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Review

Risk Factors for Contracting Invasive Meningococcal Disease and Related Mortality: A Systematic Literature Review and Meta-analysis

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ABSTRACT

Objectives: To describe risk factors (RFs) and quantify their effects in invasive meningococcal disease (IMD) and associated mortality across all age groups based on the available published literature.
Methods: A systematic literature review (SLR) was conducted via MEDLINE® and Embase. Study selection, data extraction, and quality assessment were performed by two independent reviewers. Associations between RFs and outcomes were quantified via a meta-analysis (MA).
Results: Seventy-four studies (date range 1950 – 2018) were included in the SLR. Statistically significant RFs for contracting IMD identified from the SLR (within-study) included previous IMD infection and young age (0 – 4 years). MA indicated that significant RFs for contracting IMD (11 studies) were: HIV-positive status, passive smoke exposure, and crowded living space. In the MA for IMD-related mortality risk (11 studies), age 25 – 45 years (vs. 0 – 5 years) and serogroup C (vs. serogroup B) were significantly associated with increased risk.
Conclusions: Previous findings of higher risk for IMD contraction with smoke exposure and crowded living conditions in children/adolescents have been extended by this SLR/MA to all age groups. We provide strong evidence for higher risk of IMD in HIV-positive individuals, and confirm previous findings of higher IMD-related mortality risk in adults aged 25 – 45.
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Introduction

Invasive meningococcal disease (IMD) is an acute bacterial infection, caused by *Neisseria meningitidis*, which can cause septicemia, meningitis, and can lead to potentially severe long-term sequelae, including limb amputation, neurological deficits, hearing loss, and other serious disabilities (Edmond et al., 2010). *N. meningitidis* may be found as a benign commensal bacterium in the human nasopharynx (phenomenon known as asymptomatic carriage); however, invasive disease in susceptible individuals is one of the most feared infections due to its sudden onset, rapid progression and high case fatality rates (Parikh et al., 2018). When untreated, IMD mortality may exceed 50%, and mortality despite treatment remains high at 10% (Pace and Pollard, 2012, Perez et al., 2010).

Six *N. meningitidis* serogroups are responsible for almost all IMD cases worldwide (A, B, C, W, X and Y), and there is a wide variation in serogroup distribution by geography and over time (Parikh et al., 2020). Incidence of IMD varies globally and tends to be higher in the meningitis belt of sub-Saharan Africa, spanning 26 countries where epidemics (defined as > 100 cases/100,000 population/year) occur every 5 – 12 years (Jafri et al., 2013, Parikh et al., 2020). Successful implementation of a meningococcal A (historically the most prevalent strain) conjugate vaccine program from 2010 – 2015 in this region has reduced confirmed cases by 99%, and epidemics by 59% (Mustapha and Harrison, 2018). More recently, outbreaks and epidemics in the meningitis belt have been caused by meningococcal C, W, and X (Parikh et al., 2020).

Risk factors for IMD susceptibility and severity are of considerable interest due to the potential for outbreaks and epidemics. The World Health Organization and the Centers for Disease Control and Prevention (both European and United States [US]) list age

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< 5 years, complement pathway deficiencies, asplenia, underlying chronic diseases, large group gatherings (such as Hajj or Umrah pilgrimage to Mecca), HIV infection, travel to or living in the African meningitis belt, and active or passive smoking as risk factors (Centres for Disease Control and Prevention, 2021, European Center for Disease Prevention and Control, 2021, World Health Organization, 2021).

Although there is an abundance of primary research literature on specific risk factors for contracting IMD and for IMD-related mortality, a comprehensive qualitative and quantitative overview of risk factors across all age groups is lacking. This systematic literature review (SLR) and meta-analysis (MA) sought to identify the wide range of risk factors for IMD contraction and related mortality across all age groups, to inform prevention strategies for IMD in potential high-risk groups.

Methods

An SLR was carried out by searching MEDLINE® and Embase via OvidSP from database inception to July 6, 2020. Full search strategies are provided in **Tables S1 – S2** in the **Supplementary Materials**.

A grey literature search was also conducted via manual screening of leading relevant infectious disease and clinical microbiology conference abstracts (2018 – 2020).

Study Selection, Data Extraction and Quality Assessment

Study eligibility criteria for inclusion in the qualitative synthesis of the SLR were defined using a modified version of the PICO framework. Studies that reported quantitative estimates of risk factors (e.g., odds ratio [OR], incidence rate ratio [IRR], risk ratio [RR]) on contracting IMD or IMD-related mortality were included and studies that did not include quantitative association measures were excluded. Two trained reviewers screened captured records according to pre-defined selection criteria and extracted data from the final list of included studies. Study characteristics extracted included study year(s), design, and jurisdiction; patient/exposure characteristics included patient age, serogroup status, race/ethnicity, sex, sexual orientation, comorbidities, socioeconomic status, travel history, and smoking status. Within-study statistical significance was ascertained through inspection of interquartile range or 95% confidence interval (CI). Any discrepancies in screening or data extraction decisions were resolved by a third senior reviewer. The screening process was summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Study quality was assessed using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by the same reviewers (National Institutes of Health, 2021).

Data Standardization

In the data extraction process, subgroups and risk factors (i.e., exposure and reference groups) were standardized and sorted into general categories such as age, sex, and socioeconomic status. While standardizing age for subgroups, some publications did not explicitly report age intervals in their study descriptions. Hence, the following assumptions were made based on inclusion criteria or sample characteristics: university students were assumed to be 18 – 22 years old; children 0 – 17 years old (based on the United Nations' criteria); adults or military service members 18 – 100 years old; if the study did not specify a specific population, the age interval was taken to be 0 – 100 years old. **Table S3** in the **Supplementary Materials** provides full details of the data standardization process.

Aggregate-Level Risk Factor Meta-analysis

Studies sharing a sufficient degree of homogeneity for all of the following characteristics — common exposure variable (e.g., comorbidities, smoke), reference variable, subgroup (e.g., age, socioeconomic status), association measure (e.g., OR, IRR, RR), and model (adjusted or unadjusted for selected covariates) — with at least one other study, were eligible for MA.

Random effects MA was carried out with the 'metafor' (v2.1) (Viechtbauer, 2010) package for R statistical software (v3.6.3) (R Core Team, 2018). Results were plotted using the pgfplots (v1.16) package for LaTeX. Thresholds for interpreting the I^2 statistic were as follows: 0% to 40% may not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity (Higgins et al., 2008).

Results

The search identified 11,359 records in MEDLINE® and Embase, and 19 records from grey literature. Following full-text screening, 74 records were retained for the qualitative synthesis (SLR) and 22 records were eligible for the MA (Fig. 1).

