RESEARCH PAPER

Primary immunization of meningococcal meningitis vaccine among children in Hangzhou, China, 2008–2017

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ABSTRACT

Background: Although China's Expanded Program on Immunization (EPI) provides two doses of group A meningococcal polysaccharide vaccine (MPV-A) for children younger than 2 y, more self-paying group A and group C meningococcal polysaccharide conjugate vaccine (MCV-AC) has been used as an alternative to MPV-A, to prevent *Neisseria meningitidis* serogroup C (Men-C) earlier. We evaluated the pattern of MPV-A and MCV-AC utilization to provide evidence for China to upgrade the national meningococcal meningitis vaccination strategy.

Methods: Children born between 2008 and 2017 registered in Hangzhou's Immunization Information System (HZIIS) were included. Descriptive epidemiological methods were used to characterize the data. Adverse event following immunization (AEFI) was collected from Chinese national adverse event following immunization information system (CNAEFIIS) to compare the safety of MPV-A and MCV-AC.

Results: Data of 1149,027 children from HZIIS were analyzed. The average immunization rate of meningococcal meningitis vaccine (MenV) was 97.50%. Percentages of children using MPV-A-only, MCV-AC-only, and MPV-A/MCV-AC sequential schedules were 68.20%, 29.73%, and 2.07%, respectively. The vaccination rate of MCV-AC-only increased by age and it was higher in resident children than migration children. The incidence rate of AEFI of MPV-A and MCV-AC was 53.36 per 100,000 and 62.13 per 100,000, respectively.

Conclusion: Children in Hangzhou had high MenV coverage. MCV-AC-only schedule use increased by year and was higher in urban areas among locally born children. Both MPV-A and MCV-AC were safe for children, while MCV-AC could protect against Men-C more effectively. This supports the rationale to introduce MCV-AC into China's EPI system for free instead of MPV-A.

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1. Introduction

Meningococcal meningitis is a severe acute respiratory infection caused by *Neisseria meningitidis meningitis* (Nm). Its classic clinical features are fever, rash, and meningitis. Besides meningitis and septicemia, meningococci occasionally cause arthritis, myocarditis, pericarditis, and endophthalmitis¹. Approximately 10% to 20% of the survivors of meningococcal meningitis have permanent sequelae, such as mental retardation, deafness, epilepsy, or other neurological disorders. Meningococcal disease can progress rapidly. The case fatality rate, which was 70% to 85% before the advent of antibiotics, is now 10% to 15%.² It has become one of the most significant public health problems in many countries. The majority of countries with high incidence rates belong to the African meningitis belt; many moderate-incidence countries locate in the European and African regions, and Australia, while low-incidence countries are from Europe and the America.³ There are 12 serogroups, but the majority of the invasive meningococcal infections are caused by organisms from the A, B, C, X, Y, or W-135 serogroups which account for 95% of meningococcal meningitis cases.⁴ In Asia, serogroup A and serogroup C meningococcal epidemics cause high morbidity and mortality and continue being an ongoing threat, particularly in developing countries.^{5,6} China has got several large-scale epidemics, such as the outbreak of serogroup A and

serogroup C meningitis in some provinces from the end of 2004 to the beginning of 2005.⁷ In China, most cases occurred in children under age of 15 and especially among infants of 6 months to 2 y old.⁸

For meningococcal meningitis prevention, chemoprophylaxis should be offered to household members and anyone in close contact. However, its effectiveness of lowering disease risk for a large population in response to outbreaks of meningococcal disease may be limited.⁹ Meningococcal vaccination is the most effective way for meningococcal meningitis prevention. Currently, MenV in Chinese market includes meningococcal polysaccharide vaccine (MPV) and MCV. In the 1980s, MPV-A had been widely used in China, and the incidence of meningococcal meningitis decreased significantly. In 2006, MPV-A and group A and group C meningococcal polysaccharide vaccine (MPV-AC) had been introduced to EPI in Hangzhou, China. Children aged 6–18 months were given two doses of MPV-A with at least 3-month interval time between the doses, followed by two booster doses of MPV-AC at 3 y and 6 y old. MCV-AC was available in Hangzhou in 2009 as a self-pay vaccine, mainly replacing MPV-A in children within 2 y old.

Our study is to determine the coverage rates of primary immunization of meningococcal meningitis vaccines, patterns

of use of MPV-A and MCV-AC, and occurrence of AEFI of MPV-A and MCV-AC in Hangzhou between 2008 and 2017.

