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Prevalence of *Neisseria meningitidis* serogroups in invasive meningococcal disease in China, 2010 - 2020: a systematic review and meta-analysis

Juan Xu ^{a*}, Yuquan Chen^{b*}, Mengmeng Yue^{a,c}, Jianxing Yu^a, Fuyi Han^a, Li Xu^a, and Zhujun Shao^a

^aState Key Laboratory of Infectious Disease Prevention and Control, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; ^bInstitute of Medical Information/Library, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; ^cSchool of Public Health, Nanjing Medical University, Nanjing, China

ABSTRACT

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* (*Nm*) continues to be a global public health concern. Understanding the prevalence of *Nm* serogroups in IMD is critical for developing strategies for meningococcal vaccination. We used the keywords “cerebrospinal meningitis”, “meningococcal”, “*Neisseria meningitidis*”, “meningococcal meningitis”, “serogroup” and “China” to search five databases, including PubMed, CNKI, CBM (Chinese BioMedical Literature Database), WanFang and VIP from 2010 to 2020. The age distributions, proportions of *Nm* serogroups and serogroup changes in IMD were analyzed. A total of 14 studies were included according to PRISMA guidelines. In China, from 2010 to 2020, the highest proportion of *Nm* in IMD was NmC, with 49.7% (95% CI: 35.8%–63.5%), followed by NmB with 30.2% (95% CI: 17.3%–43.0%) and NmW with 23.8% (95% CI: 7.0–40.7%). Before 2014, NmC was the major circulating serogroup, with 59.6% (95% CI: 43.8%–75.4%), followed by NmW with 24.4% (95% CI: 5.9%–42.9%). After 2015, IMD cases caused by NmB were increasing, the proportion of NmB reached to 52.4% (95% CI: 31.8%–73.1%). The age groups of children from 0 to 5 years and from 6 to 10 years represented, respectively, 29.6% (95% CI: 16.8%–42.4%) and 28.9% (95% CI: 12.1%–45.8%) of all IMD cases were reported. In China, NmB, NmC and NmW were the major serogroups causing IMD between 2010 and 2020. Since 2015, the proportion of NmB increased rapidly. The current serogroup distribution in China highlights the need of replacing the meningococcal polysaccharide vaccines that are being used in the National Immunization Program with more appropriate vaccines.

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Invasive meningococcal disease; serogroups; China; systematic review; meta-Analysis



Introduction

Neisseria meningitidis (*Nm*), a human-specific gram-negative pathogen, can cause invasive meningococcal disease (IMD).^{1,2} The fatality rate of IMD ranges to 4 to 20%, even with appropriate clinical treatment.³ 10–20% of IMD survivors reported have long-term serious sequelae, such as amputations, hearing loss, cognitive difficulties, and other neurologic disorders.^{4,5}


Nm is categorized into 12 serogroups on the basis of the capsular polysaccharide. Serogroups A, B, C, W, X and Y are responsible for most IMD cases worldwide.^{6,7} The incidence and serogroup distribution of IMD vary by geographic region and over time.^{7,8} Although IMD can occur at all ages, infants are at the highest risk, followed by adolescents and young adults.⁸ In Europe, the overall notification rate was 0.62 cases per 100,000 population in 2017, ranged from .45 (Northern and Southern Europe) to 1.33 (UK and Ireland) cases per 100,000 population.⁹ In the United States, the incidence has declined to 0.11 cases per 100,000 population in 2019.¹⁰ In African meningitis belt, with the introduction of MenA conjugate vaccine (MenAfriVac) in 2010, the IMD incidence has dramatically declined to 0.02 cases per 100,000 during 2010–2103.¹¹ In China, based on data from

the National Notifiable Disease Reporting System (NNDRS), the reported IMD average incidence was 0.0078/100,000 during 2015–2019.¹²

China has experienced several previous *NmA* meningococcal epidemics. MenA polysaccharide vaccines have been introduced into routine immunization programs since the 1980s.¹³ In 2003, serogroup C cc4821 emerged and was responsible for the meningococcal disease outbreak in Anhui Province, China, then NmC cc4821 has rapidly spread to most provinces in China.¹⁴ Therefore, the group A plus C polysaccharide vaccine was introduced into the Chinese Expanded Program for Immunization (EPI) in 2008. Chinese EPI schedule for meningococcal vaccination as follows (Figure 1): two primary doses of MenA polysaccharide vaccines were used for infants at 6 months and 9 months ages, two booster doses of group A plus C polysaccharide vaccines were inoculated for children at 3 years and 6 years. If the child aged 2 to 4 years have not received MenA polysaccharide vaccine, they would receive two dose MenA plus MenC polysaccharide vaccine for initial vaccination and the booster with an interval of 3 years.¹³ The above polysaccharide vaccines were EPI cost-free vaccines, which were paid by government.

