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Review

A review of the epidemiology of invasive meningococcal disease and vaccination strategies in North Africa

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ABSTRACT

Objective: This narrative review considered the epidemiology of invasive meningococcal disease (IMD) in North Africa and the adequacy of current preventive measures to provide guidance for future vaccination strategies.
Methods: Literature searches were conducted using PubMed for articles published from 1998 onwards to identify publications on IMD in North Africa. Additional relevant articles not included within the search results and data sources were identified from the reference lists of identified publications, authors' personal files and publicly available government or regional surveillance data.
Results: Although IMD is an endemic and notifiable disease in several North African countries, inadequacies exist regarding each country's surveillance, vaccination strategies and disease understanding. Studies showed that bacterial meningitis in North Africa caused by *Neisseria meningitidis* mostly affected young children (aged <5 years), with meningococcal serogroup B (MenB) being the most frequently identified serotype. Importantly, MenB isolates were genetically heterogeneous. Serogroup A incidence and meningococcal outbreaks decreased over time in Morocco and Egypt, possibly because of their nationwide or school-based vaccination programs. Within the region, meningococcal vaccines were only included in the national immunization program of Egypt.
Conclusions: Improving IMD diagnosis and surveillance would provide a reliable estimate of IMD burden, leading to better vaccination strategies.

Introduction

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* (*N. meningitidis*) most commonly presents as meningitis or septicemia (Rosenstein et al., 2001). Diagnosis is challenging because of the rapid onset and lack of distinguishing clinical signs. IMD has high mortality and morbidity if left untreated (World Health Organization, 2018). Although IMD occurs across ages, the highest rate is in infants, with additional peaks among adolescents and the elderly (Borrow et al., 2017a). Nearly all IMD is caused by six meningococcal serogroups: A, B, C, W, X and Y (MenA, MenB, MenC, MenW, MenX and MenY, respectively) (Borrow et al., 2017a). Capsular polysaccharide vaccines (plain and conjugate polysaccharides) are available against serogroups A, C, W, and Y (Borrow et al., 2017a), and are under development for MenX (Chilukuri et al., 2014). Protein-based vaccines are available against MenB (Borrow et al., 2017a).

Circulating meningococcal serogroups vary geographically and temporally. In a recent survey of global IMD incidence, MenW predominated in much of Africa and Latin America, and MenB was common in Europe, North America and the Western Pacific (Peterson et al., 2019). Importantly, substantial increases in MenW cases have motivated several countries, including some within sub-Saharan Africa, to implement surveillance programs and vaccination campaigns (Booy et al., 2019). Although the highest global IMD burden occurs in sub-Saharan Africa (Figure S1), information regarding IMD epidemiology in neighboring North Africa is comparatively limited and robust epidemiologic data are necessary to ensure adoption of relevant preventive strategies (World Health Organization, 2018). The current review summarized IMD epidemiology from North Africa, evaluated current preventive measures and provided guidance for future surveillance and vaccination strategies.

Methods

A PubMed search was conducted on 05 April 2019. Manuscripts published from 1998 onwards examining meningococcal disease in Morocco, Algeria, Tunisia, Libya, and Egypt were identified as

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follows: *Neisseria meningitidis* OR *N meningitidis* OR meningococc* AND (Morocco OR Algeria OR Tunisia OR Libya OR Egypt). Western Sahara and Mauritania were initially included in the search, but no relevant articles were identified. Reference lists of retrieved articles were examined to identify any additional data sources; relevant publications from authors' personal files were included, and publicly available government or regional surveillance data were obtained where possible.

Results

Among 55 articles retrieved from the search, 23 were selected for further assessment based on title or abstract relevance and five articles were obtained from authors' personal files and publicly available surveillance data (Table 1). Article summaries and overviews of each country's surveillance, reporting and vaccination practices are as follows (Table 2):

Morocco

Surveillance

Mandatory IMD surveillance in Morocco is conducted in partnership with the Institut Pasteur (Borrow et al., 2017b; Ceyhan et al., 2012). IMD is considered endemic to Morocco, and periodically emerges as micro-outbreaks (Borrow et al., 2017b). Using Global Health Data Exchange data, the 2017 estimated incidence and death rates for meningococcal meningitis were 13.24/100,000 and 0.22/100,000, respectively (Institute for Health Metrics and Evaluation, 2018).

Vaccination strategy and policy

The Moroccan immunization schedule does not currently include meningococcal vaccines (World Health Organization, 2019), but the Global Meningococcal Initiative (GMI) worldwide recommends MenACWY vaccination for pilgrims (Acevedo et al., 2019).

Literature search findings

Six articles were identified, including characterization studies of *N. meningitidis* isolates through whole genome sequencing, and serotyping and subtyping analyses (Razki et al., 2018; Zerouali et al., 2006; Zerouali et al., 2002). Retrospective and prospective studies on hospitalized children and a review of GMI roundtable discussions of meningococcal surveillance and preventative programs were also included (Borrow et al., 2017b; Gueddari et al., 2017; El Mdaghri et al., 2012).

