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Sero-survey of polio antibodies and quality of acute flaccid paralysis surveillance in Chongqing, China

A cross-sectional study

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Abstract

Serums were collected from people to assess whether polio immunity level was high enough to satisfy the polio vaccine immunization switch in Chongqing.

People in 7 age groups (<1 year, 1–2 years, 3–4 years, 5–6 years, 7–14 years, 15–19 years, ≧20 years) were randomly selected in 3 areas by different geographical features in 2015. Peripheral venous blood samples were obtained and assays to detect poliovirus (PV) –neutralizing antibodies were performed. Acute flaccid paralysis (AFP) data was collected from 2012 to 2016 in Chongqing to evaluate the performance of AFP surveillance system by indicator analysis.

A total of 636 people were tested for PV neutralization antibodies (NA). Overall NA seroprevalence for PV1, PV2 and PV3 were 93.40%, 96.38% and 91.82%, and geometric mean titers (GMTs) were 61.14, 66.78 and 21.47, respectively. GMTs and NA seroprevalence for PV1, PV2 and PV3 in older people were lower than young people. There were significant differences in seroprevalences of PV1 and PV3 among geographic areas ($P < .05$) in Chongqing.

High seroprevalence for PV1, PV2, and PV3 and qualified capability for monitoring AFP cases showed that the polio eradication program has made positive achievements in Chongqing and established a stable base for a polio vaccine immunization switch. Nevertheless, GMTs were negatively associated with age in the geographic districts with poor economical features, which will increase the risk of emergence of vaccine-derived PV after polio vaccine switch. More than 1 dose of inactivated polio vaccine should be introduced into the polio vaccine schedule, and the supplementary immunization of polio should still be annually carried out after polio vaccine switch, especially among elder children and the adults.

Abbreviations: AFP = acute flaccid paralysis, bOPV = bivalent oral polio vaccine, CDC = Center for Disease Control and Prevention, CI = confidence interval, EPI = expanded immunization program, GMTs = geometric mean titers, IPV = inactivated polio vaccine, NA = neutralizing antibodies, OPV = oral attenuated polio vaccine, PV = poliovirus, SIAs = supplementary immunization activities, tOPV = trivalent oral polio vaccine, VDPV = vaccine-derived polioviruses, WPV = wild poliovirus.

Keywords: geometric mean titers, polio, seroprevalence, surveillance of acute flaccid paralysis neutralized antibodies

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1. Introduction

Poliomyelitis is an acute communicable disease caused by any serotypes of 3 poliovirus (PV) (types 1, 2 or 3). In 1988, the annual global burden of paralytic poliomyelitis was estimated to be > 350,000 cases, with wild PV (WPV) transmission reported in >125 countries.[1] The Global Polio Eradication Initiative was established and the attenuated viruses in live oral attenuated polio vaccine (OPV) (containing types 1, 2, and 3) had been invited in the expanded immunization program (EPI) in most countries.[2,3] Since the global polio eradication initiative was launched in 1988, the number of polio cases has declined rapidly. Of the 3 types of WPVs, the last case of poliomyelitis caused by naturally circulating WPV type 2 (WPV2) was recorded in India in 1999 and global eradication of WPV2 was certified in 2015.[4] In the absence of cases of polio caused by WPV2 for >16 years, type 2 vaccine viruses, which are the component of the current live OPV, have become a significant cause of paralytic polio. During 2011–2015, almost 90% of reported circulating vaccine–derived PV cases (VDPVs) (204/230) were associated with the type 2 component of trivalent OPV (tOPV).[5] WPV and VDPV do similar harm to people. Once infected, people may have permanent disability and public health safety will be in danger.

Therefore, WPV and VDPVs are included in the management of public health emergencies in many countries, including China. To eliminate this vaccine-related disease burden and to eradicate polio, WHO proposes the Polio Eradication and Endgame Strategic Plan 2013–2018, which includes the introduction of at least 1 dose of inactivated polio vaccine (IPV) into routine immunization schedules, and the tOPV was substituted by bivalent oral polio vaccine (bOPV), withdrawal of Sabin type 2 strains, synchronously globally on May 1, 2016.[3,6,7]

Sequential schedules of IPV followed by 2 or more doses of OPV have been used or studied in several countries including Israel, Oman, Pakistan, UK, and USA. Such schedules reduce the number of doses of IPV and may theoretically optimize both the humoral and mucosal immunogenicity of polio vaccines.[8] This approach effectively prevented poliomyelitis caused by vaccine associated paralytic polio in Denmark[9] using a schedule of 3 doses of IPV followed by 3 doses of OPV, in Hungary[10] using a schedule of 1 dose of IPV followed by 3 doses of OPV, and in the USA[11] which recommended 2 doses of IPV prior to 2 doses of OPV during the period of transition from use of an OPV-only schedule to an IPV-only schedule. China had adopted an IPV-bOPV-bOPV-bOPV series in 2016.

