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Review

Meningococcal disease and control in China: Findings and updates from the Global Meningococcal Initiative (GMI)

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ABSTRACT

The Global Meningococcal Initiative (GMI) is a global expert group, including scientists, clinicians and public health officials from a wide range of specialities. The goal of the GMI is to prevent meningococcal disease worldwide through education, research, and co-operation. The Chinese GMI roundtable meeting was held in June 2017. The GMI met with local experts to gain insight into the meningococcal disease burden in China and current prevention and vaccination strategies in place. China experienced five epidemics of serogroup A meningococcal disease (MenA) between 1938 and 1977, with peak incidence of 403/100,000 recorded in 1967. MenA incidence rates have significantly declined following the universal introduction of the MenA polysaccharide vaccine in China in the 1980s. Further, surveillance data indicates changing meningococcal epidemiology in China with the emergence of new clones of serogroup B from serogroup C clonal complex (cc) 4821 due to capsular switching, and the international spread of serogroup W cc11. The importance of carriage and herd protection for controlling meningococcal disease was highlighted with the view to introduce conjugate vaccines and serogroup B vaccines into the national immunization schedule. Improved disease surveillance and standardized laboratory techniques across and within provinces will ensure optimal epidemiological monitoring.
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Introduction

Neisseria meningitidis (Nm) is an obligate human pathogen, and is the cause of invasive meningococcal disease (MD).[1] Nm strains can be classified into 12 serogroups (A, B, C, E, H, I, K, L, W, X, Y, Z) based on the immunochemistry of its capsular polysaccharides. Six serogroups (A, B, C, W, X and Y) account for the majority of all cases of MD worldwide.[2,3] The remaining serogroups (E, H, I, J, L and Z) are usually only found in carriage, but can cause invasive disease in immuno-compromised individuals, such as patients with complement deficiencies.[4]

The Global Meningococcal Initiative (GMI) was established in 2009 and is a multidisciplinary group of over 50 scientists and clinicians dedicated to the prevention of MD worldwide through education, research and international co-operation. A number of global and regional GMI meetings have been held since its inception,[5] including this regional meeting in Chengdu, Sichuan province, China in June 2017. Experts were not available to attend the GMI meeting

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from all 34 provinces across China; however, attendees included several representatives from the Chinese Center for Disease Control and Prevention (CDC; Beijing, Shanghai, Guangdong and Liaoning), as well as scientists and clinicians from hospital-based departments relating to infectious disease. Members from Public Health England (United Kingdom [UK]), Institute Pasteur (France) and the World Health Organization also attended to share their experiences and the lessons learned from their vaccination and outbreak programs.

The specific meeting objectives were to: (i) review the global incidence and epidemiology of MD, including China; (ii) provide an update on MD surveillance, prevention and control strategies from both a provincial (Liaoning province and Guangdong province) and national perspective; (iii) discuss the issues faced regarding MD and bacterial meningitis (BM) surveillance, prevention and control strategies with a focus on current barriers to implementation; (iv) highlight the importance of conjugate vaccines and their impact on the prevention of MD; and (v) discuss key learning points from immunization programs used worldwide in outbreak control and preparedness. This paper summarizes the key discussion points and subsequent recommendations from the meeting to help inform global and regional recommendations for MD prevention.

Review of the global incidence and epidemiology of meningococcal disease

The global distribution and incidence of MD varies from 0.11 to 2 cases per 100,000 population in Europe and North America,[6,7] to more than 100 cases per 100,000 population in the "meningitis belt" of sub-Saharan Africa.[8] The incidence of MD in Africa subsequently fell to 0.02 cases per 100,000 between 2011 and 2013 after the introduction of the MenAfriVac® vaccine in 2010.[8] In China, the MD incidence rate is 0.047 cases per 100,000 population based on data from 2006 to 2014 from the National Notifiable Disease Reporting System (NNDRS).[9] However, recent subnational estimates indicate an incidence rate of 1.84 cases per 100,000 population, suggesting that the overall incidence rate for China is underestimated.[10] Historically, China has experienced five epidemics of MD between 1938 and 1977.[10,11] The peak incidence of MD was recorded in 1967 with 403 cases per 100,000 population, >3,040,000 recorded cases and >160,000 deaths with a case fatality rate of approximately 5.5%. Following the universal use of serogroup A MD (MenA) polysaccharide vaccines in China in the 1980s and the introduction of MenA polysaccharide vaccines in to the Expanded Programme for Immunization (EPI) in China in 2008, the reported incidence of MD has steadily declined to <0.52 cases per 100,000 population in 2009[12]; this decline has been particularly evident in the last five years owing to an increasing vaccination coverage rate.

The incidence and prevalence of Nm serogroups continually varies both geographically and temporally.[10,13] Meningococcal epidemiology suggests an increased incidence and prevalence of MD during mass gatherings that involve migration and travel.[14–16] Further, Nm is susceptible to frequent genetic transformations due to natural horizontal DNA exchanges between isolates.[17]

