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Cover Photo: On January 30, a total of 83 members from 20 teams from 17 provincial CDCs and China CDC were quickly dispatched to 17 prefectures in Hubei Province to start support for local laboratory testing for 2019-nCoV.

Preplanned Studies

Pathogen Spectrum of Hand, Foot, and Mouth Disease Based on Laboratory Surveillance — China, 2018

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Summary

What is already known about this topic?

Enterovirus 71 (EV-A71) is the main causative pathogen for severe and fatal patients with Hand, Foot, and Mouth Disease (HFMD) in mainland China from 2008 to 2017. Non-EV-A71 and non-CV-A16 (other enterovirus) serotypes were the major causative-serotypes for mild HFMD in years of 2013, 2015, and 2017.

What is added by this report?

In 2018, other enterovirus serotypes replaced EV-A71 for the first time as the major cause of severe HFMD with a proportion of 70.7%. However, at the national level, only a small proportion of the other enterovirus serotypes were further identified as CV-A6 and CV-A10.

What are the limitations for public health practice?

Further identification of other enterovirus serotypes is highly recommended for provincial CDCs, especially for severe HFMD. Studies contributing to a multivalent vaccine for HFMD should be prioritized.

Hand, foot, and mouth disease (HFMD) is a common pediatric disease affecting children's health in China caused by various human enteroviruses (*1*). Enterovirus 71 (EV-A71) and Coxsackievirus A16 (CV-A16) are the most common causative serotypes (*1–2*). EV-A71 is the most frequently reported serotype responsible for severe and fatal HFMD (*1*), but other enterovirus serotypes, such as enterovirus A species, CV-A6, and CV-A10, can also lead to neurological complications (*3–4*). The results of surveillance data indicate that EV-A71 is the predominant serotype in 2008 to 2012 and 2014, and other enterovirus serotypes are predominant in 2013, 2015, and 2017 (*5*). The proportion of other enterovirus serotypes is dramatically increased in patients with mild conditions of HFMD after 2013 (*5*). This study aims to explore the spectrum of enterovirus serotypes by clinical severity in 2018, which will provide the scientific evidence for constructing HFMD control and prevention strategies in China.

The pathogen surveillance is a part of HFMD national surveillance routine work, which was launched in 31 provincial-level administrative divisions (PLADs) in China from 2008 (*6*). Pathogen surveillance data of HFMD is required to be reported monthly to the Chinese Center for Disease Control and Prevention (China CDC) via email in all 31 PLADs. The information includes basic demographic information (sex, age, and address), disease severity (mild or severe), specimen types, death status, date of symptoms onset, date of specimen collection, date of sample detection, sample detection methods, date of death, and the identified enterovirus serotypes.

To comply with the HFMD national surveillance guidelines, samples including throat swabs, anal swabs, or fecal samples were collected at the county-level from the first five patients with mild and probable HFMD who visited hospital outpatient departments every month, and specimens from all severe and fatal cases are required to be collected and tested. City-level CDC laboratories are responsible for identifying the enterovirus serotypes by real-time PCR or virus isolation (*6*). We classified the test results into four categories: enterovirus negative, EV-A71 positive, CV-A16 positive, and positive for other enterovirus (non-EV-A71 and non-CV-A16) without further serotype identification. The enterovirus serotypes of CV-A6 and CV-A10 were further identified in 18 PLADs*.

A total of 30 PLADs reported virological data of HFMD to China CDC in 2018. To avoid deviation in the study results, we excluded the incomplete data from two PLADs and unqualified data from one PLAD. The HFMD patients whose onset dates were

* 18 PLADs including administrative divisions from Anhui, Beijing, Gansu, Guangdong, Guizhou, Hebei, Henan, Hunan, Jiangxi, Liaoning, Qinghai, Shanxi, ShaanXi, Shanghai, Tianjin, Tibet, Xinjiang, and Zhejiang.

from January 1, 2018 to December 31, 2018 of 27 PLADs were finally enrolled in the study. Descriptive epidemiological method was used to analyze the data, and all analyses were conducted in SAS (version 9.3, SAS Institute Inc.).