Polio cases were recorded in Chongqing since 1958, with the highest polio incidence of 13.03/100,000 in 1963. OPV was first used in the 1960s and introduced into EPI in 1978. With the gradual improving surveillance of polio disease and construction of 3-level health care network, the OPV vaccine coverage increased significantly and the morbidity rate dropped rapidly. The last polio case cased by WPV was reported in Chongqing in 1993, and then China was certified polio free by the WHO in 2000. To maintain polio-free status, based on high vaccine coverage of polio, supplementary immunization activities (SIAs) of OPV were annually carried out in Chongqing. Since 2000, Chongqing has had no WPV cases or VDPV cases reported. Trivalent OPV is the only EPI polio vaccine since it was first used in the 1960s in Chongqing. Children receive 1 dose of OPV at 2, 3, 4 months and 4 years old, respectively. As a rechargeable vaccine, IPV (the 3 virus serotypes PV1, PV2 and PV3) was first introduced in Chongqing in 2009, which accounted for about 5% of all polio vaccine doses immunized. To answer the WHO's plan for the polio immunization strategy transformation in the world, Chongqing had switched polio immunization schedule to adopt an IPV-bOPV-bOPV-bOPV series instead of tOPV-tOPV-tOPV-tOPV in its EPI since May 1, 2016. Then, in the routine polio immunization schedule, only IPV contains type 2 vaccine viruses in Chongqing. Although there were no WPV cases and no VDPV cases reported in Chongqing for about 20 years, we still have the threat of PV2 from WPV endemics in surrounding countries and external environment with PV2.[12–16]

Seroprevalence surveys of anti-polio antibodies have served as an efficient tool to assess population immunity in areas of high risk for PV transmission.[17,18] We carried out this cross-sectional study to evaluate the neutralizing antibodies (NA) seroprevalence of PV among a broad age groups in Chongqing in December 2015 and assess the performance quality of surveillance of acute flaccid paralysis (AFP) cases to decide whether the polio immunity level in Chongqing was high enough to satisfy the switch of polio vaccine immunization schedule.

2. Methods

A hospital based cross-sectional survey was conducted using the multi-stage random sampling technique for sample collection. According to different geographical statuses in Chongqing, we divided 39 districts into 3 groups (west/middle/east) by the main city zone. One district in each area was randomly selected, and in each district, 1 general hospital was randomly selected. Finally, the following 3 areas were identified and chosen to be included in the sero-epidemiological survey:

(1) Jiangbei district (middle area);
(2) Dazu district (western area);
(3) Fengjie district (eastern area) (Fig. 1).

Patients who searched health care in admitted health facilities were invited to participate in our study. Individuals who were immunodeficient or had taken immunosuppressant drugs during the last 12 months were excluded from our study. Sample size was calculated based on an assumed seroprevalence of 90%, error margin of $\pm$ 10%, $\alpha = 0.05$ and a power of at least 1.5. The sample was further inflated by approximately 20% in order to account for potential non-response, which resulted in a final sample size of 630. There were 210 participants in each study area, who were averagely distributed in 7 age groups (<1year, 1–2 years, 3–4 years, 5–6 years, 7–14 years, 15–19 years, 20+ years). A questionnaire was used to collect subjects' personal information (sex, age, region, immunization history, etc) and 3 mL of venous blood was collected from each subject for testing NA to polio-myelitis virus. We collected AFP data from 2012 to 2016 in Chongqing through the National Immunization Program Information System to evaluate the performance of AFP surveillance by indicators analysis, including data about timely case reporting in 24 hours after seeking medical treatment, timely case investigating in 48 hours after being reported, collecting adequate stool samples, and timely delivery of samples for testing in 7 days after collecting samples.