In a 2017 review, regional GMI experts reported a 2–3.6/100 incidence rate of meningococcal disease in Morocco and a case-fatality ratio (CFR) of 7–13% (Borrow et al., 2017b). Razki et al. reported 145 suspected culture-confirmed or PCR-confirmed IMD cases in Casablanca between 2011–2016, comprising 25–40% of all suspected cases in the region (Razki et al., 2018). Of these, 105 IMD culture-confirmed isolates were obtained at the Ibn Rochd Hospital (IRH) from patients of all ages: 100 belonged to MenB, one to MenC and two each to MenW and MenY. Seventy-eight of the tested isolates (74%) belonged to clonal complex 32 (cc32); sequence type 33 (ST33) was the most frequent (59%, n = 62).

In a 3-year retrospective study at IRH (2011–2013), culture-confirmed (blood or cerebrospinal fluid [CSF]) IMD was reported in 35 of 96 hospitalized children with febrile purpura (mean age 53.3 ± 40.5 months) (Gueddari et al., 2017). Clinical symptoms that were significantly associated with IMD were lethargy (p = 0.04), convulsions and purpura (both p = 0.01); these were suggested to serve as clinical predictors for IMD (Gueddari et al., 2017).

A study conducted between September 2007 and August 2008 at IRH included all children aged ≤5 years meeting World Health Organization (WHO) criteria for meningitis, X-ray–confirmed pneumonia or sepsis (El Mdaghri et al., 2012). Among 238 children hospitalized with symptoms of invasive diseases, 185 were diagnosed with invasive bacterial infection (excluding tuberculosis). Of these, 76 had pneumonia, 59 had meningitis and 50 had sepsis. The main causative organisms were *Streptococcus pneumoniae* (*S. pneumoniae*) (24 isolates), *N. meningitidis* (18 isolates: 14 from meningitis cases and four from septicemia cases; all MenB) and *Haemophilus influenzae* (*H. influenzae*) (11 isolates).

In a study conducted between September 1999–2000, 13 B:4: P1.15 *N. meningitidis* strains isolated in Morocco were evaluated to identify epidemic clones (Zerouali et al., 2006). Strain characterization by multilocus sequence typing (MLST) showed that ST33 was the most frequent sequence type (9 of 13 strains) and most belonged to the ST32 clonal complex (12 of 13), which was consistent with data from Razki et al. (2018). The same group conducted a study between 1992–2000 to determine antibiotic susceptibility patterns of *N. meningitidis* isolates from patients at IRH (Zerouali et al., 2002). Of 171 *N. meningitidis* isolates recovered, 163 (95%) were characterized: 134 were from children (82.2%) and all were from CSF (144 isolates, 88.3%) or blood (19 isolates, 11.7%). MenB was the most common serogroup (75.5%), followed by MenA (13.5%), MenC (7.4%), MenY (1.2%) and MenW (0.6%). MenA frequency decreased over time, with no isolates from 1995 onwards, possibly because of annual nationwide vaccination for the preceding 5 years. Three-quarters of MenB isolates had the B:4: P1.15 phenotype; 4.3% of isolates showed reduced penicillin susceptibility.

Algeria

Surveillance

In Algeria, IMD surveillance is monitored by a network of laboratories and reporting is mandatory (Borrow et al., 2017b). In 2017, the estimated incidence and death rates for meningococcal meningitis were 8.01/100,000 and 0.09/100,000, respectively (Institute for Health Metrics and Evaluation, 2018).

Vaccination strategy and policy

Although not part of the Algerian national immunization program (NIP), MenACWY polysaccharide vaccination is recommended during epidemics and for pilgrims (Borrow et al., 2017b; World Health Organization, 2019).

Literature search findings

Five articles were identified: a systematic review of meningococcal serogroups and surveillance (Peterson et al., 2019), two epidemiological surveys (Institut National de Santé Publique, 2012; Institut National de Santé Publique, 2015), and two studies characterizing clinical meningococcal isolates from Algeria or MenW strains from 13 countries, including Algeria (Tali-Maamar and Rahal, 2003; Mayer et al., 2002). In a systematic review of meningococcal serogroup data from 2010, 2011 and 2015, percentages of IMD cases by serogroup distribution in Algeria were estimated at 59.3% for MenB, 11.9% for MenW, 10.8% for MenA, 6.4% for MenC, 4.2% for Men Y and 4.0% for 'other' (Peterson et al., 2019). A 2016 survey among Algerian National Ministry of Health or Surveillance Program officers found that countrywide surveillance was conducted across all ages.

A 2012 survey conducted by the Institut National de Santé Publique found Algeria's IMD incidence to be approximately 0.09/100,000, with higher incidences in children aged <5 years (0.48/100,000) in the Adrar province (Institut National de Santé Publique, 2012). The highest age-specific incidence rates for the

Table 1
Summary of published articles on IMD in North Africa.

