Meningococcal Carriage in High-Risk Settings: A Systematic Review

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Meningococcal carriage in high-risk settings: A systematic review

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ABSTRACT

Background: Historically, semi-closed populations have had high rates of meningococcal carriage and have experienced recurrent outbreaks. As such, these high-risk groups are recommended for targeted vaccination in many countries.
Methods: A systematic review of eight databases and Google Scholar forward citations was conducted to characterize serogroup-specific meningococcal carriage in university students, military personnel, and Hajj pilgrims from 2007 to 2016.
Results: A total of 7014 records were identified and 22 studies were included. Overall carriage ranged from 0.0% to 27.4% in Hajj pilgrims, from 1.5% to 71.1% in university students, and from 4.2% to 15.2% in military personnel. Among serogroups A, B, C, W, X, and Y, serogroup B was most prevalent in Hajj pilgrims, B and Y in university students, and B, C, and Y in military personnel. 'Other' serogroups were more prevalent in university students than Hajj pilgrims or military personnel. Risk factors for carriage varied by setting. Among Hajj pilgrims, a high endemicity in the country of origin increased the risk of carriage, while smoking, male sex, and frequently attending parties increased the carriage risk for university students. Similarly, smoking increased the carriage risk for professional soldiers. Data gaps remain for many regions.
Conclusions: Preventative vaccination policies for high-risk groups should be based on current disease data in individual countries, supplemented by carriage data. Meningococcal carriage studies and disease surveillance are critical for determining the local epidemiology, populations responsible for disease transmission, and the need for targeted vaccination.

Introduction

Invasive meningococcal disease (IMD) is a severe bacterial infection caused by *Neisseria meningitidis*, a Gram-negative bacterium often carried harmlessly in the pharynx of humans. IMD commonly presents as meningitis and septicaemia, but can more rarely cause diseases such as septic arthritis and pericarditis (Pace and Pollard, 2012). Despite advances in medical care, IMD case fatality is approximately 10–15%, and debilitating sequelae, such as amputation and neurological impairment, can result from infection in an estimated 10–15% of survivors (Pace and Pollard, 2012; Edmond et al., 2010). The incidence of IMD varies globally, with the highest burden in the African meningitis belt, young children and adolescents, and immunocompromised individuals (Harrison et al., 2009; McNamara et al., 2017a; Snydman et al., 2014; Jafri et al., 2013). Additionally, semi-closed populations are at high risk of infection, with numerous outbreaks reported among university students, Hajj/Umrah pilgrims, and military recruits (Brundage et al., 2002; Jean-François et al., 2002; National Foundation for Infectious Diseases (NFID), 2017). As such, preventative vaccination programmes have been introduced in these settings (National Foundation for Infectious Diseases (NFID), 2017; Yezli et al., 2016a; Michael et al., 2015).

Historically, carriage of the bacterium was estimated to occur in approximately 10% of the general population, with most people becoming a carrier multiple times in their lifetime (Cartwright et al., 1987). Transmission of the meningococcus occurs through droplet spread and thus through close contact with a carrier of *N. meningitidis* or an infected individual. Studies estimate that carriage peaks in early-to-late adolescence, depending on the region (Cooper et al., 2017; Christensen et al., 2010), indicating that persons of these ages are likely important transmitters of disease. Social behaviours, recent respiratory infections, and

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environmental factors can also increase an individual's risk of carriage (MacLennan et al., 2006; Mueller et al., 2008).

Six of the 12 capsular groups of *N. meningitidis*—A, B, C, W, X, and Y—cause the majority of disease cases, and their distribution varies globally. There are vaccines currently available targeting five of the 12 meningococcal serogroups, i.e. A, B, C, W, and Y, although the 'B' vaccines include recombinant proteins or recombinant proteins plus outer membrane vesicles, not capsular polysaccharides like the other vaccines. While conjugate vaccines have induced herd immunity for some serogroups, in part through a reduction in carriage levels (Trotter and Maiden, 2009), it is as yet unclear whether the broad-protection MenB vaccines will have similar effects (Donnelly et al., 2010; Pajon et al., 2016). Knowledge of the locally circulating serogroups and disease incidence is key for appropriate vaccine recommendations.

Hitherto, reviews have focused on select regions/populations or have provided prevalence-only carriage data, and an updated carriage review is warranted (Soriano-Gabarro et al., 2011a; Trotter and Greenwood, 2007; Agier et al., 2017; Zhang et al., 2007; Yezli et al., 2016b). No review describing serogroup-specific carriage in the three high-risk settings of university students, military personnel, and Hajj/Umrah pilgrims at a global level could be identified. Understanding the serogroups carried by high-risk populations such as these is important in gaining a better understanding of disease transmission and potential populations for vaccination (Borrow et al., 2016; Vetter et al., 2016). Therefore, the aim of this review was to summarize the carriage studies with serogroup data conducted in these defined high-risk settings for the period 2007–2016.

