



REVIEW

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Meningococcal infections among refugees and immigrants: silent threats of past, present and future

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ABSTRACT

Globally, there is an increasing number of international migrants. The majority are forced displaced refugees and children unaccompanied by a caregiver, and have limited access to essential public health interventions. Routine vaccination might be interrupted or be incomplete due to conflict areas with limited public health services or a long-unplanned journey. Refugees and migrants may bring infectious disease risks to their country of destination and may be exposed to new risk factors during transit or at their destination. There are lessons learned strategies among refugees and asylum seekers in different countries (vaccination campaign during outbreak, maintain vaccination systems for refugees and medical screening and/or vaccination on arrival) against vaccine-preventable diseases – other than meningococcal infections. Since the 1980s, invasive meningococcal disease (IMD) has been reported as a critical healthcare issue in places of humanitarian crisis such as Thailand and African's meningitis belt. Refugees and migrants are at increased risk of IMD compared with the overall population due to sero-epidemiology in their country of origin, specific characteristics of the IMD, and a number of contacts during the journey. Recently, IMD cases due to serogroups X and W have been reported and are an emerging health threat for persons arriving from Africa to refugee camps in Italy. There have been sporadic case reports of IMD due to serogroup B in Turkey; however, there has not yet been increased disease activity in this population and no outbreaks have been observed. Outbreaks of IMD in refugee camps have been and could be successfully controlled through the implementation of timely and high-coverage vaccination campaigns, and individual cases of IMD can be treated with antibiotics. Research is needed to determine the prevalence of meningococcal carriage and serogroup distribution among refugees and migrants to inform vaccine recommendations. There is no official recommendation for meningococcal vaccination of refugees. Further strategies for prevention and treatment of human immunodeficiency virus, tuberculosis and antibiotic resistance among refugees are directly related to potential prevention methods for IMD. Meningococcal vaccines have been administered only to risk groups in most host countries. Thus, further strategies for the definition of new/emerging risk factors for IMD would be helpful to guide vaccine implementation for refugees and immigrants.

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United Nations 2030 Sustainable Development Goals include the positive contributions of refugees and migrants for inclusive growth and sustainable development. There are an estimated 258 million international migrants and 763 million internal migrants worldwide; developing countries host the largest share, 86%, of the forced displaced population.¹ According to a 2019 report of the United Nations High Commissioner for Refugees (UNHCR), approximately 57% of refugees worldwide came from three countries in 2018: Syria, Afghanistan and South Sudan.² Worldwide, an estimated 70.8 million people were forcibly displaced from their homes in 2018; the greatest number of new asylum applications during that period were from Venezuelans.² Turkey hosted the largest number of refugees worldwide, approximately 3.5 million, followed by Pakistan, Uganda, Sudan and Germany.² More than 90 million migrants live in Europe, accounting for almost 10% of the total population in the European Region and almost one-third of international

migrants worldwide. Approximately 5.2 million refugees and 1.4 million asylum seekers live in the European Region,³ representing the influx of refugees and asylum seekers trying to reach European shores. In 2016, an estimated 362,000 refugees and migrants risked their lives crossing the Mediterranean Sea to reach Europe, and approximately 19,000 have lost their lives during the journey to Italy, Greece, Spain, Malta and other countries since 2013.^{3,4} Refugee children are an especially vulnerable and high-risk group. The UNHCR estimates that nearly 30 million children in the world are living outside their country of birth, 13 million as refugees or asylum seekers, and the majority were unaccompanied by a caregiver. The overwhelming majority of these children reside in countries of low or middle incomes that are neighbors to zones of armed conflict. Between 2015 and 2017, more than 30% of the total refugee population were unaccompanied child asylum seekers in the European Union geographical area. This percentage is

significantly higher in Italy (59%) and Slovenia (66%).^{2,3} In addition to the physical and psychosocial problems of unaccompanied children, health authorities are unable to ascertain the previous medical and immunization history of these patients. The recent large-scale population movement has posed epidemiological and health system challenges, including increasing infectious diseases and outbreaks.