2. Methods

2.1. Setting

Hangzhou is a supercity in Zhejiang Province in the east of China with a population of over 10,000,000. There are 15 districts in Hangzhou, 6 of which are classified as urban areas (Shangcheng, Xiacheng, Jianggan, Gongshu, Xihu, and Xihufengjingmingsheng); 6 of which are classified as suburb area (Binjiang, Xiaoshan, Yuhang, Qiantang, Fuyang, Lin'an); the other are classified as rural areas (Tonglu, Jiande, Chun'an). There are 200 vaccination clinics in Hangzhou responsible for vaccinating all children residing in Hangzhou, regardless of whether they are residents or migrants. EPI clinicians are required to inform parents of the benefits and risks of MPV-A or MCV-AC.

Since 2005, Hangzhou Center for Disease Control and Prevention (HZCDC) has operated the Hangzhou's Immunization Information System (HZIIS), which was a computerized information system registering immunization data for children aged <15 y old and adults living in Hangzhou. Children's demographic information and immunization history (vaccine type, dose, vaccination date) were recorded in this system. HZIIS contains a client application software deployed in every immunization clinic and a web-based management platform built in HZCDC. All children, including resident and migrant children, are registered in HZIIS during their vaccination in Hangzhou.

Chinese national adverse event following immunization information system (CNAEFIIS) is a passive surveillance system, which is the only official vaccine safety surveillance system that collects AEFI cases in mainland China. AEFI is defined as damages of body tissues, organs, and function, which are suspected to be the vaccination response occurred in the process of vaccination or after vaccination. According to the causes, they can be divided into adverse reactions (including common adverse reaction and rare adverse reaction), vaccine quality accidents, implementation error accidents, coincidences, and psychogenic reactions.

2.2. Vaccination and AEFI data

Our study included children who were born between January 1, 2008 and December 31, 2017 and registered in HZIIS. Information including district of residence, gender, birth date, dose number, vaccination time, and type was obtained. We defined children who were not born but living in Hangzhou as migrant children. Data were extracted from HZIIS on June 30, 2019. AEFI of MPV-A and MCV-AC was exported from CNAEFIIS.

2.3. Data analysis

We categorized MPV-A and MCV-AC vaccination patterns into MPV-A-only, MCV-AC-only, sequential MPV-A followed by MCV-A or MCV-AC followed by MPV-A. Coverage rate of

MenV was determined by dividing the number of vaccinations administered by the number of children registered in HZIIS. We described the vaccination patterns of MenV by birth year, geographical area, and migrant status. Annual incidence of AEFI in MPV-A and MCV-AC was analyzed statistically. MenV AEFI per 100,000 populations was calculated by using the number of MenV AEFI cases divided by the number of MenV recipients. All statistical analyses and graphs were made by SPSS statistical software for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). A value of $P < .05$ (2-sided) was considered statistically significant. The chi-square test was used to compare the proportion of children who used MCV-AC-only schedule in urban, suburb, or rural; in resident and migrant; the incidence of common adverse reaction and rare adverse reaction in MPV-A and MCV-AC. The chi-square trend test was used to compare the proportion of children using MCV-AC-only schedule year by year.

2.4. Ethical considerations

This study was determined to be exempt from ethical review by the Hangzhou CDC institutional review board. Data were safe when extracted from HZIIS and CNAEFIIS and were not linked to individual identifiers.

3. Results

3.1. MenV coverage

A total of 114,9027 infants born from 2008 to 2017 were registered in HZIIS, including 604,054 males (52.57%) and 544,973 females (47.43%); 705,281 (61.38%) resident children and 443,746 (38.62%) migrant children; 377,518 urban children (32.86%), 659,876 suburb children (57.43%), and 111,633 rural children (9.72%). There were 76,899, 79319, 95,384, 107,765, 123,967, 111,864, 141,509, 112,072, 150,983, and 149,265 children in each birth cohort. Coverage rates were 99.93% for receiving at least one dose of MenV, and 97.50% for receiving at least two doses. Across all 10 birth cohorts, the two-dose coverage rates were consistently over 95% (Table 1).