Currently, serogroup B MD (MenB) is the most prevalent globally.[7] Multilocus sequence typing (MLST) of MenB isolates worldwide revealed three major hyperinvasive clonal complexes (ccs) (sequence type [ST]-32, ST-41/44 and ST-269) in Europe and the United States of America (USA).[18] Further, cc ST-11 previously observed among serogroup C MD (MenC) and serogroup W MD (MenW) isolates has since occurred in cases of MenB due to capsular switching.[19,20] MenA is the most common serogroup involved in MD pandemics and is predominantly found in China and Africa.[21] The last major expansion of MenA observed in Africa and China was in the 1980s; however, both nations experienced the same clonal replacement of ST-5 with ST-7 in the 1990s.[21,22] Serogroup X MD (MenX) emerged in Africa in the 1990s, reaching epidemic levels in Niger in 2006.[23] Cases of MenX isolates related to those responsible for meningococcal outbreaks in Niger, Togo and Burkina Faso have recently been recorded in Northern Italy among African and Bangladeshi migrants living in refugee camps.[14] MenW has been known since the 1980s; however, its emergence as an epidemic serogroup was reported in 2000, in Hajj pilgrims returning to France and the UK.[24] Whole genome sequencing (WGS) data suggest a multifocal emergence of MenW isolates worldwide with the identification of two sub-lineages; one in individuals traveling to Mecca and in local South African residents, and the other in South America and the UK.[15] Recently emerging MenC strains in sub-Saharan Africa were different isolates from those previously observed in 1980 and 2012. Following genomic analysis of the new clone of MenC identified in men who have sex with men (MSM), the strain was found to have evolved to acquire the capacity to spread via sexual transmission, as well as by respiratory droplets.[25]

In China, the earliest serogroup A Nm was isolated in the 1950s (Fig. 1) and almost all isolated MenA strains since have been identified as cc1 or cc5. ST-5 and -7 are two major classifications of cc5 MenA, and ST-3 is a major classification of cc1 MenA. ST-5 (cc5 MenA) first emerged in the 1950s, however was gradually replaced by ST-3 (cc1 MenA) in the 1960s. Since 1980, MenA caused by ST-3 has continuously declined, and ST-7 has since been the predominant clone of MenA. In China, the incidence of MenB is increasing. Prior to 2000, invasive cc11, cc32 and cc8 strains were occasionally identified; however, more recently, MenB cc4821 has emerged. From 2003 to 2005, several MD epidemics occurred in the Anhui province, China; the MenC isolates attributed to such outbreaks were identified as the unique cc4821.[26] Genomic analysis

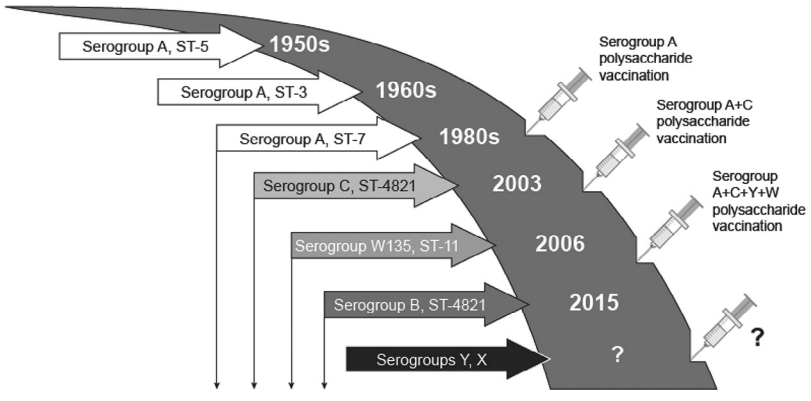


Fig. 1. Molecular epidemiology of *Neisseria meningitidis* in China.

determined a high probability that cc4821 MenB originated from cc4821 MenC.[27] The first case of MenW in China was recorded in the Fujian province of Southeast China. Subsequently, MenW has been recorded in several provinces across China with the majority of isolates identified as belonging to the cc11 lineage that developed in South Africa and caused a recent MD outbreak following the World Scout Jamboree in Japan in 2015.[16,28,29] A single case of ST-7 MenX was reported in China in 2015 and is believed to have originated from ST-7 MenA by horizontal exchange of capsule biosynthesis genes.[30–32] In 2016, a single case of serogroup Y Nm was isolated from a patient in Tianjin; however, there have since been no recorded serogroup Y MD (MenY) cases indigenous to China.[32]

Further, capsular switching has been described among meningococcal serogroups A and C,[33] serogroups A and X[34] and serogroups B and C.[27,35] Following the sequencing of whole capsular and surrounding genes and the identification of potential recombination sites, it was determined that ST-7 MenC was likely to have evolved from ST-7 MenA as a result of capsular gene rearrangement.[33] In addition, ST-7 MenX was determined as likely to have originated from ST-7 MenA via recombination leading to capsular switching following the identification of probable recombination regions during genomic analysis, however only one case was recorded.[34]

The continued epidemiological and sentinel surveillance of MD provides an overview of trends and prevalence of different meningococcal serogroups and is important in order to inform vaccination and disease planning.

Surveillance and prevention strategies of meningococcal disease in China

In China, multiple centers for immunization planning and the control and prevention of infectious disease have been established in order to conduct regular MD surveillance. Disease surveillance and treatment are initiated if there are ≥3 identified cases of MD within 14 days in any given township, or ≥5 cases recorded within one month in a county. As MD is one of 38 statutorily notifiable diseases in China, all cases, including suspected cases, must be reported to the CDC via the NNDRS. Indeed, epidemiological surveillance includes acute BM case findings, reported case surveys, outbreak surveys, and cerebrospinal fluid (CSF), blood and petechial specimen collections. Although available methods may differ between cities and provinces, laboratory tests may include isolate and serology testing, drug resistance testing, MD antibody investigations, and Nm carriage surveillance in healthy populations. However, the disease surveillance system is not sufficiently sensitive to recognize all cases of MD, as not all hospitals have the capacity to diagnose MD via laboratory tests. Therefore, it is likely that the disease burden of Nm and probable BM in China is higher than estimated. In order to improve the validity of disease burden data, technological advances with respect to pathogen detection are needed.

