococcal meningitis) were excluded. Mixed-effects logistic regression with a restricted cubic spline was used to analyse CFRs as a function of age. Random-effects meta-analyses were performed to estimate an overall CFR and CFRs by serogroup.

Results: Among 48 eligible studies reporting national CFRs, 40 studies were included in meta-analyses representing 163,758 IMD patients. CFRs ranged from 4.1% to 20.0% with the pooled overall CFR of 8.3% (95% confidence interval (CI): 7.5–9.1%). Serogroup B was associated with a lower pooled CFR (6.9% (95%CI: 6.0–7.8%)) than other serogroups (W: 12.8% (95%CI: 10.7–15.0%); C: 12.0% (95%CI: 10.5–13.5%); Y: 10.8% (95%CI: 8.2–13.4%)). The meta-analysis was not performed for serogroup A (MenA) cases due to a small number of MenA patients who were enrolled in eligible studies. For laboratory confirmed IMD cases, the predicted CFR was 9.0% in infants, gradually decreased to 7.0% in 7-year olds, subsequently increased to 15.0% in young adults aged 28 years, stabilised between 15 and 20% in mid-aged adults and reached a high in elderly people.

Conclusions: Our findings can provide useful information for better understanding the mortality risks, and quantifying the burden associated with IMD mortality.

Contents

Abbreviations: AIC, Akaike's information criterion; CFR, case fatality rate; CI, confidence interval; ICD, international classification of diseases; IMD, invasive meningococcal disease; MenA, meningococcal serogroup A disease; MenB, meningococcal serogroup B disease; MenC, meningococcal serogroup C disease; MenW, meningococcal serogroup W disease; MenY, meningococcal serogroup Y disease; MRR, mortality rate ratio; OR, odd ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

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1. Introduction

Neisseria meningitidis is estimated to be carried by around 10% of a healthy population and can result in invasive meningococcal disease (IMD), a life-threatening infection [1]. Vaccines have been developed to protect against serogroups A, B, C, W and Y, which are the most common serogroups causing IMD. The meningococcal serogroup C vaccine has been included on the national immunisation schedule for decades in many developed countries. New surface protein-based meningococcal serogroup B (MenB) vaccines have been recently developed and licensed in most developed countries. Quadrivalent (serogroups A, C, W, Y) conjugate vaccines have been included on the publicly funded immunisation schedule or are being considered for public funding in some countries. The evaluation of the cost-effectiveness of a vaccination program is one of the key inputs into the decision-making process. The cost-effectiveness of these preventive strategies depends on a number of factors including disease incidence, mortality, costs associated with the management of the disease and its sequelae, serogroup distribution, herd immunity, vaccine efficacy, and immunity duration. The case fatality rate (CFR) is not only an important parameter in cost-effectiveness evaluation, but also a key component in epidemiological studies and an essential measure of the burden of IMD. The mortality associated with IMD has been well documented in disease surveillance reports especially in developed countries [2–6], and frequently discussed in review articles [7–11]. Key factors such as age and serogroup have been reported as important factors influencing IMD outcomes [2,7,9]. However, the CFR has not been quantified and key factors such as age and serogroup in estimating CFRs have yet to be explored in a meta-analysis. In this paper, we conducted a systematic review and meta-analysis to identify published contemporary evidence worldwide, to estimate the CFR, and to investigate the impact of age and serogroup on CFRs.

2. Methods

2.1. Search strategy and selection criteria

A search of the literature was conducted using electronic databases: PubMed, Embase, and the Cochrane Library. Primary search strategies identified articles that reported the clinical and financial burden of IMD using the following keywords: meningococcal, meningococcal meningitis, meningococcal septicaemia, Neisseria meningitidis AND burden, costs, cost analysis, fees, hospital charges, economic model, economics, expenditure, utilisation, case fatality, complications, sequelae, morbidity, mortality, death rates, incidence, survival analysis, health status. The final search terms included combinations of Medical Subject Headings (MeSH)/Emtree and text words contained in the title and abstract (Supplementary Table 1). Only studies pertaining to CFRs are presented here (Fig. 1). The systematic review regarding the financial burden associated with IMD was published elsewhere [12]. Gray literature available online was searched for relevant abstracts and/or posters from the following organisations: Meningitis Research Foundation, Infectious Diseases Society of America, International Pathogenic Neisseria Conference, European Society for Paediatric Infectious Diseases, International Congress on Infectious Diseases, World Society for Pediatric Infectious Diseases, and Australian Society for Infectious Diseases. Emails were sent to the first authors for additional information as required. Reference lists of relevant review articles [7,9,11] were searched for additional citations of interest. The search was conducted by one reviewer (BW) on 3 August 2016 and updated on 3 May 2018.

The article selection process occurred in two phases: (1) title and abstract screen: titles and abstracts of articles identified from the electronic databases and from Internet searches were reviewed; (2) full text review: the full text of articles selected at the title and abstract screen were obtained and reviewed for eligibility. The screening process was completed according to a predefined protocol.

Studies were eligible if national IMD CFRs were reported through primary data collection. Studies only reporting mortality resulting from a specific symptom of IMD (e.g. meningococcal meningitis) were excluded. Comments, letters, editorials, case reports, and reviews were excluded. Following the first publicly funded meningococcal C (MenC) vaccine program in the UK in 2000, several countries have added MenC vaccine onto their national immunisation programs. Since the epidemiology of IMD might be affected by the large scale implementation of MenC vaccine programs, the search was restricted to articles published from 1 January 2000 to 3 May 2018. Studies reported in languages other than English were excluded. Several national population or surveillance-based studies replicated data by containing patient populations which were completely included in other studies; in these instances, the publication with more comprehensive information presented was selected in meta-analyses to avoid double counting of evidence.

Reporting and performing this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 statement [13] and meta-analysis of observational studies in epidemiology guidelines [14]. All analyses were performed using Stata 14.2. This systematic review was registered with PROSPERO (CRD42016043213).

2.2. Data extraction and analysis

Data were independently extracted by two reviewers (BW and RS). The following characteristics of each study were collected: type of study including study design, setting and study period, study population (sample size, mean or median age at illness, serogroup, case definition, etc), country, follow-up duration, outcomes (sequelae, CFR and costs relevant to IMD), and funding.