Study and Patient Characteristics

The present review only included observational study designs, consisting of: 28 cross-sectional studies, 28 retrospective cohort studies with study periods ranging between 1 year (Aubert et al., 2015, Hellenbrand et al., 2016, Mandal et al., 2017) and 34 years (Norheim et al., 2014), 15 case-control studies with study periods between < 1 year (Fischer et al., 1997) to 24 years (Lundbo et al., 2015), and three prospective cohort studies with study periods of 1 year (Tsolia et al., 2003), 2 years (de Greeff et al., 2008), and 9 years, (Sadarangani et al., 2015). Study periods ranged from the 1950s to 2018, with most studies including participants between the 1990s to late 2010s. Sample sizes ranged from 4 (Thabuis et al., 2018) to 16,734 subjects (Connolly and Noah, 1999) (median = 389). Among studies conducted within a single country, the two most common jurisdictions were the US and the United Kingdom (k = 10 studies each), followed by Canada and Australia (k = 8 each), Italy (k = 5), and France and the Netherlands (k = 4 each). Five studies were multi-national. **Table S4** in the **Supplementary Materials** presents full jurisdiction information with citations.

The age (median or mean, whichever was reported) of study participants ranged from 18.5 months (Lundbo et al., 2015) to 42 years, (Bloch et al., 2018) with an overall mean of 15 years. Thirteen studies examined risk factors of IMD in patient populations < 18 years old. The study with the youngest population included patients < 3 years old (Yusuf et al., 1999). Five studies investigated risk factors of IMD in young adults and included patients between the ages of 0 – 25 (De Wals et al., 2017, Hellenbrand et al., 2013, Krone et al., 2020, Mandal et al., 2017, Neal et al., 1999). Overall, the distribution of sex (reported in 32 studies) was relatively even, with the average male representation at 52%.

NIH Study Quality Assessment Tool

All 74 studies were assessed using the respective NIH tool according to study design. For the retrospective and prospective cohort, and cross-sectional studies (k = 59), there was generally a low to moderate risk of bias with three studies receiving a score ≥ 10 (max score of 14), defined as 'Good'. Fifty-three studies received a score of 5 – 9, defined as 'Fair', and three studies received

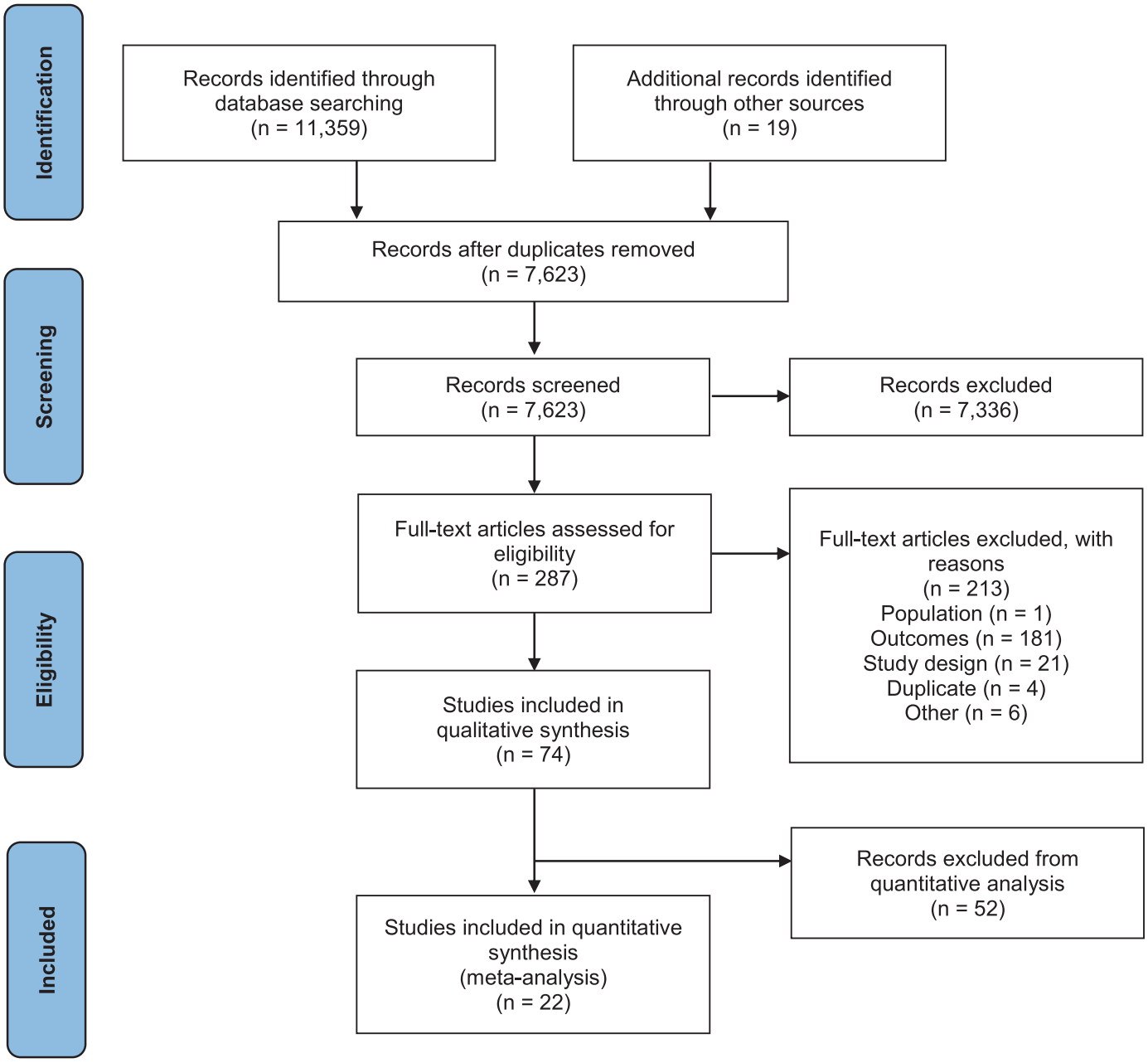


Fig. 1. PRISMA flow diagram.

a score below 5, defined as 'Poor'. Among the case-control studies (k = 15), there was a moderate risk of bias, with all studies assessed as 'Fair' (achieving a score of 4 – 8 out of a possible 10).