A total of 116,290 HFMD probable and laboratory confirmed HFMD cases were reported from January 1, 2018 to December 31, 2018 in 27 PLADs. The reported number of mild, severe, and fatal cases was 114,297, 1,780, and 7, respectively, and 206 cases were missing the disease severity variable. The epidemic peak was from May to June (Figure 1A, B). Children aged under 5 years were the mainly infected population with a proportion of 86.7%. Among the total cases, the male-to-female ratio was 1.5∶1.

The number of laboratory-confirmed cases was 80,793, and the whole enterovirus detection positive rate was 69.5%. The enterovirus positive rate of mild, severe, and fatal cases was 69.3%, 80.7%, and 71.4%, respectively. Excluding Tibet (37.3%), the enterovirus detection positive rate at the provincial level was higher than 50% in 26 PLADs.

Among laboratory-confirmed cases, the proportion of EV-A71, CV-16, and other enterovirus serotypes was 4.8% (3,913), 25.6% (20,709), and 69.3% (56,002), respectively (Figure 1B, C). In cases that were positive for other enterovirus serotypes, 13.5% and 1.2% were further identified as CV-A6 and CV-A10 infections. 0.2% of cases were identified as co-infections, including 112 as EV-A71&CV-A16, 2 of CV-A16&CV-A10, 20 of CV-A6&CV-A10, 7 of CV-A6&EV-A71, and 28 of CV-A6&CV-A16 infection (Figure 1B, C). At the provincial level, 2 PLADs were predominantly identified as CV-A16, 4 PLADs were predominantly identified as CV-A6, and 21 PLADs were predominantly identified as other enterovirus serotypes (for the enterovirus geographic distribution, Supplementary Figure S1 available in http://weekly.chinacdc.cn/).

In mild cases, 69.3% of the cases were infected by other enterovirus serotypes, and the proportion of EV-A71, CV-A16, and co-infection was 4.6%, 25.9%, and 0.2%, respectively. In severe cases, 70.7% were infected by other enterovirus serotypes, while the proportion of EV-A71, which was previously the predominant serotype, was only 15.3%. The proportion of CV-A16 and co-infection was 13.7% and 0.3%, respectively.

The age profile of laboratory-confirmed cases indicated that both mild and severe cases were mainly distributed in age groups of 12–24 months and 25–59 months with proportions of 49.0%, 27.3%, for mild cases, respectively, and 63.8%, 19.8%, for severe cases, respectively. Fatal cases occurred in the age groups of 6–11 months (20.0%) and 12–24 months (80.0%). The age distribution of probable cases showed similar compositions with the laboratory-confirmed cases (Figure 2A, C, E).

Other enterovirus serotypes were the predominant serotypes in both mild and severe cases in age groups aged under 5 years. In mild cases, CV-A6 was the second major serotype in patients aged less than 6 months, while CV-A16 was the second major serotype in age groups 6 months and older, accounting for 26.1% of cases (Figure 2B).

In severe cases, CV-A6 was mainly distributed in age groups of under 24 months years with a proportion of 69.7%. All CV-A10 infected cases were distributed in the age groups of 12–24 months. A total of 4 severe cases were identified as EV-A71&CV-A16 co-infection, including 1 patient aged 24 months and 3 patients aged 36 months (Figure 2D).

A total of 5 laboratory-confirmed case fatalities were reported. Of the 5, 3 patients had been infected by EV-A71 and were in the age groups of 12–24 months. 2 patients had been infected by CV-A16 and were in the age groups of 6–11 months and 12–24 months (Figure 2F).

Discussion

A total of 116,290 probable and laboratory-confirmed HFMD cases were reported from 27 provincial-level CDCs in 2018. The number of laboratory-confirmed cases was 80,793 and the enterovirus detection positive rate was 69.5%. Patients with HFMD were mainly aged under five years (87.6%). The epidemic peak was from May to June, and other enterovirus serotypes were the predominant serotype, mainly circulating in 21 PLADs and accounting for 69.3% of mild cases and 70.7% of severe cases in 2018. EV-A71 was still the predominant serotype in fatal cases.

