



REVIEW

Incidence and Prevention of Invasive Meningococcal Disease in Global Mass Gathering Events

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ABSTRACT

Introduction: Mass gathering events involve close contact among large numbers of people in a specific location at the same time, an environment conducive to transmission of respiratory tract illnesses including invasive meningococcal disease (IMD). This report describes IMD incidence at mass gatherings over the past 10 years and discusses strategies to prevent IMD at such events.

Methods: A PubMed search was conducted in December 2018 using a search string intended to identify articles describing IMD at mass

gatherings, including religious pilgrimages, sports events, jamborees, and refugee camps. The search was limited to articles in English published from 2008 to 2018. Articles were included if they described IMD incidence at a mass gathering event.

Results: A total of 127 articles were retrieved, of which 7 reported on IMD incidence at mass gatherings in the past 10 years. Specifically, in Saudi Arabia between 2002 and 2011, IMD occurred in 16 Hajj pilgrims and 1 Umrah pilgrim; serotypes involved were not reported. At a youth sports festival in Spain in 2008, 1 case of serogroup B IMD was reported among 1500 attendees. At the 2015 World Scout Jamboree in Japan, an outbreak of serogroup W IMD was identified in five scouts and one parent. At a refugee camp in Turkey, one case of serogroup B IMD was reported in a Syrian girl; four cases of serogroup X IMD occurred in an Italian refugee camp among refugees from Africa and Bangladesh. In 2017, a funeral in Liberia resulted in 13 identified cases of serogroup C IMD. Requiring meningococcal vaccination for mass gathering attendees and vaccinating refugees might have prevented these IMD cases.

Conclusions: Mass gathering events increase IMD risk among attendees and their close contacts. Vaccines preventing IMD caused by serogroups ACWY and B are available and should be recommended for mass gathering attendees.

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INTRODUCTION

Mass gatherings are defined by the World Health Organization and Centers for Disease Control and Prevention as concentrations of people at a specific location for a specific purpose, with the potential to strain local resources [1, 2]. These events include planned activities such as large sporting events (e.g., Olympics, FIFA World Cup), business expositions, music festivals, funerals of religious or political figures, and religious pilgrimages (e.g., the Hindu pilgrimage of Kumbh Mela in India and the annual Hajj and Umrah pilgrimages in Saudi Arabia), as well as unplanned gatherings, such as refugee camps and protests [1]. Unfortunately, the inherent properties of these events (i.e., a single location where a large number of individuals congregate who often traveled internationally) increase the likelihood of transmission of communicable diseases [1]. Transmission of such diseases not only occurs between attendees but can also occur from the local population in the host country to the mass gathering attendees, from the attendees to the local population, or from attendees infected in the host country to people in their native country on return from the event [1]. Because of the potential for rapid acquisition and spread of disease during mass gathering events, preventive measures are crucial to maintain public health and safety.

Among numerous communicable diseases associated with mass gathering events, respiratory tract infections have been designated by the World Health Organization as a public health concern [1]. Within this group, invasive meningococcal disease (IMD) has been highlighted as a specific and critical public health issue, given the emergence of outbreaks linked to mass gathering events such as the Hajj and Umrah [3, 4].

Invasive meningococcal disease is caused by the bacterium *Neisseria meningitidis* [5]. Asymptomatic colonization of the mucosal surfaces of the nasopharynx by *N. meningitidis* is common,

particularly among adolescents and young adults [6]. Transmission of *N. meningitidis* from asymptomatic carriers or people with IMD occurs through direct contact with large-droplet respiratory tract secretions [6]. Although most carriers of meningococci are asymptomatic, in a small percentage of cases (< 1%) bacteria cross the mucosa, enter the bloodstream, and cause IMD [5].

Invasive meningococcal disease causes substantial morbidity and mortality worldwide [7]. Typical IMD symptoms are fever, headache, and stiff neck as well as nausea, vomiting, photophobia, and altered mental state [5]. Onset of symptoms usually is rapid [8], and severe illness can ensue within 15–24 h after infection in infants and older children [9]; 10–15% of people with IMD die even with appropriate and timely treatment [5]. Among those who survive IMD, 3–21% could experience serious clinical sequelae, including limb loss, hearing loss, chronic pain, skin scarring, and neurologic deficits [10].

The rapidity of IMD symptom onset and disease progression poses additional challenges in mass gathering settings. Specifically, infected individuals require timely access to medical professionals in conjunction with prompt and accurate diagnosis and effective treatment; early detection requires that good surveillance systems are in place before the event [1]. Mass gatherings, by definition, strain local healthcare resources [1, 2], which complicates patient management.