Methods

Search strategy and data sources

A systematic review of the literature was conducted to identify serogroup-specific meningococcal carriage studies conducted between January 1, 2007 and December 31, 2016 in university students, military personnel, or Hajj/Umrah pilgrims (PROSPERO number CRD42017074671). Two authors (MEP and RM) searched six databases (MEDLINE, Embase, Global Health Database, WHO Global Health Library, Web of Science, Current Contents Connects) in July 2017. Search terms were developed for MEDLINE (Supplementary material, Table S1) and adapted for the remaining databases. Two Chinese literature databases (CNKI and Wanfang) were searched in June 2017 by a native speaker (YL), who translated the Chinese search terms from the English version. Google Scholar forward citations, relevant conference abstract lists, and references of identified studies and reviews were also searched. Forward searches on Google Scholar and conference abstracts were searched again in January 2018 as an update. No exclusion was made based upon language, and Google Translate was used to assist in the screening of foreign language articles. If questions remained, native speakers were contacted for assistance in translation.

Inclusion and exclusion criteria

Studies were considered for inclusion if they reported serogroup-specific pharyngeal carriage in asymptomatic individuals in a high-risk setting (Hajj/Umrah pilgrimage, university, or military), provided a clear geographic location for the participants, and were sampled only from the setting in question.

Studies were not eligible for inclusion if they were not in humans, only provided disease data, were carriage studies among cases or close-contacts of cases, only reported secondary data, were case studies, commentaries, or reviews, did not specify the geographic location or included global samples together, had unclear reporting of serogroups or participants sampled, only tested for one serogroup, could not be obtained and the author could not be contacted, or serogrouped or reported less than 75% of positive carriage specimens.

Data collection and management

Studies identified were imported into EndNote, where duplicates were removed. Two authors (MEP and RM) independently screened the titles and abstracts of all studies and the relevant full-text articles from the English databases. Data from studies selected for inclusion were independently extracted into Microsoft Access by two authors (MEP and RM). One author screened the Chinese articles (YL) with input from another (MEP). Any disagreements in eligibility or extractions were discussed and a consensus reached before moving forward.

Quality assessment

Studies identified for inclusion were assessed for quality using a modified Joanna Briggs Institute Checklist for Prevalence Studies. The quality of studies was ranked as high (0–3 no/unclear), medium (4–6 no/unclear), or low (7–9 no/unclear).

Data analysis

A narrative synthesis was performed for identified studies. Results were reported by high-risk setting and World Health Organization (WHO) region. Meta-analyses of serogroup carriage prevalence were deemed inappropriate due to heterogeneity between study populations and settings and/or insufficient data by WHO region.

Results

A total of 7014 records were identified and 331 were screened in full. Of these, 23 met the inclusion criteria (Figure 1). Three studies were among Hajj pilgrims, 14 among university students, five among military personnel, and one among university students and military personnel. Ten studies sampled participants in the high-risk settings of interest and reported serogroup-specific carriage but did not meet other eligibility criteria (Supplementary material, Table S2). Most studies received medium-level quality scores, primarily due to underreporting of study or population characteristics (Supplementary material, Table S3). Since no methodological 'gold standard' exists for carriage studies, no studies were excluded from the review based on quality scores.

Hajj pilgrims

Three studies among Hajj pilgrims met the inclusion criteria (Azeem et al., 2017; Ceyhan et al., 2013; Memish et al., 2017), and no eligible studies were conducted among Umrah pilgrims. Each of the included studies investigated serogroup-specific carriage among pilgrims both before and after the Hajj. However, the location of the 'before' and 'after' time point was inconsistent between studies and was a combination of swabbing pilgrims in their home countries and/or while in Mina. In total, 2774 pilgrims were sampled, representing 14 nationalities. One study included was a cohort study among Turkish pilgrims in 2010 (Ceyhan et al., 2013), while the other two studies were repeat cross-sectional studies with a nested cohort, one among Australian pilgrims in 2014 and the other among pilgrims from 12 countries in 2014 (Azeem et al., 2017; Memish et al., 2017).