3.2. MenV vaccination pattern

Across all birth cohorts, 68.20% of children used MPV-A-only schedule; 29.73% used MCV-AC-only schedule; and 2.07% used MPV-A/MCV-AC sequential schedules. The proportion of children who used MPV-A-only schedule decreased year by year, from 96.02% in 2008 to 58.53% in 2017 ($\chi^2 = 37180.58$, $P_{\text{for trend}} < 0.05$). The proportion of children using MCV-AC-only schedule increased year by year, from 2.73% in 2008 to 40.01% in 2017 ($\chi^2 = 40415.78$, $P_{\text{for trend}} < 0.05$). Sequential schedules were seldomly used, the rate of which varies from 1.25% to 2.86% per year.

The proportion of children who used MCV-AC-only schedule was 44.10%, highest in the urban, and it was 19.28%, lowest in the suburb ($\chi^2_{\text{urban,suburb}} = 72088.93$, $\chi^2_{\text{urban,rural}} = 50.38$, $\chi^2_{\text{suburb,rural}} = 30077.20$, all $P\text{-value} < 0.05$). The proportion was higher in resident children (33.49%) than in migrant children (23.70%) ($\chi^2 = 12344.49$, $P < .05$) (Table 2).

Table 1. Coverage of MenV^a among children born from 2008 to 2017, by birth cohort

Year of birth	No. of children	≥1 Dose		≥2 Doses	
		No. vaccinated	Rate (%)	No. vaccinated	Rate (%)
2008	76899	75399	98.05	73531	95.62
2009	79319	77957	98.28	76363	96.27
2010	95384	94204	98.76	92826	97.32
2011	107765	106595	98.91	105393	97.8
2012	123967	122558	98.86	121334	97.88
2013	111864	110756	99.01	109769	98.13
2014	141509	140333	99.17	139275	98.42
2015	112072	111070	99.11	110008	98.16
2016	150983	150023	99.36	148837	98.58
2017	149265	147785	99.01	143001	95.8
Total	1149027	1136680	98.93	1120337	97.5

^a: Meningococcal meningitis vaccine.

No matter in urban, suburb, or rural, more proportion of resident children used MCV-AC-only schedule than migrant children ($\chi^2_{\text{urban}} = 10752.31$, $\chi^2_{\text{suburb}} = 789.66$, $\chi^2_{\text{rural}} = 2356.35$, all P -value < 0.05) (Table 3).

3.3. AEFI of MPV-A and MCV-AC

For 2008 to 2017 birth cohort children, a total of 838 AEFI cases of MPV-A and 459 AEFI cases of MCV-AC were reported in CNAEFIS. The incidence of AEFI in MPV-A and MCV-AC was 53.36 per 100,000 and 62.13 per 100,000, respectively. The incidence of common adverse reaction in MPV-A and MCV-AC, mainly the injection site erythema, injection site pain, and fever, was 49.35 per 100,000 and 54.41 per 100,000, respectively ($\chi^2 = 2.53$, $P > .05$). The

incidence of rare adverse reaction in MPV-A (2.87 per 100,000) was lower than that of MCV-AC (5.14 per 100,000) ($\chi^2 = 7.26$, $P < .05$) (Table 4). Allergic rash was the main rare adverse reaction for both vaccines, and few cases of epilepsy, febrile convulsion, and angioedema were reported. There were no serious reactions or deaths.

4. Discussion

Our study showed that children in Hangzhou had a high coverage of MenV vaccination. The pattern of MenV use changed by year, and the MCV-AC only schedule was used more and more frequently for children in different areas and migrant status. Our findings demonstrate a positive safety profile of MenV with reasonable low incidences of AEFI of MPV-A and MCV-AC.

MenV has been continuously used for many years in Hangzhou. From 2008 to 2017, the coverage rates of first and second dose of MenV were all above 95%, and they were similar to the reported coverage rates of MenV in national immunization program (NIP) in China 2014 (99.39% and 99.23%).¹⁰ MenV sequential schedule was not recommended, but a small number of children used MenV sequential schedule in our study. In Hangzhou, MCV-AC vaccine was not available in a small part of vaccination clinics. If children had two doses of MenV vaccines in different clinics, they may use a sequential schedule. With the high immunization level of MenV, the incidence of meningococcal meningitis decreased. From 2006 to 2017, the morbidity and mortality of meningococcal meningitis in Zhejiang province decreased gradually by year. Since

Table 2. Use of different MenV^a schedules by birth year, geography, and migrant status