Country	Author	Study date	Number of cases or isolates	Summary
Morocco	Borrow et al. (2017b)	NR	NR	• Case fatality ratio was 7–13%
	Razki et al. (2018)	2011–2016	105 IMD culture-confirmed isolates	• Incidence rate of IMD was approximately 2–3.6/100,000 • Most of the IMD isolates were MenB, belonged to cc32, and had ST33
	Gueddari et al. (2017)	Jan 2011–Dec 2013	35 of 96 children aged <5 years	• Meningococcal infection was significantly associated with lethargy, convulsions and purpura
	El Mdaghri et al. (2012)	Sep 2007–Aug 2008	185 of 238 children aged ≤5 years	• Invasive bacterial infections were associated with pneumonia, meningitis and sepsis • All of the *Neisseria meningitidis* isolates were MenB
	Zerouali et al. (2006)	Sep 1999–Dec 2000	13 strains of *N. meningitidis*	• Most of the strains had ST33 and belonged to ST32 complex • None were epidemic clone
	Zerouali et al. (2002)	Jan 1992–Sep 2000	163 of 171 *N. meningitidis* isolates	• Most isolates (82%) were from children • MenB was the most frequent isolate (75.5%) • Decreased frequency of MenA possibly due to vaccination
Algeria	Peterson et al. (2019)	Jan 2010–Oct 2017	Data from 59 countries	• MenB was the most frequent serogroup (59.3%) • Survey results found that Algeria had countrywide surveillance for all age groups
	Institut National de Santé Publique (2012)	2012	NR	• Incidence rate of IMD was approximately 0.09/100,000 • Incidence rate of IMD in children (aged <5 years) was approximately 0.48/100,000
	Institut National de Santé Publique (2015)	2015	NR	• Incidence rate of IMD was approximately 0.07/100,000
	Tali-Maamar and Rahal (2003)	1992–2001	141 isolates of *N. meningitidis*	• Strains A:4:P1.9 subgroup III1 were predominant • MenB and MenW were equally prevalent (10.6%)
	Mayer et al. (2002)	1970–2000	76 MenW strains (26 from Hajj 2000 and from patients with meningococcal disease; 50 from 13 countries)	• MenW clone from 2000 Hajj IMD was similar to MenW isolates found in Algeria
Tunisia	Borrow et al. (2017b)	NR	NR	• MenB was the most frequent serogroup (80%) • Most IMD cases (85%) were in children (aged <5 years) • CFR was about 18%
	Saguer et al. (2016)	1998–2013	107 IMD isolates from children	• 80.4% of the IMD isolates were MenB • MenB isolates were heterogeneous and most frequently belonged to cc35
	Sfaihi et al. (2014)	2006–2011	30 cases of recorded meningitis in children (aged 3 months–13 years)	• 6% of meningitis cases were due to *N. meningitidis* (third highest cause)
	Bettaieb et al. (2013)	2003–2008	38 cases from mandatory reporting and 47 from Tunis Children's Hospital (25 cases common)	• Completeness rates: 53.5% (mandatory reports) and 66.2% (children's hospital) • Poor sensitivity for the mandatory reporting system
	Kallel-Sellami et al. (2006)	Jan 2005–Jun 2006	61 adult patients with bacterial meningitis	• 8 patients (13%) had a complement deficiency; all 8 had meningococcal meningitis • 7 of 8 had late complement component deficiencies • Half of patients reported recurrent meningitis
	Smaoui et al. (2011)	1997–2006	79 IMD pediatric cases	• MenB was the most frequent serotype (73%) o NT:NST was the most frequent phenotype

Table 1 (*Continued*)

Country	Author	Study date	Number of cases or isolates	Summary
	Khalifa et al. (2011)	1999–2006	253 isolates from recorded cases of meningitis	• 6.3% of meningitis cases were caused by *N. meningitis*
	Saguer et al. (2006)	1998–2004	23 strains isolated from IMD cases	• MenB was the most frequent isolate (83%) o B:NT:NST was the most frequent phenotype
	Maalej et al. (2006)	1993–2001	224 recorded cases of meningitis	• 10.7% of meningitis cases were caused by *N. meningitis*
Libya	Ceyhan et al. (2012)	2005	NR	• IMD incidence rate of 2.01/100,000
Egypt	Mobarak (2012)	1997–2006	1,210 cases of laboratory-confirmed meningitis	• Lower *N. meningitidis* cases (18.9–38.2%) compared with 1988–1995 (35.2–72.5%) • Case fatality: 13.4%
	Selim et al. (2007)	Apr 2004–Sep 2005	322 of suspected meningitis/encephalitis cases	• 41.7% of meningitis cases were due to *N. meningitidis*
	Shaban and Siam (2009)	1965–2004	Bacterial meningitis caused by *N. meningitidis*	• Shift of major serogroup from MenA to MenB in 1998 • High rate of resistance to trimethoprim/sulfamethoxazole (86%)
	Afifi et al. (2007)	Jun 1998 and Jun 2004	11,070 patients with suspected meningitis	• *N. meningitidis* was third most frequent bacteria that causes meningitis (16%) • MenB was the most frequent isolate (51%) • High rate of resistance to trimethoprim/sulfamethoxazole (86%)
	Klena et al. (2012)	1998–2003	67 representative *N. meningitidis* isolates	• MenB was the most frequent isolate (51%) • ST2174 were found in both MenB and MenA • ST2174 may be endemic to Egypt
	Nakhla et al. (2005)	30 years before and 11 years after 1992	National case counts reported by Egyptian MOHP, Abbassia Fever Hospital in Cairo, and surveillance data from a national network of infectious disease hospitals	• Decrease in incidence rate (2004): 0.1/100,000 • Decrease in bacterial meningitis due to *N. meningitidis* • Shift of major serogroup from MenA (1977–1992) to MenB (1998–2003)
	Farag et al. (2005)	2002–2003	310 children with meningitis/meningoencephalitis	• Of the patients infected with bacterial meningitis, 14.2% were due to *N. meningitides* • Higher CFR than meningitis caused by other bacteria
	Youssef et al. (2004)	May 1998–Dec 2000	Children aged <6 years	• 13% of bacterial meningitis due to *N. meningitidis* • CFR: 23%