Previous experiences have indicated that increased infectious diseases are often seen among refugees and migrants, though transmission from the refugee or migrant to the host country population is low.⁵ Changes for the epidemiology of infectious disease including vaccine-preventable diseases (VPDs) and non-communicable diseases are inevitable due to the highest number of refugees and migrants. Migration also influences broader aspects of public health and it also influences the use and uptake of disease prevention and health-care service utilization in general.^{5,6} Refugees and migrants may bring health risks to their country of destination (incomplete or interrupted immunization) and may be exposed to new risk factors at journey or at the host country. The displacement and migratory experience can alter the pattern of morbidity and mortality for infectious diseases. As refugees and migrants spend longer in the country of destination, their health status may converge with that of the host population.^{5,6}

Migration and infectious disease

Increased transmission of infectious disease is often seen among refugees and migrants.⁵ In terms of acute or newly acquired infections, refugees and migrants are generally at the same risk for respiratory and gastrointestinal infections, comparing the other residents. However, preexisting conditions and living environment in the host country can influence morbidity and mortality. Poor sanitation and contaminated water before or during the migratory journey increase the risk of infections. Incomplete or interrupted immunization, especially in children, can create risks of VPDs and potentially pose a public health challenge for under-immunized or unvaccinated populations in the host countries. Influenza and human papillomavirus vaccine uptakes are quite low among refugees.¹ Transmission of tuberculosis from migrants to host populations is limited, but there are no relevant data for the multi-drug resistant tuberculosis.¹ The risk of importation of HIV by migrants to Europe is low. Refugees and migrants constituted 40% of new HIV diagnoses in Europe in 2016.¹ Antibiotic resistance is also a growing concern in the context of migration. In overcrowded refugee camps and poor hygienic conditions, spread of resistant pathogens can easily occur. Disruptions in treatment and misuse of medication during transit and resettlement also increase the risk of development of disease resistance.^{7,8}

Invasive meningococcal disease

Invasive meningococcal disease (IMD) results from infection with *Neisseria meningitidis* and is associated with high case-fatality rates and long-term sequelae. IMD may occur sporadically, in small clusters or as large outbreaks or epidemics, and adequate surveillance is paramount for accurate epidemiological data and, in turn, initiation of appropriate prevention

strategies.⁹ There is limited information about the invasive meningococcal disease among the refugee population.¹⁰

Meningitis has been reported as an important health-care – or outbreak – situation in places where humanitarian crises or conflict have resulted in an influx of refugees.^{11,12} Cases of meningococcal meningitis and meningococemia have been reported in refugee camps. At the end of the 1970 s, although they did not differentiate meningococcal meningitis from other infectious causes, Feldstein and Weiss¹³ found meningitis to be the fourth-leading pediatric admission diagnosis in a Cambodian refugee camp in Thailand during a 3-month period. Reported cases were seen in the refugee camp at or after arrival or time. Some factors associated with IMD in immigrants include prevalence and incidence of the meningococcal disease in the country of origin, specific characteristics, case-fatality rate and/or serogroup distribution of meningococcal diseases, number of contacts that the migrant had during the journey and the duration of the journey.^{11–19}

To the best of our knowledge, the first meningococcal infections/outbreaks among refugees reported in the literature were in Thailand.¹¹ Over a 4-month period, serogroup A meningococcal disease outbreak at the Sakaeo refugee camp in Thailand in 1980 involved 32 refugees with an attack rate of 0.13%. The overall case-fatality rate during that outbreak was just over 28%; however, children under 5 y of age experienced a case-fatality rate of 50%.¹² A similar outbreak occurred at another camp, with 46 cases and an attack rate of 0.08% over a 3-month period.¹¹

In Africa, outbreaks of meningococcal meningitis were reported among Ethiopian refugees in eastern Sudan in 1985 and among displaced Sudanese in Khartoum and southern Sudan in 1988.¹¹ In 1994, meningococcal serogroup A epidemics occurred in refugee populations in Zaire.¹⁵ Haelterman et al.¹⁵ compared the effects of a meningococcal vaccine early in the course of epidemics and late in the course between two different refugee camps. Before the immunization campaign, the incidence of IMD was 15 cases per 100,000 people per week, and attack rates were 94 and 134 IMD cases per 100,000 people in the two camps. Within 76% of immunizations of all refugees, vaccination may have prevented 30% of the expected cases.

Heyman et al.¹⁶ studied meningococcal meningitis cases among Rwandan refugees in a field hospital. They evaluated medical records of 65 patients with meningococcal meningitis due to serogroup A and found that the mortality rate was 14%. The mortality rate was associated with the presence of dysentery, pneumonia and malnutrition.