CONTACT Zhujun Shao  shaozhujun@icdc.cn  State Key Laboratory of Infectious Disease Prevention and Control, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China

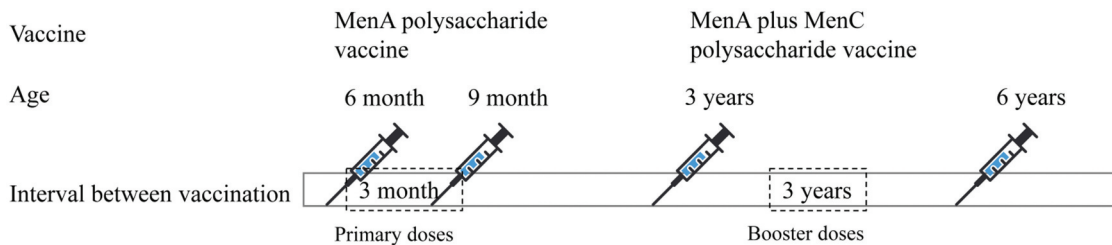
*These authors have contributed equally to this work.

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A. New Birth Cohort



B. Unimmunized Cohort

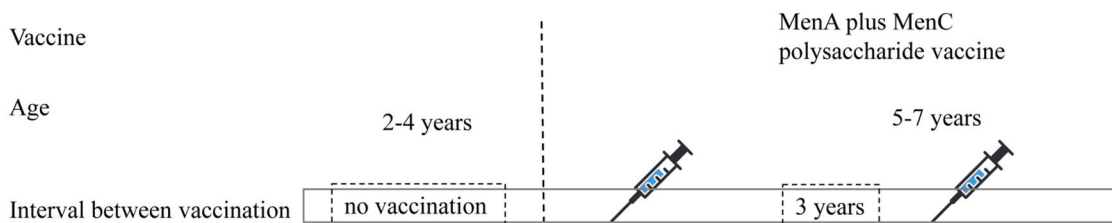


Figure 1. Expanded program for immunization schedule in China.

Ideally, the vaccination coverage rate could reach to 100% in China. The incidence of IMD caused by NmA and NmC decreased dramatically with mass vaccination. Since 2006, IMD caused by NmW cc11 and NmB cc4821 has become new challenges.¹⁵ Few IMD cases caused by NmX and NmY have been reported as sporadic cases in China in recent years.^{16,17}

Meningococcal vaccination is very beneficial for the control and prevention of IMD. To modify the strategies for meningococcal vaccination and to develop new meningococcal vaccines, such as MenB vaccines, evidence-based data including the prevalence of *Nm* serogroups and the epidemiological characteristics of the age group distribution, is necessary. In this study, we collected and systematically reviewed the published literatures related to IMD for further meta-analysis to illustrate the trends in the prevalence of serogroups in China.

Methods

Sources of data and search strategies

Following the PRISMA guidelines¹⁸ we identified articles published from 1 January 2010 to 31 December 2020 that reported invasive meningococcal disease serogroup data from 5 databases: PubMed, CNKI, CBM (Chinese BioMedical Literature Database), WanFang, and VIP. The detailed search strategies are presented in Appendix 1 (in the supplementary material). All related studies were reviewed independently by two reviewers (Juan Xu and Mengmeng Yue). To gather the required data, the following medical subject headings (MeSH) terms and text words were chosen and combined: “Cerebrospinal meningitis”, “Meningococcal”, “*Neisseria meningitidis*”, “Meningococcal meningitis”, “Serogroup”, “China” and their synonyms from the text, title, or abstract. No restriction was made based upon language. PubMed was searched in English and the other databases were searched in Chinese.

Inclusion and exclusion criteria

Preliminary screening was conducted by reading the title and abstract of the literature and clearly unqualified studies were removed, and then full-text articles were reviewed in detail against the inclusion and exclusion criteria. Questions concerning the appropriateness for inclusion in the analysis were discussed among the group members and agreed upon prior to proceeding to analysis.