cc, clonal complex; CFR, case fatality rate; IMD, invasive meningococcal disease; MenA, *Neisseria meningitidis* serogroup A; MenB, *Neisseria meningitidis* serogroup B; MenW, *Neisseria meningitidis* serogroup W; MOHP, Ministry of Health and Population; NR, not reported; ST, strain type.

city of Khenchela were 36 cases/100,000 and 28 cases/100,000 for children aged <5 years and 5–9 years, respectively. Both MenB and MenW disease were identified in incidence reports, but MenY isolates were rarely observed. In 2015, IMD incidence decreased to 0.07/100,000 (Institut National de Santé Publique, 2015). Tali-Maamar et al. collected 141 isolates between 1992–2001, 92% of which came from meningitis cases; nearly half of the cases were in individuals aged <10 years (Tali-Maamar and Rahal, 2003). A:4:P1.9 subgroup III1 was the most prevalent strain (>70%); this strain was already responsible for two pandemics in 1966 and 1983. MenB and MenW were equally frequent among cases (10.6% each). In a 2002 study, MenW isolates were evaluated using phenotypic, genotypic and subtyping approaches (Mayer et al., 2002). Molecular characterization of the MenW clone associated with the 2000 Hajj outbreak revealed high similarity with global MenW isolates, including two strains isolated from sporadic Algerian disease cases in the late 1990s.

Tunisia

Surveillance

No national surveillance network is in place in Tunisia, although IMD reporting is mandatory (Borrow et al., 2017b). The estimated incidence and death rates for meningococcal meningitis in 2017 were 6.80/100,000 and 0.08/100,000, respectively (Institute for Health Metrics and Evaluation, 2018).

Vaccination strategy and policy

Meningococcal vaccines are not currently included in the Tunisian NIP (World Health Organization, 2019). Polysaccharide

Table 2
Overview of IMD surveillance, reporting and vaccination strategies and policies in North Africa.

Country	Overview of IMD surveillance	IMD reporting	IMD vaccination strategy and policy
Morocco (Borrow et al., 2017b; Ceyhan et al., 2012; Razki et al., 2018; El Mdaghri et al., 2012)	• Surveillance of IMD is conducted in collaboration with the Meningococcal Unit of the Institut Pasteur in Paris, France • Clinically suspected cases of IMD are reported to regional health authorities and the Department of Epidemiology of the MOH • The Ibn Rochd University Hospital Center at the Children's Hospital of Casablanca served as the only sentinel site for the WHO EMRO Vaccine-Preventable Invasive Bacterial Disease Surveillance Network	Mandatory	• Meningococcal vaccination is not currently included in the NIP (World Health Organization, 2019)
Algeria (Borrow et al., 2017b; World Health Organization, 2019)	• A network of laboratories collect microbiological data in collaboration with the Algerian Pasteur Institute	Mandatory	• Meningococcal vaccination is not currently included in the NIP • Quadrivalent (MenACWY) polysaccharide vaccine is recommended for pilgrims and during epidemics
Tunisia (Borrow et al., 2017b; World Health Organization, 2019)	• No national surveillance network is in place • Conventional and molecular-based diagnoses are performed at a single hospital in Tunisia	Mandatory	• Meningococcal vaccination is not currently included in the NIP • MenACWY polysaccharide vaccine is recommended for pilgrims and children at high risk
Libya (Ceyhan et al., 2012; World Health Organization, 2019)			• Meningococcal vaccination is not currently included in the NIP • Vaccination using MenACWY polysaccharide vaccines are required for high-risk groups (eg, pilgrims, military personnel)
Egypt (Ceyhan et al., 2012; World Health Organization, 2019; Afifi et al., 2007; Nakhla et al., 2005; Youssef et al., 2004)	• The Egyptian MOHP and US Naval Medical Research began a lab-based surveillance of bacterial meningitis in 1998 • The network includes 12 infectious disease hospitals in various regions of the country • Suspected cases of bacterial meningitis are defined by sudden onset of fever, stiff neck, petechial/purpuric rash, and fever with a bulging fontanel in infants • Confirmed cases of bacterial meningitis are defined as suspected cases with a positive culture or CSF antigen detected		• A school-based vaccination program was begun in 1992 by the MOH using MenAC polysaccharide vaccines in response to the MenA outbreaks between 1988 and 1991 • Vaccination using ACWY polysaccharide vaccines are required for travelers

CSF, cerebrospinal fluid; EPI, Expanded Program on Immunization; IMD, invasive meningococcal disease; MenA, *Neisseria meningitidis* serogroup A; MenAC, *Neisseria meningitidis* serogroups A and C; MenACWY, *Neisseria meningitidis* serogroups A, C, W, and Y; MOH, Ministry of Health; MOHP, Ministry of Health and Population; NIP, national immunization program; WHO EMRO, World Health Organization Regional Office for the Eastern Mediterranean.