2.1. Laboratory procedures

Blood Samples were immediately placed in an ice box and transported to the laboratory of local Center for Disease Control and Prevention (CDC). After centrifugation of blood, the serum was separated and then stored at -20°C. Then, the samples were transported to the polio laboratory of Chongqing CDC for testing. NA against P1, P2, and P3 were determined by a standard microneutralization assay (MNA) in accordance with WHO guidelines.[19,20] Before testing, each serum sample was inactivated at 56°C for 30 minutes and then diluted from 1:4 to 1:1,024 in 2-fold serial dilutions. Each sample was incubated in duplicate wells for 3 hours at 36°C with 50% tissue culture infective doses (TCID50) of PV antigen. After incubation for 7 days, the highest dilution of serum that protected 50% of the cultures was recorded. Serum sample with a titer of $\geq$1:4 was considered positive.[20] Cell controls and a reference serum were included in each test to examine reproducibility of results.

2.2. Statistical analyses

Statistical tests were performed using SPSS 19.0 software. Seropositivity rates and geometric mean titers (GMTs) of antibodies were calculated for each group. Chi-square test was used to determine the association among demographic characteristics (sex, age, and region) and antibody seropositivity. GMTs were logarithmically transformed, and ANOVA variance was completed to compare the difference among groups with different demographic characteristics. Multiple comparisons were done

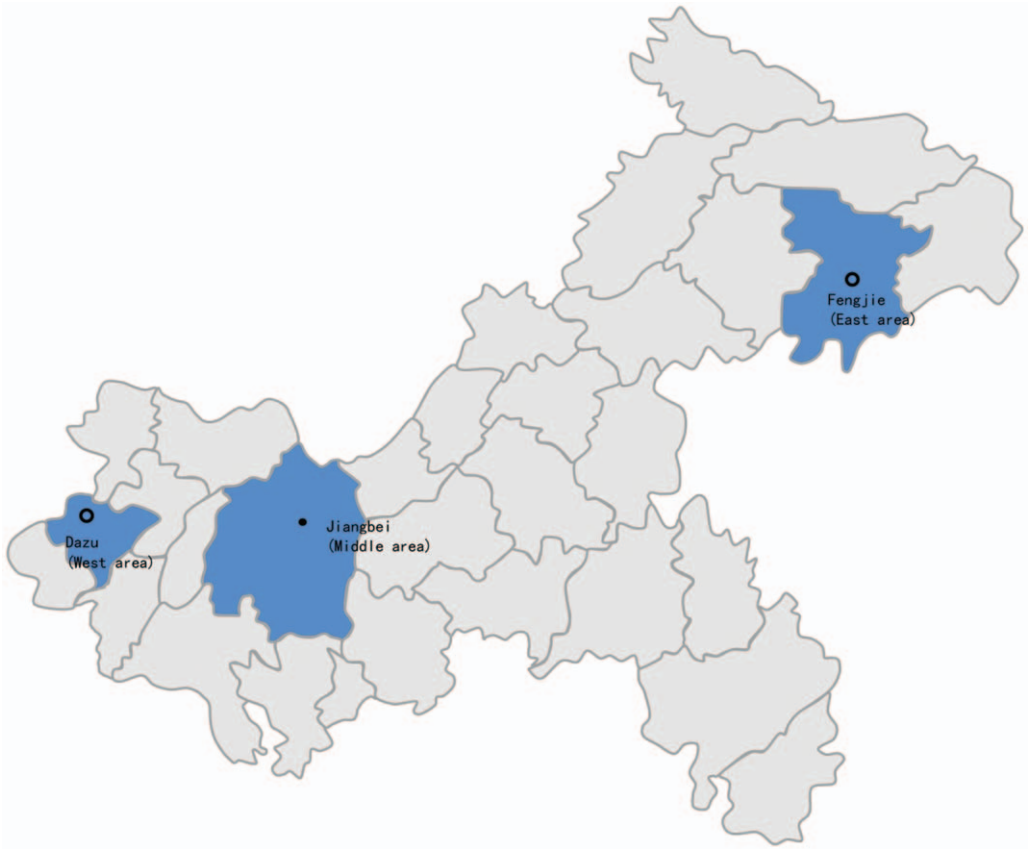

Figure 1. Seroepidemiological investigation sites in Chongqing.

using Bonferroni test to compare the difference between each group. $P < .05$ was considered statistically significant.

