

Meningococcal serogroup B disease in Turkey

A guess or reality?

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Abbreviations: CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; EU, European Union; ICD-10, International Classification of Diseases 10th Revision; IMD, invasive meningococcal disease; MCC, meningococcal group C conjugate vaccine; NIP, National Immunization Programme; PCR, polymerase chain reaction; RT-PCR, real time-polymerase chain reaction; TSI, Turkish Statistical Institute; TR, Turkey; US, United States; WHO, World Health Organization

Each country chooses the appropriate vaccine against IMD depending on the locally prevalent serogroups of *N. meningitidis*. Frequency of each meningococcal serogroup varies considerably over time and by geographical location. Despite the majority of IMD cases (85%) are caused by serogroups B and C in Europe, true prevalence of serogroup B IMD cases in Turkey is unclear. In one of the recent studies, the sharp decrease of serogroup B IMD from 35% down to 2.5% in a few years despite the absence of vaccination is confusing. Millions of European Turkish people travels from Europe to Turkey every year who could most probably carry serogroup B. It is obvious that a nationwide active surveillance is crucial to assess the true epidemiology and burden of IMD which has a major impact on the choice of vaccine type and age interval the vaccination to be implemented.

Introduction

Invasive meningococcal disease (IMD) is due to infection with the Gram-negative bacterium *Neisseria meningitidis* (*N. meningitidis*). The most common manifestation of IMD is meningitis. Although fulminant septicemia is less common, it is highly fatal, even if treated.¹ IMD still represents an important public health problem in developed and developing countries.² Approximately 500 000 cases occur worldwide annually, resulting in approximately 50 000 deaths and severe long-term complications in up to 20% of survivors.^{2–4} Deafness, intellectual and learning impairment, epilepsy, and other neurological deficits are frequent sequelae that lead to long-term reduction in quality of life.^{2,4} According to the World Health Organisation (WHO) estimates, the overall notification rate of IMD in Europe ranges from 0.2–14 cases per 100 000 in the general population.² Although the rates of IMD can be low in European and other industrialized countries, the disease is potentially devastating, with a case mortality rate that has remained at about 5–10% despite treatment.^{2,5}

In Europe, the highest numbers of confirmed IMD cases are reported in children younger than 5 y of age (7.37 per 100 000), followed by children aged 15–24 y (1.44 per 100 000).⁵ Most of these cases of IMD occur sporadically, although small local outbreaks are not uncommon.^{2,6,7}

While the majority of IMD infections are caused by *N. meningitidis* serogroups A, B, C, X, W-135, or Y, their relative prevalence has varied considerably over time and by geographical location, making trends in disease epidemiology unpredictable.² In Europe, the majority of IMD cases (85%) are caused by serogroups B and C, while serogroup Y is the third most frequently reported cause (3% in 2008, and 4% in 2009).^{2,8} Overall, the number of cases of IMD attributable to serogroup Y increased by 42% across European countries between 2007 and 2009.⁸ However, the incidence of *N. meningitidis* infection due to serogroup C has declined since the introduction of the meningococcal group C conjugate vaccine (MCC) in some European countries while the incidence of IMD across Europe has also changed.⁸

Active surveillance is crucial to assess the epidemiology and burden of IMD, as well as the impact of vaccination.⁶ In European countries, in which adequate surveillance systems have been in place for >10 y, long-term surveillance has detected large reductions in meningococcal serogroup C disease following the introduction of the MCC.² However, the scarcity of comprehensive country-specific data on the current burden of meningococcal disease in Turkey arises from the lack of homogenous surveillance system, making it difficult to understand and to predict the dynamic changes in serogroup-specific epidemiology. Meningococcal conjugate ACWY vaccine is used for both individual protection (e.g., target groups such as Hajj pilgrims, military recruits, or teenagers in the United States) and mass campaign vaccinations. It is established that MCV has a great impact in reducing meningitis if used at large scale, such as the use of MenC conjugated vaccine in the UK.⁹

While commonly used meningococcal vaccines in Europe cover serogroups A, C, Y, and W-135, an effective vaccine against serogroup B has not been available until recently. A quadrivalent protein-based serogroup B vaccine developed by Novartis Vaccines and Diagnostics has been licensed in the EU for infant vaccination. Although its use has not been implemented in