The demographic characteristics of age and sex of HFMD in 2018 were similar with results we published in *Lancet* in 2014 (*2*). The temporal pattern also did not change in 2018 when compared to surveillance results of previous years (*2*). A remarkable change in 2018 was the replacement of enterovirus serotypes in patients with severe HFMD. EV-A71 was always the

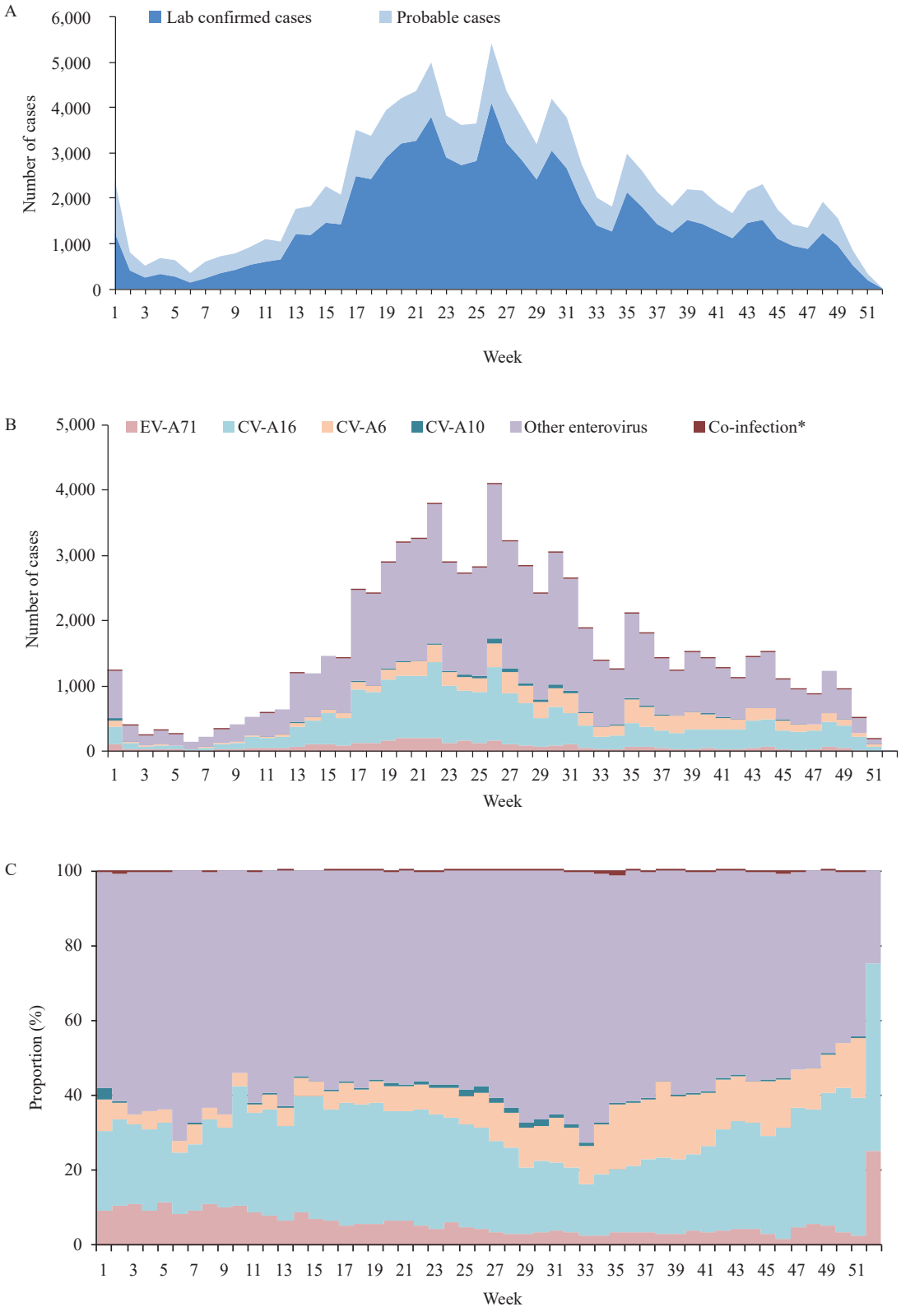

FIGURE 1. Enterovirus tested negative and laboratory-confirmed HFMD in mainland China, 2018. (A) Time series of weekly probable and laboratory-confirmed patients with HFMD. (B) Time series of weekly laboratory-confirmed patients with HFMD by enterovirus serotypes. (C) Weekly proportions of laboratory-confirmed patients with HFMD by enterovirus serotype. *Co-infection included EV-A71&CV-A16, CV-A16&CV-A10, CV-A6&CV-A10, CV-A6&EV-A71, and CV-A6&CV-A16.