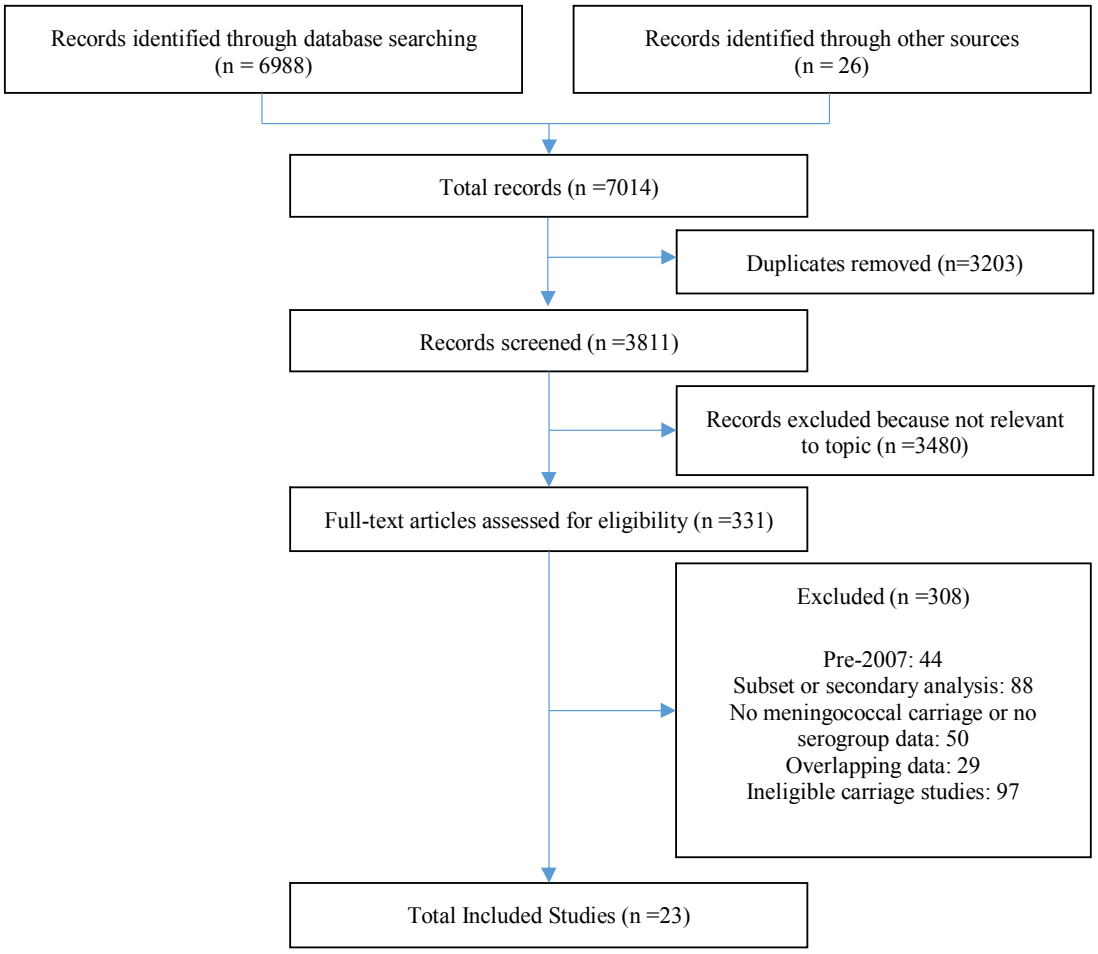

Figure 1. PRISMA flowchart of included studies.

Study variables affecting carriage prevalence also varied. Nearly all pilgrims from two studies were vaccinated with the quadrivalent (ACWY) polysaccharide vaccine prior to the pilgrimage (Ceyhan et al., 2013; Memish et al., 2017), while one study reported approximately one-third of the pilgrims were vaccinated with the quadrivalent conjugate vaccine (Azeem et al., 2017). Chemoprophylaxis was given to pilgrims from countries of the African meningitis belt upon arrival at the airport in Saudi Arabia. Most participants were at least 18 years old.

Laboratory methods also varied between studies (Supplementary material, Table S4). The site of swabbing was inconsistent between studies, with one using nasopharyngeal swabs (Memish et al., 2017), one posterior pharyngeal swabs (Azeem et al., 2017), and one both oropharyngeal and nasopharyngeal swabs (Ceyhan et al., 2013). Only one study swabbed participants both prior to and after vaccine administration (Ceyhan et al., 2013), while the other two swabbed participants only after administration (Azeem et al., 2017; Memish et al., 2017). PCR was used to identify the genogroup in all studies. However, one study used slide agglutination (SASG) to determine the 'after' pilgrimage serogroups (Azeem et al., 2017).

Carriage rates were typically below 5% (Azeem et al., 2017; Memish et al., 2017), but carriage up to 27% was reported (Ceyhan et al., 2013). Pilgrims from the Western Pacific region had the lowest carriage prevalence (before: 0.0–0.5%; after: 0.0–1.1%), while Turkish pilgrims from the European region had the highest (before: 13.4%; after: 27.4%). Serogroups A, B, W, Y, and non-groupable were identified in at least one study, with serogroup B being the most common in many regions (Table 1). In most cases, when a serogroup was detected, the change in prevalence before and after the Hajj was not substantial (median 1.3%, mean 2.6%, range 0.0–14.0%). The extent of acquisition was variable between studies. No carriers were found among pilgrims from Albania or India (Memish et al., 2017).