Summary of Risk Factors Identified from the Systematic Review

A high-level summary of the top ten risk factors with the largest effect sizes identified from within-study (subgroup vs. reference group) comparisons for contracting IMD identified in the SLR is provided in Table 1. These risk factors were not eligible for inclusion in MA (due to insufficient matching with other studies on key characteristics), but included: previous IMD infection, visits to licensed establishments (bars or other establishments where alcoholic drinks are served), *N. meningitidis* lineage 23 (in age ≥ 25 years), complement deficiency, age 0 – 4 years, visits to rave parties, university student status (either residing in a university residence with a bar opened prior to 1989, or simply attending university), and chronic underlying illness**.**

A comprehensive summary of risk factors for contracting IMD identified in the SLR is provided in **Table S5** in the **Supplementary Materials**.

Risk Factors Meta-analysis

In total, 22 studies met the criteria to be included in the MA of risk factors for contracting IMD (k = 11) and IMD-related mortality (k = 11).

See **Table S6** in the **Supplementary Materials** for details concerning the studies used for MA.

Risk Factors for Contracting IMD in the Meta-analysis

Eleven studies met the criteria for MA of risk factors for contracting IMD. The OR for IMD in subjects with chronic illness compared to those without chronic illness was reported in two studies

Table 1
Key risk factors and association measures for contracting IMD identified from the SLR (within-study).

Risk factor	Reference group	Number of IMD cases with risk factor	Statistic: point estimate (dispersion; *P*)	Publication
Previous IMD infection	General population	5,854	RR: 52.5 (IQR: 52.3 – 52.7; NR)	(Krone et al., 2020)
Visits (> 1/month) to licensed establishments[a]	Little or no visits to places serving alcohol	23	aOR: 35.2 (95% CI: 2.64 – 468; $P = .007$)	(Honish et al., 2008)
***N. meningitidis* lineage 23 (age ≥25 years; England/Wales)**	*N. meningitidis* lineage 3 (age ≥25 years)	82	aRR: 27.73 (95% CI: 12.91 – 59.56; NR)	(Hill et al., 2015)
Complement deficient (Serogroups X/Z/NG)	Complement deficient (Serogroup B)	10	RR: 22.6 (95% CI: 3.2 – 57.2; NR)	(Meiring et al., 2019)
Young age; 0-4 years	40-100 years	48	IRR: 15.4 (95% CI: 8.5 – 28.0; NR)	(Harley et al., 2002)
University student (UK; Serogroups A/C/W/Y)	Not a university student (UK; Serogroups A/C/W/Y)	NR	RR: 14.8 (95% CI, 4.3 –51.5; $P = .0001$)	(Mandal et al., 2017)
University residence bar (year opened 1970 – 1989)	University residence w/ no bar	NR	aIRR: 14.23 (95% CI, 4.55 –44.51; $P = .0001$)	(Nelson et al., 2001)
University residence bar (year opened < 1970)	University residence w/ no bar	NR	aIRR: 13.9 (95% CI, 6.56 – 29.45; $P = .0001$)	(Nelson et al., 2001)
Visits to raves	Little or no rave attendance	8	aOR: 12.8 (95% CI: 1.47 – 111; $P = .02$)	(Honish et al., 2008)
Chronic underlying illness[b]	No underlying chronic illness	11	aOR: 10.8 (2.7 – 43.3; NR)	(Fischer et al., 1997)

Abbreviations – aIRR: Adjusted incidence rate ratio; aOR: Adjusted odds ratio; aRR: Adjusted rate ratio; CI: Confidence Interval; IQR: Interquartile range; IRR: Crude incidence rate ratio; NR: Not reported; OR: Crude Odds Ratio; RR: Crude Risk Ratio.

[a] Bars or other establishments where alcoholic drinks are served

[b] Chronic illness included cancer, diabetes, renal failure, HIV-infection and agammaglobulinemia

(Honish et al., 2008, McCall et al., 2004). The pooled estimate OR was 0.54 (95% CI: 0.14 – 2.08, $I^2 = 67.43$).

Risk of contracting IMD was higher in HIV-positive subjects compared with HIV-negative subjects (RR: 4.77; 95% CI: 2.16 – 10.51, $I^2 = 96.61$; Table 2, Fig. 2**A**) (Meiring et al., 2019, Miller et al., 2014, Simmons et al., 2015) and substantially higher in HIV-positive subjects aged 25 – 44 years compared with same age HIV-negative subjects (RR: 11.88; 95% CI: 7.79 – 18.10; $I^2 = 0.00$; Table 2, Fig. 2**B**) (Miller et al., 2014, Simmons et al., 2015).

Risk of contracting IMD was also higher in subjects exposed to passive smoke compared with no passive smoke exposure (adjusted OR [aOR]: 2.37; 95% CI: 1.11 – 5.07; $I^2 = 75.18$; Table 2) (Grein and O'Flanagan, 2001, Hadjichristodoulou et al., 2016, Honish et al., 2008, Sorensen et al., 2004).

Crowding as a risk factor for contracting IMD was defined in two studies as the ratio of the number of people in the home to the number of bedrooms (crowding index), and high crowding index *versus* low crowding index conferred a higher risk (OR: 1.67; 95% CI: 1.16 – 2.41; $I^2 = 0.00$; Table 2, Fig. 2**C**) (Grein and O'Flanagan, 2001, Pereiro et al., 2004). Crowding was also defined as the absolute number of people in the house or sharing a bedroom with 2 or more people in three studies (crowded living space), and risk of contracting IMD in subjects living in a crowded living space was higher compared with living in a less crowded living space (OR: 2.78; 95% CI: 1.25 – 6.21; $I^2 = 51.82$; Table 2, Fig. 2**D**) (Grein and O'Flanagan, 2001, McCall et al., 2004, Pereiro et al., 2004).

Risk Factors for Mortality Due to IMD in the Meta-analysis

Twenty-four publications captured in the SLR reported risk factors for mortality due to IMD. Of these, 11 were appropriate for pooling in the MA, the results of which are summarized in Table 3.

