

## REVIEW ARTICLE

# Meningococcal disease in Asia: an under-recognized public health burden

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## SUMMARY

A literature search traced existing information on meningococcal disease in Asia. Reviewed data describing the epidemiology of meningococcal disease in Asia are incomplete, due in part to absence of surveillance in many countries, poor bacterial detection methods and social and healthcare barriers to disease reporting. This suggests that meningococcal disease in some Asian countries may be under-recognized, with a need to introduce/improve existing surveillance and case identification systems. Nevertheless, in some developing Asian countries, the disease burden may be significant. Serogroup A meningococcal epidemics are responsible for high morbidity and mortality in some countries and continue to be an ongoing threat, particularly in developing countries. There is an increasing role played by serogroups C, Y, and W-135 in invasive disease, indicating evolving meningococcal disease epidemiology in some countries. Multivalent meningococcal conjugate vaccines offer new opportunities in the region for reducing the meningococcal disease burden.

**Key words:** Asia, epidemic, epidemiology, meningococcal meningitis, meningococcal infection, morbidity, mortality, *Neisseria meningitidis*, vaccination.

## INTRODUCTION

Despite appropriate antibiotic and supportive therapy, invasive disease due to *Neisseria meningitidis* results in death in around 10% of cases. Higher mortality rates are often observed in developing countries and during epidemics [1]. The majority of invasive meningococcal disease globally is caused by *N. meningitidis* serogroups A, B, C, W-135, and Y. Serogroup C and combined serogroups A, C, W-135, and Y (ACWY) conjugate vaccines are now available. Better understanding of the burden of meningococcal disease in individual countries will guide

next-generation vaccine development and allow accurate assessment of the potential impact of such vaccines if introduced into vaccination calendars. This information will assist health policy-makers and healthcare professionals in allocating healthcare resources to maximize medical benefit to the population.

More than one-half of the world's population resides in Asia [2], a region characterized by densely populated countries and socioeconomic, geographic and ethnic diversity. The epidemiology of meningococcal disease in much of Asia is incompletely understood, but is likely to be diverse [3]. *N. meningitidis* serogroup A and C outbreaks are occasionally reported to the World Health Organization (WHO) Regional Office in Asia, or to national authorities.

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Anecdotal reports suggest that a considerable number of meningococcal cases may be misdiagnosed or under-reported. This review examined the available published literature and national infectious disease surveillance websites or reports where available. The aims of the review were to collate and summarize any existing information on the epidemiology of disease due to *N. meningitidis* in Asia, including GAVI (Global Alliance for Vaccines and Immunization)-eligible countries in the region, and to raise awareness about meningococcal disease in Asia, highlighting the current knowledge gap.

## METHODS

This review attempted to utilize all publicly available information relevant to the region pertaining to meningococcal disease. A literature search using PubMed was conducted. The search terms were '(meningococcal OR *Neisseria meningitidis* OR meningitis) AND Asia'. Secondary searches were performed by replacing 'Asia' with one of 20 specific Asian country names (China, India, Pakistan, Bangladesh, Sri Lanka, the Philippines, Japan, Indonesia, Singapore, Malaysia, Thailand, Taiwan, Vietnam, Cambodia, Laos, Mongolia, Myanmar, Hong Kong, Republic of Korea, Nepal). The search was limited to human studies. No restriction on publication year was applied. English- and non-English-language literature and publications were assessed for relevance by review of abstracts when available. Additional references were obtained by examination of citations in published papers. Central and regional WHO websites were searched for outbreak and epidemic information. ProMED was searched (search term 'meningitis') and websites from local Ministries of Health and Centres for Disease Control were also accessed. In view of the incomplete nature of the data, papers were not assessed using quality criteria but were included if they held any information on meningococcal disease in the region.

### Background to meningococcal disease in the region

A summary of all studies identified in this review is provided in Supplementary Tables S1 and S2 (available online). We found few studies that specifically evaluated meningococcal disease epidemiology in Asia. Most data came from (a) descriptions of outbreaks (a localized cluster of cases) or epidemics (widespread outbreaks of larger magnitude); (b) incidental detection of *N. meningitidis* during the course of studies

designed to assess the burden of a different pathogen: typically *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae*; (c) hospital-based prospective and retrospective studies assessing overall meningitis disease burden, treatment or outcome.

Official statistics were difficult to obtain. Mandatory meningococcal surveillance systems appear to operate only in Japan, Hong Kong, Korea, the Philippines, Singapore, Thailand and Taiwan, all of which rely on passive reporting. In Japan only culture-confirmed cases are required to be notified. The quality of the surveillance in these countries was difficult to judge from the available information. The lack of attention to the disease may be due to other healthcare issues and the perception that the disease is rare in much of Asia [4, 5].

*N. meningitidis* is fastidious, susceptible to cold and drying, and culture is frequently unsuccessful. Antibiotics given prior to cerebrospinal fluid (CSF) collection significantly increase the number of negative cultures [6, 7]. The technical challenges, as well as widespread availability of antibiotics (obtained 'over the counter' or by prescription) were identified by investigators as hampering attempts to describe meningococcal disease in Asia [6–9]. Economic constraints, lack of after-hours laboratory facilities, lack of laboratory expertise in detecting *N. meningitidis* and lack of available techniques aside from Gram stain and culture were also identified as obstacles to successful *N. meningitidis* identification [10, 11]. Use of polymerase chain reaction (PCR) detection techniques increases the sensitivity of detection of *N. meningitidis*, particularly in patients who have received antibiotics [12], but these techniques have been largely unavailable on a routine basis in much of Asia. The percentage of CSF or blood samples in which no bacteria could be identified was generally high in all studies we reviewed and appeared to increase over time, an observation attributed by some authors to increasing access to antibiotics.

Social and economic obstacles to investigation of meningococcal disease were also evident. In a retrospective hospital review of 435 meningitis cases in Malaysia, lumbar puncture was performed in only 71 (16.3%) children due to widespread belief in the local population that lumbar puncture leads to later paralysis or impotence [13]. In Pakistan, it is estimated that only 50% of children with meningitis may reach hospital [14]. Given all these considerations, it seems likely that meningococcal infections were under-diagnosed in the majority of studies we reviewed.