The Joanna Briggs Institute Critical Appraisal Tools were used to assess studies reporting the clinical burden of IMD including case-control, case series, cohort, quasi-experimental (non-randomised experimental studies), and randomised controlled studies [15]. Two independent reviewers (BW and RS) assessed the quality of

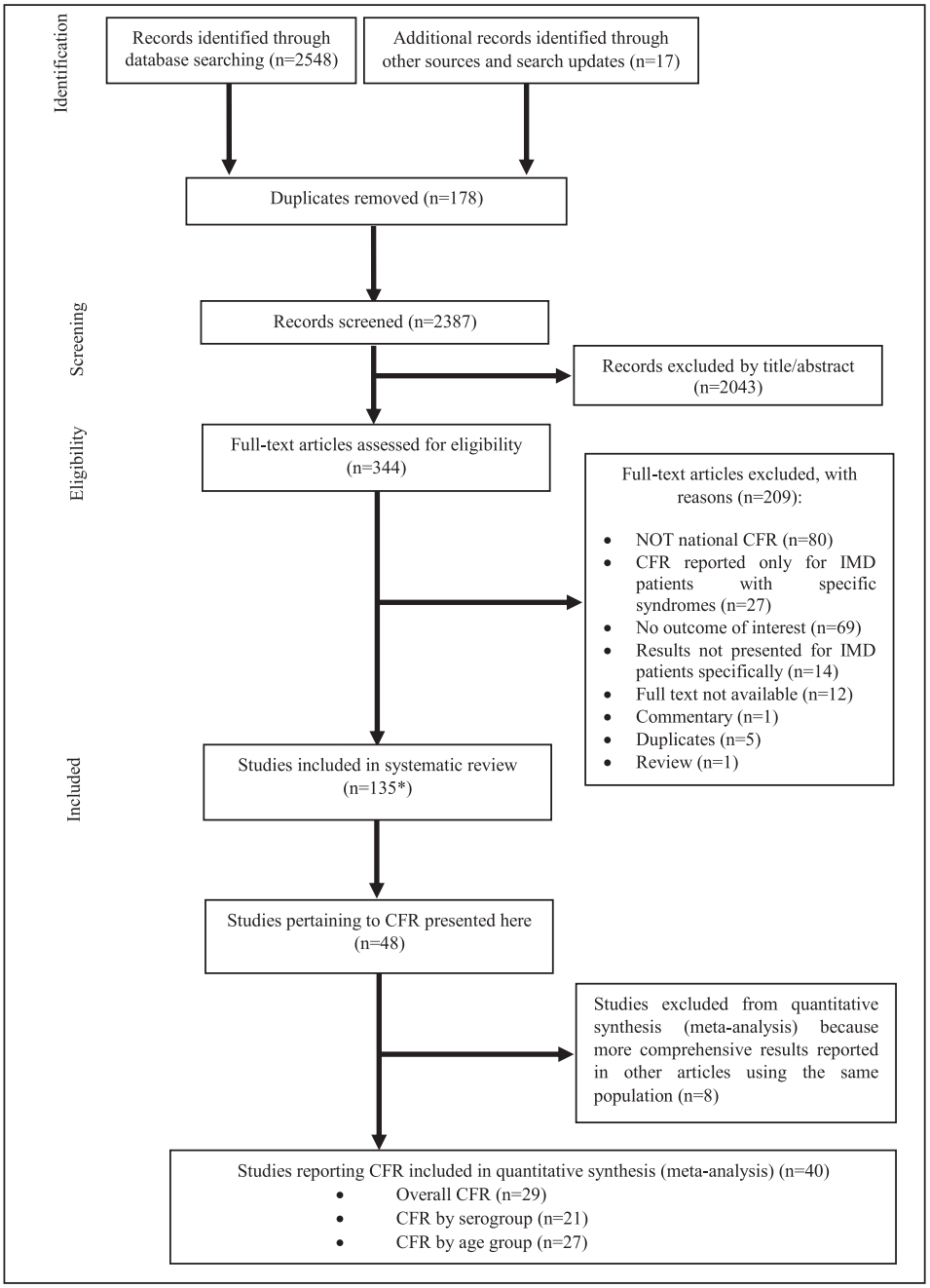


Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for article inclusion and exclusion. *The full systematic review aimed to estimate clinical and financial burden of IMD. Only studies reporting CFRs are presented here.

studies, and any divergence between them was resolved through discussion. When disagreement was not resolved, senior researchers (HM and LG) were consulted. Through quality assessment, we found demographics and follow-up period of the study patients were not reported in a large number of studies. However, most studies reported national surveillance results and surveillance networks might receive limited demographic and follow-up information.

Meta-analyses were performed for overall CFR and CFRs by serogroup. Heterogeneity was assessed statistically using the I^2 statistic. Because substantial variability (heterogeneity) was expected across studies, a DerSimonian-Laird random-effects model was used [16].

Since we expected the relationship between CFRs and age to be non-linear, multilevel mixed-effects logistic regression (QR decomposition) with a restricted cubic spline was used to model CFRs as a function of age. As patient individual level data were not available, aggregate data for each age group in a study were used. The outcome measure was the number of deaths observed in the study population recorded in binomial form, with denominator the number of IMD cases in the study population. We estimated the mean age for each age group using midpoint age of an age band if the true mean age was not presented. The model also included covariates: case definition, enrolment period, study and country. Different case definitions were used in various population studies and national surveillance networks, and therefore studies were

classified into two groups: definite laboratory confirmed cases of IMD and notified cases of IMD. The notified cases of IMD included a combination of laboratory confirmed, probable and clinically diagnosed IMD. Studies were assigned to a decade in which most of study patients were enrolled if the study spanned more than one decade. For open-ended older age bands, an upper age limit of 99 years was chosen to calculate a midpoint of this age group, as the highest age limit of 99 years was used in the included study [17]. Studies were excluded from the regression analysis if the study population was only divided into two groups, adults and children, without specific age ranges.

The model was adjusted by case definition and enrolment period as fixed effects, with study nested within country as nested random effects. Fixed effects were used for those variables based on the assumption of a constant effect across all studies. The enrolment period (decade of study) was removed from the final regression model due to a lack of statistical significance. The variables selected for random effects were assumed to have random intercepts normally distributed with common variance and population mean. The model allows for multi-levels of nested clusters of random effects, on the assumption that observations within the same cluster are correlated. This model structure was decided a priori based on previous research [1,18] and the assumption that CFR by age has the same shaped curvilinear relationship across countries but estimates in a specific country might be higher or lower than the mean value. The adequacy of models containing a restricted cubic spline with different numbers and locations of knots were assessed using Akaike's information criterion (AIC). The restricted cubic spline with five knots placed at the ages of 0.5, 7, 17, 42 and 82 years based on Harrell's recommended percentiles [19] was chosen because of the lowest AIC.

In sensitivity analyses, studies in French South Pacific Islands (New Caledonia) [20], Israel [21] and Kuwait [22] were excluded. Studies in European countries, Australia, the US and Canada were retained because these latter countries have comparable national surveillance systems. Saudi Arabia [23] was also excluded in the sensitivity analyses because the epidemiology of meningococcal disease was affected by Hajj and Umrah in Saudi Arabia.