	Year of birth	No. vaccinated	MPV-A-only ^b		MCV-AC-only ^c		Sequential schedules	
			No.	Proportion (%)	No.	Proportion (%)	No.	Proportion (%)
Year of birth	2008	75399	72400	96.02	2057	2.73	942	1.25
	2009	77957	66079	84.76	9646	12.37	2232	2.86
	2010	94204	69886	74.19	21653	22.99	2665	2.83
	2011	106595	74120	69.53	29440	27.62	3035	2.85
	2012	122558	81615	66.59	38318	31.27	2625	2.14
	2013	110756	72768	65.7	36076	32.57	1912	1.73
	2014	140333	84375	60.12	53789	38.33	2169	1.55
	2015	111070	67706	60.96	41285	37.17	2079	1.87
	2016	150023	99720	66.47	46593	31.06	3710	2.47
	2017	147785	86498	58.53	59122	40.01	2165	1.46
Area	Urban	373396	197298	52.84	164672	44.1	11426	3.06
	Suburb	652579	517884	79.36	125819	19.28	8876	1.36
	Rural	110705	59985	54.18	47488	42.9	3232	2.92
Migrant status	Resident	700224	454473	64.9	234537	33.49	11214	1.6
	Migrant	436456	320694	73.48	103442	23.7	12320	2.82
Total		1136680	775167	68.2	337979	29.73	23534	2.07

^a: Meningococcal meningitis vaccine.

^b: Children who used group A meningococcal polysaccharide vaccine (MPV-A) only.

^c: Children who used group A and group C meningococcal polysaccharide conjugate vaccine (MCV-AC) only.

Table 3. Coverage of MCV-AC^a among children born from 2008 to 2017, by geography and migrant status

		Urban			Suburb			Rural			Total		
		No. of children	No. vaccinated	Rate (%)	No. of children	No. vaccinated	Rate (%)	No. of children	No. vaccinated	Rate (%)	No. of children	No. vaccinated	Rate (%)
Migrant status	Resident	227366	114640	50.42	387560	78311	20.21	90355	41586	46.03	705281	234537	33.25
	Migrant	150152	50032	33.32	272316	47508	17.45	21278	5902	27.74	443746	103442	23.31
Total		377518	164672	43.62	659876	125819	19.07	111633	47488	42.54	1149027	337979	29.41

^a: Group A and group C meningococcal polysaccharide conjugate vaccine.

Table 4. AEFI incidence of MPV-A^a and MCV-AC^b vaccinated from 2009 to 2018

Vaccine	No. vaccinated	Common adverse reaction		Rare adverse reaction		Coincidental event		Total	
		No. of cases	Reporting rate (/100 000 doses)	No. of cases	Reporting rate (/100 000 doses)	No. of cases	Reporting rate (/100 000 doses)	No. of cases	Reporting rate (/100 000 doses)
A	1570518	775	49.35	45	2.87	18	1.15	838	53.36
A + C	738815	402	54.41	38	5.14	19	2.57	459	62.13

^a: Group A meningococcal polysaccharide vaccine.

^b: Group A and group C meningococcal polysaccharide conjugate vaccine.

2010, less than 10 cases a year have been reported in Zhejiang,¹¹ especially for Hangzhou. MenV effectively prevented the occurrence of meningococcal meningitis. No meningococcal meningitis exists in the place during the past few years. In our study, the percentage of children using MCV-AC-only schedule for primary immunization has increased year by year, which replaced the MPV-A-only schedule. This is consistent with a study in Guangxi, China that the alternative rate of MCV-AC for MPV-A vaccination increased from 2.71% in 2010 to 7.48% in 2016.¹² The epidemic microflora of meningococcal meningitis in China has changed from group A to group C, and the epidemic microflora of meningococcal meningitis is diversified.¹³ Therefore, countries should consider to introduce groups B, C, Y, W, meningococcal polysaccharide conjugate vaccine, and other related vaccines into EPI and conduct further research to explore new prevention strategies. Since serogroup C meningitis was first confirmed in Guangxi, China in 2002, it has been detected in 27 provinces in China, and the detection rate of group C Nm is increasing year by year. In 2006, group C Nm accounted for 57% of the total microflora isolated from meningococcal meningitis cases and close contacts, and group C Nm has become the dominant endemic microflora. From 2008 to 2013, more than 46% of the cases of meningococcal meningitis cluster outbreak were caused by group C Nm.¹⁴ Among the laboratory-confirmed cases of meningococcal meningitis, about 48% were meningococcal meningitis in group C, and other Nm bacteria such as group B and W135 were also detected in some areas.⁶