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Table 1. Number of injections in national immunization program (NIP) in the United States (US) compared with Turkey (TR) with and without alternative meningococcal vaccines

Vaccination schedule	Number of injected vaccine doses				
	2nd mo	4th mo	6th mo	9th mo	12th mo
Routine* in TR	3	2	3		3
Routine plus Men A, C, W, Y-CRM197 (Novartis) in TR	4	3	4		4
Routine plus Men A, C, W, Y-D (Sanofi Pasteur) in TR	3	2	3	1	4
Routine plus Men A, C, W, Y-TT (GSK) in TR	3	2	3		4
Routine plus Men A, C, W, Y-CRM197 (Novartis) and 4CMenB (Novartis) in TR	5	4	5		5
Routine in US	4	4	6		7

*Current NIP schedule.

large-scale vaccination programmes, phase III studies have demonstrated that the vaccine has the potential to protect against 78% of all IMD-causative serogroup B strains.¹⁰ Lack of systemic surveillance data on serogroup-specific meningococcal epidemiology complicates the decision to be made by health authorities with regard to implementation and choice of available meningococcal vaccines.

The purpose of this review is to provide up-to-date information on the epidemiological situation regarding the burden of IMD in Turkey.

Available Data on the Burden of IMD in Turkey

In Turkey, data available on the burden of IMD at the national level are based on records collected by the Turkish Statistical Institute (TSI) and by the Ministry of Health. According to Ministry of Health data, between 1989 and 1999, the incidence of IMD varied between 1 and 35 cases per 100 000 and the mortality rate varied between 0.71 and 2.62 per million cases.¹¹ The TSI reports that meningococcal infections were responsible for 10.2% (1336) of all deaths in children under 5 y of age in year 2008.¹² TSI reports 21, 14, and 15 deaths from meningococcal infections in all age groups in 2010, 2011, and 2012, respectively based on ICD-10 coding system.¹³ These contradictory data might be due to either the notification procedure (report of death due to IMD or report of newly identified IMD cases) or the identification of causes.¹⁴

The current situation on meningococcal epidemiology may be better reflected by the prospective multicenter sentinel surveillance for childhood bacterial meningitis conducted by 2 groups since year 2005.¹⁵⁻¹⁷ One of the investigator-initiated sentinel surveillance studies was conducted by Ceyhan et al. between February 16, 2005, through February 15, 2006, for acute bacterial meningitis among children admitted to 12 participating hospitals from 7 geographic areas and 12 health centers in 9 cities.¹⁵ This study reports that *N. meningitidis* was the leading cause of bacterial meningitis in children aged <1 y (56.5%) followed by those aged 1–4 y. Among the samples that were positive for *N. meningitidis* following PCR analysis, serogroup W-135 was the cause of most infections—59 (42.7%) cases were due to serogroup W-135, 43 (31.1%) were due to

serogroup B, 3 (2.2%) were due to serogroup Y, and 1 (0.7%) was due to serogroup A. There were no cases with a positive result for serogroup C.¹⁵ In this study, serogroup W-135 was also more common in children aged 4–16 y, while serogroup B was slightly more common in children aged <3 y. *N. meningitidis* serogroup W-135 was more prominent than the other meningococcal serogroups in the Southeast Anatolia while *N. meningitidis* serogroup B was much more common in the Marmara (northwestern Turkey) and the Central region.¹⁵ During ongoing surveillance by Ceyhan et al. between 2007–2009, while the overall IMD incidence was stable, the prevalence of IMD due to serogroup B was reported to increase to 35% and the prevalence of serogroup W-135 decreased.¹⁶ Interestingly, the same group states that during the first 9 mo of 2011, serogroup W135 was the predominant serogroup, followed by serogroup A, and serogroup B was observed in only 2.5% of cases.¹⁶

Another nationwide prospective RT-PCR-based surveillance for childhood bacterial meningitis was conducted between July 2006 and January 2009 and the Turkish Ministry of Health with participation of 37 referral hospitals located in 23 cities in 7 geographic regions of the country.¹⁷ RT-PCR detected bacterial DNA in 246 (29%) of 841 CSF specimens from children with suspected bacterial meningitis, of which 131 (53%) were due to *Streptococcus pneumoniae*, 47 (19%) were due to *Neisseria meningitidis*, and 40 (16%) were due to *Hemophilus influenzae* type b. In this study, 29 (62%) of 47 *N. meningitidis* isolates were determined as serogroup B, 2 (4%) serogroup C, 1 (2%) serogroup X, 1 (2%) serogroup A, 1 (2%) serogroup W135, and 13 (28%) other serogroups (undetermined). Sixteen (32%) of *N. meningitidis* were detected from the Marmara (north-western Turkey) region and only 5 (11%) from the Southeast Anatolia.