2.3. Ethical approval and informed consent

All procedures involving human in this study was granted by the Ethical Committee of Chongqing CDC. All information was collected after the permission of the participants. Verbal informed consent was sought and recorded from each participant. Investigators had explained to participants that their information would only be used to estimate the seroprevalence of polio NA.

3. Results

3.1. Characteristics of the study population

A total of 636 people were enrolled and stratified into seven age groups (<1, 1–2 years, 3–4 years, 5–6 years, 7–14years, 15–19years, 20+ years) and 3 regional groups (middle of Chongqing, east of Chongqing, and west of Chongqing). Among the subjects, 300 were male and 336 were female, with a sex ratio of 1:1.12. 499 subjects had immunization history of polio vaccine, and 137 subjects were uncertain or had no polio immunization history.

3.2. Distribution of PV antibody levels by age

The overall GMTs were 61.14, 66.78, 21.47 for PV1, PV2 and PV3, respectively. The GMTs ranged from 30.42 to 222.86 for PV1, from 31.19 to 183.20 for PV2, and from 13.00 to 57.90 for PV3. The antibody level of 3 polio serotypes declined as age increased, and the differences of GMTs among 3 polio serotypes were significant ($P = .000$; $P = .000$; $P = .000$). Through multiple comparison by the Student-Newman-Keul's(SNK) method, the significant difference of GMTs for PV1 was observed between <1-year group and 1–2 years group, and all the groups above 5 years had significant differences between each other. For PV2, the significant difference of GMTs was mainly found between <1-year group and 1–2-years group, 3–4-years group and 5–6-years group; and all the groups above 7 years had significant differences of GMTs for PV2. The differences of age distribution in GMTs for PV3 was same as GMTs for PV2.

The overall seroprevalences were 93.40%, 96.38% and 91.82% for PV1, PV2, and PV3, respectively. It ranged from 90% to 97.78% for PV1, from 91.11% to 100.00% for PV2, and from 85.56% to 97.78% for PV3 (Table 1). There were significant differences in seroprevalences of 2 polio serotypes (PV2, PV3) by age groups ($P = .002$, $P = .037$) except for PV1 ($P = .459$). The seroprevalence in ≥20-years group was significantly lower than other age groups for PV1 and PV2, and the seroprevalence in the 7–14-years group was lower than other age groups for PV3.

3.3. Distribution of PV antibody levels by location

According to geographical status, the subjects were divided into 3 groups (middle area, eastern area, and western area). For PV1, GMTs were 73.47 (95% CI: 59.83–90.21), 58.40 (95% CI: 46.04–74.08) and 52.83 (95% confidence interval [CI]: 40.94–

Table 1

Antibody GMTs and Seropositivity of P1, P2 and P3 by age.

		PV1		PV2		PV3	
	Number of sample	GMT* (95%CI)	Seropositivity N (%)	GMT† (95%CI)	Seropositivity N (%)	GMT‡ (95%CI)	Seropositivity N (%)
Age group (yrs)							
<1	90	141.5 (94.56–211.7)	81 (90%)	161.3 (122.9–211.6)	88 (97.78%)	45.6 (33.05–62.93)	84 (93.33%)
1~2	90	162.6 (120.2–219.9)	88 (97.78%)	166.3 (127.4–217.1)	88 (97.78%)	51.59 (38.18–69.70)	88 (97.78%)
3~4	92	104.4 (76.05–143.4)	86 (93.48%)	115.2 (93.38–142.1)	92 (100%)	28.15 (21.54–36.80)	87 (94.57%)
5~6	91	54.96 (39.09–77.26)	83 (91.21%)	89.48 (66.51–120.4)	91 (100%)	21.37 (15.82–28.88)	85 (93.41%)
7~14	90	34.30 (25.14–46.79)	87 (96.67%)	31.51 (24.28–40.89)	86 (95.56%)	10.31 (8.011–13.28)	77 (85.56%)
15~19	93	28.40 (20.36–39.63)	86 (92.47%)	27.98 (20.69–37.85)	86 (92.47%)	10.38 (8.228–13.11)	81 (87.10%)
≥20	90	25.20 (18.51–34.31)	83 (92.22%)	24.63 (18.23–33.28)	82 (91.11%)	14.15 (10.64–18.80)	82 (91.11%)
Total	636	61.14 (53.40–70.00)	93.40%	66.78 (59.32–75.18)	613 (96.38%)	21.47 (19.15–24.08)	584 (91.82%)
F/X^2		17.350	5.690	16.219	18.144	10.832	13.286
P		.000	.459	.000	.002	.000	.037

CI = confidence intervals, GMTs = geometric mean titers, PV = poliovirus.