Awareness of the incidence of IMD occurring during mass gatherings, including unplanned gatherings such as refugee camps, can provide useful information for designing and implementing appropriate preventive strategies, including recommendations for vaccination. This is especially important for planned mass gathering events, such as the Hajj pilgrimage, in which host countries can undertake a risk assessment that includes the potential for transmission of diseases such as IMD [1]. Such anticipatory planning can help ensure that procedures are in place to quickly address any disease outbreaks [1]. A better understanding of disease incidence at recent events can aid in such planning. Therefore, this review summarizes the incidence of IMD reported at mass

gathering events worldwide during the past decade and the role vaccination has in preventing outbreaks.

LITERATURE SEARCH CRITERIA AND RESULTS

A PubMed search was conducted in December 2018 using the search string: [Meningococcal OR (*N. meningitidis*) OR (*Neisseria meningitidis*) OR (*meningitis*)] AND each of the following terms: Hajj OR Umrah; Kumbh Mela; mass gather; Olympic; World Cup; refugee; funeral; concert; jamboree. Limits were human, English, and past 10 years. Articles were selected for inclusion if they described the incidence of IMD at a mass gathering event; articles that did not report data on IMD cases or did not include a mass gathering event were excluded; articles with “review” in the title also were excluded. A total of 127 articles were retrieved, of which 27 were considered for further review based on their abstract; after review of the full articles, 7 were identified as meeting the inclusion criteria and are summarized below per mass gathering event. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

INVASIVE MENINGOCOCCAL DISEASE DURING MASS GATHERING EVENTS FROM 2008–2018

Hajj and Umrah

The Hajj is an annual 5-day pilgrimage to Makkah, Saudi Arabia, undertaken by all Muslims who are physically able and have the financial means to do so [11, 12]. Although the Hajj lasts only 5 days, most pilgrims remain in Saudi Arabia for several weeks [3]. Umrah is similar to the Hajj in that it is a pilgrimage to Makkah, but travel can be completed at any time of year, and the length of the pilgrimage is shorter [11].

The Hajj pilgrimage is one of the world’s largest annual religious mass gatherings, with

about 2–3 million pilgrims from more than 184 countries participating each year [3, 11]. The Hajj brings together a geographically diverse population in close proximity, creating ideal conditions for transmission of communicable respiratory tract infections [11].

The spread of infectious diseases during the Hajj has been well documented and is attributable to crowded conditions, shared facilities, extreme heat and humidity, extended time that pilgrims spend at Hajj sites, exhaustion from performing physically demanding Hajj rites, and attendance by elderly pilgrims in poor health [11, 13, 14]. Respiratory tract infections due to viral or bacterial pathogens are commonly reported among Hajj pilgrims [15]. Meningococcal infections in particular have been associated with the Hajj, including a large outbreak in 1987 that affected pilgrims in Saudi Arabia before becoming a global outbreak when pilgrims completed the Hajj and returned home [16].

Within the 2008–2018 time frame set as an inclusion criterion for this review, one article was published that reported IMD incidence at the Hajj or Umrah between 1995 and 2011 (Table 1) [17]. During the time period of 2002–2011, IMD was confirmed in 16 Hajj pilgrims and 1 Umrah pilgrim. This is a considerable decrease from the number of cases reported during IMD outbreaks in 2000 and 2001, during which 223 Hajj pilgrims and 26 Umrah pilgrims contracted IMD. The incidence rate in 2002–2011 also was lower than that reported for the period from 1995 to 1999, when IMD occurred in 60 Hajj pilgrims and 46 Umrah pilgrims. These decreases likely reflect the diverse preventive measures instituted by the Kingdom of Saudi Arabia between 1988 and 2002, including a quadrivalent A/C/W/Y meningococcal polysaccharide vaccine requirement for all Hajj and Umrah pilgrims and meningococcal vaccination programs targeting Hajj workers and residents of Mecca, Medina, and surrounding areas [18].