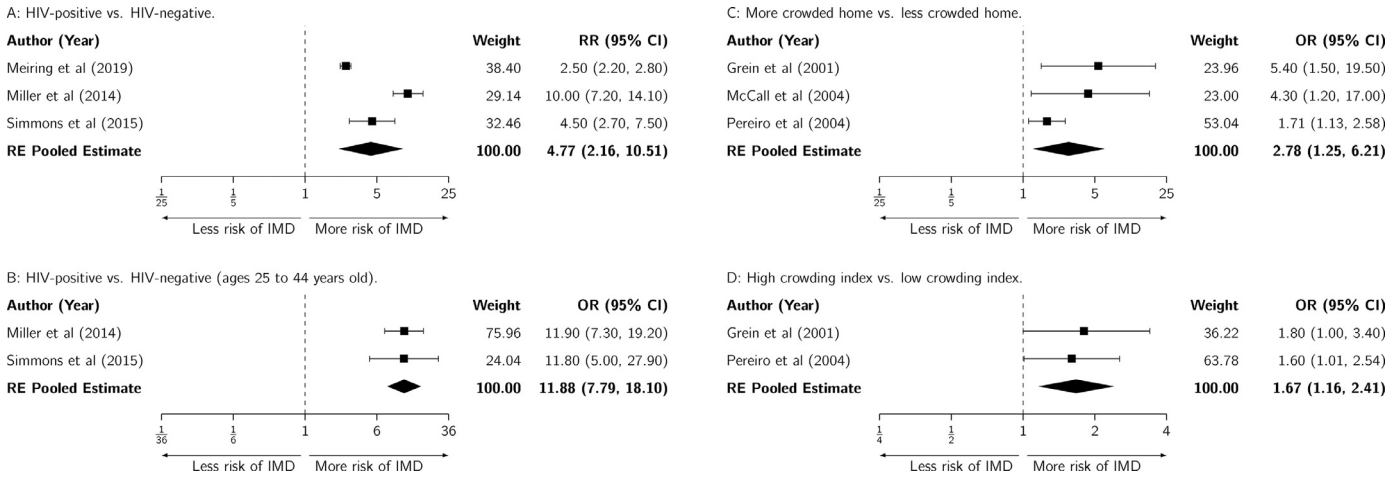
MA estimated numerically lower risks in young children (age 1 – 4) and adults (age 25 – 44), but higher risks in teenagers and young adults (age 15 – 24), when compared with infants (age < 1 year). However, none of these findings were statistically significant, with moderate to substantial heterogeneity. Point estimates for odds of mortality in adults aged 25 – 44 were significantly elevated in comparison with odds of mortality in infants and young children < 5 years; the OR for adults aged 25 – 45 years *versus* young children/infants was 3.63 (95% CI: 1.81 – 7.29; $I^2 = 0$). The reference age group in one study consisted of young children aged 1 – 4 years (Sadarangani et al., 2015) and in the other included young children aged < 5 years (Von Gottberg et al., 2008); however, it should be noted that in the Sadarangani et al (2015) study, death rates in infants (< 1 year) and young children (1 – 4 years) were virtually identical. In contrast, age 25 – 45 was not a significant risk factor for mortality when compared with age 0 – 1 years in the two relevant studies (Edge et al., 2016, Xu et al., 2012).

The RR for the risk of IMD-related mortality in subjects with serogroup C *versus* serogroup B was reported in two studies (Pugh et al., 2003, Whalen et al., 1995). Pugh et al. (2003) investigated subjects of all ages in Queensland, Australia in 2002, and Whalen et al. (1995) reported on subjects of all ages in Canada from 1985 – 1992. The RE pooled estimate was 3.18 (95% CI: 2.15 – 4.71, $I^2 = 5.02$).

Sex was not associated with any significant risk of IMD-related mortality, with a pooled estimate OR of 1.02 (95% CI: 0.24 – 1.43).

Discussion

Given the potential for IMD outbreaks and epidemics, variables associated with meningococcal nasopharyngeal carriage, susceptibility and mortality are under constant monitoring to guide the development of effective prevention strategies and to reduce disease



burden. The objective of the present SLR and MA was to identify risk factors associated with onset and mortality of IMD.

To the best of our knowledge, this is the first MA of IMD risk factors across all patient age groups. Studies identified in this SLR were predominantly large (> 100 participants), multi-center observational studies conducted from the 1990s to late 2010s. The majority of studies captured were conducted in European and North American countries. Participants' age and sex were well reported across publications, and serogroups were also commonly described.

Eleven studies were included in the MA for risk of contracting IMD. Risk factors eligible for pooling in the MA were limited to: HIV-positive status (in both a primary analysis and a subgroup analysis among participants aged 25 – 44 years old), comorbid chronic illness, passive smoke exposure, living space crowding index (high vs. low), and living space crowding (crowded vs. not crowded). Among these, all identified risk factors except comorbid chronic illness were significantly associated with increased risk of contracting IMD. Differences between participants in the two studies examining comorbid chronic illness as a risk factor for contracting IMD may have contributed to the substantial heterogeneity (I^2 = 67.43; 95% CI: 0, > 99) observed. In one study (Honish et al., 2008), patients with asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV infection were not included, and in the other, chronic conditions were not defined (McCall et al., 2004).

Household crowding and second-hand smoke exposure were also identified in the MA as significant risk factors for contracting IMD. Heterogeneity among the four studies included for pooled analysis of passive smoke inhalation was considerable (I^2 = 75.18; 95% CI: 0, 99). This degree of heterogeneity is not surprising, as the smoke exposure measures varied considerably, along with age of cases and controls. Heterogeneity among studies reporting on household crowding ranged from negligible (I^2 = 0.00; 95% CI: 0, 99) to moderate (I^2 = 52.0; 95% CI: 0, 98), depending on the measures used for defining crowding, which in themselves were variable. Therefore, much of the variability in these association measures is likely due to study design and population differences, as opposed to sampling error. The results must also be interpreted with caution in view of the wide ranges of 95% CIs for heterogeneity.

These two risk factors for IMD were also highlighted in a recent MA in pediatric populations (Spyromitrou-Xioufi et al., 2020). The present analysis provides further quantitative evidence for an association across all age groups between these environmental factors and IMD. Crowded living conditions lead to increased contact between asymptomatic carriers and more susceptible individuals, and passive smoke exposure is also known to increase carriage rates (Caugant and Maiden, 2009). A combination of crowding and smoke exposure may increase rates of carriage, as reported in studies from the era where smoking was more permitted in social situations (Bruce et al., 2001, MacLennan et al., 2006). Carriage rates are known to be highly variable; one study of Norwegian military recruits reported 91% carriage (Caugant et al., 1992), however, point-prevalence carriage rates between 10% – 35% have been estimated in young adults in the US and Europe (Cartwright et al., 1987, Caugant et al., 1994, Claus et al., 2005, Stephens, 1999). Despite relatively high carriage rates, carriage does not fully predict the occurrence of IMD, and neither can carriage be used as a proxy for vaccine efficacy (Caugant and Maiden, 2009).