Only one study assessed risk factors associated with meningococcal carriage among Hajj pilgrims (Supplementary material, Table S7) (Memish et al., 2017). The only risk factor investigated in that study was the endemicity of the country of origin and its effect on carriage at arrival. Pilgrims from high endemic countries (Ethiopia, Nigeria, and Tanzania) were found to have statistically higher carriage rates upon arrival than pilgrims from other countries (6.3% and 2.0%, respectively).

University students

Fifteen studies that sampled only university students met the inclusion criteria. Six studies were cross-sectional studies (Aliyu and Olayinka, 2017; Bali et al., 2017; Rizek et al., 2016; Rodrigues et al., 2015; Rodriguez et al., 2014; Tryfinopoulou et al., 2016; Takahashi et al., 2016), six were repeat cross-sectional studies with a nested cohort (either intentional or unintentional) (Ala'aldeen et al., 2011; Breakwell et al., 2018; Durey et al., 2012; McNamara et al., 2017b; Oldfield et al., 2017; Soeters et al., 2017), two were cohort studies (Bidmos et al., 2011; Gilca et al., 2013), and one was a randomized controlled trial investigating the impact of vaccination on carriage (Read et al., 2014). The majority of studies were conducted in the region of the Americas ($n = 6$) or the European region ($n = 6$), and no study was identified from the Eastern Mediterranean region. The sample size of the studies ranged from

Table 1
Serogroup-specific carriage prevalence in studies among Hajj pilgrims[a].

Country	Year	Number swabbed	A	B	C	W	X	Y	NG/other	Overall carriage
				African Region						
Ethiopia (Memish et al., 2017)	2014	Before: 93	**4.3**	–	–	–		–	2.2	6.5
		Before: 64*	**4.7**	ND	ND	ND		ND		6.3
		After: 64*	–	–	–	–		–		0.0
Nigeria (Memish et al., 2017)	2014	Before: 85	–	5.9	–	–		–	**10.6**	16.5
Tanzania (Memish et al., 2017)	2014	Before: 95	–	**1.1**	–	–		–		1.1
		Before: 72*	–	**1.4**	–	–		–		1.4
		After: 72*	–	**2.8**	–	–		–		2.8
				Region of the Americas						
USA (Memish et al., 2017)	2014	Before: 92	–	**2.2**	–	–		–		2.2
		Before: 40*	–	**2.5**	–	–		–		2.5
		After: 40*	–	**5.0**	–	–		–		5.0
				Eastern Mediterranean Region						
Egypt (Memish et al., 2017)	2014	Before: 98	–	**1.0**	–	–		–		1.0
		Before: 86*	–	**1.2**	–	–		–		1.2
		After: 86*	–	**1.2**	–	–		–		1.2
Pakistan (Memish et al., 2017)	2014	Before: 98	–	**1.0**	–	–		–		1.0
		Before: 89*	–	**1.1**		–		–		1.1
		After: 89*	–	–		–		–		0.0
Somalia (Memish et al., 2017)	2014	Before: 98	–	**6.1**	–	–		–	1.0	7.1
		Before: 50*	ND	**10.0**	ND	ND		ND		12.0
		After: 50*	–	**2.0**	–	–		–		2.0
				European Region						
Turkey (Ceyhan et al., 2013)	2010	Before: 472*	0.2	1.9	–	**11.0**	–	0.2	–	13.4
		After: 296*	0.3	1.7	–	**25.0**	–	0.3		27.4
				South-East Asia Region						
Bangladesh (Memish et al., 2017)	2014	Before: 79	–	**2.5**	–	–		–		2.5
		Before: 27*	–	**3.7**	–	–		–		3.7
		After: 27*	–	**3.7**	–	–		–		3.7
Indonesia (Memish et al., 2017)	2014	Before: 98	–	**2.0**	–	–		–		2.0
		Before: 59*	–	**1.7**	–	–		–		1.7
		After: 59*	–	–	–	–		–		0.0
				Western Pacific Region						
Australia (Azeem et al., 2017)	2014	Before: 183*	–	–	–	**0.5**		–		0.5
		After: 93*	–	**1.1**	–	–		–		1.1
Malaysia (Memish et al., 2017)	2014	Before: 95	–	–	–	–		–		0.0
		Before: 68*	–	**1.5**	–	–		–		1.5
		After: 68*	–	–	–	–		–		0.0

[a]Individual serogroup prevalence may not sum to overall carriage due to rounding or if select serogroup results were not reported. NG: non-groupable. (*): includes participants from a cohort or a nested cohort. (–): serogroup tested for but not identified (i.e., 0.0% prevalence). Blank: serogroup not tested for or testing of serogroup not reported. (ND): serogroup tested for but not reported. The most prevalent group identified is shown in bold.