Since reliance on culture confirmation may substantially underestimate meningitis cases due to *N. meningitidis* for the reasons given above, we considered positive bacteriological identification present if an organism was identified in CSF or blood culture specimens using any identification technique, i.e., Gram stain, culture, latex agglutination, counter-electrophoresis or PCR.

## THE BURDEN OF DISEASE IN GAVI-ELIGIBLE COUNTRIES IN ASIA

At the time of writing 11 of the 20 Asian countries we investigated (India, Pakistan, Bangladesh, Indonesia, Vietnam, Cambodia, Laos, Mongolia, Myanmar, Sri Lanka, Nepal), representing a total population of about 2 million [15], were eligible for funding from the GAVI Alliance [16]. All 11 countries currently receive GAVI support. Six of these countries (India, Indonesia, Mongolia, Nepal, Pakistan, Vietnam) have suffered major serogroup A (or C in Vietnam) meningococcal epidemics in the last 30 years (Table 1). Available data suggest that these poorer countries represent a disproportionately high fraction of the overall meningococcal disease burden in Asia. The population incidences of meningococcal disease in countries with available data are given in Table 2. Serogroup distributions by country are given in Figure 1. While some published data were available for GAVI-eligible countries, these were limited and of varying quality.

### Bangladesh

Many sick children are not brought to hospital and die at home in Bangladesh [17], suggesting that meningococcal disease cases are likely to be undetected. Five studies were identified during this review. Results from four retrospective hospital-based studies conducted between 1982 and 1994 [49–52], showed *N. meningitidis* present in up to 35% (28/79) of positive cultures in all ages, and up to 18% in children aged <2 years with bacterial meningitis. In 48 meningococcal-positive CSF specimens between 1987 and 1994 in children aged <5 years, 33 (69%) were from children aged <12 months [49].

More recently, of 628 blood and CSF samples sent to the International Centre for Diarrhoeal Disease Research in Bangladesh between 1999 and 2006, *N. meningitidis* was detected in 24.8% ( $n=136$ ), of which 97.7% were serogroup A [17]. Almost 60% of

cases occurred in 6- to 24-year-olds, 20.6% occurred in 25- to 39-year-olds, 7.4% in 1- to 5-year-olds and 2.9% of cases were in children aged <1 year. Between 2002 and 2004 a higher number of samples were processed by the laboratory compared to previous years. Isolation rates of other bacteria did not change over this time. However, the percentage of *N. meningitidis* positive isolates in 2002–2004 was 15 times higher than in 1999–2000, suggesting that local serogroup A outbreaks had occurred. The number of *N. meningitidis* cases then decreased over 2005 and 2006, suggesting that this was not a spurious result linked to improved detection or awareness.

In 2009 an unpublished outbreak of meningococcal disease (serogroup unconfirmed) was reported (ProMED) to have spread from India to the Chittagong Hill Tracts of Bangladesh [53, 54]. Morbidity and mortality data were not retrievable.

### India

#### *Epidemic meningococcal disease*

India has experienced repeated meningococcal serogroup A epidemics over the last century [8], most recently in 2005 in Delhi and surrounding districts. Between March and July 2005, 444 cases and 62 deaths [case-fatality rate (CFR) 16.9%] were recorded [55]. The majority of cases (44%) and deaths (62%) were in adolescents and young adults aged between 15 and 29 years, and 71% of those affected were males [21]. The peak attack rate in Delhi was 13.23/100 000 [56]. Serogroup A disease re-appeared in Delhi in between January and March 2006, with 177 cases reported (CFR 9.6%) [20].

Other unpublished reports (ProMED) describe suspected meningococcal outbreaks in the regions of Nawada (2000) [57] and Meghalay, Tripura and Mizoram (2009, thought to be serogroup A), with more than 2000 cases and 257 deaths reported in 2008–2009 [54, 58, 59].

#### *Endemic meningococcal disease*

The burden of meningococcal disease between outbreaks in India is difficult to quantify. Studies in non-outbreak settings performed since 1990 have detected little meningococcal disease [7, 60–66], but very low bacterial detection rates in many studies, considered to be the result of both technical laboratory aspects and high levels of antibiotic use prior to hospitalization (up to 79% in one study [63]), have prevented firm conclusions [7, 8]. In a 10-year retrospective

Table 1. *Meningococcal epidemics in Asian countries*

Country	Year of epidemic	Serogroup	Cases	CFR	Rate per 100 000	Ref.
Cambodia						
China	1984	A			11.7	[18]
	1977	A		~5%	59	[19]
	1967	A*	3 million	~6%	150–800	[19]
	1959	A*		~10%	~55	[19]
Hong Kong	1918	—				[19]
India	2006	A	177	9.6%		[20]
	2005	A	426	13.6%	13.23	[21]
	1985	A	6133	13%		[22]
	1966	A*	616	20.9%		[22]
Indonesia						
Japan						
Korea						
Laos						
Malaysia						
Mongolia	1994–95	A	1754	9.3–12.4%	90 (overall) 179 (capital city)	[23] [23]
	1973–74	A or B			359 (2–18 yr) 704 (<9 yr)	[23] [24]
Myanmar						
Nepal	1982–84	A	1475	7–9% 26%	103 (overall) 221 (<1 yr)	[25] [25]
Pakistan	1988	A	112	11%		[26]
Philippines	2004–2005	A	98	33%		[27]
Singapore						
Sri Lanka						
Taiwan	1933–46	A				[28]
	1919–26	A				[28]
Thailand						
Vietnam	1977–79	C		27.4–34.7%	>20	[29]

CFR, Case-fatality rate.

Shaded areas indicate none reported/no data.

\* Serogroup unconfirmed.

review of acute bacterial meningitis cases in a tertiary hospital in Bangalore, *N. meningitidis* accounted for only 1.4% of microbiologically proven cases [62]. All cases occurred in individuals aged >12 years. In Delhi between the non-epidemic years 2002 and 2004, 971 meningococcal cases with 118 deaths (CFR 12%) were reported [64].

*N. meningitidis* serogroup A is most commonly isolated in India but serogroup B [67] and serogroup C [68] also play a role in sporadic disease cases.