Another report evaluated a meningococcal meningitis outbreak in a Sudanese refugee camp in Northern Uganda in 1994.¹⁷ During this outbreak, 291 cases of the disease were recorded. The epidemic reached its peak within 3 weeks; the attack rate was 0.30% and CFR was 13.3%. While the sampling was limited, the identified meningococcal serogroup A isolates were serotype 21:P1-9, clone III-1. During the outbreak period, 37,547 doses of meningococcal vaccine were administered between February and March 1994 (the camp's refugee population was 96,860), and the outbreak was under control by August 1994. However, new cases were reported after a massive refugee influx after this period.¹⁷

Italy

Italy is an important entry point for refugees to Europe.³ Stefanelli and colleagues¹⁸ reported meningococcal serogroup X cases in a refugee camp in Italy. According to data from the Italian Reference Laboratory for IMD, four unlinked case-patients (migrants living in refugee camps or reception centers) with serogroup X IMD have been reported. The first case was reported in 2015 in a 15-y-old girl from Eritrea who had arrived in a refugee camp in Lombardy, Italy, 3 d before onset of the disease, which manifested as septicemia. The other three cases were reported in 2016: two in Lombardy (in a 20-y-old man from Mali and a 31-y-old man from Niger) and another in a Tuscan camp (in a 24-y-old man from Bangladesh). These cases were characterized by meningitis with fever over 40°C and loss of consciousness. All patients were treated with ceftriaxone and survived. Chemoprophylaxis with rifampin or ciprofloxacin was administered to all persons directly exposed to the index case-patients. The man from Bangladesh lived in a camp with other African refugees for several months before disease onset, but symptoms developed in the other three patients shortly after their arrival in Italy. CC181 genomes were resolved in three main groups: group 1, finetype X:P1.5-1,10-1:F1-31:ST181 (CC181); group 2, finetype X:P1.5-1,10-1:F4-23:ST5789 (CC181); and group 3, finetype X:P1.5-1,10-1:F4-23:ST181 (CC181). Two of the strains identified in Italy in 2016 clustered in group 1 with seven MenX strains isolated from 2005 to 2016 in Niger, Burkina Faso, Benin and the United Kingdom. Notably, the UK MenX CC181 strain clustered close to the Italy strains. The strain diagnosed in Italy in 2015 clustered in group 2 with three strains isolated in 2006 in Niger. MenX isolates from Africa belonged to CC181 and formed a single main lineage. MenX strains from Italy were found to have similar characteristics to those already described.¹⁸ Stefanelli et al.¹⁸ suggest that MenX represents an emerging health threat for persons arriving in Italy from Africa.

Stefanelli and colleagues¹⁹ have also reported three cases of meningococcal meningitis caused by the ST-11/ET-37 strain of *N. meningitidis* serogroup W. Two of the three cases, detected in Sicily in June and July 2014, were migrants from Mali and Eritrea. The third case was fatal meningitis that occurred in November 2014 in a 37-y-old man working in an immigrant center in Calabria.

Turkey

Turkey is the primary host country of Syrian refugees.² According to the official registry (March 2019), 3,642,738 Syrian (registered) refugees live in Turkey – approximately 4.5% of the population in Turkey – 141,627 (3.8%) of whom live in refugee camps. A large portion (45.5%) of Syrian refugees in Turkey are under 18 y old and the mean age is 22.7 y (younger than the mean age, 31.7 y, of Turkish citizens). During the last 8 y, 405,521 Syrians were born in Turkey. While the majority of the refugees in Turkey are of Syrian origin, the country also hosts refugees from Afghanistan, Iraqi and other Middle Eastern countries.²⁰

Before the Syrian Civil War, there were no relevant epidemiological data for IMD. There is limited information regarding invasive meningococcal infections in refugee populations; only case reports are available. Tezer and colleagues²¹ reported one such case of an 11-y-old Syrian refugee girl living in Turkey for 3 months. She had a 2-d history of headache, fever, vomiting, petechiae which was more prominent on the lower extremities, and laboratory examinations revealed leukocytosis, elevated serum CRP levels and prolonged activated partial thromboplastin time. Cerebrospinal fluid (CSF) examination: polymorphonuclear leukocytes in Giemsa stain and gram-negative cocci in gram stain increased CSF protein levels as 341 mg/dl and polymerase chain reaction (PCR) study of CSF yielded *N. meningitidis* serogroup B. Patient was cured after 10 d of ceftriaxone therapy. Authors stated that due to 3 months of accommodation in Turkey, it could not be estimated whether the patient acquired this strain in her country or in Turkey.²¹ The second reported case was a 2-y-old Turkoman refugee boy living in Turkey admitted with a fever and 2-d history of vomiting.²² Upon admittance, petechiae were more prominent in the upper extremities but unnoticed by her mother. CSF examination showed gram-negative cocci, glucose as 28 mg/dL and protein as 242 mg/dL. PCR evaluation of CSF yielded *N. meningitidis* capsular group B. Clinical and laboratory findings were recovered after 10 d of ceftriaxone therapy.²² Recently published new case from the same group in Turkey showed a 2-y-old Syrian refugee with meningococcal meningitis due to serogroup B, complicating with empyema.²³

Anecdotally, there have been other meningococcal infections among refugees (not published); however, there is no increased disease activity in this population and no outbreak has been observed.