MenACWY vaccine is the only available meningococcal vaccine in Tunisia and is recommended for pilgrims and travelers to endemic areas and to children considered at high risk (Borrow et al., 2017b; Institut Pasteur de Tunis, 2012).

Literature search findings

Nine articles were identified: two of which characterized *N. meningitidis* isolates by serogroup and subtype (Saguer et al., 2006; Saguer et al., 2016). Articles also included retrospective studies on pediatric patients, examining bacterial meningitis, IMD epidemiology and the sensitivity of surveillance reports (Sfaihi et al., 2014; Smaoui et al., 2011; Bettaieb et al., 2013). A prospective study screened adult patients with bacterial meningitis for complement deficiency and two studies evaluated meningitis-causing bacteria (Kallel-Sellami et al., 2006; Khalifa et al., 2011; Maalej et al., 2006). The review of the GMI discussion was also included (Borrow et al., 2017b). Regional experts from the GMI reported that 85% of Tunisian IMD cases occurred in children aged <5 years; 38% of cases were in infants (Borrow et al., 2017b). The most prevalent serogroup was MenB (80%), with a CFR of approximately 18%.

Saguer et al. characterized 107 IMD isolates from patients (aged 3 days–13 years) in the Tunis Children's Hospital during 1998–2013; 80.4% were MenB, 12.2% were MenC, 5.6% were MenA, and 1.8% were MenY (Saguer et al., 2016). Isolates collected before February 2007 (n = 56) were genotyped by *porA* sequencing and MLST, showing that all MenA isolates were A:4:P1.9 (similar to the clone causing epidemics within sub-Saharan Africa from 1990–1997) and belonged to cc5. MenC isolates were from several serosubtypes and clustered into three ccs. MenB isolates were heterogeneous, had six serotypes and eight serosubtypes, and showed 23 STs that clustered into 12 ccs. MenB and MenC isolates most frequently belonged to cc35, and 25% of all genotyped isolates were cc35.

In a retrospective study from 2006 to 2011, 30 cases of bacterial meningitis were recorded in children (aged 3 months–15 years) at

Hedi Chaker Hospital in Sfax (Sfaihi et al., 2014). Of the 27 culture-confirmed cases of bacterial meningitis, *N. meningitidis* was the third most frequent cause, comprising two cases, of which one was fatal. Bettaieb et al. used a two-source capture-recapture method to evaluate IMD surveillance during 2003–2008 (Bettaieb et al., 2013). The first source identified all cases reported by mandatory notification (n = 38) and the Tunis Children's Hospital laboratory (n = 47; 25 cases common to both). Completeness rates were 53.5% and 66.2% from mandatory reporting and hospital records, respectively. The study concluded that the sensitivity of the mandatory notification system was poor.

A study during 2005–2006 found that among 61 adult patients with bacterial meningitis, eight (13%) carried a complement deficiency, all of whom had meningococcal meningitis (Kallel-Sellami et al., 2006). Seven of these patients (aged 17–32 years) had late complement (C5–C9) component deficiencies. About half of patients had recurrence of meningococcal meningitis. A retrospective study in children (aged 3 days–11 years) in Tunis during 1997–2006 identified 79 cases of IMD, with higher frequency in winter and spring (Smaoui et al., 2011). Overall, 57.3% of patients were aged <4 years and meningitis was the most common clinical presentation. Of the 46 *N. meningitidis* isolates characterized, MenB was the most common serotype (73%; most frequent phenotype, NT:NST), followed by MenC (most frequent phenotype, 4:P1.13) and MenA. Additionally, 54% of isolates had reduced susceptibility to penicillin and 10% to amoxicillin. Another study analyzed bacteriologically confirmed cases of meningitis recorded between 1999–2006 at the University Hospital of Monastir (Khalifa et al., 2011). Of 253 isolated strains, *N. meningitidis* accounted for 6.3% of cases.

Saguer et al. characterized 23 strains isolated from IMD cases during 1998–2004; 86.9% were recovered from children aged <4 years (Saguer et al., 2006). MenB isolates were the most frequent (83%; major phenotype, B:NT:NST). MenC isolates were found in 17% of isolates, and the major phenotype was C:4:P1-14.

In a study during 1993–2001, 224 recorded cases of bacteriologically confirmed, community-acquired meningitis were reported, with *N. meningitidis* accounting for 10.7% of cases (Maalej et al., 2006). Diagnosis was by culture in 208 cases and demonstration of soluble bacterial antigens in 16 cases. For patients aged <5 years, *S. pneumoniae* and *H. influenzae* were predominant causes of meningitis. *N. meningitidis* strains were isolated from patients aged ≥1 month, with a serogroup distribution of 80.9% for MenB and 19.1% for MenC.

Libya

Surveillance

Surveillance systems for IMD are not in place in Libya (Ceyhan et al., 2012). In 2017, the estimated incidence and death rates for meningococcal meningitis were 8.02/100,000 and 0.09/100,000, respectively (Institute for Health Metrics and Evaluation, 2018).