Studies were eligible for inclusion with the following items: 1. the studies were peer-reviewed and published from 1 January 2010, to 31 December 2020, 2. reported cases were limited to China, 3. the study included humans, 4. the serogroup prevalence was reported, and at least one or more of the following indicators, such as age, time, and vaccine type, 5. it was published in Chinese or English.

Studies with the following items were excluded: 1. studies that targeted the *N. meningitidis* carrier population rather than IMD, 2. the articles were systematic reviews, meta-analyses or case reports, 3. reporting data from outbreak investigations, 4. the study data were incomplete and did not include serogroup information or were unable to calculate the proportion of serogroups based on the study data, 5. duplicated publications of the same study, 6. the publication year of the case report was before 2010 or did not explicitly exclude data from prior to 2010.

Quality assessment

Quality assessment of the studies was performed by two reviewers (Juan Xu and Mengmeng Yue) independently using an existing checklist modified by Hoy D.¹⁹ The checklist has nine questions. Each question could be answered “yes” or “no”, and the “yes” answer could get one score. Thus, final scores for each study could range from zero to nine. If the score was 0 to 3, it was low quality, 4 to 6 was moderate quality and 7 to 9 was high quality.

Data extraction and data collection

Two reviewers (Juan Xu and Mengmeng Yue) independently conducted data extraction and collection from the literature. For each included article, two researchers extracted the following data into an Excel sheet: title, study region, publication date, study design, research period, age groups of the individuals, sample type, identification method, sample size, number of IMD cases, number of *N. meningitidis* serogroups (A, B, C, Y, X, W and others), and serogroup distribution in different years and age groups. If any of the desired data were not found in the publications, they were marked as “UN (unknown)”.

Data analysis

The age distribution of IMD, proportions of different serogroups (A, B, C, Y, X, W, and others) and changing trends of serogroups of the IMD cases were analyzed. R software (version 4.0.3, Auckland University, USA) was used for the meta-analysis. First, the Shapiro-Wilk statistic was used to test the normality of the original data. According to the results of the normality test, a data form close to the normal distribution was selected for the meta-analysis. When the original data were normally distributed according to the Shapiro-Wilk test, we

used the original rate directly in the meta-analysis. Otherwise, the nonnormally distributed data were transformed using the following methods (log, logit, arcsine, or Freeman-Tukey double arcsine transformation). The *chi-square-based heterogeneity test* (Q test) was used to analyze the heterogeneity ($\alpha = 0.10$). We used a random-effects model for pooled prevalence estimation. Heterogeneity was measured using I^2 values. Publication bias was analyzed by funnel plots and Egger's test with linear regression or Peters test (for a sample size less than 10). All *P* values were bilateral, and $P < .05$ indicated statistical significance.

Results

Study selection

A total of 3954 publications were reviewed in the systematic search, and 2665 duplicates were excluded after the first screening. According to the title, abstract and full text, the literature was screened. Finally, 14 studies were included in the meta-analysis and reported relevant data (Figure 2).

Among the 14 studies that received a “high” quality assessment score, the results are shown in Figure 3 and Table S1 (in the supplementary material). The 14 studies included 12