### Indonesia

Six reports were identified that included a WHO report, and five studies that described meningitis aetiology or treatment in Indonesia [69–74]. Between 1995 and 1996, *N. meningitidis* was identified as the cause of meningitis in 16.7% (1/6) of bacteriologically

confirmed cases in children aged <5 years [69]. In a population-based study between 1998 and 2002 of Hib vaccination in 818 hamlets encompassing 744 000 individuals, *N. meningitidis* was detected in 3/17 (17.6%) culture-positive meningitis cases in children aged <2 years [70]. In 30/47 (63%) cases of probable bacterial meningitis the causative organism could not be identified, probably due to the high previous antibiotic use and technical aspects related to sample storage [70]. During 2000, 14 cases of meningococcal meningitis with six deaths (43% mortality) were reported to the WHO in Indonesia [71]. Serogroup B was detected in one individual.

### Mongolia

Five publications were identified: four described past epidemics and one was a prospective study of

Table 2. Rate of meningococcal disease per 100 000 population in countries with available data (non-outbreak settings)

Country	Years studied	Age	Baseline rate per 100 000	Ref.
China	2003–2007	Overall	2.09 (Hefei)	[30]
	Before 2003	Overall	0.18 (Hefei)	[30]
	2005	Overall	0.18–0.2	[31]
	2000–2002	Overall	0.25 (Nanning)	[32]
	1989	Overall	1.22	[18]
	1988	Overall	1.97	[18]
	1987	Overall	3.21	[18]
	1986	Overall	7.56	[18]
	1985	Overall	10.73	[18]
	1984	Overall	11.69	[18]
	1983	Overall	7.81	[18]
	1982	Overall	8.65	[18]
	1981	Overall	13.21	[18]
	1980	Overall	23.44	[18]
Hong Kong	1984–1993	≤ 24 m	≤ 0.24/13.0*	[33]
Japan	1980–current	Overall	< 0.02†	[34]
Korea	2004–2008	Overall	0.002–0.017†	[35]
	2002–2003	Overall	0.06–0.08†	[36]
	2000–2001	Not specified (Army recruits)	2.2	[39]
Mongolia	2002–2005	< 5 yr	13	[37]
	1971	Overall	17	[24]
Philippines	2004	Overall	0.04	[38]
	2005	Overall	0.1	[38]
	2006	Overall	0.03	[38]
	2007	Overall	0.02	[38]
	2008	Overall	0.0	[38]
Singapore	2005–2009	Overall	0.11–0.23†	[40]
	2000–2001	Not specified (Hajj pilgrims)	25	[41]
Taiwan	2001	Overall	0.19	[42, 43]
	2000	Overall	0.07	[42]
	1991	Overall	0.22	[28]
Thailand	2008	Overall	0.02	[44]
		< 5 yr	0.10	[44]
	2007	Overall	0.05	[44]
		< 5 yr	0.30	[44]
	2000–2001	< 5 yr	1.8	[45]
	1981–1990	Overall	≤ 0.2	[46]
Vietnam	Pre-epidemic	Overall	< 5	[29]
	2000–2002	< 5 yr	2.6	[47]
		7–11 mo.	21.8	[47]

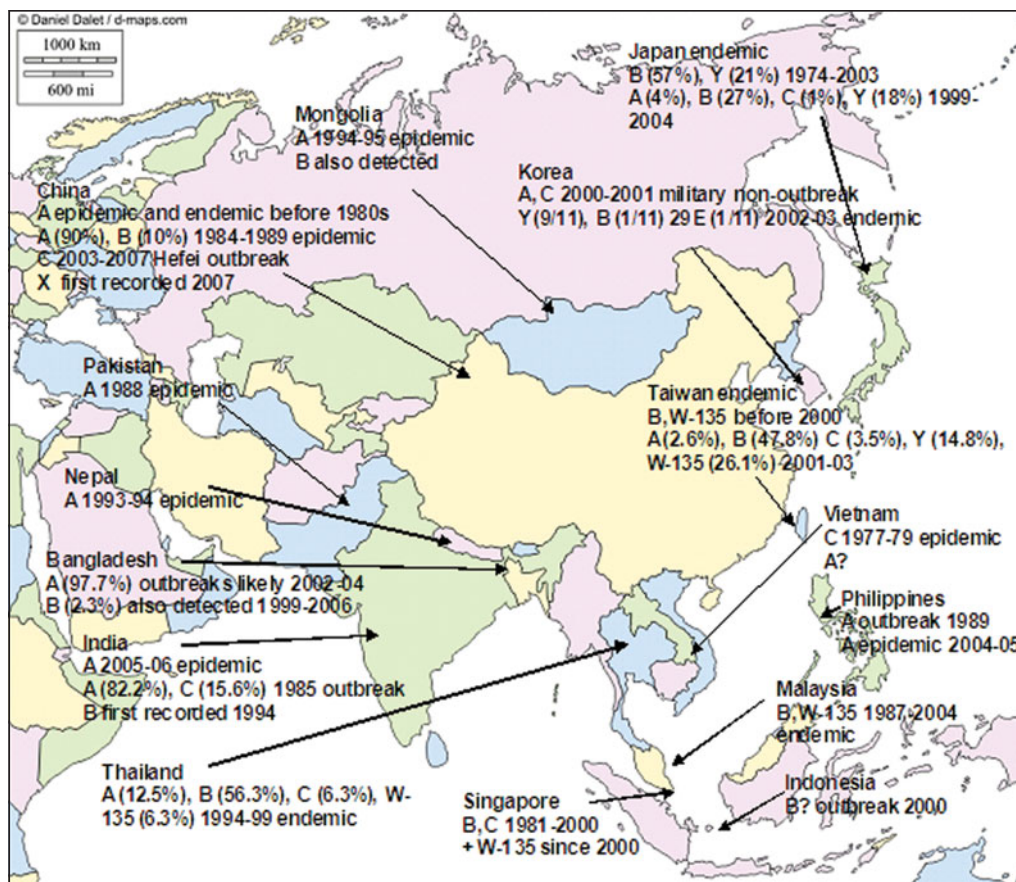
\* Rate in Chinese and Vietnamese communities respectively.

† Calculated using the UN 2008 Revision Population Database [15] (median variant).

meningitis aetiology. Large meningococcal serogroup A epidemics originating in China spread to Mongolia in 1973–1974 and 1994–1995 [75, 76]. During the 1994–1995 epidemic, the overall attack rate ranged between 80 and >90/100 000, but reached 179/100 000 in the capital city of Ulaanbaator [23]. The highest incidence was in children aged between 2 and 18 years (attack rate 359/100 000) [23]. The fatality

rate was 7–9%, with 122 deaths, and 165 deaths in the first 4 months of 1994 and 1995, respectively [23].