3. Results

Forty-eight studies met inclusion criteria and reported national CFRs in 34 countries (Table 1). Seven studies [24–30] were not included in meta-analyses due to data overlapping with other published reports that were included in the meta-analyses. IMD cases in these seven studies were completely included in other studies. Another study was excluded from meta-analysis because all-cause mortality rates within the first year of diagnosis of IMD were reported [31]. One article was available as a conference abstract and additional information was provided by the first author [32]. In total, 11,807 deaths were observed in 163,758 IMD patients. Although the review was limited to articles published after 2000, the observation time reported in studies spanned the period from 1974 to 2017 with most data reported from developed countries (e.g. the EU, the US, Canada, and Australia). Around half of studies (n = 19, 47.5%) enrolled laboratory confirmed IMD patients only. Among 40 studies [2,4–6,17,20–23,32–62] included in the meta-analyses, 29 studies [4–6,17,20–23,32,34,35,38,42,43,45,46,48,49,51–58,60–62] were used to estimate the overall CFR with 21 studies [4–6,17,20,23,32,33,39,44,46,48,49,52–56,58,61,62] used to derive pooled estimates of CFRs by serogroup, and 28 studies [2,4,17,20,21,23,33,35–37,39–43,47,48,50–55,58–62] used to examine the age effect on CFR.

The overall CFR was estimated to be 8.3% and the included studies were very heterogeneous (I^2 = 96.3% (95% confidence interval (CI): 95.7–96.8%)) (Supplementary Fig. 1). Among 21 studies, 19 [4,6,17,20,23,32,33,44,46,48,49,52–56,58,61,62] reported CFRs in MenB cases (n = 67324) (Fig. 2A); 17 [4,6,17,20,23,33,44,46,48,52–56,58,61,62] reported CFRs in MenC cases (n = 18954) (Fig. 2B); 13 [4–6,17,23,39,48,49,53,54,56,58,62] reported CFRs in serogroup W (MenW) cases (n = 3017) (Fig. 2C); 10 [4–6,23,39,53,54,56,61,62] studies reported CFRs in serogroup Y (MenY) cases (n = 3356) (Fig. 2D). The pooled estimate of MenB CFR was lower than serogroups W, C and Y. Heterogeneity reduced when meta-analyses were stratified by serogroup, especially in MenW and MenY cases. The number of serogroup A (MenA) cases was low in the identified studies. Only two of six studies enrolled more than ten MenA cases with CFRs ranging from 3.9% [48] to 21.8% [23]. Therefore, meta-analysis was not performed for MenA disease.

CFRs by age group were reported in 28 studies, including 83,649 IMD cases. Among those cases, 22,308 were definite laboratory confirmed cases with 61,341 were defined as notified IMD cases (a combination of laboratory confirmed, probable and/or clinically diagnosed cases). Besides the variables created for the spline function of age, the type of case definition was significantly associated with CFR, after adjusting the nested random-effects of country and study (likelihood ratio test $P < 0.0001$). At a given age, the chance of death for patients with laboratory confirmed IMD was double in comparison with those notified IMD cases (Table 2). The estimated variance in CFRs was higher for between studies than between countries. For laboratory confirmed cases, the predicted CFRs were highest in Saudi Arabia and lowest in Australia.

Predicted CFRs by age were non-linear (Fig. 3). Predicted CFRs for laboratory confirmed cases decreased from 9.0% in infants to 7.0% in 7-year olds, stayed stable in children aged 7–10 years, gradually increased to 10.4% in adolescents aged 16 years, reached a peak of 15.0% in young adults aged 28 years, remained steady in adults aged between 28 and 45 years, rose rapidly in older adulthood, and reached 32.8% in 80-year olds (Supplementary Table 2).

In the sensitivity analysis of studies reporting CFRs by age in the EU, the US, Canada and Australia only (n = 25), laboratory confirmation of case was still a significant factor affecting CFRs (odd ratio (OR): 1.92; 95%CI: 1.48–2.49; $p < 0.0001$). However, the predicted CFRs tended to be slightly lower in general compared with the main analysis, increasing to 10.1% in 16-year olds, remaining stable through young adulthood, and increasing to 32.2% in elderly patients aged 80 years. Similar to the main analysis, variation in CFRs was still lower between countries (0.092; 95%CI: 0.019–0.445) than between studies (0.137; 95%CI: 0.058–0.322).

After removing studies in New Caledonia, Israel, Kuwait and Saudi Arabia, the pooled estimates of overall, MenB and MenY CFRs were slightly lower: 7.8% (95%CI: 7.0–8.6%; I^2 = 96.3% (95%CI: 95.6–96.8%)), 6.8% (95%CI: 5.9–7.6%; I^2 = 92.7% (95%CI: 90.3–94.3%)), 10.6% (95%CI: 8.1–13.2%; I^2 = 69.8% (95%CI: 19.2–83.7%)), respectively. The pooled estimate of the MenW CFR dropped from 12.8% to 11.3% (95%CI: 10.1–12.5%; I^2 = 0.0% (95%CI: 0.0–49.8%)). The pooled estimate of MenC CFR stabilised at 12.0% (95%CI: 10.4–13.5%; I^2 = 85.7% (95%CI: 77.8–89.8%)).

4. Discussion

This is the first meta-analysis to estimate the CFR and to quantitatively examine the effect of age and serogroup on CFRs.

The meta-analysis showed the greatest CFRs in MenW and MenC cases, which highlighted the significant impact of the recent increase in incidence of MenW disease in many countries. After removing fatality data reported in the Saudi Arabia, the pooled MenW CFR decreased and became lower than MenC in the sensitivity analysis. The reduction in the pooled estimate may reflect very high fatality associated with the MenW outbreak during Hajj

Table 1
Characteristic of eligible studies identified through systematic review.

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
1.	Archer et al. [33]	Australia	1999–2015	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B & C	All	4774 (B&C)	By age and serogroup: <5 years: B: 5%, C: 5%; 5–9 years: B: 2%, C: 8%; 10–14 years: B: 1%, C: 2%; 15–24 years: B: 2%, C: 6%; 25 + years: B: 6%, C: 12%; all ages: B: 4%, C: 8%
2.	Baker et al. [34]	New Zealand	1991–2000	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	3547	Overall: 4.5%; laboratory confirmed cases: 4.9%
3.	Ben-Shimol et al. [21]	Israel	1989–2010	Hospital based national surveillance	Laboratory (culture) confirmed cases	All	<15 years	743	Overall: 9.9%; by age: <1 year: 9.2%, 1–4 years: 12.3%, >4 years: 7.7%; yearly mean CFR: 9.9% ± 4.1%
4.	Brotherton et al. [35]	Australia	2001–2002	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	1355	88 deaths in 1355 cases; by age: 0–4 years: 26/393, 5–14 years: 8/213, 15–24 years: 21/391, 25–59 years: 24/286, 60 + years: 9/72
5.	Brotherton et al. [36]	Australia	2003–2005	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	1355 (2003–2005); 955 (2003–2004)	69 deaths in 1355 cases in 2003–2005; 46 deaths in 955 cases in 2003–2004 (using IMD notification numbers reported from national notifiable diseases surveillance system): 0–4 years: 12/292, 5–14 years: 1/116, 15–24 years: 12/273, 25–59 years: 10/199, 60 + years: 11/74
6.	Chiu et al. [37]	Australia	2005–2007	National surveillance based on notification and hospital data	Laboratory confirmed and probable cases	All	All	622 (2006–2007); 700 (2005–2006)	32 deaths in 700 cases in 2005–2006 (using IMD notification numbers reported from national notifiable diseases surveillance system): 0–4 years: 15/242, 5–14 years: 2/84, 15–24 years: 3/177, 25–59 years: 7/153, 60 + years: 5/44; 21 deaths in 622 cases in 2006–2007
7.	Cizman et al. [38]	Slovenia	1993–1999	Hospital based national surveillance	Laboratory confirmed cases	All	<15 yrs (1993–1999); all (1995–1999)	75	4.1%
8.	Darton et al. [39]	England and Wales, UK	1999–2001	National surveillance based on laboratory data	Laboratory confirmed cases	All	All	1910 (EDTA-treated blood samples were received by theMeningococcal Reference Unit)	Overall: 10%; by age: <1 year: 45/482, 1–3 years: 15/397, 4–11 years: 12/272, 12–17 years: 33/315, 18–20 years: 7/90, 21–60 years: 40/274, 61 + years: 18/59; by serogroup: A: 0/1, B: 62/1010, C: 94/616, Y: 0/8, W: 2/31, ungrouped: 10/202