In the present analysis, HIV positivity was associated with a substantially elevated risk of IMD. Considerable heterogeneity (I^2 = 96; 95% CI: 87, > 99) was evident in pooled estimates of relative risk (4.77; 95% CI: 2.16 – 10.51) for contracting IMD in HIV-infected *versus* HIV-uninfected individuals. Age distribution may be a factor contributing to heterogeneity, as point estimates of IMD risk for HIV-infected *versus* non-infected individuals of all ages appear relatively scattered compared with point estimates from subgroups aged 25 – 44. It should be noted that the subgroup analysis in subjects aged 25 – 44 excluded a South African study in which 44% of all subjects were aged < 5 years (Meiring et al., 2019). To the best of our knowledge, no prior MA has confirmed an association of HIV positivity with IMD susceptibility. It is known that individuals with HIV, regardless of CD4+ cell counts, have an increased risk of developing bacterial infections compared to the general population (Vaillant et al., 2020). In line with this, all studies included in our MA on HIV concluded that this is a population that is at increased risk of meningococcal disease and policy makers and clinicians should consider this when making decisions about meningococcal vaccine recommendations (Meiring et al., 2019, Miller et al., 2014, Simmons et al., 2015). Additionally, Miller et al (2014) suggest that cost-effectiveness analyses of vaccine options should be conducted for HIV-positive patients to better serve this population.

Eleven studies were appropriate for pooling in the MA for IMD-related mortality risk. Among the factors assessed, age between 25 and 45 years (vs. < 5 years) and serogroup C (vs. serogroup B), were each significantly (p < 0.001) associated with increased risk of IMD-related mortality. Two studies included for MA reported higher case-fatality rates and risk of mortality in adults compared to younger children (Sadarangani et al., 2015, Von Gottberg et al., 2008). Sadarangani et al (2015) examined outcomes and associated risk factors for death and complications from IMD in 868 Canadian hospitalized cases between 2002 and 2011. In their study, mortality was independently associated with age groups 20 – 24

Table 2
Random-effects meta-analysis pooled estimates for contracting IMD.

Risk factor	Reference group	IMD cases with risk factor	Statistic	Point estimate (95% CI)	I^2, % (95% CI)	*k*	Publications
Chronic illness[a]	No chronic illness	15	OR	0.54 (0.14 – 2.08)	67 (0, >99)	2	(Honish et al., 2008, McCall et al., 2004)
HIV-infected	HIV-uninfected	421	RR	**4.77 (2.16 – 10.51)**	96 (87, >99)	3	(Meiring et al., 2019, Miller et al., 2014, Simmons et al., 2015)
HIV-infected (25 – 44 years)	HIV-uninfected (25 – 44 years)	25	RR	**11.88 (7.79 – 18.10)**	0.00 (incalculable)	2	(Miller et al., 2014, Simmons et al., 2015)
Passive home smoke exposure	No passive home smoke exposure	NR	aOR[b]	**2.37 (1.11 – 5.07)**	75 (0, 99)	4	(Grein and O'Flanagan, 2001, Hadjichristodoulou et al., 2016, Honish et al., 2008, Sorensen et al., 2004)
Crowding index, high[c]	Crowding index, low	79	OR	**1.67 (1.16 – 2.41)**	0 (0, 99)	2	(Grein and O'Flanagan, 2001, Pereiro et al., 2004)
Living space, crowded[d]	Living space, less crowded	143	OR	**2.78 (1.25 – 6.21)**	52 (0, 98)	3	(Grein and O'Flanagan, 2001, McCall et al., 2004, Pereiro et al., 2004)

[a] The category "chronic illness" was defined as "conditions other than asplenia, complement disorder, diabetes, cancer, kidney disease requiring dialysis, or HIV" in Honish et al., 2008 and simply as "chronic condition" with no further elaboration in McCall et al., 2004.
[b] Adjustment factors: Grein and Flanagan, 2001 (day-care, ≥2 children under 6 years of age in household, number of adults in home, crowding index ≥2); Hadjichristodoulou et al., 2016 (recent symptoms of viral respiratory infection, relocation or vacation during the previous month, density: ≥ 4.4 (number of people per 100 m^2 house), age, gender); Honish et al., 2008 (use of external humidifier in home, attended raves, more than one visit per month to bars, mother's education less than high school diploma, visits to places where smoking is allowed); Sorenson et al., 2004 (maternal age, birth order, per capita income, crowding, and calendar year of hospitalization).
[c] High crowding index was defined as ≥2 and ≥1.5 persons/number of bedrooms in Grein and O'Flanagan et al., 2001 and Pereiro et al., 2004, respectively.
[d] Crowded living space was defined as ≥5 adults/household, ≥4 household members, and sharing bedroom with 2 or more people in Grein and O'Flanagan et al., 2001; Pereiro et al., 2004; and McCall et al., 2004, respectively.**Abbreviations** – aOR: Adjusted odds ratio; aRR: Adjusted risk ratio; CI: Confidence interval; k: Number of studies; OR: Crude odds ratio; RR: Crude risk ratio.Significant estimates (i.e., 95% CI does not include 1) are in **bold**.**NR:** Number of cases could not be determined accurately from reported data.

Table 3
Random-effects meta-analysis pooled estimates for IMD-related mortality.

Risk factor	Reference group	IMD deaths with risk factor	Statistic	Point estimate (95% CI)	I^2, % (95% CI)	*k*	Publications
Age, 1 – 4 years	Age, <1	NR	OR	0.26 (0.02 – 2.85)	91 (56, <99)	2	(Sadarangani et al., 2015, Xu et al., 2012)
	Age, <1	NR	RR	0.84 (0.37 – 1.93)	70 (0, >99)	2	(Memish et al., 2013, Whalen et al., 1995)
Age, 15 – 24 years	Age, <1	NR	aOR[a]	1.97 (0.89 – 4.38)	38 (0, >99)	2	(Edge et al., 2016, Xu et al., 2012)
Age, 25 – 45 years	Age, <1	NR	aOR[a]	0.55 (0.03 – 9.37)	98 (88, >99)	2	(Edge et al., 2016, Xu et al., 2012)
	Age, <5	NR	OR	**3.63 (1.81 – 7.29)**	0 (0, >99)	2	(Sadarangani et al., 2015, Von Gottberg et al., 2008)
Age, 5 – 20 years	Age, <5	NR	OR	1.81 (0.76 – 4.29)	0 (0, 98)	2	(Sadarangani et al., 2015, Von Gottberg et al., 2008)
Serogroup, C	Serogroup, B	NR	RR	**3.18 (2.15 – 4.71)**	5 (0, >99)	2	(Pugh et al., 2003, Whalen et al., 1995)
Serogroup, W	Serogroup, B	41	aOR[b]	2.60 (0.57 – 11.88)	46 (0, 99)	2	(Campbell et al., 2020, Loenenbach et al., 2020)
Serogroup, Y	Serogroup, B	15	aOR[c]	1.86 (0.99 – 3.50)	0 (0, 98)	2	(Campbell et al., 2020, Stoof et al., 2015)
Sex, Male	Sex, Female	NR	OR	1.02 (0.24 – 1.43)	0 (0, 63)	3	(Duarte et al., 2005, Loenenbach et al., 2020, Sadarangani et al., 2015, Von Gottberg et al., 2008)
Strain not susceptible to penicillin	Strain susceptible to penicillin	NR	OR	1.21 (0.59 – 2.45)	36 (0, 99)	3	(Sadarangani et al., 2015, Von Gottberg et al., 2008, Xu et al., 2012)