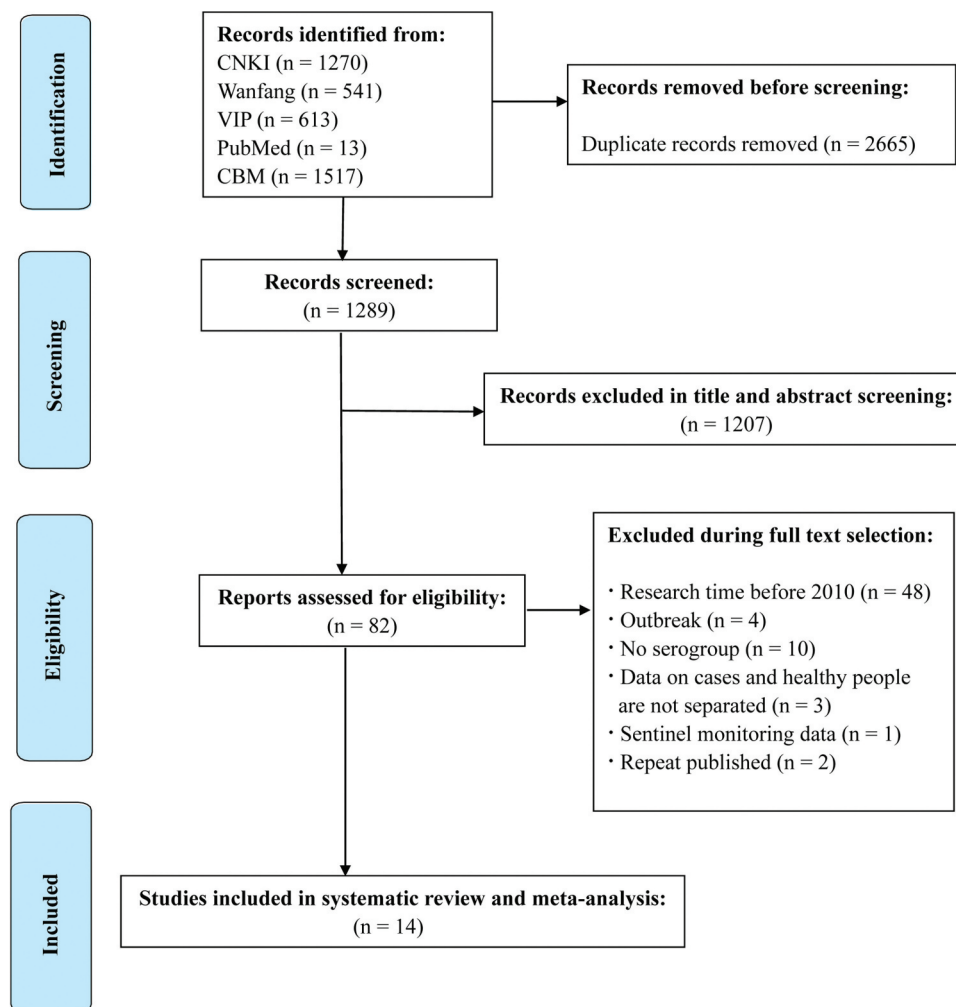


Figure 2. Flow diagram of the literature search and study selection.

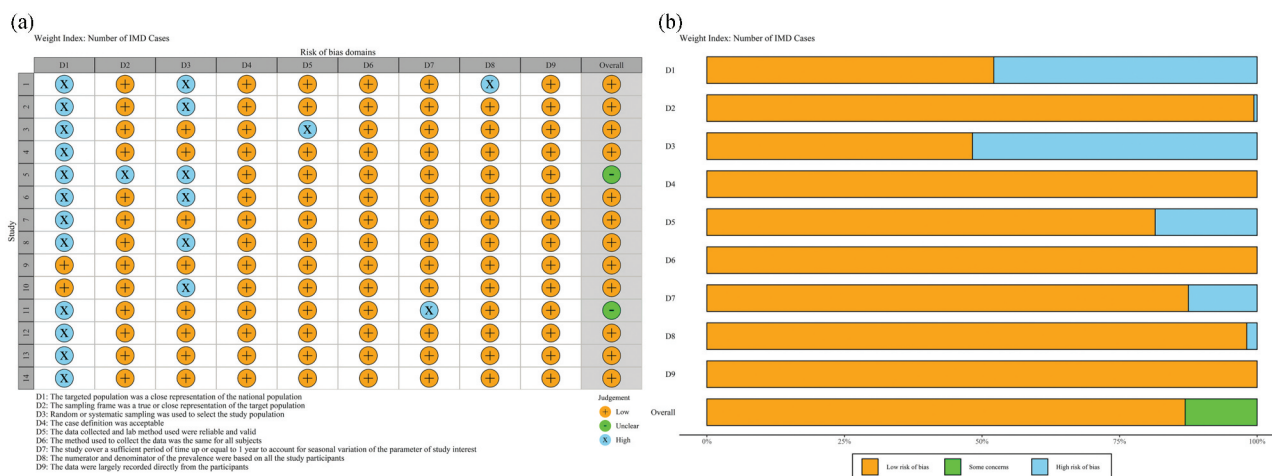


Figure 3. Quality assessment of the included studies. (a) Summary plot of risk bias; (b) Traffic light plot of risk bias.

articles with data from 8 provinces and 2 studies were national data. The characteristics of the selected articles are summarized in Table 1. All studies reported serogroup prevalence by year after 2010 (Table S2 in the supplementary material), and 4 studies clearly reported the number of IMD cases in the different age groups. The average number of *N. meningitidis* isolates from each study included in the meta-analysis were 42 (specimens or subjects), with a range of 4–296 isolates. Three studies reported that the sample type was CSF (cerebrospinal fluid) and blood, and 11 did not report the sample type.