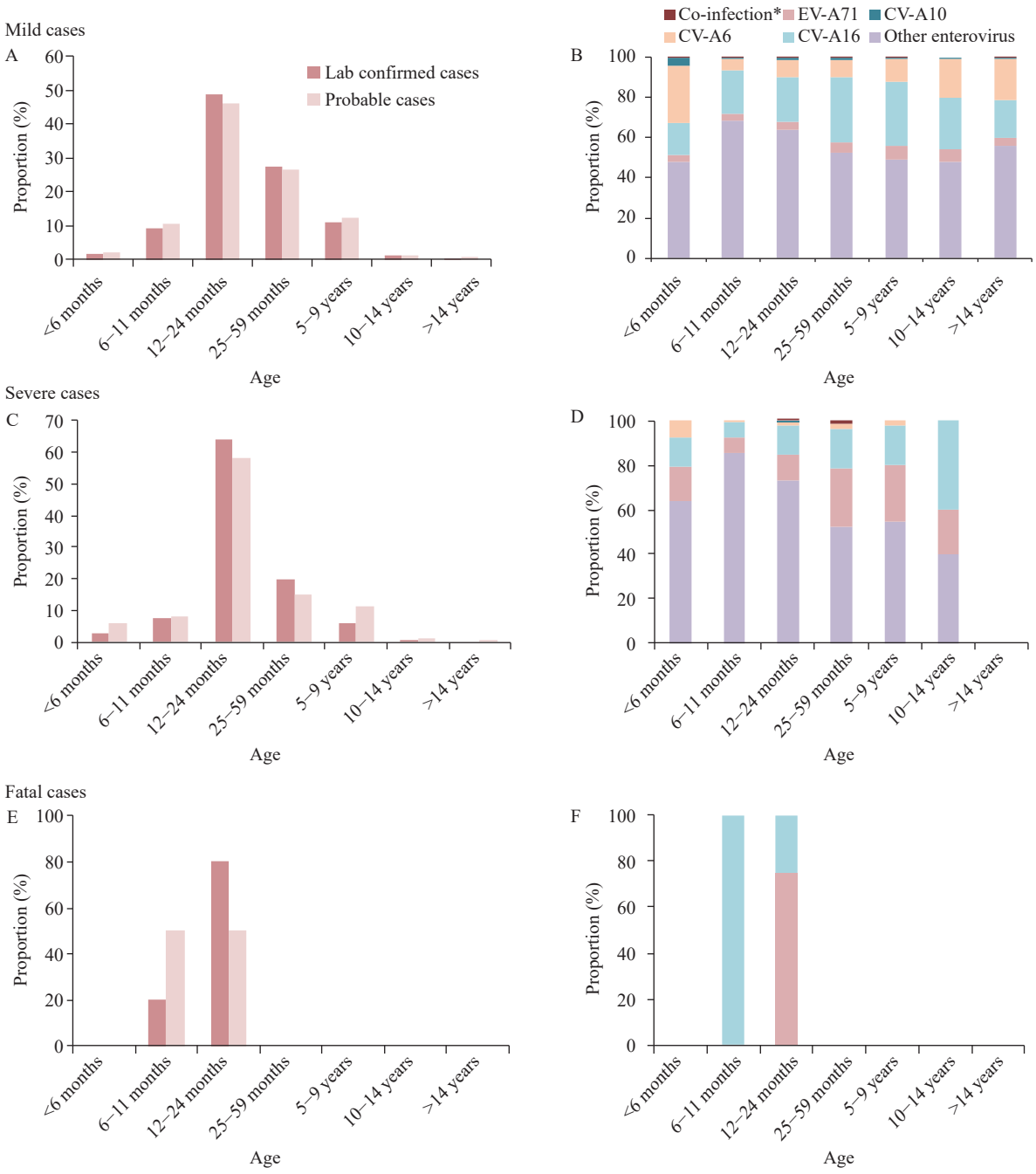

FIGURE 2. Age profile and enterovirus serotypes distribution in the laboratory-confirmed HFMD based on clinical severity in mainland China, 2018. (A)&(B), Mild cases; (C)&(D), Severe cases; (E)&(F), Fatal cases.
*Co-infection included EV-A71&CV-A16, CV-A16&CV-A10, CV-A6&CV-A10, CV-A6&EV-A71 and CV-A6&CV-A16 in the mild cases. Among severe cases, Co-infection refers to EV-A71&CV-A16.

main causative serotype for severe and fatal HFMD, which has accounted for 70.0% of severe and 92.3% of fatal cases from 2008 to 2017 (*5*). In 2018, other enterovirus serotypes were the predominant serotypes with a proportion of 69.3%, which caused 69.3% of mild cases and 70.7% of severe cases. The epidemic activities of EV-A71 and CV-A16 were very low, especially for the EV-A71, which only accounted for a proportion of 4.8%. Although EV-71 being replaced by other enterovirus serotypes had been observed before, this marks the first time other enterovirus serotypes became the predominant serotype for severe HFMD since HFMD was classified as a notifiable disease in China in 2008.

CV-A6 and CV-A10 circulations have been reported from several PLADs in China, such as Hunan and

Hebei (*7–8*). Four PLADs were affected by CV-A6 the most in 2018, however, at the national level, the CV-A6 and CV-10 were not required to be identified. Among positive cases due to other enterovirus serotypes, only 13.5% and 1.2% of the cases were identified as CV-A6 and CV-A10. Most of the other enterovirus serotype infected cases, especially for the severe cases (96.5%), were not further to be identified. Considering