Discussion

To prevent IMD among young infants, protection needs to be achieved early in life. Since the introduction of the first meningococcal conjugate vaccines in 1999, remarkable progress has been made in reducing the morbidity and mortality caused by meningococcal disease.¹⁸ Studies have demonstrated that Meningococcal C Conjugate (MCC) vaccination confers protection in infancy (0–12 mo) from the first dose but this protection

is short-term.⁹ However, administration of a booster dose early in the second year of life results in longer protection.¹⁹

The burden of IMD is the highest among infants aged <1 y (2.6 cases per 100 000 persons) in the US.¹⁹ Among infants younger than 1 y of age, more than 50% of cases are caused by serogroup B in the US.²⁰ In Turkey, the burden of meningococcal disease is the highest among infants.¹⁵ It was recently reported that bacterial meningitis was most frequently observed in the first 7 mo of life, regardless of the etiologic agent.²¹ All meningococcal meningitis cases occurred in those <6 mo of age and mostly in those <3 mo of age. All cases in the youngest infants were due to meningococcal serogroup B and W135 in Turkey.²² If meningococcal vaccines against Men B and serogroups A, C, W135, Y with early infant indications may also be registered, we would have an opportunity to protect young infants starting from 2 mo of age in Turkey.

The growing-complexity of National Immunization Programme (NIP) in Turkey has resulted in as many as 4 required injections during a single healthy baby visit. The number of injections in a well-baby visit in the US is up to 7.²⁰ Protecting against vaccine preventable meningococcal serogroups will result in an increase in the number of injections up to 6 in Turkey, but this is acceptable when we compare with developed countries (Table 1)

Contrasting data obtained from different surveillance studies may be related to regional differences in the weight of subjects enrolled from different regions of the country or methods used. Ceyhan et al. argues that higher rates of serogroup W-135 since 2005 in their earlier study¹⁵ is due to 100 000 Turkish Hajj pilgrims traveling to Saudi Arabia every year,¹⁶ which was also seen in Malaysia and Singapore.²³ The results reported by Bakir et al.¹⁷ showing the predominance of serogroup B may be explained by the millions of the Turkish diaspora living in Europe, where serogroup B is predominant, who travel back and forth to the country many times annually. This is a more likely explanation of the existing sero-epidemiology because

other explanations of the sharp decrease of serogroup B IMD from 35% down to 2.5% in only a few years¹⁶ in the absence of serogroup-specific vaccination are unlikely.

The distribution of serogroups varies among age groups and over time. This variation may also reflect the introduction and implementation of detection techniques such as the PCR. Sero-epidemiology data on IMD in 2 different surveillance studies in Turkey at the same time periods had different results. This complicates the decision to be made by health authorities on the implementation and the type of meningococcal vaccine to be chosen. In the light of available surveillance data in Turkey, a vaccine effective against meningococcus serogroup B as well as serogroup W-135 should be considered in early infancy. Systematic continuous surveillance is warranted to measure the urgency of need and effectiveness of a vaccination program for IMD.

The WHO recommends the introduction of appropriate large-scale meningococcal vaccination programmes in countries with high (>10 cases/100 000 population/year) or intermediate (2–10 cases/100 000 population/year) IMD incidence rates, and in countries with frequent epidemics.² In countries with lower IMD incidence rates (<2 cases/100 000 population/year), vaccination is recommended for defined risk groups, including children and young adults residing in close communities, laboratory workers at risk of exposure, travelers to high-endemic areas and immunodeficient individuals.²

Overall, each country should choose the appropriate vaccination program depending on the locally prevalent serogroup of *N. meningitidis*.² Conjugate vaccines are preferred over polysaccharide vaccines due to their potential for herd protection, immunologic memory and their increased immunogenicity, particularly in children <2 y of age.²

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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