Nasopharyngeal Carriage

Between 8–25% of the general population are asymptomatic nasopharyngeal carriers of *N. meningitidis* [19]. Hajj pilgrims typically have

Table 1 Incidence of invasive meningococcal disease at mass gathering events, 2008–2018

Event	Outbreak location, year	Attendance, <i>n</i>	Age of attendees, years	IMD cases, <i>n</i>	Attack rate per 100,000	Attendee country of origin	Age, years	Serogroup	Serogroup/isolate found in country of event (yes/no)	Secondary IMD cases (non-attendees)
Cummiskey [23]	Spain, 2007	1500	NA	1	NA	NA	16	B	NA	NA
	European Youth Olympic Sports Festival									
Memish [17]	Saudi Arabia, 2002–2011	NA	NA	16 (Hajj) 1 (Umrah)	0.21 (2002) 0.01 (2010)	NA	NA	NA	NA	NA
Tezer [25]	Refugee camp	NA	NA	1	NA	Syria	11	B	NA	NA
Kanai [24]	World Scout Jamboree	> 33,000	14–17 (scouts)	6	19.5	Scotland (4 cases) Sweden (2 cases)	NA	W	No	1
Stefanelli [26]	Refugee camp	NA	NA	4	NA	Eritrea Mali Niger Bangladesh	15 20 31 24	X	NA	NA
Patel [28], Docdeh [27]	Funeral	NA	NA	14	NA	Liberia	NA	C (13 cases) NA (1 case)	NA	NA

NA not available

meningococcal nasopharyngeal carriage rates of 5–10% [20]. Studies of residents living near the Haram (Holy Mosque) in 1992 [21] and 2001 [22] reported overall meningococcal carriage rates of 86% and 7.4%, respectively. Overcrowded conditions, humidity, and air pollution are implicated in these rates [15].

Other Mass Gathering Events

Cases of IMD at mass gathering events other than the Hajj and Umrah published within the 2008–2018 time frame were reported at one sports festival [23]; the World Scout Jamboree [24]; two refugee camps, one in Turkey [25] and the other in Italy [26]; and one funeral [27, 28] (Table 1).

Sporting Events

A European Youth Olympic Sports Festival was held in January 2008 in Spain and was attended by 1500 athletes from 43 countries [23]. At this event, a 16-year-old ice hockey player became unwell, complaining of a stiff neck and fever. While in Spain, he was diagnosed with meningitis caused by serogroup B and treated with antibiotics. The patient recovered fully, had no early sequelae resulting from IMD, and was transported back to his native country.

The World Scout Jamboree held in Japan in the summer of 2015 was attended by more than 33,000 scouts and leaders from 155 countries [24]. After the jamboree concluded, six cases of IMD were reported by public health agencies in the attendees' native countries [three scouts and one household contact (parent) from Scotland and two scouts from Sweden]. All patients recovered with treatment. All six cases were attributable to serogroup W, an uncommon serogroup in Japan where the jamboree took place.

Refugee Camps

In Turkey, IMD caused by serogroup B was reported in an 11-year-old refugee girl from Syria [25]. The patient responded to a 10-day course of antibiotics. Whether the serogroup B

strain was acquired in Turkey or Syria could not be determined because the patient had resided in Turkey for only 3 months at the time IMD developed.

In refugee camps in Italy, four cases of IMD caused by serogroup X were reported, one in 2015 and three in 2016 [26]. The affected patients were a 15-year-old female from Eritrea, a 20-year-old male from Mali, a 31-year-old male from Niger, and a 24-year-old male from Bangladesh. Three of the affected patients developed symptoms shortly after arriving in Italy; the remaining patient (a Bangladeshi male) was in a camp with other African refugees for several months before disease onset. All four patients recovered with antibiotic treatment.

Funerals

Across 3 counties in Liberia, 31 cases of unexplained illness and death were reported among individuals that attended a 2-day funeral in 2017 [27, 28]. The onset of unexplained illnesses was tightly clustered over 10 days and included 13 deaths. Subsequent laboratory testing of 24 patients detected *N. meningitidis* in 14 patients, with serogroup C linked to 13 patients. Further, *N. meningitidis* was identified in 100% (11/11) of the fatal cases with available specimens. Reports from one of the three affected counties show that patients recovered with supportive treatment including antibiotics.

Kumbh Mela

No specific cases of IMD were identified for Kumbh Mela, a large pilgrimage that occurs once every 3 years to one of four river banks in India [29]. However, several serogroup A meningococcal outbreaks affecting mainly the northern cities of India have been reported. Although not confirmed, overcrowding during the Kumbh Mela has the potential to result in meningococcal transmission. Other infections such as influenza, measles, chicken pox, pertussis, and mumps also have the potential to spread during the Kumbh Mela [29].