* Significant difference in GMT between < 1 yr group and 1 to 2 yr group, and all the groups above 5 yr for type 1 based on Student-Newman-Keuls test.

† Significant difference in GMT between < 1 yr group and 1 to 2 yr group, 3 to 4 yr group and 5 to 6 yr group, and all the groups above 7 yr age group for type 2 based on Student-Newman-Keuls test.

‡ Significant difference in GMT between < 1 yr group and 1 to 2 yr group,3 to 4 yr group and 5 to 6 yr group, and all the groups above 7 yr age group for type 3 based on Student-Newman-Keuls test.

68.16) in the middle area, eastern area, and western area, respectively; for PV2, GMTs were 66.14 (95% CI: 54.09–80.87), 61.94 (95% CI: 50.77–75.58) and 72.66 (95% CI: 58.58–90.13); for PV3, GMTs were 27.60 (95% CI: 22.47–33.51), 20.38 (95% CI: 16.87–24.62) and 17.53 (95% CI: 14.24–21.58) (Table 2). There was no significant difference of GMTs for each polio serotype among 3 areas.

There were significant differences of seroprevalences for PV1 and PV3 in 3 locations ($P = .002$, $P = .018$) (Table 2). The seroprevalence of PV1 ranged from 86% to 99% among 0–6 years old age group, and from 91% to 97% among≥ 7 years group. Seroprevalence of PV2 was nearly 100% among 0 to 6 years group, and it ranged from 91% to 96% among ≥ 7 years group. For PV3, it ranged from 89% to 97% among 0 to 6 years group, and 87% to 90% among ≥ 7 years group (Fig. 2).

Furthermore, we found there were significant differences of reciprocal titers for PV1 and PV3 in different areas in both 0 to 6 years group and ≥ 7 years group. Distribution of reciprocal titers demonstrates the differences among areas (Fig. 3).

3.4. The quality of AFP surveillance

389 local AFP cases were reported from 2012 to 2016 in Chongqing. The reported incidence of AFP was higher than 1/100,000, which is requested by the China AFP monitoring program. The average day (median) for timely reporting AFP cases was 1 day (0–72d) after patients visited the hospital. The average day (median) for timely investigating AFP cases was 0d (0–40d) after patients reported. In total, the indicators of AFP cases surveillance from 2012 to 2016 showed the monitoring capability in Chongqing for AFP cases were annually improved (Table 3).

4. Discussion

Lower antibody seroprevalences and GMTs were observed for PV3 in each age group. The decrease of seroprevalence for PV3 was also reported in other similar serological studies,[21–24] which might attribute to low content of PV3 in OPV. The seroprevalences of PV1, PV2 and PV3 were all around 90% in each age group, but the GMT for each serotype was significantly lower in older age groups. The preschoolers had highest seroprevalences and GMTs, which were due to EPI and the compulsory vaccination certificate for school admission in China. The GMTs and seroprevalences decreased rapidly from 7 years old and dropped to a relatively stable level in those under 20 years old. The subjects older than 20 years old, who had not participated in the intensified large-scale SIAs in Chongqing, had the lowest seroprevalences. Much more attention should be paid to the polio immunity status of elder age groups. In 2011, 52.38% cases infected by imported WPV from Pakistan were older than 19 years old in Xinjiang,[25] this event also suggested that we should

Table 2

Neutralized antibody of polio in different geographical districts.