Little is known about the epidemiology of endemic disease in Mongolia. The estimated incidence rate during the 1970s non-epidemic period was about 10/100 000 population [24]. A prospective hospital-based study conducted between 2002 and 2005 in



**Fig. 1.** Serogroup distribution of meningococcal disease cases in Asian countries with available data (map outline reproduced from [48]). % = percentage of serogroupable isolates.

Ulaanbaator identified *N. meningitidis* in 25/111 (23%) of children aged 2 months to 5 years with confirmed bacterial meningitis, giving a population-based incidence of 13/100 000 [37]. Mortality was 12% [37].

### Myanmar

A single brief report from the WHO indicated that during 1995, 479 cases of meningococcal disease were reported in Myanmar, with 113 deaths (CFR 24%) [77].

### Nepal

Epidemic meningococcal disease was not reported in Nepal until 1982 when a large meningococcal serogroup A outbreak occurred in the Kathmandu Valley with an overall attack rate of 103/100 000 [25, 75, 77]. Incidence and mortality was highest in infants aged <1 year (221/100 000 and 26%, respectively).

Incidences in other age groups were 104/100 000 (CFR 19%) in the 1-4 years age group, 141-156/100 000 (CFR 6-12%) in the 5-9, 10-14 and 15-19 years age groups, and between 32 and 95/100 000 (CFR 5-16%) in adults [25]. After resolution of the epidemic, meningococcal disease continued to be reported in tourists, primarily hikers, with an attack rate in 1985 of 19/100 000 [78].

Three studies of meningitis aetiology or treatment were identified. A single prospective study performed in a children's hospital in Kathmandu during 1993 and 1994 showed that *N. meningitidis* accounted for 26% (6/23) of pyogenic meningitis cases in those aged 5 months to 5 years [79]. In two prospective hospital-based studies between 2001 and 2007, *N. meningitidis* accounted for 5.4% (2/37 bacteriologically confirmed cases) of bacterial meningitis in all age groups [80], and 2/151 (1.3%) culture-positive meningitis cases in the <5 years age group, of whom 26.7% of the 151 individuals had received prior antibiotics [81].

### Pakistan

A meningococcal serogroup A epidemic occurred in Karachi, Pakistan, in 1988 [26] with 112 cases of which 20% had septicaemia and 80% had meningococcal meningitis. Children aged between 5 and 10 years were primarily affected. Overall mortality was 11% but reached 55% in individuals with meningococcaemia.

Bacterial meningitis has been described as a major health problem in Pakistan [10]. Four studies conducted prior to 2002 suggested that over 30% of bacterial meningitis in adults and 20% in children was attributable to *N. meningitidis* [10, 82–84]. In both children [82] and adults [10], *N. meningitidis* was the second most common cause of bacterial meningitis after Hib and pneumococcus, respectively. In contrast, in a prospective hospital-based study of meningitis in <5-year-olds conducted between 2005 and 2006, 3.6% (3/83 bacteriologically confirmed cases) were due to *N. meningitidis* [85]. Notably, a causal aetiology could not be identified in 80% of specimens. The authors noted high rates of prior antibiotic use, as well as evidence that only 50% of children with meningitis might reach hospital in Pakistan. Serogroup data were not available.

### Vietnam

A serogroup C epidemic occurred in the southern provinces of Vietnam between 1977 and 1979 [29, 75]. The overall incidence rate of meningococcal disease during the epidemic rose from <5/100 000 in the preceding years to >20/100 000. The mortality rate was between 27.4% and 34.7% [29]. Seventy percent of cases occurred in children aged between 3 and 15 years.

Four prospective studies of meningitis have been conducted since the 1977 epidemic covering the years 1993–2005 [47, 86–88]. Meningococcal disease accounted for 0.5% of positive blood cultures and around 4–8.5% of bacterial meningitis cases where an aetiology was identified. Between 2000 and 2002 the estimated incidence of meningococcal meningitis in Hanoi, Vietnam, was 21.8/100 000 (95% CI 5.0–94.4) in children aged 7–11 months and 2.6/100 000 in children aged <5 years (95% CI 0.8–8.5) [47]. Serogroup data were not available.

### Laos, Sri Lanka and Cambodia

We found no information on meningococcal disease from these countries.

## BURDEN OF DISEASE IN NON-GAVI ELIGIBLE COUNTRIES IN ASIA

Although generally more information was available for non-GAVI eligible countries, the published data were still incomplete. Incidence rates have been calculated where possible. However, systematic presentations of epidemiological estimates were not feasible.

### China

#### *Epidemic meningococcal disease*

Meningococcal disease is endemic in China, and regional or nationwide epidemics have occurred periodically over the last century. Much of the published literature describes these epidemic cycles. In the past epidemics occurred every 8–10 years, lasting 3–5 years [89] with the majority of cases occurring between October and June [90]. During the worst epidemics, incidence rates of up to 2000/100 000 were recorded in affected unvaccinated communes [91]. In a review of seasonal variation of meningococcal meningitis incidence rates in Hunan Province, it was noted that between 1959 and 1990 there were 16 years where the incidence was <10/100 000, 14 years where the overall disease incidence was between 10 and 99.99/100 000, and 2 years where the incidence was >100/100 000 [90]. During the observation period a total of 38 148 cases were recorded. The last epidemic in 1984 was largely attenuated due to widespread use of meningococcal polysaccharide serogroup A vaccine in adolescents and children [92].

Locally produced meningococcal polysaccharide serogroup A vaccines have been available in China since the 1950s [93]. Their widespread use since the 1970s has been associated with reductions in the incidence of meningococcal disease, particularly in older children, as well as loss of epidemic cyclic activity [89, 90, 93–95]. Prior to vaccination in Zhengzhou, children aged between 4 and 15 years represented 68.22% of all meningococcal cases, and routine vaccination of children aged <15 years began in 1984 and 1985 [94]. Estimates of efficacy at 1 year were more than 94% after vaccination in this population [95]. In 1984 in Zhengzhou, meningococcal disease incidence was 36.35/100 000. In 1985 the incidence was 10.08/100 000, decreasing to 0.67/100 000 by 1991 [94].