Table 2 Available meningococcal vaccines

Serogroup	Vaccine formulation	Vaccine type	Vaccine name	Manufacturer
A	MenA-TT	Conjugate	MenAfriVac [58]	Serum Institute of India
B	MenB-FHbp	Recombinant (FHbp subfamily A and B)	Trumenba [59]	Pfizer
	MenB-4C	Recombinant (FHbp subfamily B, NadA, NHBA, OMV)	Bexsero [45, 60]	GlaxoSmithKline
C	MCC-TT	Conjugate	NeisVac-C [61]	Pfizer
	Hib-MCC-TT	Conjugate	Menitorix [62]	GlaxoSmithKline
	MCC-CRM	Conjugate	Menjugate [63]	Novartis
	MCC-CRM	Conjugate	Meningitec [64]	Pfizer
C + Y	Hib-MenCY-TT	Conjugate	MenHibrix [65]	GlaxoSmithKline
ACWY	MenACWY-DT	Conjugate	Menactra [41]	Sanofi Pasteur
	MenACWY-CRM	Conjugate	Menveo [66]	GlaxoSmithKline
	MenACWY-TT	Conjugate	Nimenrix [67]	Pfizer

CRM cross-reactive material, *DT* diphtheria toxoid, *FHbp* factor H binding protein, *Hib Haemophilus influenzae* type B, *MCC* meningococcal serogroup C conjugate, *NadA* neisserial adhesin A, *NHBA* neisserial heparin-binding antigen, *OMV* outer membrane vesicles, *TT* tetanus toxoid

VACCINATION AS A TOOL TO PREVENT INVASIVE MENINGOCOCCAL DISEASE AT MASS GATHERINGS

Vaccines Available

Vaccination is an effective strategy of reducing the incidence of meningococcal disease because of serogroups included in the vaccine formulation [30]. *N. meningitidis* is categorized into 12 serogroups according to the biochemical composition of the capsular polysaccharide; however, only 6 serogroups (A, B, C, W, X, and Y) are responsible for most meningococcal disease

[7], and vaccines are available for 5 of these serogroups [6, 31]. No vaccine is currently available against disease caused by serogroup X, although multivalent vaccines that cover serogroup X are in development [32, 33]. Moreover, studies suggest that serogroup B vaccines may provide some protection against serogroup X disease [34, 35], as described below.

Polysaccharide-based vaccines in bivalent and quadrivalent forms that target serogroups A, C, W, and/or Y have successfully protected mass gathering attendees [20]. However, there are major limitations to polysaccharide vaccines, including insufficient protection for toddlers and children as well as an inability to provide long-lasting or substantial herd

immunity [36, 37]. More recently, polysaccharide-based conjugate vaccines with improved immunogenicity [38, 39] targeting serogroups A, C, W, and Y have been used in both monovalent and polyvalent forms to successfully prevent disease due to these serogroups; monovalent vaccines for serogroups A and C are not commonly used for vaccination of mass gathering attendees. Three quadrivalent vaccines are available for prevention of IMD caused by serogroups A, C, W, and Y [39, 40]: MenACWY-DT (Menactra[®], conjugated to diphtheria toxin; Sanofi Pasteur Inc., Swiftwater, PA, USA) [41]; MenACWY-CRM (Menveo[®], conjugated to C-reactive protein; Novartis Vaccines and Diagnostics Srl, Sovicille, Italy) [42]; and MenACWY-TT (Nimenrix[®], conjugated to tetanus toxoid; Pfizer Ltd, Sandwich, UK) [43] (Table 2).

Two recombinant protein-based vaccines specifically targeting serogroup B also are available: MenB-FHbp (Trumenba[®], bivalent rLP2086; Pfizer Inc, Philadelphia, PA, USA) [44] and MenB-4C (Bexsero[®], 4CMenB; GlaxoSmithKline Vaccines, Srl, Siena, Italy) [45] (Table 2). Notably, both serogroup B vaccines contain one or both variants of the factor H binding protein (FHbp) [46], a meningococcal outer membrane protein found in most IMD strains [47, 48]. Therefore, these vaccines could potentially provide protection against additional meningococcal serogroups [48]. Recent work has highlighted that MenB-4C elicited immune responses against serogroup X strains [34], while MenB-FHbp demonstrated immune responses greater than the serologic correlate of protection against serogroup C, W, Y, and X strains [49]. However, these results are preliminary, and additional clinical studies are required to fully evaluate the potential applicability of serogroup B vaccines in broad IMD protection.

Vaccination Strategies Previously Used at Mass Gathering Events

The incidence of IMD due to serogroups A, B, C, W, X, and Y varies globally; therefore, awareness of the local epidemiology at the site of the mass gathering is important. However, the

nature of mass gathering events, which involves attendees traveling to the host country, can introduce new isolates or serogroups that change the local epidemiology.