Surveillance data from Chinese provinces indicate that there remains a higher prevalence of MD in the Anhui, Xinjiang and Guizhou provinces compared with national levels among children and adolescents.[36] In China an increase in MD prevalence among adolescents may, in part, be due to university living conditions such as co-habitation in dormitories. During 2004–2006, an outbreak of MenC in the Anhui province resulted in >500 recorded cases with a mortality rate of 7.8%. MenC accounted for the majority of MD cases in China from 2008 to 2010, and was recorded in >80% of provinces; during this time, MenB occurred relatively infrequently.[37] From 2011 onwards, the proportion of MenC cases began to decline and MenB to rise, with the majority of recorded cases in children <1 year. In 2015, MD caused by MenY began to emerge. While there are many recorded cases of serogroups A, B and C across China,[38] MenX has only been identified in MD patients in two provinces.[30,34]

Currently, 12 vaccines are freely available via the Chinese EPI for the control of 15 infectious diseases, including MD and hepatitis A. The MenA polysaccharide vaccine and the MenA plus MenC polysaccharide vaccine are available via the routine immunization program at no extra cost to individuals. There is a wider range of MD conjugate vaccines available in China, but the cost must be covered by the individual. Currently available vaccines include: the MenA plus MenC polysaccharide-protein conjugate; serogroup ACWY meningococcal polysaccharide vaccine; and MenA, MenC and *Haemophilus influenzae* type b (Hib) conjugate vaccines.

The routine MD immunization schedule for children in China (Fig. 2) is as follows: children aged 6–18 months are given two doses

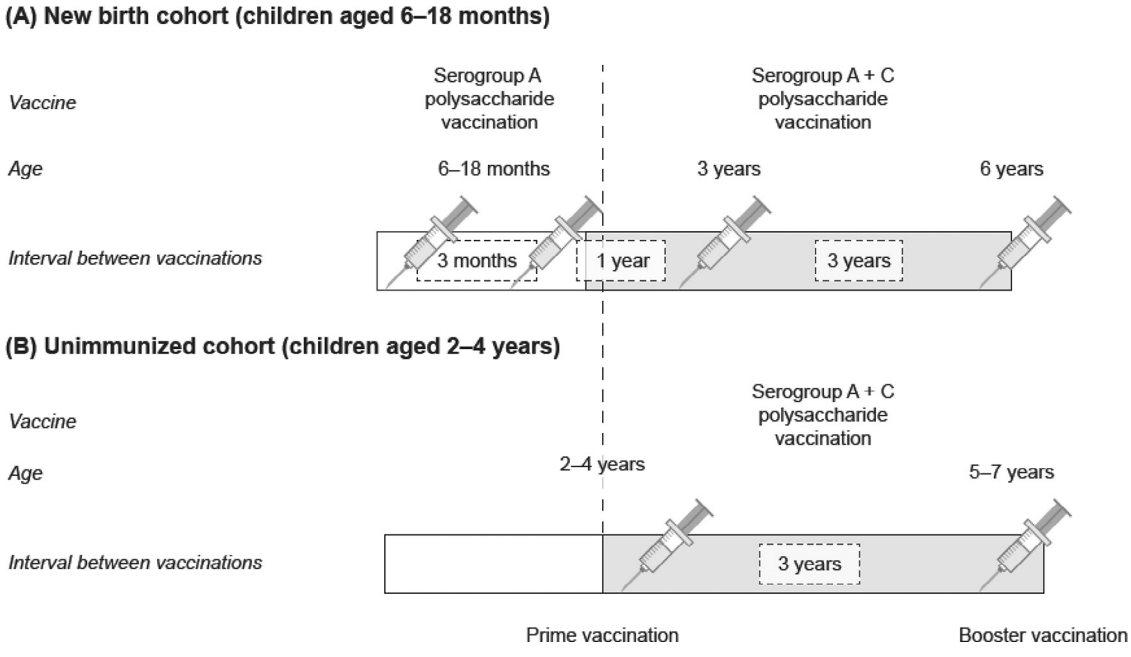


Fig. 2. Routine immunization schedule in China.