		PV1		PV2		PV3	
Location	Number of sample	GMT \(95%CI)	Seropositivity N (%)	GMT (95%CI)	Seropositivity N (%)	GMT (95%CI)	Seropositivity N (%)
M	211	73.47 (59.83–90.21)	203 (96.21%)	66.14 (54.09–80.87)	203 (96.21%)	27.60 (22.47–33.51)	201 (95.26%)
E	212	58.40 (46.04–74.08)	202 (95.28%)	61.94 (50.77–75.58)	208 (98.11%)	20.38 (16.87–24.62)	196 (92.45%)
W	213	52.83 (40.94–68.16)	188 (88.26%)	72.66 (58.58–90.13)	202 (94.84%)	17.53 (14.24–21.58)	187 (87.79%)
Total	636	61.14 (53.40–70.00)	593 (93.24%)	66.78 (59.32–75.18)	613 (96.38)	21.47 (19.15–24.08)	584 (91.82%)
F/X2		0.203	12.723	1.263	3.302	1.836	8.040
P		.816	.002	.283	.192	.160	.018

CI = confidence interval; GMTs = geometric mean titers; PV = poliovirus.

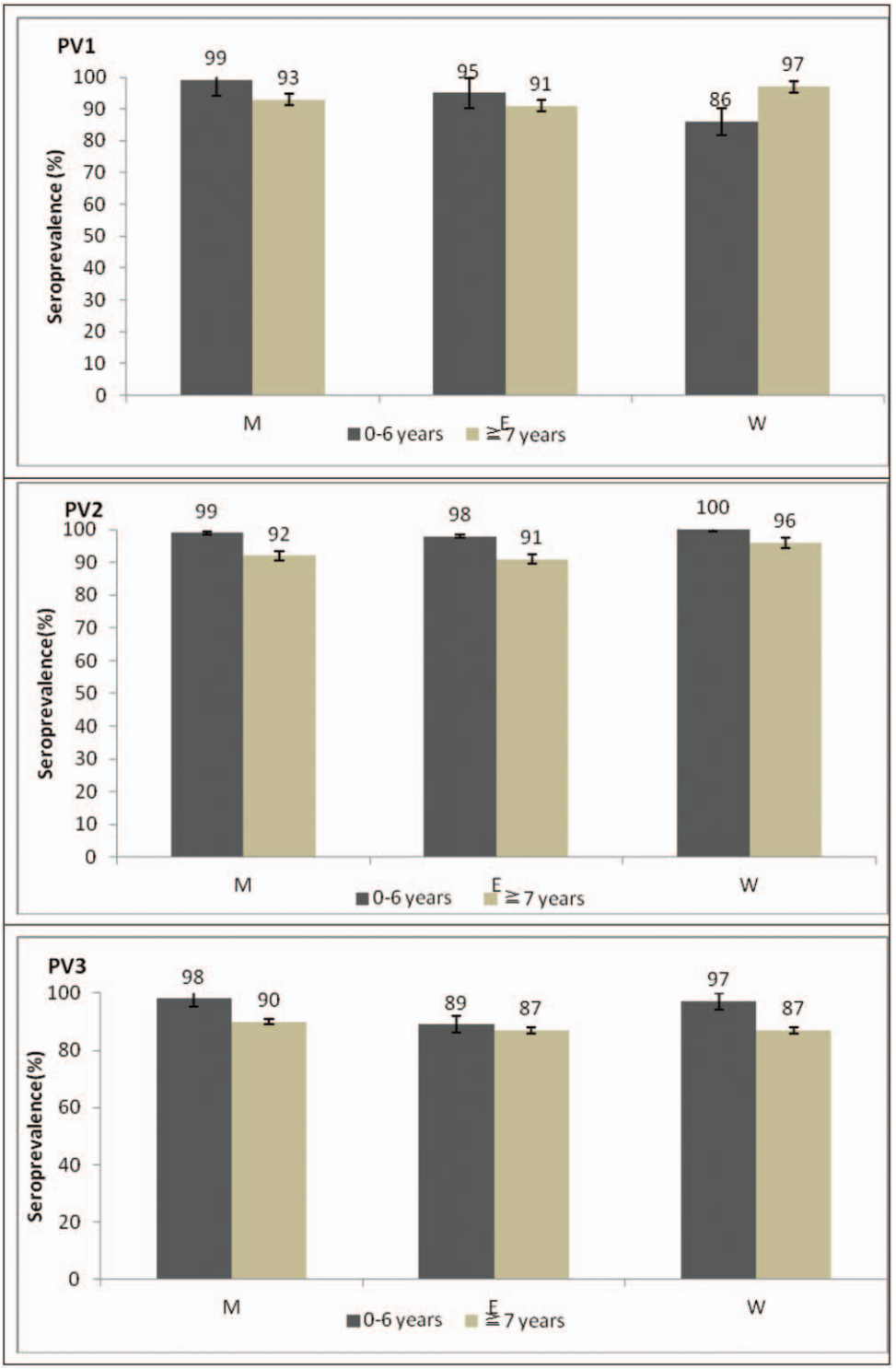

Figure 2. Seroprevalence value reported for each poliovirus serotype, age group, and sampling site.