Table 1 (*continued*)

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
9.	Daures et al. [20]	French South Pacific Islands (New Caledonia)	2005–2011	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	66 episodes including 2 recurrences (n = 64)	Overall: 7.8%; by age: <1 year: 2/4, 1–4 years: 2/12, 5–9 years: 0/10, 10–14 years: 0/11, 15–19 years: 0/10, 20–24 years: 0/9, 25–34 years: 0/1, 35–44 years: 1/2; 45–54 years: 0/1, 55–64 years: 0/3, 65–74 years: 0/2, 75 + years: 0/1; by serogroup: B: 3/29
10.	Davison et al. [40]	England and Wales, UK	July 1993–June 1998	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	C	All	Actual laboratory confirmed MenC cases: 2782; estimated confirmed MenC cases: 3360	CFRs in estimated laboratory confirmed cases by age: <1 year: 5.3%, 1–4 years: 7.3%, 5–9 years: 4.7%, 10–14 years: 7.9%, 15–19 years: 13.9%, 20–24 years: 12.9%, 25–29 years: 14.6%, 30–34 years: 13.3%, 35–39 years: 17.9%, 40 + years: 18.3%
11.	de Greeff et al. [24]	Netherlands	January 2003–May 2005	National surveillance based on notification data	Laboratory confirmed cases	All	All	752	Overall: 6.7%; by serogroup: B: 6.3%, C: 5.2%
12.	Dey et al. [41]	Australia	2008–2011	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	1015	Overall: 48/1015; by age: <1 year: 10/163, 1–4 years: 5/184, 5–14 years: 1/118, 15–24 years: 9/266, 25–49 years 10/154, 50–64 years: 5/77, 65 + years: 8/53
13.	Edge et al. [2]	England, UK	2007–2011	National population linkage study	Laboratory confirmed cases	All	All	4619	30-day CFR: 4.5%; overall CFR (after 30 days): 4.7%; by age: <1 year: 3.3%, 1–4 years: 3.0%, 5–14 years: 2.2%, 15–24 years: 5.4%, 25–44 years: 3.7%, 45–64 years: 4.7%, 65 + years: 18.0%; by serogroup: B: 4.2%, C: 3.4%, W: 9.5%, Y: 9.9%, other: 0.7%
14.	Gil-Prieto et al. [42]	Spain	1997–2008	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on International Classification of Diseases (ICD) codes	All	All	11,611	Overall: 7.3%; by age: <1 year: 5.2%, <2 years: 5.1%, 0–4 years: 5.0%, 5–9 years: 3.6%, 10–14 years: 4.6%, 15–19 years: 8.7%, 20–24 years: 9.5%, 25–29 years: 10.2%, 30–49 years: 9.8%, 50–54 years: 12.6%, 55–59 years: 12.4%, 60–64 years: 15.1%, 65–69 years: 15.2%, 70–74 years: 14.7%, 75–79 years: 20.2%, 80–84 years: 29.5%, 85 + years: 37.7%
15.	Goldacre et al. [43]	England, UK	1999–2010	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on ICD codes	All	All	19,113	30-day CFR: 4.9%; by age: <1 year: 3.0%, 1–4 years: 2.9%, 5–9 years: 1.6%, 10–14 years: 3.8%, 15–19 years: 5%, 20–24 years: 4.1%, 25–29 years: 5.5%, 30–34 years: 7.2%, 35–39 years: 8.7%, 40–44 years: 8.0%, 45–49 years: 9.5%, 50–54 yeas: 7.5%, 55–59 years: 14.3%, 60–64 years: 12.9%, 65–69 years: 20.8%, 70–74 years: 16.5%, 75–79 years: 19.0%, 80 + years: 32.5%
16.	Gottfredsson et al. [44]	Iceland	1977–2004	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	362	Overall: 8.6%; by serogroup: B: 14/204, C: 14/144, others: 3/14

(*continued on next page*)

Table 1 (*continued*)

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
17.	Gottfredsson et al. [45]	Iceland	1975–2004	Population based study	Laboratory confirmed cases	All	All	541	30-day CFR: 7.9%
18.	Gray et al. [46]	England and Wales, UK	July 1993–June 2004	National surveillance based on laboratory data	Laboratory confirmed cases	All	All	21,712	Overall: 6.7%; by serogroup: B: 5.1%, C: 11.6%, others: 5.0%
19.	Hanquet et al. [47]	Belgium	2004–2010	National surveillance based on hospital discharge and laboratory data	Laboratory confirmed cases	All	All	933	Overall: 7.0%; by serogroup: B: 5.4%, C: 15.6%; by age: <1 year: 6.7%, 1–4 years: 4.9%, 5–9 years: 3.2%, 10–19 years: 4.2%, 20–64 years: 10.3%, 65 + years: 16.3%
20.	Howitz et al. [48]	Denmark	1974–2007	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	5924	31-day CFR: 7.6%; by age: <1 year: 5.9%, 1–4 years: 7.5%, 5–9 years: 3.5%, 10–19 years: 5.6%, 20–49 years: 9.4%, 50 + years: 17.9%; by serogroup: A: 3.9%, B: 7.9%, C: 9.1%, W: 10.3%, other known: 17.0%
21.	Husain et al. [22]	Kuwait	1987–2013	National surveillance study	Laboratory confirmed cases	All	All	293	13.5%
22.	Knol et al. [25]	Netherlands	July 2015–March 2017	National surveillance based on notification and laboratory data	Laboratory confirmed cases	W	All	79	11%
23.	Knol et al. [49]	Netherlands	2015–2017	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B, W	All	215 (B); 138 (W)	W: 12%, B: 4%
24.	Ladhani et al. [26]	England and Wales, UK	July 2006–June 2011	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	5471	Overall: 5.3%; by serogroup: B: 5.2%, C: 9.9%, Y: 9.2%, W: 5.5%
25.	Ladhani et al. [27]	England and Wales, UK	2007–2009	National surveillance based on notification and laboratory data	Laboratory confirmed cases	Y	All	143	19% for all MenY cases in 2009; 13% for 114 genotypically characterized isolates in 2007–2009
26.	Ladhani et al. [50]	England and Wales, UK	July 2008–June 2014	National surveillance based on notification and laboratory data	Laboratory confirmed cases	W	All	270	Number of death: 30/270; by age: <5 years: 2/65; 5–19 years: 5/43, 20–44 years: 5/35, 45–64 years: 4/49, 65 + years: 14/78
27.	MacNeil et al. [4]	US	2006–2015	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	7924	Overall: 14.9%; by age: <1 year: 8.6%, 1 year: 5.9%, 2–4 years: 11.8%, 5–10 years: 10.5%, 11–15 years: 11.5%, 16–20 years: 14.3%, 21–25 years: 16.7%, 26–44 years: 16.8%, 45–64 years: 16.9%, 65–84 years: 17.4%, 85 + years: 28.0%; by serogroup: B: 11.5%, C: 20.2%, W: 20.9%, Y: 13.7%