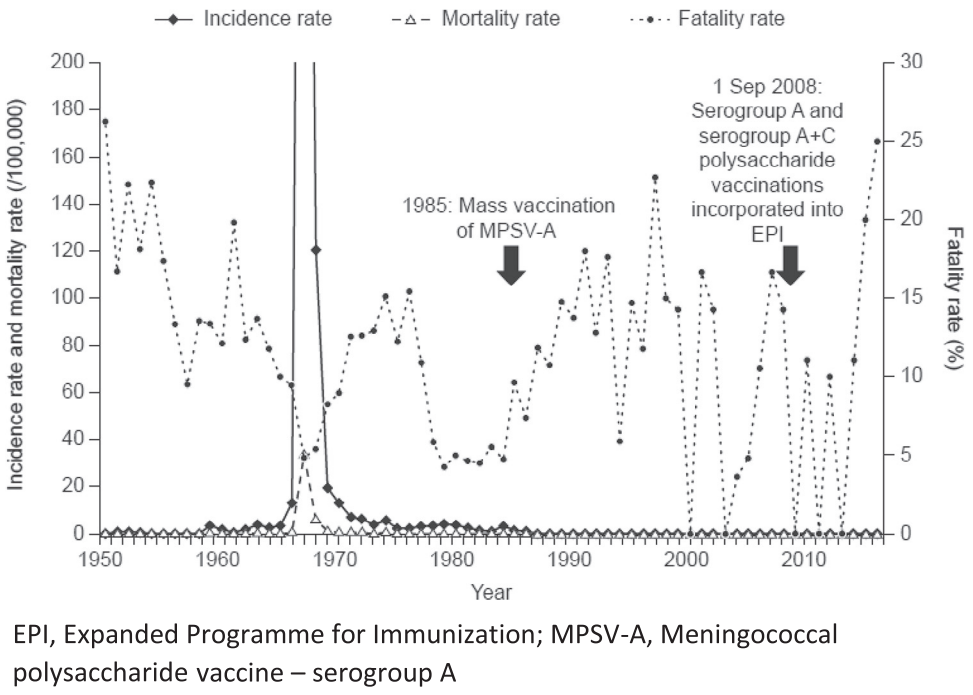


Fig. 3. The incidence of MD in the Guangdong province between 1950 and 2016.

of the MenA polysaccharide vaccine separated by three months, and subsequently receive a single dose of the MenA plus MenC polysaccharide vaccine at ages 3 and 6 years. If the child has not received the MenA polysaccharide vaccine between the ages of 2 and 4 years, they will receive the MenA plus MenC polysaccharide vaccine, with an interval of 3 years between the initial immunization and booster vaccine.

Liaoning province

Liaoning province is located in the northeast of China, with a population of approximately 43 million people.[39] Currently, the incidence rate of MD is <1 case per 100,000 population, with the majority of cases recorded during the springtime, and in the cities of Shenyang and Dalian, from 2004 to 2016. MD mainly affects individuals aged 0–15 years, while children, students and farmers (defined as laborers that travel from rural areas into cities for work) are the three main groups affected.

Surveillance data has demonstrated that serogroup A represents the highest number of meningococcal strains isolated from patient cases and close contacts of individuals with MD. From 2004 to 2016, serogroup A accounted for 75% of patient cases among 20 isolated strains of Nm, while serogroups B and C were detected less frequently. Further, 52 strains of Nm were observed among 922 close contacts of individuals with MD sampled by pharyngeal swab detection from 2004 to 2016, representing a 5.64% detection rate. Serogroup A accounted for 69.23% of close contacts, and serogroups B, C, W and Y were detected less often. In healthy carriers of meningococci, serogroup B and non-serogroupable represents the majority of recorded strains.

In accordance with national policy, the MenA polysaccharide vaccine and the MenA plus MenC polysaccharide vaccine have been freely available in Liaoning since 1985 and 2008, respectively, and conjugate vaccines are available only for private purchase. Vaccines are administered via the EPI as previously described (Fig. 2). Due to the expansion of the national immunization program, there is a continuing decrease in the incidence of MD in Liaoning; however, meningococcal vaccines for serogroups B, X, W and Y are not licensed, or incorporated into the EPI schedule, in China. Therefore, continued disease surveillance and close monitoring, as well as ensuring high rates of immunization coverage, are important for continuing disease control.

Guangdong province

Guangdong is a province located on the South China Sea coast. Guangdong has a permanent population of approximately 108,490,000 accounting for 7.9% of the total population of China.[40] The peak prevalence of MD cases in Guangdong was reported in 1967 with 705.04 cases per 100,000 population (Fig. 3). In 2016, Guangdong had an MD incidence rate of 0.0037 cases per 100,000 persons, with a case fatality rate of 25% (i.e. one reported death).

From 2012 to 2016, 32 sporadic cases of MD and four fatalities were reported in 11 cities across the Guangdong province. MenB accounted for the majority of reported isolates. Although MD cases were reported year round, disease incidence was highest in the winter and spring with 25% of cases reported in January. Patients' age ranged from 10 days to 56 years: 46.9% of patients were <6 months old and not yet eligible for immunization, and 68.8% of patients were <14 years old. The remainder of patients were adults in whom meningococcal vaccinations were not routinely offered.

The MenA polysaccharide vaccine was introduced into the Guangdong province immunization policy from 2000. In 2008, the MenA polysaccharide vaccine and the MenA plus MenC polysaccharide vaccine were made freely available to patients via the EPI. The MenA plus MenC conjugate vaccine and the serogroup ACWY meningococcal polysaccharide vaccine became available for private purchase in 2007 and 2008, respectively. Meningococcal vaccines in the Guangdong province are administered via the Chinese immunization schedule for children (Fig. 2).

MD prevention measures in Guangdong province include immunization, surveillance, raising awareness among the general public, and physician training, along with routine reporting, sentinel surveillance and the management of epidemics. From 2005 to 2013, sentinel surveillance was carried out in Guangdong to determine

meningococcal carriage rates, antibody prevalence and antibiotic resistance among healthy participants across several age groups (<1, 1–2, 3–4, 5–6, 7–14, 15–19 and ≥20 years). Data demonstrated that positive and protection rates of antibody levels against MenC were low in children <1 year, yet increased in children aged ≥3 years.[41] For the prophylaxis and treatment of MD, resistance tests are conducted annually to determine the effectiveness of antibiotics; however, there is a need for national guidelines advising on which antibiotics should be used in control of the disease. Again, continued disease surveillance alongside high rates of immunization coverage are imperative for the continued control and future prevention of MD.

Overall, the prevalence rates of MD in China continue to decrease annually due to the increasing coverage of vaccination and immunization. In order to decrease the incidence of MD further, China may benefit from the integration of conjugate vaccines in to the EPI and from increased immunization among high-risk groups and target populations in specific areas known to suffer from frequent meningococcal epidemics.