Vaccination before attendance at a mass gathering event, such as Hajj, Umrah, Kumbh Mela, and sport gatherings, can lower the risk of IMD. The benefits of vaccination and its effect on IMD incidence at a mass gathering were exemplified by the response of Saudi Arabia after the 1987 Hajj meningococcal serogroup A outbreak. Beginning in 1988, Saudi Arabia required mandatory serogroup A and C vaccination for all pilgrims and all other Hajj attendees and workers [18]. Free vaccination was also offered to residents living in neighboring areas [18]. In 1997, in response to an increase in cases of serogroup A disease, vaccination was coupled with antibiotic prophylaxis of Hajj pilgrims traveling from areas with endemic disease, which decreased IMD incidence until 1999 [18]. In 1987, the year of the meningococcal serogroup A outbreak, the incidence rate of IMD in Saudi Arabia was 12.83 cases per 100,000 people [20]. Between 1995 and 1999, the mean annual incidence was 0.20 cases per 100,000 (range 0.25 cases per 100,000 in 1995 to 0.06 cases per 100,000 in 1999) [20].

Mandatory vaccination of Hajj pilgrims against serogroup A in the late 1990s saw the emergence of IMD caused by serogroup W-135. In 2000, an IMD outbreak caused by serogroup W occurred among Hajj pilgrims and their close contacts, ultimately spreading globally and to people with no connection with the Hajj attendees; 90 cases were reported in 9 countries between March and July of that year [50]. In May 2001, a quadrivalent meningococcal vaccine against serogroups A, C, Y, and W became a requirement for all Hajj pilgrims [50].

Considerations for Optimizing Vaccination Strategies for Mass Gatherings

Preventing IMD among mass gathering attendees requires a high rate of vaccine uptake, particularly among those at highest risk for transmission, such as travelers from areas with endemic disease and those with a high rate of

carriage (e.g., adolescents). Importantly, however, vaccination during a mass gathering event may not be efficacious because of the 7- to 10-day lag in development of protective antibodies [51]. Therefore, attendees must be vaccinated before rather than during the event. Moreover, vaccination efforts need to target not only those attending the mass gathering event but also event staff, healthcare workers, and residents of areas near the event location.

Compliance with meningococcal vaccination before traveling to Hajj is a key aspect of prevention. A survey conducted in Saudi Arabia in 2009 revealed that only 75% received meningococcal vaccination before traveling to Hajj [52]. Meningococcal vaccination compliance may be less for pilgrims traveling for Umrah, despite mandatory recommendations.

Vaccine recommendations for mass gathering attendees must also account for changes in local epidemiology. Although the availability of quadrivalent vaccines allows for broader coverage compared with monovalent and bivalent formulations, these vaccines do not cover serogroup B disease. Therefore, it is important to continually monitor local serogroup B epidemiology and update recommendations for vaccination with a recombinant serogroup B vaccine as needed.

As of December 2018, travelers aged ≥ 2 years to Saudi Arabia who are Hajj or Umrah pilgrims, seasonal workers, or workers in contact with pilgrims are required to show proof of vaccination with a polysaccharide or conjugate quadrivalent ACWY vaccine administered at least 10 days and not more than 3 years (polysaccharide vaccine) or 5 years (conjugate vaccine) before arrival in the country [53]. Travelers from countries in the meningitis belt of Africa are vaccinated on arrival in Saudi Arabia [53]. Vaccination with a serogroup B vaccine is not currently required for entry to Saudi Arabia.

In Japan and Spain, which had IMD outbreaks at mass gathering events, and in Italy and Turkey, countries hosting refugees from the Middle East and Africa in whom IMD has occurred, meningococcal vaccine is recommended depending on the traveler's age, health, lifestyle, and occupational risk, but it is not required for entry [54–57].

CONCLUSIONS

Mass gathering events predispose attendees of the event and the local population to communicable diseases, including IMD. Within the past decade, IMD has been reported at the annual Hajj and Umrah pilgrimages [17], the World Scout Jamboree in Japan [24], and a European youth sports festival in Spain [23], in refugee camps in Turkey [25] and Italy [26], as well as a funeral in Liberia [27, 28]. Vaccination is the best option for preventing IMD at mass gathering events. Communicating the need for meningococcal vaccination to mass gathering attendees through print and online communications or by travel agents is key to increasing the number of vaccinated travelers.

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