#### *Endemic meningococcal disease*

In a survey of bacterial meningitis in children aged ≤5 years in Nanning City (Yining County), Guangxi

Province between 2000 and 2002, no cases of *N. meningitidis* meningitis were observed in 303 clinically confirmed cases of bacterial meningitis out of a local population of over 141 000 children [32]. However, a causative organism was identified in only 14% of cases [32]. The regional incidence of *N. meningitidis* disease was 0.25/100 000 at the time of the study, attributed to widespread routine use of serogroup A polysaccharide vaccination. In 2005, the incidence of meningococcal disease in China was reported to be 0.18–0.2/100 000 [31] (Table 2).

#### *Evidence for changing meningococcal serogroup distribution over time*

Historically, meningococcus serogroup A has been largely responsible for sporadic and epidemic disease in China. Since the 1980s, the proportion of cases caused by serogroups B and C has increased [18, 89, 94]. Between 1990 and 1992, 60.9% of 23 meningococcal meningitis cases in children aged  $\leq 15$  years were due to serogroup B and 39.1% to serogroup A [96].

The first recorded serogroup C outbreak in China was in a village in Guangxi Province during 2002 in which 3/15 cases died (CFR 20%) [89]. Between 2003 and 2007, serogroup C outbreaks were reported in Anhui Province [30, 97]. Using data from the Hefei (capital city of Anhui Province) Center for Disease Control and Prevention (CDC), the incidence of meningococcal disease in the region was 2.09/100 000, with a greater proportion of cases (60.9%) occurring in urban regions [30]. In total, 386 cases were reported in the region of Hefei between 2003 and 2007. Of 135 laboratory-confirmed cases, all were serogroup C. The age-specific incidences were 6.57/100 000 in the 12–17 years group (1.4% of all cases), 5.55/100 000 in those aged  $< 6$  years (18.4% of all cases) and 4.71/100 000 in the 6–11 years group (18.4% of all cases). The CFR was 7.3% with the highest CFR in the 0–5 years age group (16.9%). Implementation of a serogroup A and C polysaccharide vaccination programme was not successful [30]. Carriage and serogrouping studies suggest that serogroup C has spread through many provinces in China [31, 98]. The first case of serogroup X invasive disease was reported in Beijing in 2007 [99].

#### **Hong Kong**

Epidemic meningococcal disease was reported in Hong Kong as early as 1918 [19]. No recent epidemics

have occurred. In four hospital-based surveillance studies conducted between 1984 and 2001, only five cases of meningococcal meningitis were reported, all of which occurred in the Vietnamese minority population [33, 100–102]. All affected children were aged  $< 5$  years. All cases were due to serogroup B and one child died [33]. The incidence rate in the  $< 5$ -year-old Vietnamese migrant population in Hong Kong was estimated to be 13.0/100 000 (95% CI 4.2–30.3). Government data cited in Sung *et al.* [33] and French *et al.* [102] give a meningococcal disease incidence rate in the overall population of 0.02–0.24/100 000 during the same period. Medical practitioners are required to notify the Hong Kong Centre for Health Protection of all suspected and confirmed cases of invasive meningococcal disease [103]. Notifications between 2005 and 2009 numbered between 0 and 6 [103]. No recent serogroup data are available in the literature; however, a case of serogroup C disease has been reported [104].

#### **Japan**

##### *Historical meningococcal disease burden in Japan*

Bacteriologically confirmed meningococcal disease must be reported to the national register of notifiable diseases in Japan. Records available since before 1920 show between 300 and 1500 meningococcal cases per year between 1920 and the early 1960s, with a peak in 1945 and around 1947 with about 4500 cases and 3500 cases, respectively [34, 105]. After 1970 the number of reported cases fell to  $< 100$ , with fewer than 30 cases per year reported since 1980 [34, 106, 107]. There is little seasonal variation in case numbers or mortality [34].

##### *Meningococcal disease in retrospective hospital surveys*

Nationwide and local retrospective surveys of bacterial meningitis have been performed regularly via questionnaires sent to medical institutions [105, 107–120]. According to these surveys, the proportion of bacterial meningitis cases due to *N. meningitidis* since the 1990s has remained below 2%. Since 2000, the proportion has been less than 1%. Low rates of meningococcal disease have also been observed in hospital-based studies [121]. Under-reporting has been suggested due to problems associated with handling and laboratory detection of *N. meningitidis* and use of antibiotics prior to culture [105, 107, 120]. However, in a study of 168 CSF samples obtained from patients of all ages throughout Japan from 2005



to 2007 that were evaluated using PCR, no *N. meningitidis* was identified (0/121 positive samples) [122]. It has been estimated that fewer than 30 cases of meningococcal disease occur per year in Japan [123] (Table 2), with the majority of cases occurring in children aged  $\leq 5$  years [34].

A large-scale surveillance study of invasive meningococcal disease conducted by the Ministry of Health is currently ongoing [124]. However, underestimation of the true disease burden is still considered a possibility, since only culture-proven meningococcal cases (less likely to be successful when antibiotics have been administered) are reported to the health authorities [124].

#### *Meningococcal serogroup distribution*

A retrospective survey examined 182 Japanese isolates collected over 30 years between 1974 and 2004 [125] using multi-locus sequence typing (MLST). Of these samples, 49.2% were from patients, 47% were from nasopharyngeal samples collected from healthy individuals and 4% were of unknown source. Of the 182 samples, 57% (103) were serogroup B, 21% (39) were serogroup Y, 1% (1) were W-135 and 21% (39) were non-groupable. This is in line with official data concluding that although serogroup data is sparse, serogroup B followed by serogroup Y make up the majority of meningococcal disease cases in Japan [34]. Three serogroup A cases have been reported in Japan since 1999. These strains were identical to Chinese strains and all three individuals had either travelled to China or had relatives that had travelled there prior to illness [34]. Only one case of serogroup C disease has been reported from Tokyo (2003) [34]. The apparently very low disease incidence is supported by carriage data suggesting very low population carriage prevalence (0.4% prevalence between 2000 and 2002) [126].

#### **Korea**

Five publications were identified. In a review of 140 culture-positive bacterial meningitis cases from 13 hospitals in and around Seoul between 1986 and 1995, *N. meningitidis* was the third most common cause of bacterial meningitis (nine cases, 6.4%) in children aged  $< 15$  years [127], with the highest proportion of cases in children aged  $> 5$  years [127, 128]. In a later, prospective population-based surveillance of Hib disease in Korea between 1999 and 2001, no *N. meningitidis* was isolated in 2176 children evaluated for

possible meningitis [129]. However, a causative organism was only identified in 4% of abnormal CSF samples in this study for reasons that are not clear, although early use of antibiotic therapy may have contributed.