[a] Adjustment factors: Edge et al., 2016 (age group, gender, capsular group, diagnostic method, clinical presentation and year of diagnosis); Xu et al., 2012 (not reported)
[b] Adjustment factors: Campbell et al., 2020 (age group); Loenenback et al., 2020: (age, gender, and comorbidity, clinical manifestation)
[c] Adjustment factors: Campbell et al., 2020 (age group); Stoof et al., 2015: (age, clinical manifestations, serogroups, clonal complex, comorbidity groups [none, immunocompromising, non-immunocompromising])Significant estimates (i.e., 95% CI does not include 1) are in **bold**.**Abbreviations** – aOR: Adjusted odds ratio; aRR: Adjusted risk ratio; CI: Confidence interval; k: Number of studies; NR: Number of cases could not be determined accurately from reported data; OR: Crude odds ratio; RR: Crude risk ratio.

years and 60 – 99 years (vs. 1 – 4 years), shock, admission to the intensive care unit, and symptom onset within 24 hours of admission. Von Gottberg et al (2008) examined 185 IMD cases (35 deaths) in Gauteng, South Africa between 2003 and 2005. Independent risk factors for death included age 25 – 44 years (vs. < 5 years) and meningococcemia *versus* meningitis. In their study, serogroup (W135 vs. A) was not a factor affecting mortality. The age-dependence of mortality risk was explored in a recent global SLR/MA, indicating case fatality rates gradually decreasing from infancy through childhood, subsequently increasing from age 10 – 25, with a stable elevated plateau between age 25 – 45, and exponentially increasing thereafter (Wang et al., 2019). Our MA results are consistent insofar as the risk for mortality was significantly higher from age 25 – 45 compared with age < 5 years, but we did not capture data for MA of ages > 45. Wang et al (2019) estimated that case fatality rates doubled from 15% in young adults to 30% in elderly aged 75 years.

The present analysis confirmed an increased risk of death for serogroup C, W and Y, relative to serogroup B; however, only the risk associated with serogroup C was significant (RR = 3.18; 95% CI: (2.15 – 4.71), with negligible heterogeneity between studies (I^2 = 5; 95% CI: 0, > 99; Table 3) (Pugh et al., 2003, Whalen et al., 1995). This is also consistent with findings from the recent SLR/MA by Wang et al (2019), where serogroups C, Y, and W were associated with higher case fatality rates (12.0%, 10.8%, and 12.8% respectively) relative to serogroup B (6.9%) (Wang et al., 2019). By way of comparison, the finding for mortality of serogroup C *versus* serogroup B from Wang et al (2019) translates to an RR of 1.74. It should, however, be noted that associations between serogroups and clonal complexes may vary over time, such that one particular serogroup may have predominance of hyper-virulent clonal complex explaining its high mortality rate at that time. These results on serogroups should therefore be interpreted with caution.

One limitation of this MA relates to the limited availability of data appropriate for pooling and MA, mainly due to variation across included studies in exposure or reference categories, patient subgroups, or effect measures and/or models used. The studies included potentially captured results which were not estimating the same quantity from the same populations. However, one strength of this SLR consists of identification of a large number of observational studies as an evidence base for summarizing and describing IMD risk factors in the real world. Most studies were of "fair" quality based on the relevant NIH Quality Assessment tools, lending weight to the reliability of the evidence base. Additionally, as our review captured publications on both adult and pediatric patients, our findings may be more broadly applicable to a wider range of at-risk populations. Nonetheless, given the number of studies conducted in Europe and North America, our results underscore a persistent lack of reporting on IMD risk factors in developing countries. The relatively low number of studies that could be matched for MA could conceivably introduce imprecision in the I^2 statistic estimating heterogeneity (von Hippel, 2015). More consistent analytical methods of future studies would perhaps help mitigate these limitations, though this may not always be feasible.

Even though we identified a large number of risk factors and evaluated them as reported in eligible studies via MA, as well as at the level of individual studies, we did not capture interactions, additive or relative, of mixed effects of multiple risk factors. For example, socioeconomic status can independently impact parental level of education, family size, and crowding in the home; while age and comorbidities can have a synergetic effect on IMD. Similarly, our review and analyses necessarily spanned different jurisdictions and time periods; however, regional and temporal trends in IMD could not be accounted for here. These may be considered limitations, but they reflect the current state of the IMD literature, which generally does not report on interactions between known risk factors, geography, and temporal trends.

Conclusions

This review and meta-analysis identified a number of host-related and environmental variables across a wide range of categories from studies reporting on risk factors for contracting IMD and IMD-related mortality. This MA quantified the substantial and significant risk in HIV-infected individuals for contracting IMD, and extended previous findings identifying crowded living environments and passive smoke exposure as risk factors in children and adolescents, as well as older age groups. This study also confirms findings from a previous MA associating higher risks of IMD-related mortality with age (25 – 44 years) and serogroup C. Further studies are warranted to understand the critical range of factors, singly or in combination, contributing to IMD transmission, susceptibility, and clinical outcome. This understanding would benefit public health interventions to reduce the burden of IMD.

Declaration of Competing Interest

Himanshu Dubey, Philipp Oster, Sandra Guedes, and Amine Amiche are, or were, employees and shareholders of Sanofi Pasteur at the time of this study. Mir Sohail Fazeli, Paul Serafini, and Lisa Leung are employed by Evidinno Outcomes Research Inc. (Vancouver, BC, Canada), which was contracted by Sanofi Pasteur to conduct this study.

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Ethical approval was not required.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.03.032.

References

Aubert L, Taha MK, Boo N, Le Strat Y, Deghmane AE, Sanna A, et al. Serogroup C invasive meningococcal disease among men who have sex with men and in gay-oriented social venues in the Paris region: July 2013 to December 2014. Eurosurveillance 2015;20(3) (no pagination)(21016).

Bloch D, Murray K, Peterson E, Ngai S, Rubinstein I, Halse TA, et al. Sex Difference in Meningococcal Disease Mortality, New York City, 2008-2016. Clinical Infectious Diseases 2018;67(5):760–9.