Meningococcal carriage

The literature provides only limited information about the meningococcal carriage status among refugees. Tafuri and colleagues²⁴ evaluated the prevalence of *N. meningitidis* carriage among migrants in Italy in 2008. They enrolled 253 refugees (25.1% of them in the Asylum Center during 2008) between the ages of two and 41 y (mean 19.8 y). All migrants came from Africa and 201 (79.4%) originated from countries within the meningitis belt. They found that meningococcal carriage was 5.1%; 30.8% strains belonged to serogroup W and 23.1% to serogroup Y.²⁴

Meningococcal vaccines

There is no official recommendation for meningococcal vaccines for refugees. Migrants are moving throughout host countries, and many vaccines must be given in consecutive doses, at regular, pre-scheduled time intervals.²⁵ A majority of host countries immunize refugees with their national immunization program (NIP). As meningococcal vaccines are not a part of NIPs in most countries,⁹ refugees are not immunized with these vaccines. War and conflict areas are also important factors for low vaccine coverage.³ The World Health Organization (WHO) estimates that levels of immunization – vaccines in general – in Syria are

currently around 60%, while they were greater than 90% before the war. In Turkey, Syrian children are vaccinated free of charge (vaccine coverage is 95%) according to the Ministry of Health Expanded Immunization Program (13 antigens, not including meningococcal vaccines). Nine rounds of mop-up campaigns among Syrian refugees and children from Turkey were also conducted.⁸

Lessons learned in the implementation of other vaccines for refugee and migrant populations

Forty-five studies among refugees/migrants showed that the burden of VPDs is higher and immunization rates are lower as 70%.²⁶ In the past, there are lessons learned strategies against VPDs – other than meningococcal infections – among refugees and asylum seekers in different countries. These strategies are vaccination campaign during outbreak, maintain immunization systems for refugees according to host country's national immunization program and medical screening and/or immunization at arrival.^{27,28} Based on more than 20 yof experience in the development and monitoring of a health assessment framework for the United States-bound immigrants and refugees, successful strategies are to improve health during planned migrations, including overseas screening, treatment and vaccination programs. These strategies have reduced tuberculosis rates; decreased transmission and importation of VPDs; prevented morbidity from parasitic diseases; and saved domestic health costs in the United States.²⁸

In August 2017, nearly 900,000 Rohingya refugees have migrated from Myanmar and settled in Bangladesh.²⁹ Given the crowded conditions in the refugee camps and the low rates of measles immunization among the Rohingya population, a large measles outbreak broke out in the Rohingya refugee camps in late 2017, with over 1700 cases of measles. Two vaccination campaigns with measles-rubella vaccines (135,519 children aged 6 months to 15 y old at first phase and 323,940 children aged 6 months to 15 y at second phase) were conducted in response to the outbreak. Evaluation of this period showed reactive vaccination campaigns with high vaccination coverage rates, a remarkable public health achievement given the very low rates of prior immunization and higher birth rate among the refugee population. Vaccination coverage is the key indicator for the number of cases averted and maintaining ongoing surveillance is essential.²⁹

Thijssen et al.³⁰ stated that by establishing a well-prepared infrastructure for screening, vaccination and treatment against hepatitis B for refugees in an opportunity for elimination of this virus. Vaccination policies for refugees are also important for the disease with ongoing global eradication program like polio. In Denmark, among 475 children and adult refugees (from mainly Syria, and the rest from Eritrea, Congo, Lebanon, Somalia, Afghanistan, Iran, Iraq, Ethiopia and Columbia), 5.6% have negative serology for a least one polio serotype. Ensuring poliovirus immunity among refugees remains a priority until polio has been eradicated worldwide.³¹

Ravensbergen et al.³² analyzed vaccination policies for migrants in Europe, and there is considerable variation in policies. In 2018, the main strategies for migrant vaccination are in place in nearly all European countries, and the strategies are generally in line with international recommendations and mainly focused on children.³³ Freidl et al.³⁴ assessed the

immunity of adult asylum seekers against VPDs including measles, mumps, rubella, varicella, diphtheria, tetanus, polio types 1–3 and hepatitis A and B, and highlighted prioritizing vaccination of susceptible subgroups of adult asylum seekers, in general and in outbreak situations. Seedat et al.³⁵ showed that majority of the European countries prefer to screen only-predominantly active or latent tuberculosis infection, and HIV, hepatitis B and C.