Addressing surveillance/diagnostic challenges of meningococcal disease in China

Microbiological laboratory analyses play a critical role in the diagnosis of MD and the identification of causative strains of the disease. Laboratory analyses help in the detection of outbreaks: both in establishing the local or regional spread of infective strains and subsequent guidance of appropriate therapy, and in the identification of emerging pathogenic or virulent variants of the disease. Common laboratory techniques used in the isolation, identification and characterization of Nm include both blood and CSF cultures, serogrouping (using antisera and polymerase chain reaction [PCR]) and the creation of stock for future analysis. In China, the main methods used for confirming a diagnosis of Nm are by blood culture, CSF culture and real-time PCR (rtPCR).

Shanghai is a region of China with a traditionally high incidence of MD due to Nm. In Shanghai, laboratory methodologies currently available for confirming a diagnosis of Nm are blood cultures, CSF, latex agglutination and rtPCR. Isolates collected from patients with Nm, close contacts of individuals with Nm and carriers of Nm can undergo serogrouping, MLST and pulse-field gel electrophoresis (PFGE) to investigate serogroup prevalence, cc prevalence and genetic relationships. Antibiogram and gyrA sequencing were used to investigate the changes in Nm quinolone susceptibility from 1965 to 2013 that were associated with the introduction and expanding use of quinolones in Shanghai. Quinolones have been widely used in China since the end of the 1980s, and have been recommended for Nm prophylaxis since 2005. The use of antibiogram and gyrA sequencing demonstrated a high prevalence of Nm quinolone non-susceptibility in Shanghai, which was associated with hyper-virulent MD lineages cc4821 and cc5 in turn due to two quinolone-resistant clones; China$^{cc4821\text{-}R1\text{-}C/B}$ and China$^{cc5\text{-}R14\text{-}A}$.[42] In Shanghai, the average incidence rate of MD decreased from 43 cases per 100,000 population between 1965 and 1985, to 0.08 cases per 100,000 population between 2005 and 2013. Conversely, the case fatality rate has increased from 3% between 1961 and 1970 to 10% between 2001 and 2013.[42]

When culture results are negative, rtPCR can be used in the diagnosis of Nm and identification of causative serogroups.[43] For further strain characterization beyond the serogroup, nested MLST can then be used to identify the strain cc and ST.[44]

Laboratory methods in Shanghai are very robust and ongoing methods for comprehensive MD strain characterization throughout China involve the continuous analysis of WGS data, including characterizing the aforementioned quinolone-resistant clones.

Pediatric bacterial meningitis in China

Globally, BM is a major cause of illness among infants and children and is among the top ten causes of death in children <5 years.[45] Between 2007 and 2016, Beijing Children's Hospital saw high numbers of BM, with incidence peaking in 2014 and 2016.[45] There are many cases of BM recorded in Northern China with unknown causative pathogens, and atypical clinical manifestations; of 148 BM patients admitted to Beijing Children's Hospital between 2007 and 2008, the most commonly reported clinical characteristics were fever, lethargy and convulsion.[45] Neurological sequelae commonly associated with BM include hearing loss, mental retardation, delayed language acquisition, visual impairment and behavioral problems.[45]

A recent study reported that the estimated incidence of BM was 1.84–2.93 cases per 100,000 within the entire population and 6.95–22.30 for children <5 years from 2006 to 2009, with half of all patients aged <15 years.[46] The causative pathogens identified within these cases were Nm (35.1%), Hib (12.2%) and *Streptococcus pneumoniae* (52.7%), with BM caused by *S. pneumoniae* most prevalent in children <2 years and adults >45 years accounting for 30.8% and 20.5% of cases, respectively.[46] Further, all confirmed cases of Hib were in children <2 years.[46] Similarly, in Hefei, China the estimated incidence of BM was 9.3 cases per 100,000 for children aged 1 month–15 years, and 19.2 cases per 100,000 for children aged 1 month–5 years between 1990 and 1992.[47] In the same study, the predominant causative pathogens of BM observed were Hib, Nm and *S. pneumoniae*, which accounted for 51.7%, 38.3% and 8.3% of cases, respectively.[47] Other common BM-causing isolates in China are coagulase negative *Staphylococcus*, *Enterococcus, Escherichia coli* (*E. coli)* and *Acinetobacter baumannii*.[48,49]

As discussed in the case of Shanghai, China with prophylaxis for Nm, high levels of antibiotic resistance have also been reported in cases of BM. From 2010 to 2014, the main causative pathogens among 507 children with BM in Beijing were identified as *S. pneumoniae* (33.2%), *E. coli* (10.9%), *Enterococcus* (10.0%) and group B *Streptococcus* (8.2%).[48] Following penicillin susceptibility testing, high levels of antibiotic resistance rates were reported, and the total non-susceptibility rate of *S. pneumoniae* to penicillin was 47.6%. The resistance rates of *S. pneumoniae* isolates to ceftriaxone, cefepime and ceftazidime antibiotics were 75%, 55.6% and 40%, respectively.[48] Further, the five most common BM isolates were coagulase negative *Staphylococcus* (58.9%), *Micrococcus* (5.5%), *S. pneumoniae* (5.1%), *E. coli* (4.8%) and *Enterococcus faecium* (3.9 %) were reported between 2007 and 2014. *S. pneumonia* had a 77.7% resistance rate to penicillin and 100% sensitivity rates to vancomycin and *E. coli* to piperacillin, tazobactam and meropenem.[50]