In Korean army recruits, the incidence of meningococcal disease was 2.2/100 000 (95% CI 1.3–3.8) in 2000–2001: 1/12 cases was identified as serogroup A and three cases were serogroup C [39].

A laboratory-based study of *N. meningitidis* serogroups in Korea, citing Korean Ministry of Health data, stated that between 1990 and 2001, between 2 and 13 cases of meningococcal disease occurred annually [36]. A substantial increase in disease cases occurred in 2002 (27 cases) and 2003 (38 cases) [36]. Of nine clinical isolates from across Korea during these 2 years, seven were serogroup Y, with one each being serogroups B and 29E, suggesting locally evolving meningococcal epidemiology. Since 2003, the number of *N. meningitidis* cases notified to the Korean CDC was eight in 2004, seven in 2005, 11 in 2006, four in 2007 and one in 2008 [35] (Table 2).

#### **Malaysia**

Four retrospective reviews from hospitals in various regions within Malaysia have been published [5, 13, 130, 131]. The most recent of these reviewed microbiologically confirmed meningococcal disease occurring between 1987 and 2004 in a large university hospital in Kuala Lumpur [5]. Only 17 cases (12 with data) were noted during the observation period. Seven cases occurred in the 20–35 years age group, three cases in the 10–15 years group and one case in a child aged 10 months. Mortality was 25%. Of six cases where the serogroup was identified, one case was identified as serogroup B and five cases as serogroup W-135. These data contrast with other earlier studies that suggest a significant burden of disease due to *N. meningitidis*, including infants aged  $< 1$  year [130]. The low detection rate in later studies may be due in part to low acceptance of lumbar puncture [13] and/or because some cases might go unrecognized.

An outbreak of suspected meningococcal disease was reported (ProMED) in trainees of the Road Transport Department (JPJ) Academy in Malacca in 2009, with 20 cases and one death [132].

#### **The Philippines**

Available information sources included five publications, a report from the WHO and annual reports

from the Department of Health (2004–2008). Between 17 and 35 cases of meningococcal disease were reported annually to the Department of Health between 2004 and 2008, with the exception of 2005 when 115 cases were reported [38]. This increase was due to a meningococcal serogroup A outbreak that occurred in the regions of Baguio City, Mt Province and Ifuga in the Philippines in 2004 and 2005, with 98 cases (33% mortality) reported to the WHO up to January 2005 [27]. The incidence per population in the non-outbreak years ranged between 0.0 and 0.04/100 000 (Table 2) but there was marked variability between regions [38]. In non-outbreak years between 34% and 50% of cases were reported in children aged <5 years. In 2005 most cases (88/115) were reported in the 5–49 years age group [38].

An outbreak of meningococcal disease, probably due to serogroup A, of 10 cases (incidence 65/100 000 population) was reported in 1989 in San Jose, Sipalay, Negros Occidental [133]. All but one case had meningococcaemia and mortality was 50%. Seven of 10 cases occurred in individuals aged  $\leq 19$  years [133].

Three prospective hospital-based studies in children, carried out between 1991 and 2000, failed to identify *N. meningitidis* in Filipino children with serious infections including meningitis [134–136]. Notably, in two of these studies, culture was successful in only around 8% of cases [134, 136]. Earlier retrospective hospital-based studies conducted during the 1980s detected *N. meningitidis* in up to 16.7% of children aged <15 years with meningitis, with most cases occurring in children aged <5 years [137, 138].

### Singapore

The number of invasive meningococcal disease cases reported to the Singapore Ministry of Health over the last 5 years was five in 2009, six in 2008, five in 2007, ten in 2006 and five in 2005 [40] (Table 2). Estimations of the proportion of meningitis cases caused by *N. meningitidis* have been made in adults and children in five retrospective hospital-based studies carried out between 1975 and 2000 [139–144]. In studies with available data, the proportion of culture-negative meningitis cases was high (between 30% and 55%) and in one study [139], 55% of subjects had received antibiotics prior to admission to hospital. In adults, *N. meningitidis* was present in up to 20% of community-acquired cases of bacterial meningitis [139]. In children, *N. meningitidis* accounted for

between 0% and 12.5% of cases, with decreasing frequency over time from the 1970s to the 1990s.

Little data about prevailing serogroups are available. Cases of meningococcal disease identified between 1975 and 1979 were a result of serogroups X, Y or Z [144]. Between 1981 and 2000, 66 cases of meningococcal disease were described [140]. The age of the patients ranged from 3 weeks to 81 years; 28/58 serogroupable strains were serogroup B (53%), 10 (18%) serogroup C and nine (16%) serogroup W-135. Mortality was 22.7%.

Disease due to serogroup W-135 was not detected in Singapore prior to 2000 but has since been observed, mainly affecting Hajj pilgrims and their contacts [41]. Twelve cases of serogroup W-135 meningitis were documented in Singapore between 2000 and 2001 (age range 1–75 years), eight of whom were Hajj pilgrims or their contacts [41, 145, 146]. There was one death and the attack rate for serogroup W-135 disease in Singaporee Hajj pilgrims was estimated at 25/100 000.

### Taiwan

#### *N. meningitidis as a cause of all bacterial meningitis*

Prospective [147, 148] and retrospective [149–156] hospital-based studies conducted between 1981 and 2005 show *N. meningitidis* to be a relatively uncommon cause of bacterial meningitis in all age groups. *N. meningitidis* was responsible for between 0% and 2.5% of meningitis cases in adults (with the exception of one study showing 6% [155]), and 3.5–4.95% of cases in children aged <15 years. Nevertheless, in one prospective study, *N. meningitidis* was the third most common cause of meningitis in children aged >2 months [147].