Table 1 (*continued*)

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
28.	Martin et al. [5]	Australia	2003–2015	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	3720 (all IMD); 159 (W)	Overall: 4.7%; by serogroup: B: 4.2%, C: 9.1%, W: 10.7%, Y: 4.1%
29.	McDonald et al. [32]	Scotland, UK	1999–2013	National surveillance based on notification and laboratory data	Laboratory confirmed cases	B	All	1028	B: 5.7%
30.	McIntyre et al. [51]	Australia	1998–2000	National surveillance based on notification and laboratory data	Laboratory confirmed, probable and clinically diagnosed cases	All	All	1655 (1998–2000)	103 deaths in 1655 cases (1998–2000) (using IMD notification numbers reported from national notifiable diseases surveillance system in 1998): 0–4 years: 33/588, 5–14 years: 8/208, 15–24 years: 25/492, 25–59 years: 28/289, 60 + years: 9/78
31.	Memish et al. [23]	Saudi Arabia	1995–2011	National surveillance based on notification data	Laboratory confirmed cases	All	All	1103	Overall: 18.0%; by age: <1 year: 6.8%, 1–4 years: 9.4%, 5–14 years: 9.3%, 15–45 years: 19.4%, 46 + years: 32.6%; by serogroup: A: 21.8%, B: 21.2%, C: 20%, W: 19.7%, Y: 33.3%
32.	Montero et al. [28]	Spain	1997–2005	National surveillance based on hospital discharge data	All hospital discharges of meningococcal infections based on ICD codes	All	All	9479	Overall: 6.5%; by age: 0–4 years: 4.7%, 5–9 years: 3.4%, 10–14 years: 3.8%, 15–19 years: 7.9%, 20–24 years: 8.7%, 25–29 years: 11.8%, 30 + years: 12.2%
33.	Muscat et al. [52]	Malta	1994–2007	National surveillance based on notification data	Laboratory confirmed, probable and possible cases	All	All	233	Overall: 12%; by age: < 1 year: 7%, 1–9 years: 6%, 10–19 years: 13%, 20–44 years: 13%, 45 + years: 23%; by serogroup: B: 13/87, C: 5/18
34.	Parent du Chatelet et al. [53]	France	2006–2015	National surveillance based on notification data	Laboratory and clinically diagnosed cases	All	All	5894	Overall: 10.4%, by age: <1 year: 9.9%, 1–4 years: 8.9%, 5–14 years: 5.9%, 15–24 years: 10.3%, 25–59 years: 9.3%, 60 + years: 20.0%; by serogroup: B: 8.8%, C: 13.2%, W: 11.9%, Y: 15.5%
35.	Parikh et al. [54]	England, UK	January 2011–June 2015	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	3411	28-day CFR: 6.9%; by age: <1 year: 4.0%, 1–4 years: 4.8%, 5–14 years: 4.8%, 15–24 years: 6.2%, 25–44 years: 7.8%, 45–64 years: 6.3%, 65–74 years: 12.7%, 75–84 years: 17.0%, 85 + years: 31.9%; by serogroup: B: 5.4%, C: 10.1%, W: 11.9%, Y: 12.1%
36.	Perrocheau et al. [17]	France	2001–2003	National surveillance based on notification data	Laboratory and clinically diagnosed cases	All	All	1707 (2001–2003)	Overall: 14.0%; by age: < 2 years: 15.3%, 2–14 years: 11.2%, 15–24 years: 9.6%, 25–99 years: 21.1%; by serogroup: B: 11.3%, C: 17.9%, W: 20.0%
37.	Piscopo et al. [29]	Malta	1994–1998	National surveillance based on hospital data	Lab confirmed and probable cases	All	All	60	20.0%
38	Roed et al. [31]	Denmark	1977–2006	National surveillance based on hospital register data	All hospital discharges of meningococcal infections based on ICD codes	All	All	5356	All-cause mortality: within the first year of diagnosis of IMD: 8.3%; during the observation period: 6.4%: overall mortality rate ratio (MRR): 1.27 (95%CI: 1.12–1.45), adjusted MRR: 1.21 (95%CI: 1.06–1.37),

(*continued on next page*)

Table 1 (*continued*)

	Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
									adjusted MRR for death due to nervous, digestive and genitourinary system diseases, respectively: 3.15 (95%CI: 1.59–6.23), 1.99 (95%CI: 1.16–3.43), 6.26 (95%CI: 1.58–24.81)
39.	Ruedin et al. [55]	Switzerland	1999–2002	National surveillance based on notification data	Laboratory confirmed and probable cases	All	All	626	Overall: 9.1%; by age: <1 year: 6.8%, 1–4 years: 15.1%, 5–9 years: 2.8%, 10–19 years: 4.0%, 20–29 years: 11.9%, 30 + years: 12.2%; by serogroup: B: 8.3%, C: 8.5%, other or unknown: 10.8%
40.	Sadarangani et al. [56]	Canada	2002–2011	Population based surveillance study	Laboratory confirmed cases	All	All	868	Overall: 8.4%; by serogroup: A: 50.0%, B: 6.1%, C: 12.8%, W: 8.7%, Y: 9.5%
41.	Schrauder et al. [57]	Germany	2003	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	779 cases reported to the Robert Koch Institute; 565 laboratory confirmed cases isolated/typed at the National Reference Centre for Meningococci	8.8%
42.	Shigematsu et al. [58]	England, Wales and Northern Ireland, UK	January1999–June 2001	National surveillance based on notification and laboratory data	Laboratory confirmed and probable cases	All	All	12,074	Overall: 5.8%; laboratory confirmed cases: 8.2%; probable cases: 2.5%; laboratory confirmed CFR by age: <1 year: 6.1%, 1–4 years: 4.3%, 5–14 years: 4.8%, 15–17 years: 7.6%, 18 + years: 15.3%; by serogroup: B: 5.8%, C: 13.8%, W: 15.0%
43.	Skoczynska et al. [59]	Poland	2010–2011	National surveillance based on notification and laboratory data	Laboratory confirmed cases	All	All	458 (2010–2011)	During the period 2010–2011, overall: 10.0%; by age: 0–5 years: 10.3%, 5–9 years: 12.5%, 10–14 years: 5.6%, 15–19 years: 3.7%, 20–24 years: 15.4%, 25–44 years: 7.9%, 45–64 years: 2.9%, 65 + years: 46.2%; by serogroup: B: 10.3%, C: 8.8%
44.	Squires et al. [61]	Canada	1997–1998	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	439	Overall: 8.9%; by serogroup: B: 5.4%, C: 12.4%, Y: 14.3%, others: 4.8%, clinical cases: 9.2%; number of death by age group for the year 1997 and 1998, respectively: <1 year: 1/47, 0/21; 1–4 years: 4/43, 0/39; 5–14 years: 1/39, 1/20; 15–19 years: 6/39, 1/24; 20–64 years: 9/73, 9/54; 65 + years: 6/24, 1/14
45.	Squires et al. [60]	Canada	1999–2001	National surveillance based on notification and laboratory data	Laboratory confirmed and clinically diagnosed cases	All	All	805 (214 in 1999, 241 in 2000, 350 in 2001)	Overall: 10.7%, 8.7%, and 9.4% in 1999, 2000, and 2001 respectively; in 1999 by age: <1 year: 2.6%, 1–4 years: 8.30%, 5–9 years: 15.4%, 10–14 years: 20.0%, 15–19 years: 6.5%, 20–24 years: 12.5%, 25–64 years: 15.4%, 65 + years: 18.7%; in 2000 by age: <1 year: 10.5%; 1–4 years: 4.0%; 5–9 years: 11.8%; 10–14 years: 10.0%; 15–19 years: 6.0%; 20–24 years: 3.8%; 25–64 years: 12.3%, 65 + years: 11.1%; in 2001 by age: <1 year: 10.0%, 1–4 years: 9.1%, 5–9 years: 9.1%, 10–14 years: 6.2%, 15–19 years: 2.6%, 20–24 years: 6.5%, 25–64 years: 15.2%, 65 + years: 15.2%

Table 1 (*continued*)

Paper	Country	CFR data collection period	Study setting	Case definition	Serogroup	Age group	Sample size	Case fatality rate
46. Steindl et al. [30]	Austria	2010	National surveillance based on notification and laboratory data	laboratory confirmed cases	All	All	80	12.5%
47. Stoof et al. [62]	Netherlands	June 1999–June 2011	National surveillance based on hospital and laboratory data	Laboratory confirmed cases	All	All	939	30-day CFRs: 8%; by age: 0–6 months: 2%, 6–24 months: 7%, 2–4 years: 5%, 5–9 years: 4%, 10–19 years: 4%, 20–64 years: 8%, 65 + years: 39%; by serogroup: B: 8%, C: 9%, W: 13%, Y: 13%
48. Whittaker et al. [6]	EU	2004–2014	National surveillance based on notification data	Laboratory confirmed cases	All	All	41,206	Overall: 8.6%; by serogroup: B: 7.4%, C: 14.3%, W: 10.3%; Y: 10.2%

in Saudi Arabia [63]. As we expected, a high level of heterogeneity was found in the synthesis of overall CFR. After analyses stratifying by serogroup, heterogeneity reduced especially in cases due to serogroup W and Y disease. This finding is reassuring as we expected serogroup was an important factor in predicting CFRs. However, heterogeneity was still high in MenB related cases. In our review, almost 70% of IMD cases were caused by MenB disease with diverse age groups and study design reflecting the epidemiology of MenB disease. Especially for endemic MenB disease, organisms causing the infection are genetically diverse, which may explain the heterogeneity in CFRs [64]. Previous research has demonstrated that certain serotypes/serosubtypes and clonal complexes were associated with a higher CFR [65–68]. For example, MenC disease of the phenotype 2a:P1.2,5 was associated with an increased risk of mortality [48]. MenW disease has traditionally been caused by strains of the ST-22 clonal complex which is usually associated with fatal disease outcomes in the elderly population. However, the recent rise in cases of MenW disease, which is caused by strains of the ST-11 clonal complex in many countries, can also be fatal in children and young adults [50].

Although the disease incidence peaks in infants and IMD remains a leading infectious cause of death in early childhood in developed countries [69], our regression model indicated that CFRs were lower in infants compared to adolescents and young adults. In addition to the highest carriage rate estimated in young adults aged 19 years [1], our finding of an increased CFR in young adults would help researchers and policy makers to further understand the potential impact of vaccination strategies. CFR doubled with age from 15% in young adults to 30% in those aged around 75 years. Reasons for the significant variation in CFR by age are not fully understood [9]. Higher prevalence of serogroup W and Y disease was observed in older people especially with underlying medical conditions [5,27,50,70,71]. The highest mortality rate may be explained by predominant serogroups and frailty. The highest CFR in elderly patients may also be associated with delay in appropriate treatment, because the symptoms may be more difficult to recognise in frail older patients coupled with a relatively lower prevalence of IMD in this age group. Moreover, factors related to host may explain different CFRs. For example, previous research reported genetic factors were clearly associated with mortality and severe outcomes of meningococcal disease [72,73].

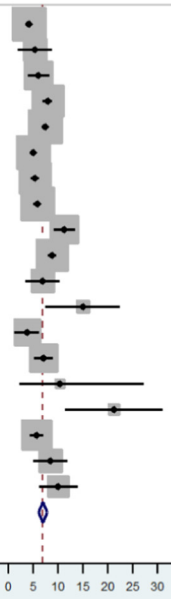
Our regression model showed an increased variance between studies compared with between countries. After removing data collected in Israel, New Caledonia and Saudi Arabia in sensitivity analysis, the results still revealed the same trend. Although we did not limit our search to Western countries, most included studies were conducted in developed countries. The low variance between countries might be due to similar healthcare setting and comparable epidemiological transition across developed countries. Case definitions used by different studies varied substantially. For example, some studies [2,42] enrolled patients based on ICD codes at hospital discharge without laboratory confirmation; some studies used national surveillance or notification data. Even for surveillance data, a number of studies [23,44,55] restricted IMD notification to laboratory confirmed cases, but several studies had included probable or clinically diagnosed cases [34–37,60,61]. Furthermore, laboratory confirmed cases were defined inconsistently in different studies [8]. Although our regression model was adjusted by case definition and we only categorised case definitions into two groups, variation between studies may still result from inconsistent case definitions used in different studies. Our regression model could not be adjusted by serogroup due to very limited serogroup data for each age group. Although we only included papers published after 2000, the enrolment period still spanned from 1974 to 2015 for included studies. The decade of study was not statistically significant in our initial regression model, which may support previous research [48,74] and confirm CFR has not significantly decreased despite improvements in diagnostic techniques, clinical management and healthcare access. This is likely to be due to the pathophysiology of the disease process with an overwhelming effect of the cytokine storm limiting effectiveness of current treatment strategies.