The proportion of IMD cases in the different age groups

A total of 4 studies reported IMD cases by age. As shown in Table 2, the random-effects model was used to combine the proportion of cases at different ages. As shown in the table, the proportion of IMD cases in children from 0 to 5 years was 29.6% (95% CI: 16.8%–42.4%), followed by children in 6–10 years age group with 28.9% (95% CI: 12.1%–45.8%).

The proportion of *N. meningitidis* serogroups in invasive meningococcal disease

As shown in Table 3, a random-effects model was used to evaluate the proportion of *Nm* serogroups in IMD. In China, during 2010–2020, the highest proportion of *Nm* serogroups in IMD was NmC with 49.7% (95% CI: 35.8%–63.5%), followed by NmB with 30.2% (95% CI: 17.3%–43.0%) and NmW with 23.8% (95% CI: 7.0%–40.7%). Heterogeneity was high ($I^2 \geq 75\%$) in NmB, NmW, NmC, NmA and the others.

N. meningitidis serogroup in the different periods

The results of *N. meningitidis* serogroups in IMD is shown in Table 4. The results showed an increasing proportion of NmB and others in China, while the proportion of serogroups A, C, and W decreased. In 2010–2014, NmC was the predominant circulating serogroup with 59.6% (95% CI: 43.8%–75.4%), followed by NmW with 24.4% (95% CI: 5.9%–42.9%) and others with 23.1% (95% CI: 6.4%–39.8%). However, after 2014, the proportion of NmB increased and reached to 52.4% (95% CI: 31.8%–73.1%),

while NmC declined to 22.8% (95% CI: 18.2%–27.4%), followed by NmW and NmA with 16.8% (95% CI: 0%–36.9%) and 4.7% (95% CI: 2.6%–7.8%), respectively.

Publication bias

Publication bias analysis was conducted for the included studies in each serogroup, and funnel plots and Egger's test linear regression were used for analysis. NmC had publication bias ($P < .05$), and the results are shown in Table 5 and Figure S1 (in the supplementary material). For publication bias, the trim-and-fill method was used for correction. After filling in the missing studies, the proportion of NmC was 27.3% (95% CI: 13.2%–41.4%), which was lower than the original results.

Discussion

The proportion of *Nm* serogroups in IMD varied in different countries. In this study, we systematically reviewed the prevalence of *Nm* serogroups causing IMD in China from 2010 to 2020. Meta-analysis indicated that the highest overall proportion in IMD was NmC with 49.7% in the last decade. Since 2015, IMD cases caused by NmB were increasing. Similarly, a meta-analysis based on global *Nm* serogroups in IMD in 2019 showed that the overall proportion of NmB in IMD was 48.5%, and NmB became the major *Nm* serogroup in IMD worldwide.³³ In Africa, since 2010, the conjugate vaccine MenAfriVac was deployed extensively for persons aged 1–29 years in all countries of the meningitis belt. The implementation of this programme led to nearly 99% decline in confirmed MenA cases during 2010–2015.^{34,35} Consequently, with the dramatic decline of MenA, the circulating serogroups have shifted and most disease is now caused by MenC, MenW and MenX.³⁴

Vaccination is regarded as the optimal strategy of preventing IMD. The first vaccines based on capsular polysaccharide against serogroups A, C, W and Y were successful for the prevention of IMD. However, polysaccharides are T-cell-independent antigens that result in short-lived immunity and could not induce immune memory.³⁶ And apart from group A polysaccharide, other vaccines components are poorly

Table 1. Characteristics of the included studies.