Sentinel surveillance and etiological analysis in Shandong from 2006 to 2012 confirmed 309 cases of BM.[51] Of 61 patients with laboratory-confirmed BM, 32 cases were due to serogroups B, C, W and unspecified Nm, and 29 cases were due to *S. pneumoniae*. Up to 87% of BM cases were successfully treated or had a positive disease prognosis.[51]

The continued presence of BM among the Chinese population is attributed to a number of risk factors, including lack of immunity to specific pathogens, close contact with patients, absence of breastfeeding among infants aged 2–5 months and crowding. In a follow-up study of 33 patients with recurrent purulent meningitis, the risk factor responsible for the greatest proportion of cases was congenital abnormal anatomic structure (75%), followed by trauma in cephalic or vertebral region or operation (15%), and congenital immunodeficiency (9%).[52] Further, PCR-based sequencing used to analyze blood samples taken from 218 child patients with confirmed BM and 330 healthy adult controls indicated that polymorphisms in toll-like receptor 2 and toll-like receptor 9 are associated with BM severity and poor prognosis in Chinese children.[53]

The treatment of BM in China depends on the pathogen, disease severity, complications and antibiotic treatment response. For

example, antibiotics are discontinued when associated symptoms are no longer observed, normal temperature has been achieved for >1 week, normal CSF levels are present and protein/glucose and pathogenic tests are negative. In China, pediatric BM incidence data indicates that cases attributable to Nm are declining, whereas *S. pneumoniae* cases are increasing despite the availability of conjugate vaccines. China still faces many challenges in the treatment of acute BM, such as the notifiable diseases reporting system, etiology and surveillance, antibiotic resistance, societal and governmental awareness and vaccination status.[10,54]

Importance of conjugate vaccines in the prevention of meningococcal disease

In 1999, the UK became the first country to implement the meningococcal serogroup C conjugate vaccine into the national vaccination schedule.[55] Unlike polysaccharide vaccines, conjugate vaccinations have the ability to impart herd protection via the prevention of the acquisition of carriage among the healthy population[56] and have been shown to reduce the acquisition of nasopharyngeal carriage of Hib,[57] *S. pneumoniae,*[58] MenC,[56] MenA[59] and MenY.[60] Conjugate vaccines are currently available for MenA and MenC, Hib and *Nm*. Mono- and multi-valent conjugate vaccines are recommended in UK national immunization programs for infants, adolescents and "at risk" groups.

The MenC conjugate vaccine was introduced in the UK as the primary vaccine for all infants aged 2, 3 and 4 months, and as a single dose "catch-up" program for all adolescents up to 18 years.[55] From 1999 to 2015, the incidence of MD declined significantly. Indeed, epidemiological surveillance revealed that ≥1 year after primary infant immunization the efficacy of the MenC vaccine (estimated as direct protection afforded to vaccinated rather than unvaccinated individuals in the same population) significantly declined from 97% to 68%.[61] Data from infants who received three doses of the MenC conjugate vaccine, at ages 2, 3 and 4 months, indicated that serum bactericidal antibody (SBA) titers significantly increased over three doses in early infancy, before falling to pre-vaccination levels by 4 years of age.[62] Although the MenC conjugate vaccine was priming for immune memory, the booster response was too slow to prevent disease, confirming that immunological memory alone was insufficient to provide long-term disease protection.[63] The UK immunization schedule subsequently evolved in 2006, to include a booster dose at age 12 months in addition to two primary doses at ages 3 and 4 months (2 + 1 schedule).[64]

As antibody levels still rapidly declined following a 2 + 1 dosing schedule, the immunization schedule was altered to include adolescent vaccination in an effort to maintain the herd protection.[55] The effect of both direct and indirect immunization provided a marked reduction in MD carriage rates in the UK (71% reduction from 1999 to 2000, further reducing to 81% by 2001 in a cohort of 15,000 immunized teenagers aged 15–19).[56] A 67% reduction in the incidence rate of MenC in an unvaccinated UK cohort demonstrated an immunoprotective effect of the MenC vaccination program, and successful herd protection.[65]

The success of the MenC conjugate vaccine in the UK in reducing the incidence of MD can be attributed to the combined efficacy of the vaccine against disease and carriage, and the nature of the vaccine introduction strategy. Indirect protection is a significant component of disease control in the UK. In UK students, the Nm carriage rate increases dramatically within the first week of university due to an increase in the number of "high-risk" behaviors, such as attending bars, night clubs and places with overcrowding, and smoking.[66,67] The use of a "catch-up" campaign among adolescents was paramount to the successes of the MenC conjugate vaccine in reducing the prevalence of the disease in the UK, providing both direct and indirect protection to immunized and unimmunized individuals, respectively. The vaccination policy in China is currently under review, and the introduction of conjugate vaccinations into the EPI schedule is being considered to increase the proportion of the population protected against MD.