age as a risk factor for HFMD, we find that the severity risk is higher in younger age groups and decreases with increasing age (*9*). Our results indicate CV-A6 and CV-A10 are the main infection for children aged 2 years and under in the severe cases. In addition, CV-A6 and CV-A10 are also reported to potentially cause neurological complications such as encephalitis and meningitis (*3–4*). Therefore, including CV-A6 and CV-A10 into the routine detection serotypes could be largely beneficial.

A small proportion of co-infections was found both in mild and severe HFMD. The co-infection of severe HFMD was also reported from an outbreak analysis of Shandong province in 2012 (*10*). The results of co-infection were needed to be further validated, since the detection method was critical for co-infection identification. The relationship between co-infection and HFMD, especially the pathogenesis of HFMD severity, also requires further study.

This study is subject to at least a few limitations. Although we provided the enterovirus serotype spectrum in 2018, the spectrum was not complete at the national level due to a lack of pathogen data in four PLADs. Only a small part of the other enterovirus serotypes were further identified as CV-A6 or CV-A10, and a large proportion of other enterovirus serotypes were still unknown. Another limitation was that the proportion of EV-A 71 or other enterovirus serotypes might be underestimated because 0.2% of the data lacked disease severity information. Due to the limited information we collected, we cannot explain the shift in enterovirus serotypes in patients with severe HFMD.