Vaccination strategy and policy

The WHO found that meningococcal vaccines are not currently included in the NIP of Libya (World Health Organization, 2019). However, targeted vaccination is mandatory for high-risk groups, including pilgrims and military personnel (Ceyhan et al., 2012).

Literature search findings

No articles were identified in the literature search. However, a review of meningococcal disease in the Middle East and North Africa, which was identified from the authors' files, reported an IMD incidence rate of 2.01/100,000 in 2005 in Libya (Ceyhan et al., 2012).

Egypt

Surveillance

In 1998, a laboratory-based surveillance of bacterial meningitis was initiated in a national Egyptian network of infectious disease hospitals (Afifi et al., 2007). Meningococcal meningitis was found to be endemic to Egypt (Mobarak, 2012; Nakhla et al., 2005), with estimated incidence and death rates of 13.68/100,000 and 0.08/100,000, respectively, in 2017 (Institute for Health Metrics and Evaluation, 2018).

Vaccination strategy and policy

In response to MenA outbreaks in earlier years, the Egyptian Ministry of Health and Population (MOHP) established a school-based vaccination program in 1992 using MenAC polysaccharide vaccines that is currently in place (Ceyhan et al., 2012; World Health Organization, 2019; Nakhla et al., 2005). Egypt also currently recommends MenACWY polysaccharide vaccination of travelers to risk areas (World Health Organization, 2019).

Literature search findings

Eight articles were identified, including a study characterizing *N. meningitidis* isolates by serogroup and subtype and a review of meningococcal meningitis in Egypt before and after the introduction of the school-based vaccination program (Nakhla et al., 2005; Klena et al., 2012). Other articles examined bacterial meningitis, including epidemiological studies (Mobarak, 2012; Farag et al., 2005), analyzed bacterial etiology of meningitis/encephalitis (Selim et al., 2007), evaluated surveillance data, (Afifi et al., 2007; Youssef et al., 2004), and reviewed bacterial meningitis epidemiology (Shaban and Siam, 2009). Mobarak evaluated all 1,210 cases of laboratory-confirmed meningitis admitted to the Alexandria Communicable Diseases Hospital during 1997–2006 (Mobarak, 2012). Case numbers peaked during colder seasons. Excluding cases in which no organism was detected (45.6%), *N. meningitidis* was the most common bacterial pathogen overall (28.9% of cases) for each year and in all studied age groups. The percentages of meningitis cases caused by *N. meningitidis* (18.9–38.2%) during this period decreased compared with cases during 1988–1995 (35.2–72.5%). The CFR of *N. meningitidis* was 13.4%.

Selim et al. studied 322 cases (aged 2 months–75 years) of acute febrile illness and neurologic signs admitted to three Egyptian hospitals (Damanhour, Alexandria and Kafr El-Sheikh) from April 2004 to September 2005 (Selim et al., 2007). Of 322 suspected meningitis/encephalitis cases, 165 were diagnosed as meningitis. Seventy-two of these meningitis cases were bacterial, of which 30 cases (41.7%) had a final diagnosis of *N. meningitidis*.

Another study reviewed the epidemiology of bacterial meningitis in Egypt during 1965–2004 (Shaban and Siam, 2009). A gradual decrease was seen in the percentage of bacterial meningitis cases caused by *N. meningitidis*. While MenA was the major serogroup identified (95% of cases) in earlier studies, MenB (51–54.5%), MenA (31.8–35%), MenW (4–4.5%), and MenY (2–2.3%) became more prominent in later studies (1998 onwards). This shift in meningococcal cases was attributed to a school-based MenAC polysaccharide vaccination commencing in 1992. Resistance of *N. meningitidis* to sulphonamides was detected in the 1960s, and three studies reported antibiotic susceptibilities of *N. meningitidis* isolates during 1998–2004. Reported rates of resistance varied among these studies, although a high rate of resistance (86%) to trimethoprim/sulfamethoxazole was apparent.

Between 1998 and 2004, Afifi et al. reported on 11,070 patients with suspected meningitis, of whom 8% had culture-confirmed meningitis (Afifi et al., 2007). The most commonly isolated bacteria was *S. pneumoniae* (42%), followed by *H. influenzae* serotype b (20%) and *N. meningitidis* (16%). Purulent culture-negative CSF samples

were tested by PCR, 90 (5%) of which were positive for *N. meningitidis*. Consequently, the overall percentage of *N. meningitidis* cases increased from 16% to 23%. Of *N. meningitidis* isolates, 51% were MenB, 35% MenA, 4% MenW, 2% meningococcal serogroup D (MenD), 2% MenY, and 8% untypeable. Additionally, 86% of meningococcal isolates were resistant to trimethoprim-sulfamethoxazole, >40% had intermediate ampicillin resistance and 55% had intermediate penicillin resistance.