ID	Study	Publication date	Research period	Province/Region	Median/range age (year)	Sample Type	Identification method	Number of IMD cases	Number of <i>N. meningitidis</i>	Contribution To Analysis	Reference
1	Lingping Chen	2019	2005–2018	Zhejiang	UN	UN	UN	13	5	NmB, NmX	20
2	Jianhong Wu	2013	2005–2011	Zhejiang	All ages	UN	UN	4	4	NmW, Others	21
3	Xiaoying Shan	2018	2005–2018	Shandong	UN	UN	UN	129	129	NmA, NmB, NmC, NmY, NmW, Others	22
4	Lei Feng	2014	2006–2013	Shandong	UN	CSF, Blood	PCR	9	7	NmA, NmC, NmW	23
5	Meng Yang	2018	2005–2015	Jiangxi	UN	UN	Antiserum	4	4	NmC	24
6	Yinqi Sun	2012	2005–2011	Hebei	All ages	UN	UN	12	7	NmA, NmB, NmC, Others	25
7	Baohua He	2015	2012–2013	Hebei	UN	CSF, Blood	PCR	21	21	NmB, NmC, NmW	26
8	Feng Jiang	2014	2011–2013	Guizhou	0-16	UN	UN	31	9	NmA, NmC	27
9	Junhong Li	2015	2005–2010	China	UN	UN	UN	67	67	NmA, NmB, NmC, Others	28
10	Junhong Li	2020	2015–2019	China	All ages	UN	UN	296	296	NmA, NmB, NmC, NmY, NmW, Others	12
11	Lili Fang	2017	2014–2016	Heilongjiang	UN	CSF, Blood	UN	87	10	NmB, NmC	29
12	Yahui Zhan	2018	2011–2016	Jiangsu	UN	UN	Antiserum	5	5	NmB, NmW	30
13	Shengwei Wu	2020	2006–2017	Guizhou	UN	UN	Antiserum	4	4	NmB, NmC	31
14	Defang Dai	2017	2008–2016	Hunan	0-14	UN	UN	14	14	NmB, NmC, NmW	32

Table 2. The proportion of cases of invasive meningococcal disease of different ages.

Item	Age group			
	0–5 years	6–10 years	11–18 years	>18 years
Number of studies	4	4	4	4
Total number of cases	202	149	175	215
Sample size	741	741	741	741
I^2 (P value)	90% (P < .01)	96% (P < .01)	66% (P > .01)	98% (P < .01)
Model	Random	Random	Random	Random
Proportion (%)	29.6	28.9	21.1	19.2
95% CI	16.8 ~ 42.4	12.1 ~ 45.8	14.9 ~ 27.3	1.2 ~ 37.2

Table 3. The proportion of *N. meningitidis* serogroups in IMD in China, 2010–2020.

Item	NmA	NmB	NmC	NmY	NmW	Others
Number of studies	6	10	11	2	7	5
Total number of cases	32	158	189	6	83	112
Sample size	515	558	568	425	476	503
I^2 (P value)	80% (P < .01)	90% (P < .01)	88% (P < .01)	0% (P > .01)	91% (P < .01)	91% (P < .01)
Model	Random	Random	Random	Random	Random	Random
Proportion (%)	7.1	30.2	49.7	1.2	23.8	24.9
95% CI	1.8–12.4	17.3–43.0	35.8–63.5	0.2–2.3	7.0–40.7	11.0–38.8

Table 4. Time trend of *N. meningitidis* serogroups in IMD in China, 2010–2020.

Item	NmA		NmB		NmC		NmW		NmY		Others	
	2010–2014	2015–	2010–2014	2015–	2010–2014	2015–	2010–2014	2015–	2010–2014	2015–	2010–2014	2015–
Study	5	1	7	5	10	3	5	3	1	1	4	2
Case	18	14	37	120	116	73	57	23	1	5	25	87
Sample size	206	296	229	322	246	317	159	312	116	296	194	309
I^2	79%	-	80%	69%	81%	-	80%	57%	-	-	83%	-
P-value	<.01	-	<.01	= .01	<.01	>.01	<.01	>.01	-	-	<.01	>.01
Model	random	random	random	random	random	random	Random	Random	-	-	Random	Random
Proportion (%)	14.0	4.7	22.3	52.4	59.6	22.8	24.4	16.8	0.9	1.7	23.1	28.1
95% CI	1.1–26.9	2.6–7.8	9.8–34.8	31.8–73.1	43.8–75.4	18.2–27.4	5.9–42.9	0–36.9	0.0–4.7	0.6–3.9	6.4–39.8	23.1–33.1

Table 5. Bias test for each serogroup.