Outbreak control

Learnings from routine MenB immunization in the UK

Bexsero®, a multicomponent MenB vaccine (4CMenB),[68] was introduced into the UK national immunization schedule in 2015 in infants aged 2, 4 and 12 months. Following the implementation of this vaccine, the number of recorded cases of MD dropped in the vaccination eligible cohort and vaccine effectiveness was reported at 83%.[69] While the MenB vaccine does not provide protection against all strains of MenB, it is estimated to protect against 88% of MenB strains in the UK and, as such, provide vaccine effectiveness of 94%. To date, there have been no reported safety concerns associated with the use of the vaccine. Current published data suggested that the MenB vaccine does not show a significant effect on the carriage of MenB; however, surveillance efforts are ongoing to accurately assess the impact of the vaccine on meningococcal carriage rates.[60]

Trumenba® is a bivalent MenB vaccine that contains two fHbp variants.[70,71] Trumenba® has been licensed in the USA since 2014, and is given to adolescents aged 10–25 years; as such, the vaccine is predominantly used in outbreaks.[70] In the European Union (EU), Trumenba® has been licensed since 2017 for individuals aged >10 years, and it is likely, in the USA, that the vaccine will be used in outbreak settings.[70–72]

Conjugate vaccines against serogroups A, C, Y and W are highly effective in the prevention of MD, especially via the interruption of the acquisition of carriage.[56,59,60] Broad coverage vaccines for serogroup B disease are now licensed in the USA, EU and elsewhere. As MenB is a highly prevalent MD serogroup worldwide, and incidence rates are increasing in China[10] would be advantageous for there to be a licensed serogroup B vaccine in China that could be considered for future use in the Chinese National Immunization Programme.

Learnings from routine MenB immunization in Seine-Maritime, Northern France

MLST and phenotyping determined that MenB isolates from Seine-Maritime were B:14:P1.7,16 and cc32; B:14:P1.7,16 accounted for approximately 50% of the total MenB strains observed in Seine-Maritime, but only 5% of the total MenB cases in France, indicating varying global and temporal incidence with a specific localization of this strain in Seine-Maritime. The case fatality rate for this strain was significantly higher than that of other serogroup B cases at 19% compared with 8%; as such, urgent action was required to reduce the spread of MenB.[73]

Due to similarities in the PorA protein between the B:14:P1.7,16 Seine-Maritime strain and the Norwegian B:15:P1.7,16/ST32 isolate used to develop the outer membrane vesicles (OMV)-based vaccine, the MenB vaccine (MenBvac®) developed in Norway, was determined as effective against the French isolate.[74] The vaccine was therefore able to eradicate the Seine-Maritime strain at a level not significantly different from that of the original vaccine strain.[74]

More than 26,014 individuals were identified as eligible for vaccination with the MenB vaccine; however, due to a shortage of the vaccine, individuals aged 1–5 years were initially targeted (as this age group showed the highest incidence of B:14:P1.7,16 cases).[73] Individuals living in Seine-Maritime aged 1–19 years were vaccinated from June 2006 onwards. The vaccine campaign was halted in 2013, as the incidence of the strain reverted to pre-vaccination levels. It was confirmed that the MenB vaccine produced short-lived responses (showed by a similar percentage of patients with an SBA titer of ≥4 before and five years after the vaccination).[75,76]

Approximately 200 isolates were obtained in a carriage study of volunteers between 1 and 25 years; however, only five had the outbreak strain (B:14:P1.7,16/ST-32). As the carriage rate is 0.31% among vaccinated children versus 2.10% in non-vaccinated children, this suggested that the vaccine may impact carriage regardless of serogroup. Subsequently, there were no cases of B:14:P1.7,16 in the Seine-Maritime between 2014 and 2015 and only one reported case in 2016; however, the strain is still present in France. Further, since the outbreak of MenB in Seine-Maritime, France Bexsero® has become widely available and Trumenba® is expected shortly.

Learnings from routine MenA immunization in Africa

China and Africa differ in many senses; however, both have regions that are overcrowded. Further, both countries have reported inexplicable similarities in the 10-yearly cycles of MD epidemics.[10,77] The "meningitis belt" of sub-Saharan Africa consists of 26 countries with extremely high prevalence rates of Nm: from 1986 to 2015, there were approximately 1.3 million cases of MD, accounting for approximately 80% of the global burden of the disease. In the "meningitis belt", epidemics occur periodically every 3–4 years. The high incidence of MD is thought to be due to the windy sub-Saharan climate, which favors colonization and transmission of Nm in the nasopharynx. Historically, >80% of Nm outbreaks in the "meningitis belt" were caused by serogroup A compared with serogroups C, W or X.

Licensed in 2009, the monovalent MenA conjugate vaccine MenAfriVac® initiative was designed to eliminate MenA epidemics from Africa and provide long-term efficacy against the disease at an affordable price.[78] The introduction strategy of the monovalent MenA conjugate vaccine was to provide indirect disease protection via the induction of herd protection by immunizing the population aged 1–29 years with a 10 μg dose of the vaccine. A 5 μg dose of the vaccine was then introduced into the EPI in order to provide direct protection of the new birth cohort. The highest priority for vaccination was given to countries with the highest incidence of MenA, and a multi-phase approach was used in order to target as much of the population as quickly as possible. To date, over 270 million people have been vaccinated across the majority of countries in the "meningitis belt" and enhanced surveillance is in place in order to detect potential outbreaks and monitor the impact of the MenA vaccine on incidence levels.

The introduction of the MenAfriVac® campaign has successfully reduced the incidence of meningitis and carriage due to Nm serogroup A; overall, enhanced surveillance indicates a 60% decline in the incidence of Nm and a 90% decline in MenA.[79,80] The monovalent MenA conjugate vaccine has a number of properties that contribute to its success. The vaccine is thermostable and can be kept in a controlled temperature chain at temperatures of less than 40 °C for up to four days. The vaccine is well tolerated, with few adverse events seen following immunization, and inexpensive at around $0.50 per dose. Finally, the national campaigns had 95% coverage rates on average; although the vaccination program easily captured infants, adolescents were less well covered and as such, "mop-up" campaigns were launched in countries with low coverage rates.