Bruce MG, Rosenstein NE, Capparella JM, Shutt KA, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. Jama 2001;286(6):688–93.

Campbell H, Andrews N, Parikh S, Ribeiro S, Gray S, Lucidarme J, et al. Variable clinical presentation by the main capsular groups causing invasive meningococcal disease in England. Journal of Infection 2020;80(2):182–9.

Cartwright KAV, Stuart JM, Jones DM, Noah ND. The Stonehouse survey: Nasopharyngeal carriage of meningococci and Neisseria lactamica. Epidemiology and Infection 1987;99(3):591–601.

Caugant DA, Hoiby EA, Magnus P, Scheel O, Hoel T, Bjune G, et al. Asymptomatic carriage of Neisseria meningitidis in a randomly sampled population. Journal of Clinical Microbiology 1994;32(2):323–30.

Caugant DA, Hoiby EA, Rosenqvist E, Froholm LO, Selander RK. Transmission of Neisseria meningitidis among asymptomatic military recruits and antibody analysis. Epidemiol Infect 1992;109(2):241–53.

Caugant DA, Maiden MC. Meningococcal carriage and disease–population biology and evolution. Vaccine 2009;27(Suppl 2):B64–70.
Centres for Disease Control and Prevention. Bacterial Meningitis; 2021. Available from: https://www.cdc.gov/meningitis/bacterial.html. [Accessed October 17, 2021].
Claus H, Maiden MCJ, Wilson DJ, McCarthy ND, Jolley KA, Urwin R, et al. Genetic analysis of meningococci carried by children and young adults. Journal of Infectious Diseases 2005;191(8):1263–71.
Connolly M, Noah N. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993-6. Epidemiology and Infection 1999;122(1):41–9.
de Greeff SC, de Melker HE, Schouls LM, Spanjaard L, van Deuren M. Pre-admission clinical course of meningococcal disease and opportunities for the earlier start of appropriate intervention: a prospective epidemiological study on 752 patients in the Netherlands, 2003-2005. Eur J Clin Microbiol Infect Dis 2008;27(10):985–92.
De Wals P, Deceuninck G, Lefebvre B, Tsang R, Law D, De Serres G, et al. Impact of an immunization campaign to control an increased incidence of serogroup B meningococcal disease in one region of Quebec, Canada. Clinical Infectious Diseases 2017;64(9):1263–7.
Duarte MCMB, Amorim MR, Cuevas LE, Cabral-Filho JE, Correia JB. Risk factors for death from meningococcal infection in Recife, Brazil. Journal of Tropical Pediatrics 2005;51(4):227–31.
Edge C, Waight P, Ribeiro S, Borrow R, Ramsay M, Ladhani S. Clinical diagnoses and outcomes of 4619 hospitalised cases of laboratory-confirmed invasive meningococcal disease in England: Linkage analysis of multiple national databases. Journal of Infection 2016;73(5):427–36.
Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2010;10(5):317–28.
European Center for Disease Prevention and Control. Factsheet about meningococcal disease; 2021. Available from: https://www.ecdc.europa.eu/en/meningococcal-disease/factsheet. [Accessed October 16 2021].
Fischer M, Hedberg K, Cardosi P, Plikaytis BD, Hoesly FC, Steingart KR, et al. Tobacco smoke as a risk factor for meningococcal disease. Pediatric Infectious Disease Journal 1997;16(10):979–83.
Grein T, O'Flanagan D. Day-care and meningococcal disease in young children. Epidemiology and Infection 2001;127(3):435–41.
Hadjichristodoulou C, Mpalaouras G, Vasilopoulou V, Katsioulis A, Rachiotis G, Theodoridou K, et al. A case-control study on the risk factors for meningococcal disease among children in Greece. PLoS ONE 2016;11(6) (no pagination)(e0158524).
Harley D, Hanna JN, Hills SL, Bates JR, Smith HV. Epidemiology of invasive meningococcal disease in north Queensland, 1995 to 1999. Communicable diseases intelligence 2002;26(1):44–50.
Hellenbrand W, Claus H, Schink S, Marcus U, Wichmann O, Vogel U. Risk of invasive meningococcal disease in men who have sex with men: Lessons learned from an outbreak in Germany, 2012-2013. PLoS ONE 2016;11(8) (no pagination)(e0160126).
Hellenbrand W, Elias J, Wichmann O, Dehnert M, Frosch M, Vogel U. Epidemiology of invasive meningococcal disease in Germany, 2002-2010, and impact of vaccination with meningococcal C conjugate vaccine. Journal of Infection 2013;66(1):48–56.
Higgins JPT, Green S, Cochrane C. Cochrane handbook for systematic reviews of interventions. Chichester, England; Hoboken, NJ: Wiley-Blackwell; 2008.
Hill DMC, Lucidarme J, Gray SJ, Newbold LS, Ure R, Brehony C, et al. Genomic epidemiology of age-associated meningococcal lineages in national surveillance: An observational cohort study. The Lancet Infectious Diseases 2015;15(12):1420–8.
Honish L, Soskolne CL, Senthilselvan A, Houston S. Modifiable risk factors for invasive meningococcal disease during an Edmonton, Alberta outbreak, 1999-2002. Canadian Journal of Public Health 2008;99(1):46–51.
Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013;11(1):17.
Krone M, Lam TT, Claus H, Vogel U. Recurrent invasive meningococcal infections - quantifying the risk, Germany, 2002 to 2018. Euro Surveill 2020;25(25).
Loenenbach AD, van der Ende A, de Melker HE, Sanders EAM, Knol MJ. The Clinical Picture and Severity of Invasive Meningococcal Disease Serogroup W Compared With Other Serogroups in the Netherlands, 2015-2018. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2020;70(10):2036–44.
Lundbo LF, Sorensen HT, Clausen LN, Hollegaard MV, Hougaard DM, Konradsen HB, et al. Mannose-binding lectin gene, MBL2, polymorphisms do not increase susceptibility to invasive meningococcal disease in a population of Danish children. Open Forum Infectious Diseases 2015;2(4) (no pagination)(ofv127).
MacLennan J, Kafatos G, Neal K, Andrews N, Cameron JC, Roberts R, et al. Social behavior and meningococcal carriage in British teenagers. Emerging Infectious Diseases 2006;12(6):950–7.
Mandal S, Campbell H, Ribeiro S, Gray S, Carr T, White J, et al. Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine. Vaccine 2017;35(43):5814–18.
McCall BJ, Neill AS, Young MM. Risk factors for invasive meningococcal disease in southern Queensland, 2000-2001. Intern Med J 2004;34(8):464–8.
Meiring S, Cohen C, De Gouveia L, Du Plessis M, Kularatne R, Hoosen A, et al. Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003-2016. Clinical Infectious Diseases 2019;69(3):495–504.