We aimed to estimate CFR with minimum bias by searching publications and grey literature, contacting authors for additional information, and not restricting our search to developed countries. However, national surveillance networks are well established in developed countries, but very little data were identified from developing countries in Asia and South America. Countries with high endemic rates of IMD in Africa often reported mortality data associated with meningococcal meningitis only. Those studies were not included in this review as per the inclusion and exclusion criteria. The CFRs may be generally underestimated, as timely, reliable, and affordable health services may not be available in some countries especially in remote areas, which could substantially increase mortality from IMD [9]. Also, sudden deaths caused by IMD without hospitalisation

A

Publication	N. deaths (B)	N. cases (B)	CFR data collection period	Study location	Case fatality rate (95% CI)	% Weight
Archer et al (2017)	153	3675	1999-2015	Australia	4.2 (3.5, 4.8)	7.87
Squires et al (2000)	9	166	1997-1998	Canada	5.4 (2.0, 8.9)	3.69
Sadarangani et al (2015)	29	478	2002-2011	Canada	6.1 (3.9, 8.2)	5.57
Howitz et al (2009)	256	3237	1974-2007	Denmark	7.9 (7.0, 8.8)	7.54
Whittaker et al (2017)	2407	32529	2004-2014	EU	7.4 (7.1, 7.7)	8.15
Gray et al (2006)	685	13448	Jul 1993-Jun 2004	England and Wales, UK	5.1 (4.7, 5.5)	8.10
Parikh et al (2018)	134	2489	2011-2015	England, UK	5.4 (4.5, 6.3)	7.60
Shigematsu et al (2002)	242	4168	Jan 1999-Jun 2001	England, Wales and Northern Ireland, UK	5.8 (5.1, 6.5)	7.81
Perrocheau et al (2005)	90	799	2003	France	11.3 (9.1, 13.5)	5.48
Parent du Chatelet et al (2017)	310	3518	2006-2015	France	8.8 (7.9, 9.7)	7.53
Gottfredsson et al (2006)	14	204	1977-2004	Iceland	6.9 (3.4, 10.3)	3.66
Muscat et al (2009)	13	87	1994-2007	Malta	14.9 (7.5, 22.4)	1.21
Knol et al (2018)	8	215	2015-2017	Netherlands	3.7 (1.2, 6.3)	4.94
Stoof et al (2015)	50	711	Jun 1999-Jun 2011	Netherlands	7.0 (5.2, 8.9)	6.01
Daures et al (2015)	3	29	2005-2011	New Caledonia	10.3 (2.2, 27.4)	0.47
Memish et al (2013)	14	66	1995-2011	Saudi Arabia	21.2 (11.3, 31.1)	0.74
McDonald et al (2014)	59	1028	1999-2013	Scotland, UK	5.7 (4.3, 7.2)	6.79
Ruedin et al (2004)	21	248	1999-2002	Switzerland	8.5 (5.0, 12.0)	3.65
MacNeil et al (2017)	23	229	2006-2015	US	10.0 (6.2, 13.9)	3.20
Overall (I-squared = 92.1%, p = 0.000)					6.9 (6.0, 7.8)	100.00

NOTE: Weights are from random effects analysis



B

Publication	N. deaths (C)	N. cases (C)	CFR data collection period	Study location	Case fatality rate (95% CI)	% Weight
Archer et al (2017)	87	1099	1999-2015	Australia	7.9 (6.3, 9.5)	9.38
Squires et al (2000)	13	105	1997-1998	Canada	12.4 (6.1, 18.7)	3.80
Sadarangani et al (2015)	21	164	2002-2011	Canada	12.8 (7.7, 17.9)	4.86
Howitz et al (2009)	95	1041	1974-2007	Denmark	9.1 (7.4, 10.9)	9.19
Whittaker et al (2017)	940	6573	2004-2014	EU	14.3 (13.5, 15.1)	10.11
Gray et al (2006)	627	5419	Jul 1993-Jun 2004	England and Wales, UK	11.6 (10.7, 12.4)	10.11
Parikh et al (2018)	13	129	2011-2015	England, UK	10.1 (4.9, 15.3)	4.77
Shigematsu et al (2002)	269	1950	Jan 1999-Jun 2001	England, Wales and Northern Ireland, UK	13.8 (12.3, 15.3)	9.46
Perrocheau et al (2005)	97	541	2003	France	17.9 (14.7, 21.2)	7.15
Parent du Chatelet et al (2017)	163	1236	2006-2015	France	13.2 (11.3, 15.1)	9.02
Gottfredsson et al (2006)	14	144	1977-2004	Iceland	9.7 (4.9, 14.6)	5.14
Muscat et al (2009)	5	18	1994-2007	Malta	27.8 (7.1, 48.5)	0.53
Stoof et al (2015)	15	180	Jun 1999-Jun 2011	Netherlands	8.3 (4.3, 12.4)	6.08
Memish et al (2013)	2	10	1995-2011	Saudi Arabia	20.0 (2.5, 55.6)	0.33
Ruedin et al (2004)	16	193	1999-2002	Switzerland	8.3 (4.4, 12.2)	6.26
MacNeil et al (2017)	27	146	2006-2015	US	18.5 (12.2, 24.8)	3.81
Daures et al (2015)	0	6	2005-2011	New Caledonia	(Excluded)	0.00
Overall (I-squared = 84.7%, p = 0.000)					12.0 (10.5, 13.5)	100.00

NOTE: Weights are from random effects analysis

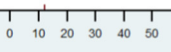


Fig. 2. Forest plots for CFRs by serogroup.

were not considered in most studies. As notification or hospital discharge data were usually used to identify IMD cases, those studies only included IMD patients who were admitted to hospital. Goldacre et al. found 616 deaths with meningococcal disease as a cause on the death registration record but those deaths did not have a corresponding hospital admission in a UK study [43]. During the same study period, 940 deaths occurred within 30 days after hospital admissions. The true mortality rate of IMD might be much higher than we estimated. A large proportion of CFR data were collected in young children aged less than 5 years. The concentration of data on this age group is likely to be due to the incidence peaking in young children. Only articles