Klena et al. characterized representative *N. meningitidis* isolates recovered from major Egyptian infectious disease hospitals during 1998–2003 (Klena et al., 2012). Of 67 isolates, 34 (51%) were MenB, 23 (34%) MenA, three (4%) MenW, and one each were MenD and MenY, with the remaining five isolates being nongroupable. Intermediate resistance to penicillin and ampicillin was found in 40% and 20% of MenA isolates, respectively. Of MenB isolates, 71% had intermediate resistance to penicillin and 46% to ampicillin. MLST revealed ST2174 and ST7 as the most frequent ST (37% and 21% overall, respectively). Thirteen different STs were observed within the MenB isolates; 50% (17/34) of MenB isolates were ST2174. Of the five sequence types found in MenA isolates, the most common STs were ST7 (14/23) and ST2174 (6/23). STs comprised seven ccs, with ST8 complex cluster A4 (37%) and ST5 complex subgroup III (22%) being the most common. The authors concluded that the ST2174 clone may be endemic to Egypt and recommended regular monitoring.

A review of meningococcal meningitis data in Egypt from 30 years before and 11 years after the 1992 introduction of MenAC vaccination in schools used national case counts reported by the MOHP, Cairo's Abbassia Fever Hospital (AFH) and surveillance data from a national network of infectious disease hospitals (Nakhla et al., 2005). Large meningococcal meningitis outbreaks occurred in 1973–1974 and 1988–1991, and a smaller outbreak in 1982–1984. By 2004, the incidence of meningococcal meningitis had decreased to 0.1/100,000. During 1967–1985, 65–90% of characterized cases of bacterial meningitis were *N. meningitidis*. Conversely, a survey carried out from 1998 to 2000 identified *N. meningitidis* in only 16% of patients with culture-confirmed bacterial meningitis. Data from AFH further showed that MenA was the predominant serotype (95%) during 1977–1992 and MenB was predominant (66%) during 1998–2003.

Farag et al. studied the cases of children admitted to Alexandria Hospital with meningitis/meningoencephalitis in 2002–2003 (Farag et al., 2005). Approximately 65% of the 310 patients (aged 3 months–15 years) were infected with bacterial meningitis, and 14.2% of these cases were caused by *N. meningitidis*. The CFR was higher in *N. meningitidis* cases compared with *S. pneumoniae* or *H. influenzae* cases. Enhanced surveillance for meningitis in children aged <6 years from 1998 to 2000 at 12 Egyptian hospitals was reported by Youssef et al. (2004); *N. meningitidis* accounted for 30 of 228 cases (13%) of bacterial meningitis. The average age of patients with IMD was 1.5 years, and the CFR was 23%. Disease distribution was highest during late autumn and winter.

Discussion

While the global burden of IMD is highest in sub-Saharan Africa, limited IMD data are available from neighboring North Africa because of insufficient surveillance (World Health Organization, 2018). Accordingly, IMD epidemiology in North Africa remains unclear, and it is difficult to develop effective preventative strategies. Thus, this review investigated IMD epidemiology, surveillance and vaccination practices of these countries to highlight knowledge gaps. It found considerable variability in surveillance practices between North African countries. Available data suggest that MenA predominated in North Africa up to the early 1990s, with genotypes such as A:4:P1.9 subgroup III-1 circulating in sub-Saharan Africa (Tali-Maamar and Rahal, 2003; Saguer et al., 2016; Nakhla et al., 2005; Shaban and Siam, 2009), thereby explaining why IMD epidemiology in North Africa was thought to be linked to that of sub-Saharan Africa (Ceyhan et al., 2012). Although some countries have IMD surveillance programs (Morocco, Algeria and Egypt), others have no or limited surveillance data available (Tunisia and Libya). Few of these systems meet the recommended standards by the WHO for IMD surveillance (World Health Organization, 1998). Although IMD is a notifiable disease in some North African countries, an insufficient or lack of a surveillance network, as seen in Tunisia, likely results in an overall underestimation of IMD cases (Borrow et al., 2017b). In Libya, data on surveillance practices are sparse, despite high disease incidence (Ceyhan et al., 2012). Conversely, nationwide meningococcal vaccination and surveillance have been implemented in Morocco and may account for the dramatic decrease in MenA incidence (Borrow et al., 2017b; Zerouali et al., 2002). Laboratory-based surveillance networks were established in Egypt and Algeria (Borrow et al., 2017b; Nakhla et al., 2005), and data from Egypt reveal a shift in frequency from MenA to MenB disease (Afifi et al., 2007; Klena et al., 2012; Shaban and Siam, 2009). Despite efforts in Algeria, data on current serogroup distribution remain limited, aside from studies on the outbreak-causing MenW clone (Mayer et al., 2002).

A recent study conducted in Tunisia identified after the literature search was performed further adds to the body of literature describing the epidemiology of IMD in North Africa (Brik et al., 2019). A total of 59 meningococcal isolates from children in the Hamza Children's Hospital of Tunis from 2009 to 2016 were characterized (Brik et al., 2019). Overall, 88.8% of isolates were MenB, 4.7% were MenY, 1.6% were MenA, 1.6% were MenC, and 1.6% were MenW (Brik et al., 2019). Findings from an analysis of the level of expression of fHbp by enzyme-linked immunosorbent assay suggested that 92.4% of MenB isolates were expected to be killed by anti-fHbp antibodies (Brik et al., 2019).

One obstacle to obtaining a clear representation of IMD in North Africa is identifying national and comprehensive databases clearly attributing disease to *N. meningitidis*. Moreover, a standardized and common case definition across countries, essential for making reliable comparisons across countries and for improving diagnosis, is lacking. Current surveillance systems often rely on clinical reporting that defines cases based on meningitis rather than IMD. Current systems also have a low percentage of biologically confirmed cases and limited matching between notified cases and biological data. Consequently, limited usable epidemiologic data are available.