pay close attention to the immunization status of adolescents and adults other than preschoolers, especially for the susceptible population without immunization history. If we don't expand the age of the target population for SIAs, the antibody levels of polio in older people remain low and this is a risk for us to keep polio free. So, it is suggested that in our routine SIAs for polio vaccine, we should not only immunize children ≤4 years, but also take the older age groups into account.

There was no difference of GMTs for PV1, PV2, and PV3 in 3 areas, and there was no difference in seroprevalence for PV2 in 3 areas. According to the age groups covered by EPI, we divided the participants into 2 age groups of 0 to 6 years old and >7 years

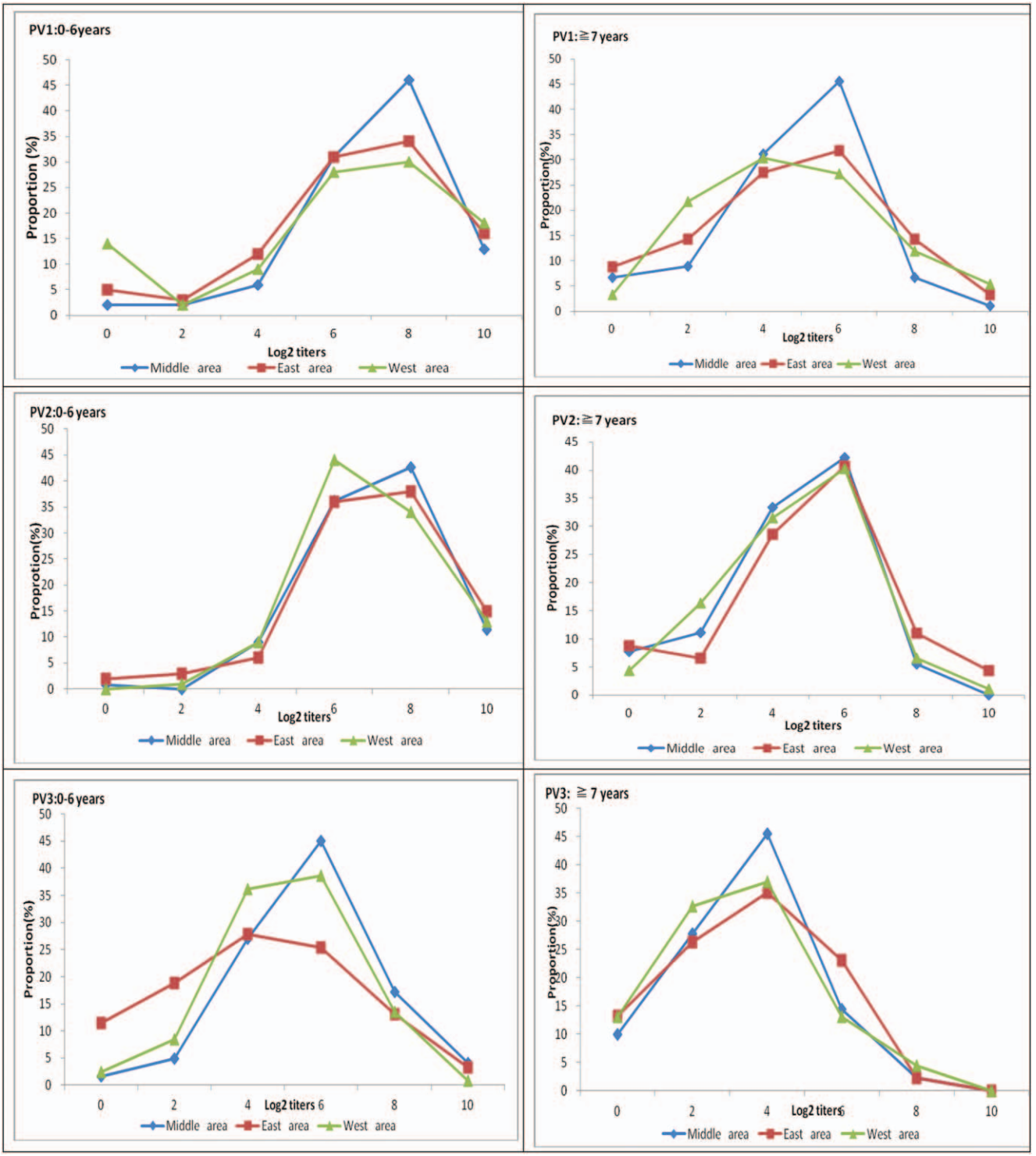

Figure 3. Titer distribution for each poliovirus serotype, age group, and sampling site.

old, we found that 0–6 years group had lower polio antibody titers for PV1 and PV3 in western and eastern Chongqing. Although 0 to 6 years group is covered by EPI and the vaccination rate is higher than 95%, the difference in antibody titers of poliomyelitis varied from region to region. The eastern area in Chongqing with mountainous features has poorer economic conditions, and their vaccination work is carried out by village doctors. Usually they take part-time on vaccination, which is performed less than 3 times a week, even only once a month in remote areas. The western area has better economic geographical condition and intensive immunization services, but antibody titers are still low among young people in western areas. So, to

Table 3

Performance indicators of AFP cases surveillance in Chongqing, 2012-2016.

			Timely reporting		Timely investigating		Collecting adequate stool samples	Timely delivering samples for test	
Year	No. of cases	incidence rates of reported AFP cases (1/100,000)	N (%)	Median	N (%)	Median	N (%)	N (%)	Median
2012	73	1.52	39 (53.42)	1	70 (95.89)	1	62 (84.72)	67 (91.55)	5
2013	82	1.74	31 (37.80)	1.5	80 (97.56)	1	78 (95.12)	78 (95.12)	4
2014	71	1.55	43 (60.56)	1	71 (100)	1	68 (95.89)	68 (95.89)	4
2015	78	1.61	47 (60.26)	1	78 (100)	0	76 (97.37)	74 (94.67)	4
2016	85	1.79	53 (62.35)	0	85 (100)	0	77 (90.59)	83 (97.62)	3
Total	389	1.59	213 (54.76)	1	384 (98.71)	0	361 (92.78)	370 (95.12)	4

AFP = acute flaccid paralysis.

National Poliomyelitis Action Plan: 2003–2010 requires the rate of below indexes reach at 80%.