#### *N. meningitidis occurrence and changing incidence over time*

Epidemics of serogroup A meningococcal disease occurred in Taiwan between 1919 and 1926, and 1933 and 1946 [28] with about 300 cases reported in each outbreak year. Meningococcal disease has been notified to the Taiwan CDC since the 1950s [157]. Between 1950 and 2001, 659 meningococcal cases were reported with peaks in 1953 (incidence rate 0.94/100 000) and 1959 (0.52/100 000), dropping to very low levels over the ensuing decades [157]. In 1991 the incidence of meningococcal disease was estimated by the CDC to be 0.22/100 000, with the highest rate in

20- to 24-year-olds (0.38–0.71/100 000 according to region [158]) (Table 2). Prior to 2001, between 17 and 34 meningococcal disease cases were reported each year [43] and in 2000 the incidence rate in Taiwan was estimated to be 0.07/100 000 [41]. The mean age was 19.4 years, 33.6% were aged between 11 and 30 years and 31.3% were <1 year old.

In 2001 and 2002, changes in the epidemiology of meningococcal disease in Taiwan were observed in terms of incidence, serogroup distribution and possibly the age distribution of cases. The overall incidence more than doubled in 2001 (0.19/100 000) [41, 43] with an overall mortality of 25.6% [157]. Cases were geographically dispersed and none had travelled to the Hajj or had contact with Hajj pilgrims [157]. The age distribution of 115 cases collected between 2001 and 2003 was: <1 year, 27 cases (23.5%); 1–9 years, 16 cases (13.9%); 10–19 years, 16 cases (13.9%); 20–54 years, 37 cases (32.2%); ≥55 years, 19 cases (16.5%) [41].

In recent years the incidence of meningococcal disease cases appears to have gone back to levels observed prior to 2001–2002. The number of meningococcal disease cases reported to the Taiwan CDC from 2006 was 13 in 2006, 20 in 2007, 19 in 2008, two in 2009 and one case to date in 2010 [159].

#### *Evidence for changing meningococcal serogroup distribution over time*

Serogroups B and W-135 predominated in Taiwan prior to 2001 [43, 160, 161]. Serogroup B was responsible for 48.8% of meningococcal cases between 1995 and 1999 [160] and for 84.6% (11/13) in 1999 [43]. Concurrent with an increase in disease incidence in 2001 and 2002 has been an apparent change in the serogroup distribution of cases. Of 115 confirmed cases collected between 2001 and 2003, 55 (47.8%) were serogroup B, 30 (26.1%) were serogroup W-135, 17 (14.8%) were serogroup Y, six (5.2%) were non-groupable, four (3.5%) were serogroup C and three (2.6%) were serogroup A [41]. Serogroup Y appeared for the first time in 2001, and cases of disease due to serogroups A and C also started to emerge at this time [43, 157]. These serogroups A, C and Y meningococcal strains were identified as worldwide epidemic clones [43].

#### **Thailand**

Between 1981 and 1990 the incidence of meningococcal disease was cited as 0.03–0.2/100 000 population

by government sources (Annual Epidemiology Surveillance Report 1990 cited in [46]). In 2007 and 2008 the incidence rates were unchanged, with 30 and 15 meningococcal disease cases reported to the Bureau of Epidemiology, respectively (incidence of 0.02–0.05/100 000 population) [44]. The highest incidence was observed in children aged <5 years (0.1–0.3/100 000), and case fatality was 33.3% in 2007 and 13.33% in 2008. Most notifications came from regions in the south. No seasonality was observed and serogroup B was the only serogroup identified [44].

Retrospective hospital-based studies have also detected few meningococcal disease cases [4, 11, 46, 162–165]. Of 36 culture-positive meningococcal cases observed in 13 government hospitals throughout Thailand between 1994 and 1999, 22/36 (61.1%) cases occurred in children aged <15 years, with a peak in children aged <5 years. Of 16 serogrouped isolates, serogroup B was most frequently represented (9/16); serogroup A was identified in two cases and serogroups C and W-135 in one case each. A meningococcal carriage study between 1983 and 1984 showed that 14.23% of children aged between 5 and 15 years were nasopharyngeal carriers of *N. meningitidis*. The authors postulated that the apparently very low incidence of meningococcal disease in Thailand was spurious, due to over-the-counter availability of antibiotics and technical problems in laboratories such as lack of after-hours facilities [11]. Corroborating this hypothesis, a well conducted prospective population-based survey of bacterial meningitis in two northern provinces (Lampang, Phitsanulok) of Thailand between 2000 and 2001 estimated a rate of meningococcal meningitis that was tenfold higher in children aged <5 years (1.8/100 000) [45]. In this study, health workers and laboratory staff were trained and laboratory methods optimized. Lumbar puncture was performed in 76.1% of 598 enrolled children and 94.3% of samples were tested by PCR, including testing for *N. meningitidis*.

#### **SUMMARY**

Data describing the epidemiology of meningococcal disease in Asia are incomplete. Yet it is apparent that the burden of disease due to *N. meningitidis*, and prevailing serogroups, are highly heterogenous across Asia. This is not surprising given variations across the region in climate (from temperate to tropical to dry desert), socio-demography (with overcrowding in some regions and variable access to health care

facilities), economic settings (reflecting the spectrum of developed and developing countries), and religious practices (including a substantial Muslim population in some countries that attend Hajj, which is associated with meningococcal disease outbreaks). All of these factors can influence meningococcal disease epidemiology, as well as the ability to detect and treat cases and implement surveillance.

Widespread devastating meningococcal serogroup A epidemics have occurred in China, Hong Kong, India, Mongolia, Nepal, Pakistan, the Philippines and Taiwan over the last century. Since 1980, six serogroup A epidemics have been reported in Asian countries, including India (two epidemics, most recently in 2005), Mongolia, Nepal, Pakistan and the Philippines (also in 2005). Almost 10 000 cases of epidemic meningococcal disease have been reported during these epidemics. Reported epidemic mortality ranged between 7% and 33%. More recently, other serogroups have been responsible for local outbreaks in China (serogroup C [30]), Singapore (serogroup W-135 [41]) and Taiwan (serogroup Y [43]). Although some countries (Thailand, Malaysia, Indonesia) require vaccination of Hajj pilgrims against meningococcal disease with tetravalent ACWY polysaccharide vaccines, we found evidence of routine mass meningococcal vaccination only in China [166]. Polysaccharide serogroup A vaccines were used for outbreak/epidemic control during the late 1970s and 1980s. Since the 1980s, vaccination of children with two doses of serogroup A vaccine between 6 and 18 months of age, and vaccination with serogroup A and C vaccine at 3 and 6 years of age is recommended [165]. Coverage is reported to be very high [167]. In Korea, the Korean Paediatric Society recommends meningococcal vaccination for high-risk groups (asplenia, complement deficiency, travellers to endemic areas) [168], although no meningococcal polysaccharide or conjugate vaccine is currently available. No meningococcal conjugate vaccines are currently routinely recommended in any of the other countries we studied in this review.