MenAfriVac® has been progressively introduced into the immunization schedules of countries in the "meningitis belt"; however, there is much work yet to be done. The monovalent MenA conjugate vaccine is not yet implemented into routine immunization schedules in all countries in the "meningitis belt". Further, there remains a continued risk of a meningitis outbreak due to an alternative serogroup; serogroups X, W and C are still present in Africa and the re-emergence of MenC is a growing concern, particularly in Niger and Nigeria. The ideal vaccine would be a five-valent conjugate vaccine that protects against serogroups A, C, X, Y, and W and that is affordable, thermostable and well tolerated.

The MenA vaccine reduced carriage rates and invasive disease inducing herd protection and direct protection, respectively. The key characteristics responsible for the success of the vaccine initiative were its continued efficacy outside of the cold chain, the development of tailored doses for campaign or routine settings and the low manufacturing costs. It is tempting to speculate that a similar approach could be adopted in China for the production of conjugate vaccines against MenA, MenC and MenA/C plus Hib to improve cost-effectiveness and increase the likelihood of introduction into the EPI.

Outbreak preparedness

Key WHO recommendations for the outbreak response and preparedness are relevant to all countries, including China, and as such, universal standard operating procedures should be defined and implemented globally. Adequate MD surveillance is paramount to the detection of disease outbreak and aids with a timely and effective response. During an MD outbreak, the correct identification of the causative serogroup is important to identify the most appropriate antibiotic prophylaxis if needed. Further, epidemiological data are needed to estimate disease burden, geographical location and to identify "at-risk" populations. Once the vaccination response has occurred, epidemiological data collected via surveillance networks are required to determine vaccine effectiveness.

Although surveillance in China should cover the whole country, provinces may have different surveillance objectives and therefore sentinel surveillance may be sufficient. The aim of the invasive Bacterial Vaccine-Preventable Disease (IBVPD) surveillance network is to assess the impact of vaccination. A laboratory component is essential (e.g. culturing or PCR) to disease surveillance, as rapid identification of the serogroup is critical in determining the response needed at a local and national level. Lumbar puncture for CSF is the most accurate way to confirm meningitis; however, future diagnostic methods may include the collection of other fluids (e.g. blood), as in many regions lumbar puncture kits may not be available, as is true in Africa. Furthermore, laboratory capacities vary at a local, provincial and national level and various aspects of surveillance require standardized, country-specific protocols in order for the provision of timely disease data to support case management and reactive vaccination and treatment strategies. Once in place, there is a need to define and continuously monitor surveillance indicators to ensure optimal quality. The use of a weekly national bulletin in which all laboratory data are provided to all provinces to monitor epidemiology, and a support network within and among neighboring countries may be beneficial in disease surveillance. This approach has worked well in Africa following the introduction of MenAfriVac®, and a similar approach may be effective in China.

The definitions for alert and epidemic thresholds will vary among countries and are directly related to the level of disease burden; for example, in Africa 3 per 100,000 persons per week trigger "alert" actions. Similar to Africa, China is hugely populated and this approach may prove effective. For example, an epidemic threshold level could be defined for each Chinese sub-county, at which neighboring counties would be alerted to a rising incidence of MD. This would lead to the reactive vaccination of the target population in response to epidemic threshold, which when complete would in turn lead to the cessation of the alert. It is tempting to speculate that this would be a very effective method in the prevention of future epidemics in China.

The most important aspect of reactive protocols for vaccination and antibiotic prophylaxis is speed. In Africa, vaccination should occur within 4 weeks after having reached the threshold, and similar time constraints could be developed in China. Polysaccharide vaccines are usually given due to a lower cost compared with conjugate vaccines; however, global supply is limited. Antibiotics should be given early (within 72 hours) in order to prevent death and complications; although, the antibiotic used is subject to antibiotic

resistance. The development of rapid bedside diagnostic tests may be useful for the global community to enable a better response to meningitis outbreaks and several prototypes are currently in development.[81,82]

Standardized protocol for procedures to outline actions during an MD epidemic are needed within and among countries (including defined alert and epidemic thresholds), which emphasize the importance of disease surveillance. These could be developed for provinces across China in order to standardize outbreak response and disease control.

Conclusions and key recommendations

Based on the surveillance, diagnosis and confirmation data presented at this GMI meeting, it is clear that meningococcal epidemiology is changing in China with the decline of serogroup A disease, emergence of new clones of serogroup B and C, and as a consequence of the international spread, an increase in serogroup W cc11.[16,26–29] As MenB is responsible for an increasing number of MD cases in China, an effective vaccination strategy should be in place should an outbreak occur; this further emphasizes the importance of standardized laboratory procedures across China. Indeed, there is a need for improved disease surveillance and standardized laboratory techniques across and within provinces to ensure optimal epidemiological monitoring. Further, incidence data relating to pediatric BM in China indicates that Nm cases are declining, whereas *S. pneumoniae* cases are increasing, despite the availability of conjugate vaccines[48]; therefore, new vaccination strategies may be required including the use of conjugate vaccines and a MenB vaccine to reduce the carriage and induce herd protection acknowledging important lessons from the prior use in the control of MD outbreaks.

Conflict of interest

RB and XB perform contract work for Public Health England on behalf of GSK, PATH, Sanofi Pasteur and Pfizer.

MKT performs contract work for the Institut Pasteur funded by GSK, Pfizer and Sanofi Pasteur.

JL, ZS, GL, MC, QG, YH, YL, Xihai Xu, Xin Xu and HZ have no conflicts of interest.

Author's contributions

Authors discussed and agreed to the scope of the manuscript and contributed to the development of the manuscript at all stages. All authors read and approved the final manuscript.

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