Therefore, further identification of other enterovirus serotypes is highly recommended for provincial CDCs, especially for severe HFMD cases. The testing of CV-A6 and CV-A10 should be included in routine HFMD surveillance and researches contributing to a multivalent vaccine for HFMD should be prioritized.

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Outbreak Reports

Detection and Initial Response to a Type 2 Vaccine-Derived Poliovirus — Sichuan Province, China, 2019

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Summary

What is already known about this topic?

After the type 2 strain of the live, attenuated poliovirus vaccine was withdrawn globally in 2016, any identification of a type 2 poliovirus is a Public Health Emergency of International Concern. A vaccine-derived type 2 poliovirus (VDPV2) was identified in Sichuan, prompting an urgent, comprehensive investigation and response.

What is added by this report?

Type 2 monovalent, live, attenuated oral poliovirus vaccine (mOPV2) is being used to respond to the numerous VDPV2 outbreaks seen around the world. In contrast, the response in Sichuan used Sabin strain inactivated poliovirus (sIPV) to stop circulation of the VDPV2. In the 6 months following the vaccination response, there have been no VDPV2s detected in Sichuan, despite extensive search.

What are the implications for public health practices?

Further search for the VDPV2 must continue in order to determine whether transmission has been stopped. The ongoing investigation and response to the Sichuan VDPV2 is providing evidence to the Global Polio Eradication Initiative on managing VDPV2 outbreaks.

Background

In 2015, the World Health Organization (WHO) declared that type 2 wild poliovirus was eradicated. In April 2016, the type 2 oral poliovirus vaccine (OPV) strain was withdrawn globally from trivalent live attenuated oral poliovirus vaccine (tOPV) to avoid the inherent risk of seeding type 2 vaccine-derived polioviruses (VDPV2). China withdrew OPV2 in synchrony with other tOPV-using countries, changing the routine immunization schedule to one dose of inactivated polio vaccine (IPV) followed by three doses of bivalent (I+III) OPV (*1*). After OPV2 withdrawal from all countries, routine protection of subsequent birth cohorts from type 2 polioviruses only comes from IPV, which is trivalent. A very small number of VDPV2 outbreaks were anticipated following OPV2 withdrawal, and these would have to be stopped with monovalent OPV2. The detection of any type 2 poliovirus (wild, vaccine-derived, or Sabin) in any sample from any source is generally considered to be a global public health emergency (*2*), necessitating urgent investigation and a comprehensive response.

In June 2019, VDPV2 was detected in stool specimens from an acute flaccid paralysis (AFP) case in Liangshan Prefecture, Sichuan Province. The Chinese Center for Disease Control and Prevention (China CDC) joined Sichuan provincial and local CDCs to investigate and respond. We report investigation results and responses to date.

Investigation

The AFP case was of a 4-year-old boy born in November 2014 in a remote village of Leibo county, Liangshan Prefecture, Sichuan Province (Figure 1). Illness onset was April 25, 2019, when both of his legs and his left arm were found to be paralyzed 7 days after symptoms first appeared. By vaccination record and the parents' recall, the child had received tOPV in March 2015 and May of 2015, approximately one year prior to the switch from tOPV to bOPV.

Stool specimens were collected on May 17 and 18, 2019. The provincial CDC laboratory found a type 2 poliovirus; China CDC confirmed the VDPV2 and determined it had 28 nucleotide changes from the vaccine strain and shared 9 nucleotide changes with a VDPV2 isolated from sewage in Urumchi, Xinjiang Autonomous Region on April 18, 2018 (the Xinjiang VDPV2 had 13 nucleotide changes from the vaccine strain) (*3*). The child recovered without residual

paralysis and was discharged from the hospital. His subsequent stool specimens were negative for VDPV2 (Table 1).