190 to 2954. The timing of studies varied, with four studies commencing within the first week of a new academic term and the remainder at various points in the academic year.

As with studies in Hajj pilgrims, participant characteristics varied between studies (Supplementary material, Table S5). For example, high coverage rates of conjugate MenACWY and MenC were reported in the USA and the UK, respectively. MenB-fHbp and MenB-4C were used only among students in the USA. Most studies did not have strict inclusion or exclusion criteria, but three studies excluded participants for factors such as recent antibiotic use or a previous history of meningococcal disease (Bali et al., 2017; Rodriguez et al., 2014; Read et al., 2014). Where ages were reported, the majority of studies included only students of typical university age, about 18–26 years old ($n = 6/7$). The three studies in the USA were conducted after recent serogroup B outbreaks at the university but not as a means to determine the carriage among close contacts of cases.

Although there were differences in methodologies between studies, the swab sites and methods used to detect the capsular group in carriers were similar. Only one study described swabbing the nasopharynx, while the remaining used pharyngeal swabs. All studies, except one, in university students used a genotypic method such as PCR or whole genome sequencing to categorize the genogroup in carriers. One study used SASG to serogroup the positive results, but used multilocus sequence typing for further characterization. Seven studies reported the results from SASG and PCR testing, and PCR was universally more sensitive.

Overall carriage rates varied substantially between studies and regions, with the highest carriage in the region of the Americas (range 4.0–71.1%) and European region (range 10.4–61.9%). At the country level, the highest carriage rates among university students were in England and ranged from 14.3% to 61.9%. Low levels of carriage were identified in Chile (4.0%), Nigeria (5.1%), and India (1.5%). Non-groupable, capsule null locus (cnl), or other serogroups that are typically non-disease causing, were the most commonly identified among carriers in most regions. Exceptions included studies from Brazil, England, and India, where the most

prevalent capsular groups identified were C (46.3%), Y (21.1%), and B (1.5%), respectively, at baseline (Table 2).

Seven studies assessed risk factors associated with increased carriage among university students, the methodology of which is detailed in Supplementary material Table S7 (Aliyu and Olayinka, 2017; Rodriguez et al., 2014; Tryfinopoulou et al., 2016; Breakwell et al., 2018; Durey et al., 2012; McNamara et al., 2017b; Soeters et al., 2017). Risk factors investigated included demographic data and social behaviours, such as age, sex, smoking, recent respiratory infections, and attending crowded social settings. Smoking, male sex, and attending parties or clubs at least once per week were most frequently reported as risk factors in the study populations. Additional risk factors identified included recent upper respiratory infection and age or graduation year representative of students halfway through university. One study included both university students and military recruits in their risk factor assessment (Tryfinopoulou et al., 2016); therefore, these associations are not reported as it cannot be determined which setting contributed to the increased risk.

Military personnel

Five cross-sectional studies and one cross-sectional study with nested cohorts conducted among military personnel met the inclusion criteria, four of which were from the European region. Four studies were among new recruits in Greece (Tryfinopoulou et al., 2016), Iran (Ataee et al., 2016), Turkey (Celal Basustaoglu et al., 2011), and the Republic of Korea [48] and two studies were among professional soldiers in Poland (Korzeniewski et al., 2015; Korzeniewski et al., 2017). Sample sizes ranged from 226 to 1995. In the studies among new recruits, when reported, the initial time point of swabbing varied from day 1 to day 7 after military entrance; only one study swabbed recruits again to evaluate changes in carriage (Heo et al., 2014).

Similar to the other high-risk settings in this review, study participants differed between studies (Supplementary material, Table S6). Three studies swabbed participants immediately prior to or post-vaccine administration (Ataee et al., 2016; Celal Basustaoglu et al., 2011; Heo et al., 2014), and at least a portion of the

Table 2
Serogroup-specific carriage prevalence in studies among university students[a].