Endemic meningococcal disease epidemiology is even less well described across Asia. In individual studies *N. meningitidis* was one of the three most common causes of meningitis in children in India [169], Korea [127], Pakistan [82] and Taiwan [147] and in adults in India [170] and Pakistan [10]. Ready access to antibiotics and laboratory-related technical issues have clearly influenced *N. meningitidis* detection rates in Asia. Widespread availability and use of

more precise tools such as PCR, as well as the establishment of ongoing surveillance systems, are needed to improve disease ascertainment in many countries.

In countries with available historical time series data (India, China, Japan, Korea, Singapore, Taiwan), the contribution of *N. meningitidis* to childhood and adult meningitis has apparently fallen to very low levels per 100 000 population over the last century (Table 2). In China this has been largely attributed to widely implemented polysaccharide vaccine immunisation programmes. In other countries the reason for the reduction in cases is less clear, but may be linked to improving socio-economic conditions, although similar variability in Hib and pneumococcal disease across Asia has been observed [171, 172]. Understanding the reasons behind this apparently very low disease incidence in these countries remains an epidemiological challenge and is an important topic of future epidemiological research. These apparent reductions are in marked contrast to the situation in developing GAVI-eligible countries where the available data suggest an important, ongoing meningococcal disease burden affecting children and adults. The disease burden appears both epidemic and endemic, but remains poorly described.

Available estimates for meningococcal disease in developed countries in the 21st century are no more than 2.6/100 000 population in any country, although higher rates are observed in some specific groups, such as the Vietnamese immigrant community in Hong Kong and Hajj pilgrims in Singapore (Table 2). Notably, disease incidence estimates were not available for 12 of the 20 countries we studied, including 9/11 GAVI-eligible countries. Based on the limited available evidence, population disease incidence rates in GAVI-eligible countries are expected to be higher than those in industrialized countries within Asia. In 1997 the WHO estimated that 160 000 cases of meningitis occurred in South East Asia, of which 55 000 were due to non-epidemic meningococcal disease [173].

The available serogroup data indicate that all of the five major disease-causing meningococcal serogroups are present in Asia, albeit with wide variability in their distribution across the region. Serogroup A dominates in Bangladesh, and in China and India during epidemic years, while serogroups B and C are present in sporadic cases, with evidence of more serogroup B and C disease in China since the 1980s [18, 89, 94]. Serogroup B is most commonly implicated as a cause of sporadic disease in Japan, Singapore, Thailand and

Taiwan, and is present in Malaysia, Mongolia and Indonesia. Important contributions to disease are made by serogroup Y in Japan and Taiwan, serogroup C in Singapore and serogroup W-135 in Singapore and Taiwan.

We found evidence of evolving meningococcal disease epidemiology in Mongolia, Nepal, China, India, Korea, Japan, Singapore and Taiwan, with strain importation clearly implicated in some countries. Epidemics of serogroup A disease were first described relatively recently in Mongolia [77] and Nepal [61] in the 1970s and 1980s. In China and India where serogroup A has historically dominated, there is some evidence that serogroup B meningitis has subsequently emerged [67, 96]. Additionally, serogroup C has become established in some regions of China since 2002 [30]. In Japan, serogroup A was first identified in 1999 and was probably imported from China, while the first serogroup C case was identified in 2003 [34]. In Taiwan, serogroups A, C and Y have been observed since 2000 [43]. In Singapore, serogroup W-135 appeared for the first time in 2000 in Hajj pilgrims and their contacts [41]. The large Asian Muslim population points to an ongoing risk of future Hajj-related outbreaks. Circulation of multiple serogroups, as well as evidence of changing serogroup distribution, argue for use of meningococcal vaccines giving broad coverage, such as tetravalent ACWY conjugates, in many countries in Asia. Furthermore, broad coverage by tetravalent vaccines may be the vaccination strategy of choice in those countries as yet without routine surveillance and precise serogroup information.

The absence of high-quality disease surveillance systems among many countries in Asia is likely to contribute to delays in making informed decisions about the potential benefits of introducing vaccination programmes. This has been the case for both Hib and *S. pneumoniae*, where implementation of universal mass vaccination has been slow in Asian countries due to lack of epidemiological data [172, 174]. This review has highlighted problems that are manifested across most of the region for detecting cases of meningococcal disease. As observed for studies describing the burden of Hib and pneumococcal disease in Asia, under-detection is a major problem due to high levels of prior antibiotic use and suboptimal procedures associated with sample handling and laboratory testing in some countries [172, 174]. Access to more sensitive molecular technologies such as PCR is needed, and country-specific issues

such as fears surrounding lumbar puncture, and lack of access to hospital care for many sick children, will also need to be overcome in order to more accurately assess the true disease burden. A further problem is that the ability to apply standardized meningococcal case definitions such as those advocated by WHO [175] will differ regionally, with clinical diagnoses most likely in rural areas and case confirmation only possible in areas with well-equipped laboratories [3, 175].

There is currently only limited information available to assess the burden of meningococcal disease in much of developing Asia, and it is likely to be under-recognised. Therefore, there is a need for introducing and improving surveillance capacity across the region to more accurately assess the disease burden and determine serogroup distribution. Meningococcal serogroup A outbreaks represent an ongoing threat, and importation of previously unseen serogroups poses a continuing potential epidemic risk in Asia. Multivalent meningococcal conjugate vaccines targeting the major disease-causing serogroups (e.g. A, C, W-135 and Y conjugate vaccines that are now available), particularly if licensed for use in younger children, may offer opportunities for disease control in the region. There may also be a role for a serogroup B vaccine in the region once one becomes available that can provide broad protection against serogroup B disease.

#### NOTE

Supplementary material accompanies this paper on the Journal's website (<http://journals.cambridge.org/hyg>).

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#### DECLARATION OF INTEREST

A.V. and J.C. are employees of GlaxoSmithKline Biologicals, a vaccine company that manufactures

meningococcal vaccines. T.N., M.S-G. and J.M.W. are previous employees of GlaxoSmithKline Biologicals. J.M.W. received payment for her contribution to the writing of this manuscript.

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