Medical screening is another key strategy to reduce the risk of infectious diseases.²⁸ The American Academy of Pediatrics recommends medical screening for all newly arrived refugee children and linkage to primary care as soon as possible after arrival.³⁶ Health-care providers caring for refugee children must be aware of communicable diseases that are endemic to the refugee's country of origin. Priority infectious diseases affecting refugees and other newly arriving migrants to high-income countries include tuberculosis (active and latent), HIV, hepatitis B, hepatitis C, VPDs (such as polio, tetanus, diphtheria toxoids, pertussis, *Haemophilus influenzae* type b, rotavirus, mumps, measles, rubella, hepatitis A, hepatitis B, meningococcal disease, influenza, pneumococcus and varicella) and parasitic infections.²⁸

Recommendations of serology screen for some VPDs (e.g. hepatitis A, hepatitis B, varicella) are most cost efficient than systematic immunization regardless of serostatus.^{27,28,37} Fahrni et al.³⁷ showed that for hepatitis A, serology-based immunization in specific age groups or countries with >25.7% of seropositivity and systematic vaccination for the others is the most cost-efficient immunization strategy. Vaccination without obtaining serologic tests for VPD may be a consideration in some settings since tests may be expensive, have a delayed turnaround time, and patients may be lost to follow-up due to re-location.³⁸

Pneumococcal infections and prevention strategies might be an example of meningococcal infection and immunizations. WHO Framework lists include pneumococcal conjugated vaccine (PCV) as one of the vaccines to be considered for use in humanitarian crises. WHO recently recommended to use PCV in children under 1 y of age and consider for children under 5 y of age during humanitarian crises and other emergencies.³⁹

Refugees and asylum seekers' perspectives on infectious disease screening and vaccination policies are another important factor for the control of VPDs. According to the study by Louka et al., among refugees from Afghanistan, Syria and Eritrea in Greece and the Netherlands, 72.1% of refugees were willing to be vaccinated after arrival in Europe, 26% preferred vaccination and screening to be performed at the point of entry. Screening and vaccination programs could be more effective when implemented shortly after arrival.⁴⁰

Concerns about refugee health potentially associated with meningococcal infections

- (1) VPDs result from domestic acquisition rather than importation. Refugees and asylum seekers are particularly vulnerable due to disrupted or poor-quality health services, low coverage of vaccinations, long and dangerous journeys and conditions experienced in transit or at reception, such as overcrowding and poor sanitation facilities.

- (2) Screening services for VPDs and vaccination are not always provided to migrants or are not easily accessible or centered on migrants' needs.²⁵
- (3) There is often no information on the immunization status of migrants and refugees. Hosting countries are facing economic crises and exacerbating their risk of infectious disease. In Turkey, there is a well-organized system for immunization. Syrian children have been vaccinated free of charge (vaccine coverage is 95%), according to the Ministry of Health Expanded Immunization Program (13 antigens, not including meningococcal vaccines). Nine rounds of mop-up campaigns among Syrian refugees and children from Turkey were also conducted.⁸
- (4) Migrants often refuse vaccination and registration by medical authorities for fear of legal consequences. Lack of coordination among public health authorities of neighboring countries may determine either duplications or lack of vaccine administration.²⁵
- (5) There is an increased percentage of health-care-associated infections in migrants. In Turkey, the percentage and/or mortality of health-care-associated infections increased in the last 3 y, and the first isolate of New Delhi Metallo-Beta-Lactamase-1 (NDM-1) was reported from a Syrian refugee.⁸
- (6) HIV and tuberculosis are critical diseases in refugee populations.³ HIV infection is a new risk factor of meningococcal infection; for this reason, refugees might be appropriate candidates for meningococcal vaccines.⁹ Tuberculosis has also been commonly detected among host country entry points, including multi-drug resistant tuberculosis. Rifampicin is a key agent of the treatment of tuberculosis and is also an important antibiotic to fight meningococcal infections.

Detection and surveillance systems for imported infections are routine components of national health systems, especially for IMD; early diagnosis, treatment and prophylaxis should be ensured to protect vulnerable populations, including migrants, refugees and the host community. There are no clear signs of the effect of immigration on a host country's IMD distribution; however, regarding the experience in Italy, uncommon serogroups, such as serogroups X and W, might be entering the country with immigrants. Thus, the importance of having rapid meningococcal diagnostics is of utmost importance. There are no official immigrant vaccination recommendations for IMD. However, due to overcrowding and limited health-care facilities, refugees should be included in risk groups for IMD. Meningococcal vaccines have been administered only to risk groups in a majority of host countries; thus, further strategies for the definition of new/emerging risk factors would help to increase vaccine implementation.

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No potential conflicts of interest were disclosed.

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