Country	Year	Number swabbed	A	B	C	W	X	Y	NG/other	Overall carriage
African Region										
Nigeria (Aliyu and Olayinka, 2017)	2014	336	0.9		0.9	0.3		**1.5**	**1.5**	5.1
Region of the Americas										
Brazil (Rizek et al., 2016)	2010	190	–	1.6	**46.3**	–		–	20.5	71.1
Canada (Gilca et al., 2013)	2011–12	360*	ND	**6.9**	ND	ND	ND	ND	ND	28.8
Chile (Rodriguez et al., 2014)	2012	500	–	0.8	–	0.6	–		**2.6**	4.0
USA (Breakwell et al., 2018)	2015	1st: 1067*	–	1.8	0.2	–	0.2	0.7	**9.9**	12.8
		2nd: 761*	–	2.6	0.3	–	0.3	0.7	**10.8**	14.6
USA (McNamara et al., 2017b)	2015–16	1st: 1173*	–	1.2	0.3	0.2	0.1	0.3	**12.3**	14.2
		2nd: 1069*	–	2.2	0.1	–	0.1	0.2	**14.6**	17.1
		3rd: 1045*	–	1.9	0.3	–	–	0.3	**8.0**	10.5
		4th: 938*	–	2.3	0.1	0.1	–	0.5	**14.3**	17.4
USA (Soeters et al., 2017)	2015–16	1st: 717*	–	4.3	1.1	–	0.1	0.4	**18.4**	24.4
		2nd: 878*	–	4.1	0.3	–	0.2	0.5	**18.9**	24.0
		3rd: 622*	–	4.2	–	0.2	–	0.2	**15.3**	19.8
		4th: 626*	–	3.5	–	0.2	0.8	0.3	**16.0**	20.8
European Region										
England (Bidmos et al., 2011)	2008–09	1st: 190*	–	6.3	0.5	1.1	0.5	**21.1**	17.4	46.8
		2nd: 91*	–	4.4	1.1	–	–	**24.2**	20.9	50.6
		3rd: 74*	–	4.1	1.4	–	–	24.3	**25.7**	55.4
		4th: 63*	–	7.9	1.6	3.2	–	**25.4**	23.8	61.9
England (Ala'aldeen et al., 2011)	2009–10	1st: 1585*	ND	**8.0**	ND	ND	ND	5.7	ND	27.8
		2nd: 1049*	ND	9.3	ND	ND	ND	**17.6**	ND	46.3
		3rd: 678*	ND	10.9	ND	ND	ND	**13.9**	ND	48.7
England (Read et al., 2014)	2010	1st: 2954*	–	**9.4**	0.3	1.7		6.9		32.6
England (Oldfield et al., 2017)	2015–16	1st: 769*	ND	3.3	ND	0.7	ND	1.8	**5.3**	14.3
		2nd: 353*	ND	8.5	ND	6.8	ND	2.3	**11.6**	38.5
		3rd: 288*	ND	5.9	ND	8.0	ND	3.8	**17.8**	46.2
Greece (Tryfinopoulou et al., 2016)	2015	740	–	3.4	–	0.7	0.5	1.9	**3.9**	10.4
Portugal (Rodrigues et al., 2015)	2012	601	–	5.3	0.3	0.2	0.2	1.7	**5.7**	13.3
South-East Asia Region										
India (Bali et al., 2017)	2014	274	–	**1.5**	–	–		–	–	1.5
Western Pacific Region										
Republic of Korea (Durey et al., 2012)	2009	1st: 136*	–	2.2	3.7	–	–	–	**5.9**	11.8
		2nd: 128*	–	3.1	4.7	0.8	–	–	**5.5**	14.1

[a]Individual serogroup prevalence may not sum to overall carriage due to rounding or if select serogroup results were not reported. NG: non-groupable. (*): includes participants from a cohort or a nested cohort. (–): serogroup tested for but not identified (i.e., 0.0% prevalence). Blank: serogroup not tested for or testing of serogroup not reported. (ND): serogroup tested for but not reported. The most prevalent group identified is shown in bold.

Table 3
Serogroup-specific carriage prevalence in studies among military personnel[a].

Country	Year	Number swabbed	A	B	C	W	X	Y	NG/other	Overall carriage
European Region										
Greece (Tryfinopoulou et al., 2016)	2014	680	–	**6.8**	0.3	0.4	0.3	1.3	6.0	15.2
Poland (Korzeniewski et al., 2015)	2013	559	–	**1.6**	1.3	–		1.4	1.4	5.7
Poland (Korzeniewski et al., 2017)	2016	1246	–	**2.7**	0.5	0.2		0.5	1.4	5.2
Turkey (Celal Basustaoglu et al., 2011)	2008	1995	0.1	0.3	0.4	0.5		0.7	**2.3**	4.2
Eastern Mediterranean Region										
Iran (Ataee et al., 2016)	2014–15	226	1.8		**4.0**	0.4	0.4	1.3		8.0
Western Pacific Region										
Republic of Korea (Heo et al., 2014)	2013–14	1st: 434*	–	**4.1**	1.4	–	–	0.2	3.2	9.0
		2nd: 434*	–	2.1	–	0.5	1.2	–	**10.1**	13.8
		3rd: 443*	–	2.5	3.8	0.2	0.2	–	**5.9**	12.6
		4th: 443*	–	1.4	0.9	0.2	–	–	**2.7**	5.2

[a]Individual serogroup prevalence may not sum to overall carriage due to rounding or if select serogroup results were not reported. NG: non-groupable. (*): includes participants from a cohort or a nested cohort. (–): serogroup tested for but not identified (i.e., 0.0% prevalence). Blank: serogroup not tested for or testing of serogroup not reported. The most prevalent group identified is shown in bold.

participants from the other three studies had previously been vaccinated with a conjugate meningococcal vaccine (range 15–55% coverage) (Tryfinopoulou et al., 2016; Korzeniewski et al., 2015; Korzeniewski et al., 2017). The age of the participants was reported in five of the studies and all were among adults, typically aged 20–50 years. In the three studies that reported the sex of participants, the study populations were more than 98% male.