Serogroup	Method for publication bias	df	t	se.bias	Intercept	P > t	Normality test (P)	Data transformation methods*	Raw result	Calibration results
A	Peters	4	2.39	0.665	0.0781	0.0753	0.6905	PRAW	7.1(1.8–12.4)	-
B	Linreg	8	1.14	1.5249	0.1352	0.2857	0.5605	PRAW	30.2(17.3–43.0)	-
C	Linreg	9	2.75	1.046	0.1951	0.0224	0.3891	PRAW	49.7(35.8–63.5)	27.3(13.2–41.4)
W	Peters	5	0.26	1.7013	0.2811	0.803	0.5453	PRAW	23.8(7.0–40.7)	-
Other	Peters	3	1.09	1.4059	0.2392	0.355	0.6616	PRAW	24.9(11.0–38.8)	-

*PRAW, untransformed proportions.

immunogenic in children younger than 2 years of age.³⁷ To overcome the problem of short duration protection and inability of memory response against the meningococcus, vaccines that conjugated the polysaccharide to a carrier protein were used.³⁸ In 1999, the UK first introduced the MenC polysaccharide conjugate vaccine into national immunization programs (NIPs) for routine infant immunization and as a booster vaccination for children and adolescents up to 18 years of age, then there was a marked decline in MenC disease.^{38,39} Furthermore, MenC conjugate vaccines also could decrease carriage among teenagers and induce herd protection.^{38,40} Polysaccharide-conjugate vaccines for

serogroups A, C, W, and Y gradually replace polysaccharide vaccines and have been recommended or introduced into NIPs in many countries worldwide for years.³⁸ However, in Chinese routine national immunization programs, infants (6 months and 9 months) received two doses MenA polysaccharide vaccine and children (3 years and 6 years) received two doses MenAC polysaccharide vaccine, there was no longer booster for those over 6 years of age. In addition, polysaccharide conjugate vaccine was not introduced into EPI. But some conjugate vaccines could be available, including MenAC and MenACWY conjugate vaccine for infants older than 3 months of age, which should be paid for the cost by parents.

Polysaccharide vaccines could not be available for MenB vaccines because of their polysaccharide structure's similarity to the *N*-acetylneuraminic acid structure of human nerve cells, which may lead to not only poor immunogenicity but also potential autoimmune antibodies.⁴¹ The development of MenB vaccine was protein-based. Two MenB vaccine including 4CMenB (*Bexsero*, GSK) for infants, toddlers and children at 2–10 years of age or person aged 10–25 years^{42,43} and rLP2086 (*Trumenba*, Pfizer) for persons aged 10 to 25 years have been recommended for NIPs in many countries.^{44,45} MenB vaccines exhibited broad coverage and effectiveness. In the UK, the effectiveness of 4CMenB could reach 83% after two doses of inoculation, and the protective effect could persist for over 3 years among 75% of vaccinated individuals.^{46,47} In China, MenB became the predominant IMD serogroup, but no MenB vaccines are currently available.

In this study, we found the proportion of NmB, NmW and NmY are increasing, but the polysaccharide vaccines included in EPI currently cannot cover these serogroups. Vaccines targeting more serogroups should be introduced into EPI, and polysaccharide conjugate vaccines should gradually replace polysaccharide vaccines. Furthermore, new vaccines for NmB need to be developed in the future.

Strengths and limitations

This study included almost all studies about the distribution of IMD serogroups in China in the past 10 years, and we systematically reviewed the prevalence of *Nm* serogroups causing IMD in China. It provided preliminary estimate of the current serogroup and age groups distribution of IMD cases in China.

The main obstacle for this study was that most studies calculated the incidence rate of IMD based on different regions, not age groups. With the limitation of data, we only calculated the proportion of each age group, rather than the incidence rates. In addition, in some studies, the *Nm* serogroups may not be reported due to lack of laboratory diagnostic kits or insufficient laboratory capacity for culture and PCR. The publication bias and heterogeneity detected in the present analysis cannot be ignored, and all of these factors must be considered when interpreting the results.

Conclusion

This systematic review showed that NmC was still the major prevail serogroup between 2010 and 2020, but the proportion of NmB in IMD was increasing rapidly since 2015. The current serogroup distribution in China highlights the need of replacing the meningococcal polysaccharide vaccines that are being used in the National Immunization Program with more appropriate vaccines.

Disclosure statement

Nopotential conflict of interest was reported by the author(s).

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ORCID

Juan Xu  <http://orcid.org/0000-0003-1752-0443>

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