Memish Z, Al Hakeem R, Al Neel O, Danis K, Jasir A, Eibach D. Laboratory-confirmed invasive meningococcal disease: effect of the Hajj vaccination policy, Saudi Arabia, 1995 to 2011. Euro Surveill 2013;18(37):12.
Miller L, Arakaki L, Ramautar A, Bodach S, Braunstein SL, Kennedy J, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Annals of Internal Medicine 2014;160(1):30–7.
Mustapha MM, Harrison LH. Vaccine prevention of meningococcal disease in Africa: Major advances, remaining challenges. Human Vaccines and Immunotherapeutics 2018;14(5):1107–15.
National Institutes of Health. Study Quality Assessment Tools - Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies; 2021. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. [Accessed Nov 24 2021].
Neal KR, Nguyen-Van-Tam J, Monk P, O'Brien SJ, Stuart J, Ramsay M. Invasive meningococcal disease among university undergraduates: Association with universities providing relatively large amounts of catered hall accommodation. Epidemiology and Infection 1999;122(3):351–7.
Nelson SJ, Charlett A, Orr HJ, Barker RM, Neal KR, Taylor C, et al. Risk factors for meningococcal disease in university halls of residence. Epidemiology and Infection 2001;126(2):211–17.
Norheim G, Sadarangani M, Omar O, Yu LM, Molbak K, Howitz M, et al. Association between population prevalence of smoking and incidence of meningococcal disease in Norway, Sweden, Denmark and the Netherlands between 1975 and 2009: A population-based time series analysis. BMJ Open 2014;4(2) (no pagination)(e003312).
Pace D, Pollard AJ. Meningococcal disease: clinical presentation and sequelae. Vaccine 2012;30:B3–9.
Parikh SR, Campbell H, Bettinger JA, Harrison LH, Marshall HS, Martinon-Torres F, et al. The everchanging epidemiology of meningococcal disease worldwide and the potential for prevention through vaccination. J Infect 2020;81(4):483–98.
Parikh SR, Campbell H, Gray SJ, Beebeejaun K, Ribeiro S, Borrow R, et al. Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015. Vaccine 2018;36(26):3876–81.
Pereiro I, Diez-Domingo J, Segarra L, Ballester A, Albert A, Morant A. Risk factors for invasive disease among children in Spain. J Infect 2004;48(4):320–9.
Perez AE, Dickinson FO, Rodriguez M. Community acquired bacterial meningitis in Cuba: a follow up of a decade. BMC Infectious Diseases 2010;10:130.
Pugh RE, Smith H, Young M. Surveillance of invasive meningococcal disease in Queensland, 2002. Communicable diseases intelligence 2003;27(3):342–51.
R Core Team. R: A language and environment for statistical computing. Vienna, Austria.: R Foundation for Statistical Computing; 2018 Available from: https://www.r-project.org/ [Accessed Nov 24 2021].
Sadarangani M, Scheifele DW, Halperin SA, Vaudry W, Le Saux N, Tsang R, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: A prospective cohort study. Clinical Infectious Diseases 2015;60(8):e27–35.
Simmons RD, Kirwan P, Beebeejaun K, Riordan A, Borrow R, Ramsay ME, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: A population-based cohort study. BMC Medicine 2015;13(1) (no pagination)(297).
Sorensen HT, Labouriau R, Jensen ES, Mortensen PB, Schonheyder HC. Fetal growth, maternal prenatal smoking, and risk of invasive meningococcal disease: A nationwide case-control study. International Journal of Epidemiology 2004;33(4):816–20.
Spyromitrou-Xioufi P, Tsirigotaki M, Ladomenou F. Risk factors for meningococcal disease in children and adolescents: a systematic review and META-analysis. European Journal of Pediatrics 2020;179(7):1017–27.
Stephens DS. Uncloaking the meningococcus: dynamics of carriage and disease. Lancet 1999;353(9157):941–2.
Stoof SP, Rodenburg GD, Knol MJ, Rumke LW, Bovenkerk S, Berbers GAM, et al. Disease Burden of Invasive Meningococcal Disease in the Netherlands between June 1999 and June 2011: A Subjective Role for Serogroup and Clonal Complex. Clinical Infectious Diseases 2015;61(8):1281–92.
Thabuis A, Tararbit K, Taha MK, Dejour-Salamanca D, Ronin V, du Chatelet IP, et al. Community outbreak of serogroup B invasive meningococcal disease in Beaujolais, France, February to June 2016: From alert to targeted vaccination. Eurosurveillance 2018;23(28) (no pagination)(1700590).
Tsolia MN, Theodoridou M, Tzanakaki G, Kalabalikis P, Urani E, Mostrou G, et al. The evolving epidemiology of invasive meningococcal disease: A two-year prospective, population-based study in children in the area of Athens. FEMS Immunology and Medical Microbiology 2003;36(1-2):87–94.
Vaillant AAJ, Naik R. HIV-1 associated opportunistic infections. StatPearls [Internet] 2020.
Viechtbauer W. Conducting meta-analyses in R with the metafor package. Journal of statistical software 2010;36(3):1–48.
Von Gottberg A, Du Plessis M, Cohen C, Prentice E, Schrag S, De Gouveia L, et al. Emergence of endemic serogroup W135 meningococcal disease associated with a high mortality rate in South Africa. Clinical Infectious Diseases 2008;46(3):377–86.
von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Methodol 2015;15:35.

Wang B, Santoreneos R, Giles L, Haji Ali Afzali H, Marshall H. Case fatality rates of invasive meningococcal disease by serogroup and age: A systematic review and meta-analysis. Vaccine 2019;37(21):2768–82.
Whalen CM, Hockin JC, Ryan A, Ashton F. The changing epidemiology of invasive meningococcal disease in Canada, 1985 through 1992. Emergence of a virulent clone of Neisseria meningitidis. JAMA 1995;273(5):390–4.
World Health Organization. Meningitis; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/meningitis. [Accessed October 17 2021].
Xu XH, Ye Y, Hu LF, Jin YH, Jiang QQ, Li JB. Emergence of serogroup C meningococcal disease associated with a high mortality rate in Hefei, China. BMC Infectious Diseases 2012;12:205.
Yusuf HR, Rochat RW, Baughman WS, Gargiullo PM, Perkins BA, Brantley MD, et al. Maternal cigarette smoking and invasive meningococcal disease: A cohort study among young children in Metropolitan Atlanta, 1989-1996. American Journal of Public Health 1999;89(5):712–17.