While the swabbing site differed between studies, the methods for detecting the capsular group were more similar in studies conducted in military personnel than the previously described university setting. The site of swabbing varied between studies; three studies swabbed the nasopharynx and two the pharynx. PCR was used in all studies to detect the genogroup, except in Turkey where SASG was used. The study among Korean recruits primarily used SASG, but used PCR for isolates that could not be characterized using SASG (Heo et al., 2014).

Carriage was relatively low in most studies, with the highest carriage rate among Greek new recruits (Table 3). Serogroups A, B, C, W, X, Y, and non-groupable were identified in at least one study. The only study from the Eastern Mediterranean region identified serogroup C as the most prominent, while serogroup B was the most common throughout much of the European region. In the Western Pacific region, B was the most common at one time point and non-groupable for the other three.

Three studies investigated risk factors associated with increased meningococcal carriage in military personnel (Supplemental material Table S7) (Tryfinopoulou et al., 2016; Korzeniewski et al., 2015; Korzeniewski et al., 2017). Risk factors investigated in these studies included both demographic data and social behaviours. Among professional soldiers, both studies found smoking increased the risk for carriage. One study included both university students and military recruits in their risk factor assessment (Tryfinopoulou et al., 2016); therefore, these associations are not reported as it cannot be determined which setting contributed to the increased risk.

Discussion

It was observed that the majority of carriage studies in high-risk settings were conducted among university students, with few studies reporting serogroup data among Hajj pilgrims or military personnel. It was also observed that the majority of carriage studies were conducted in the region of the Americas or the European region. In the three studies among Hajj pilgrims, serogroup B was the most prevalent across regions. Carriage was highest among university students compared to the other two risk groups included in this review, and non-groupable or 'other' serogroups were the most prevalent in the majority of studies. Only five carriage studies reporting serogroup data were identified among military personnel. Carriage was found to be low in most of these studies, with serogroups B and non-groupable or 'other' serogroups being most prevalent.

Several global outbreaks have been associated with the Hajj pilgrimage, such as the one in 2000 caused by a hyperinvasive W strain (Jean-François et al., 2002). Protective measures have been introduced to help protect pilgrims, including a mandatory quadrivalent vaccine and chemoprophylaxis to clear carriage in pilgrims from the African meningitis belt (Yezli et al., 2016a). The study among Turkish pilgrims in 2010 was consistent with results from the Hajj carriage review from Yezli, Wilder-Smith (Yezli et al., 2016b) describing serogroups B and W as the most prominent. However, in the studies identified from 2014, only serogroup B predominated among Hajj carriers. This is, perhaps, not surprising given the mandated quadrivalent (ACWY) vaccine prior to the pilgrimage—although most pilgrims included in studies in this review reported receiving the polysaccharide vaccine, which does not prevent carriage acquisition (Borrow et al., 2016). Continued research is needed to ascertain whether a broad coverage serogroup B vaccine is warranted in the future (Memish et al., 2017).

Carriage was highest in university students, especially students from the region of the Americas and European region. Interestingly, university students in these regions were the only population to carry such high levels of non-groupable or 'other' serogroups compared to other high-risk settings and populations in this review. However, with limited data, it is not possible to say whether this is simply due to variability within the studies or a possible explanation for the high carriage levels in this setting. While most of the carriage was of non-groupable or 'other' serogroups, there was still considerable carriage of disease-causing serogroups in some studies, especially if students were living in dormitories. Outside of these regions, few studies were conducted, but reported lower carriage levels compared to the Americas and Europe. University students should continue to be evaluated as a potential source of IMD transmission and considered for targeted vaccination to decrease disease burden.

Few studies were conducted in military personnel and these were primarily from Europe. Carriage prevalence was less than previously identified in this region (Soriano-Gabarro et al., 2011b), but this is perhaps due to the timing of the studies included in this review. Most of the studies sampled recruits on day 1 of entry or professional soldiers who did not live in barracks. Therefore, the

majority of the results are likely not indicative of high-risk setting acquisition. The one study that sampled from the same cohort on day 1 and again 5 weeks later reported variable results, with increased overall carriage prevalence in one cohort and decreased overall carriage prevalence in the other. Notably, the increase in carriage prevalence among the first cohort was primarily due to increased non-groupable carriage. Additional studies are needed to determine whether the risk of increased carriage in new recruits remains.