Timely reporting: AFP cases should be reported in 24 hours.

Timely investigating: AFP cases were timely investigated within 48 hours after cases reported.

Collecting adequate stool samples: Two qualified stool specimens should be collected in 14 days after case reported.

Timely delivering samples for test: AFP cases of stool samples should be delivered to the provincial polio laboratory within 7 days after samples collected.

strengthen the immunity of the entire population, we should carry out SIAs with IPV in Chongqing in time. The result also reminded us that when we explain the immunization level, we should not only evaluate the vaccination rate and service quality, but also assess the quality of vaccination and cold chain which may influence the effectiveness of vaccines.

One limitation in our study is that the sample population investigated in our study was from hospital outpatients, who may not be truly representative of the general population. Notwithstanding, we consider this bias will not be large, because there has been no wild polio case since 1993 in Chongqing, the polio immunity status mostly relates to vaccination, and there is no significant difference in vaccination rates between outpatients and the general population.

5. Conclusion

Chongqing has set up and maintained high and effective population immunity to polio, and the polio immunity status is ready for the new polio immunization schedule. To better protect the whole population against potential VDPV2 threats and prevent the recession of the polio antibody, especially in the older population and immune blank group in the Western Pacific, we should at least introduce 1 or more doses of trivalent IPV for the older population. We should not only concern the vaccination rate of polio vaccines but also to evaluate the vaccination quality of vaccines.

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Author contributions

Qing Wang, Rong Rong, and Wenge Tang planned the study. Jiawei Xu, Yuanyuan Zhang and Shanshan Kuang were in chargeo of data collection and blood samples collection. Jiawei Xu carried out the immunoassays and performed the statistical analysis. Jiawei Xu drafted and Yuanyuan Zhang edited the manuscript. Yuanyuan Zhang participated in data analysisted. All authors read and approved the final manuscript.

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