Standard diagnosis and confirmation of IMD cases must be established throughout North Africa to clearly attribute disease to *N. meningitidis*. The classic diagnostic approach, commonly implemented in North Africa (Razki et al., 2018; Khalifa et al., 2011; Maalej et al., 2006; Afifi et al., 2007; Nakhla et al., 2005), uses bacterial culture; however, sensitivity can be low (Rosenstein et al., 2001). Diagnostic sensitivity is especially problematic if patients received prior antibiotic treatment. Conversely, molecular-based methods offer considerable advantages: living organisms are not required for a positive test result and genogroup-specific DNA can be detected, offering opportunities to further characterize *N. meningitidis*. Therefore, implementing molecular diagnostic techniques, coupled with properly trained laboratory personnel, should greatly improve the accuracy of available datasets, allowing development of effective health strategies to prevent IMD in North Africa.

From the limited available data, *N. meningitidis* appears to be one of the most common causes of bacterial meningitis across North Africa. It was identified as the second or third most frequent cause of bacterial meningitis cases in Tunisia, following *S.*

pneumoniae and *H. influenzae* (Saguer et al., 2016; Sfaihi et al., 2014). Studies from Egypt identified *N. meningitidis* as the most common pathogen causing meningitis and had the highest CFR compared with other pathogens (Mobarak, 2012; Farag et al., 2005). Importantly, MenB was the most frequent serogroup among IMD isolates in North Africa, yet considerable genetic heterogeneity exists across the region. For example, most MenB isolates in Morocco had the B:4:P1.15 phenotype (Zerouali et al., 2002), whereas B:NT:NST was the most frequent in Tunisia (Saguer et al., 2006; Smaoui et al., 2011). Additionally, MenB isolates in Tunisia were diverse, with six serotypes, eight serosubtypes and 23 STs identified (Saguer et al., 2006; Saguer et al., 2016). MenB isolates in Egypt also varied, with 13 STs noted in surveillance data (Klena et al., 2012). This heterogeneity may result from geographic location and travel patterns (Saguer et al., 2016). These recent data on MenB prevalence in North Africa emphasize that meningococcal epidemiology should be analyzed at the serogroup level.

Notably, North Africa seems to share greater similarity in serogroup distribution with Europe than with neighboring sub-Saharan Africa. In North African countries with available distribution data, MenB was the most frequently identified isolate in nearly all studies. Similarly, MenB is the predominant disease-causing serogroup in most European countries, comprising 41–92% of all IMD cases (Peterson et al., 2019). However, the recent rise in MenW cases in Europe is not similarly reported in North Africa (Peterson et al., 2019; Borrow et al., 2017b; Razki et al., 2018; Zerouali et al., 2002; Shaban and Siam, 2009; Krone et al., 2019). These findings contrast with those of sub-Saharan Africa, where MenA or MenW predominate (Peterson et al., 2019) and further emphasize the unpredictability of IMD.

Currently, meningococcal vaccination in North Africa relies on nonconjugated vaccines, such as the polysaccharide MenACWY vaccine, with only Egypt currently including polysaccharide meningococcal vaccine in its NIP (ie, MenAC for children and MenACWY for travelers) (Borrow et al., 2017b; Ceyhan et al., 2012; World Health Organization, 2019). Algeria, Tunisia and Morocco also use meningococcal polysaccharide vaccines for high-risk groups (eg, children and pilgrims); Algeria uses the vaccine during epidemics (Borrow et al., 2017b; Acevedo et al., 2019). Notably, economic and budgetary considerations are critical factors regarding inclusion of meningococcal vaccines within immunization programs in the region.

Although the MenACWY polysaccharide vaccine provides protection against four IMD serogroups, effectiveness wanes over short periods (Cohen and Levy, 2012). Conversely, meningococcal conjugate vaccines offer longer immunogenicity and, unlike plain polysaccharide vaccines, do not induce hyporesponsiveness (Poolman and Borrow, 2011). Because MenB disease seems to predominate in North Africa, meningococcal vaccines targeting this serogroup should also be considered for more complete protection. It is therefore important to conduct studies evaluating vaccine coverage of currently circulating MenB isolates in North Africa. As annual pilgrimages cause major meningococcal transmission and large-scale outbreaks, there is great incentive for establishing MenB vaccination programs to prevent the spread of IMD (Mayer et al., 2002).

Conclusion

Meningococcal epidemiology in North Africa appears variable, with MenB as the predominant serogroup identified in IMD cases. Improving diagnosis and PCR-based surveillance of IMD within the region would provide a more reliable burden estimate. By implementing rational meningococcal vaccine programs based on these improvements, more effective protection might be provided to the greater population.

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Author contributions

MKT, JP and LS analyzed and interpreted the data, drafted the manuscript and/or revised it critically for important intellectual content, have given final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical approval

No ethical approval was required.

Conflict of interest

MK Taha carries out contract work for the Institut Pasteur funded by GSK, Pfizer Inc., and Sanofi Pasteur. J Presa and L Serra are employees of Pfizer Inc and may hold stock or stock options.

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