No single risk factor was universally associated with carriage, but several were identified including male sex, attending clubs or parties at least once a week, and smoking, which are consistent with the previous literature (MacLennan et al., 2006). Although it cannot be said with certainty that these risk factors are consistent in all regions, the ones highlighted in this review can, nonetheless, be useful to inform public health practice. Knowledge of these risk factors has encouraged protective meningococcal vaccination in other at-risk populations, such as Norwegian teenagers participating in the annual russ celebrations (Norwegian Institute of Public Health (NIPH), 2017). Policymakers and researchers should continue to evaluate whether additional groups within their local demographics share similar risk factors and, thereby, increased risk of carriage and IMD.

Study design, participant characteristics, laboratory methodology, and local epidemiology can all impact the detected carriage prevalence and the risk factors associated with it. Factors such as recent antibiotic use and immunization with a conjugate vaccine are associated with decreased carriage (Borrow et al., 2016; Breakwell et al., 2018; McNamara et al., 2017b; Soeters et al., 2017), while outbreaks can occasionally increase carriage rates (Safadi et al., 2014). Certain methods are more sensitive for detection, such as swabbing the posterior pharynx instead of the nasopharynx or using PCR instead of SASG for genogroup classification (Roberts et al., 2009; Borrow, 2012). Therefore, use of these methodologies would be beneficial when assessing meningococcal carriage. Study design can also affect the risk factor analyses in studies that have small sample sizes or unexpectedly low carriage rates, and thus, decreased power to detect differences. It is advisable that future carriage studies use methods sensitive for detection and consider local epidemiological factors when calculating a necessary sample size.

Data gaps by region were prevalent across all settings, with few studies conducted in the African, Eastern Mediterranean, South-East Asia, and Western Pacific regions. Additional research should be considered in these regions to understand how carriage levels and serogroups in these regions differ from those of the Americas and the European region. There are several ongoing studies that will help partially fill this gap. Two studies are among university students, one in Australia and the other in Japan (trial registration numbers ACTRN12617000233325 and JPRN-UMIN000026546, respectively). Additionally, there are two ongoing studies in Hajj pilgrims, one investigating the effect of quadrivalent conjugate vaccination on carriage in Australian, Saudi Arabian, and Qatari pilgrims (trial registration number ACTRN12616001230448) and another assessing before and after carriage in French pilgrims (trial registration number NCT02868541).

The strengths of this study include the comprehensive literature search, including Chinese language databases. Additionally, this appears to be the first review analyzing the serogroup-specific carriage in university students and military personnel in regions outside of Europe and updates a previous review of carriage in Hajj pilgrims (Yezli et al., 2016b; Soriano-Gabarro et al., 2011b).

However, this review is not without limitations. As with all systematic reviews, this review was limited by the studies conducted and the data available. As such, there are considerable data gaps in many world regions in this review. The methodologies varied widely among studies, which could have affected the carriage prevalence detected. Limitations notwithstanding, it is believed that this review will be beneficial to researchers and policymakers who wish to gain an understanding of the serogroup-specific carriage studies conducted in the previous decade in the high-risk settings included in this review.

This review provides a comprehensive evaluation of the serogroup-specific carriage studies conducted between 2007 and 2016, providing a further understanding of the *N. meningitidis* epidemiology in specific regions and risk groups. There is a need for more well-designed carriage studies to continue answering questions about carriage acquisition, transmission, risk factors, and duration of carriage. This understanding is important for vaccination policy, as countries may consider vaccinating the portion of the population with the highest carriage levels, and thus, those most responsible for transmission (Borrow et al., 2016). Carriage data, such as those presented in this review, should be used as a supplement to disease data when developing vaccination policies, as a low prevalence of carriage does not necessarily correlate with a decreased risk of disease. This is evident within Africa, where a large multi-country carriage study found relatively low carriage prevalence in the region with the highest burden of IMD (Ali et al., 2015). Further work is also required to assess the efficacy of newly introduced vaccines to decrease *N. meningitidis* carriage and develop indirect herd immunity.

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Ethical approval

No human subjects or animals were involved in this study. As such, additional ethical approval was not applicable.

Conflict of interest

MHK is an employee of Sanofi Pasteur. All other authors declare no conflict of interest.

Author contributions

HN and MHK conceptualized the study and provided critical comments on the manuscript. MEP led the systematic review, acquired and analyzed the data, and drafted the manuscript. RM and YL assisted with the systematic review and provided critical comments on the manuscript. All authors read and approved the final draft.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.05.022.

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