MCV is especially suitable for the current situation in China.^{14–16} The Nm polysaccharides in MPV are t cell-independent (TI) antigens. The level of antibodies produced by MPV-A vaccination in infants under 2 y old is low and the duration of antibody is short.¹⁴ The immune effect and the coverage of the bacteria cannot adapt to the current epidemic situation of cerebral meningitis. MPV-AC or groups A, C, Y, W135 MPV (MCV-ACYW135) could not reliably induce the generation of protective antibodies in infants and young infants.¹⁴ If MPV is given to young infants, it will also cause the immune tolerance to antigens when they are vaccinated again.¹⁴ But regardless of the debate over the MPV, the effectiveness and safety of the MCV have been recognized. MCV is a combination of Nm polysaccharides and protein carriers, whose antigens are converted into T cell-dependent (TD) antigens, thus inducing the body to produce high levels of antibodies. MCV can enhance the immune memory response to infants under 2 y old and increase the immunogenicity and immune persistence of antibodies.¹⁴ Serological results showed that at 16 months after receiving one dose of MCV, 88% of children aged 1 to 2 still had protective antibodies, and up to 96% of adolescents aged 15 to 17 had protective antibodies. Infants receiving three doses of MCV at

2-month intervals produced high levels of protective antibodies. Practical experience in the UK showed that MCV-C had a good overall performance.¹⁷ MPV-C previously inoculated will not affect the immune response of MCV, and MCV-C will not interfere with other vaccines in the immunization program.¹⁷ In recent years, foreign studies have shown that MCV-ACYW135 also has good protection and safety.^{18,19} Some experts suggest replacing MPV-A with MCV-AC in China, so as to further strengthen the protection of infants and reduce the incidence of meningococcal meningitis.²⁰ It is also consistent with the views of Chinese experts.²¹

Our study showed that the coverage rate of children using MCV-AC-only schedule was higher in urban area than in other areas. This is consistent with a study in Shandong province, China that the coverage rate of MCV-AC in resident was higher (24.71%) than that in migrant (21.91%).²² Economic cost is an important barrier for the accessibility of self-pay vaccination in China. Parents with high income would like to pay for self-pay vaccine.²³ Another study also showed that parents in urban area had more chance to know vaccine-related knowledge than in rural areas. The parents of urban are more willing to choose self-pay vaccine for children to prevent infectious diseases.²⁴

The incidence of AEFI in MPV-A and MCV-AC in Hangzhou was lower than in previous studies.²⁵ Despite the incidence of rare adverse reaction in MCV-AC was higher than in MPV-A, such cases were mainly allergic rashes, urticaria, etc., which did not cause more serious damage. MPV-A and MCV-AC are relatively safe for children.

This study also has some limitations. In China, the price of MCV is higher than that of MPV. Although research by the Chinese preventive medicine association has shown that vaccination with MCV is cost-effective in countries such as the United Kingdom, the United States and Canada,²⁶ no relevant studies have been conducted in Hangzhou. When the incidence of meningococcal meningitis is low, a cost-benefit analysis is needed to include MCV-AC or MCV-ACYW135 in EPI. MenV has more varieties in China and sequential schedules are more complicated. The effect of sequential schedules on antibody production was not investigated in Hangzhou. The AEFI data used in this paper were passively monitoring data, which may not truly reflect the occurrence of AEFI of MPV-A and MPV-AC to some extent.

Conclusions and key recommendations: To sum up, we believe that MCV has the advantages of simultaneously preventing a variety of diseases, reducing the number of injections, simplifying immunization procedures, etc., and we suggest to update the current meningococcal meningitis immunization strategy in China. It is also suggested to use MCV for primary immunization in children before 2 y old and MPV for enhanced immunization in children after 3 y old, which can save money and solve the problem

of insufficient production.

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Disclosure of potential conflict of interest

The authors declare no conflicts of interest.

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Authors' contributions

Conceived and designed the study: Yan Liu, Xinren Che, Yuyang Xu. Obtained and organized the data: Jun Wang, Xinren Che, Wenwen Gu. Analyzed the data: Yan Liu, Wei Jiang. Contributed reagents/materials/analysis tools: Jian Du, Xiaoping Zhang, Xuechao Zhang. Wrote the manuscript: Xinren Che, Yan Liu.

Ethical considerations

This study was determined to be exempt from ethical review by the Hangzhou CDC institutional review board. Data were de-identified when extracted from HZIS and were not linked to individual identifiers.

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