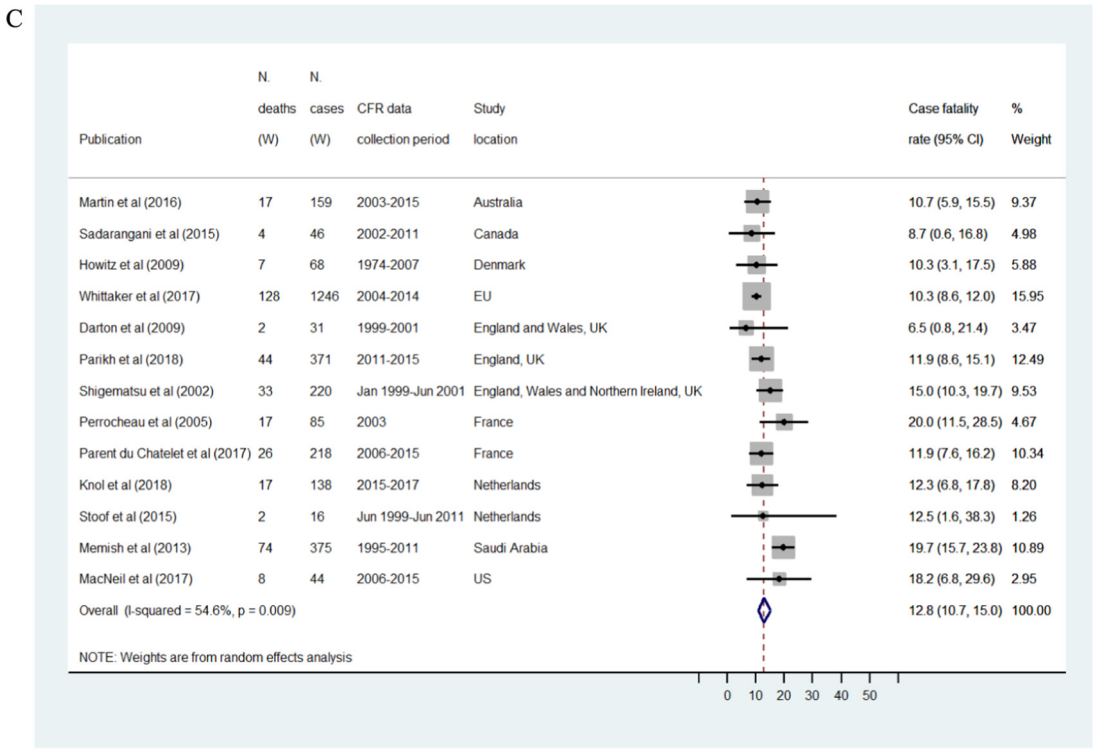


Fig. 2 (*continued*)

published in English were included which may result in publication bias. Historically *N. meningitidis* serogroup A has been the cause of the epidemics in the meningitis belt of sub-Saharan Africa. Since eligible studies in our review were conducted in non-African countries, the number of studies reporting MenA cases was small and most studies only enrolled one or two patients. Therefore, the meta-analysis was not performed for serogroup A related disease.

5. Conclusions

Despite those limitations and differences between countries, our review explored factors influencing CFR and emphasised the importance of age and serogroup as key factors determining CFRs by using different meta-analytic techniques. Our meta-analyses can provide clear, informative and contemporary results, advance our understanding of the disease burden and epidemiology of

Table 2
Fixed and random effect estimates from the main analysis.

Fixed effect parameter estimates:		
	Estimates	95%CI (p value)
Notified IMD cases (a combination of laboratory confirmed, probable or clinically diagnosed cases)	OR: 1	
Laboratory confirmed IMD cases	OR: 1.906	1.491–2.434 (p < 0.0001)
Random effect parameter estimates		
Country	Variance: 0.080	0.020–0.331
Study	Variance: 0.127	0.057–0.284

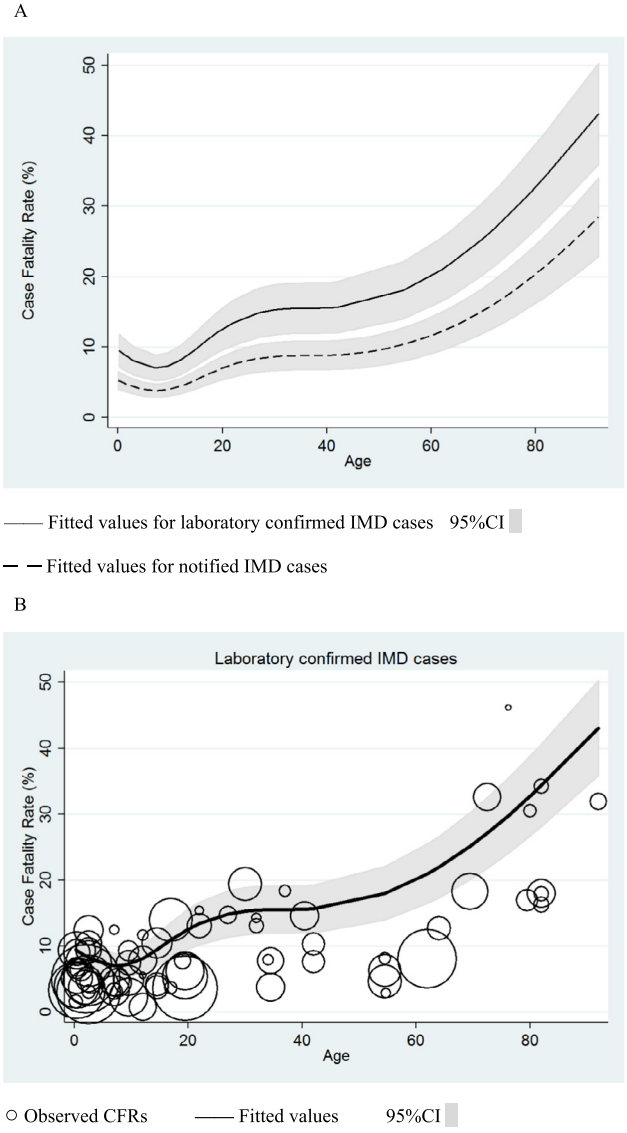


Fig. 3. Estimates of CFR by age. The size of circles is proportional to the number of cases included in each study, with the larger circles indicating a larger sample size.

IMD, and assist in evaluating the potential benefits of new meningococcal vaccine programs.

Author contribution

BW, HM, LG and HHAA conceived and designed the study. BW conducted the searches. BW and RS extracted data and performed critical appraisal. HM and LG resolved divergencies. BW prepared the first draft of the manuscript under the direct supervision of HM, LG and HHAA. HM, RS, LG, and HHAA contributed to, reviewed and edited the manuscript.

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Conflict of interest

HM is an investigator on clinical trials of investigational vaccines sponsored by Industry. Her institution receives funding from Industry (GSK, Pfizer, Novavax) for Investigator led research. She does not receive any personal payments from Industry. There are no other conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.020.

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