We tested stool specimens for poliovirus from children under 5 years old in the affected child's neighborhood and village and the hospital that treated

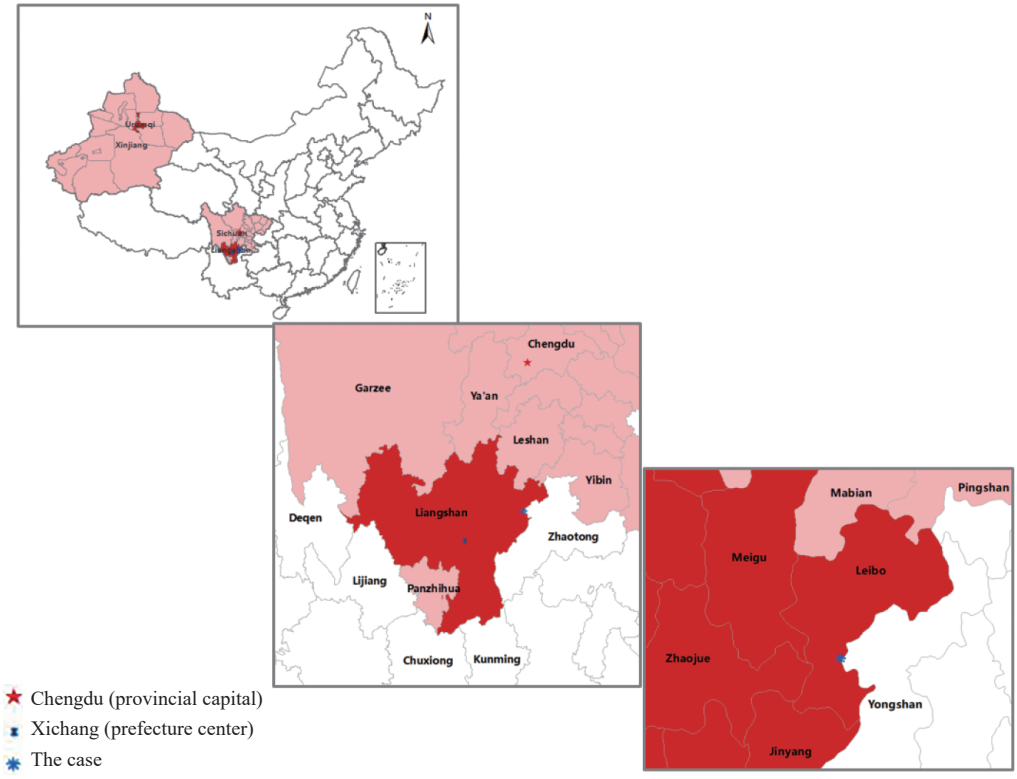

FIGURE 1. Location of the 2 VDPV2 events - Sichuan (2019) and Xinjiang (2018).

TABLE 1. Stool sample results from the acute flaccid paralysis (AFP) case, his contacts, and one other child.

Sample		AFP case	Contact 1	Contact 2	Healthy child
1st	Collection date	2019.5.7	2019.6.14	2019.6.27	2019.8.18
	Isolation result	PV type 2	PV type 2	PV type 2	PV type 2
	Nucleotide changes*	28	27	33	27
2nd	Collection date	2019.5.18	2019.6.27	2019.7.7	2019.9.18
	Isolation result	PV type 2	NPEV	NPEV	Negative
	Nucleotide changes	28	–†	–†	–†
3th	Collection date	2019.6.17	2019.7.7	2019.7.15	2019.9.25
	Isolation result	NPEV	NPEV	Negative	Negative
4th	Collection date	2019.6.22	2019.7.15	2019.7.24	2019.10.9
	Isolation result	Negative	Negative	Negative	Negative
5th	Collection date	2019.6.30	2019.7.24	–§	2019.10.18
	Isolation result	NPEV	Negative	–§	Negative
6th	Collection date	2019.7.7	–§	–§	–§
	Isolation result	NPEV	–§	–§	–§

Abreviation: PV=Poliovirus, NPEV=Non-polio enterovirus.
* Nucleotide changes from vaccine strain.
† Because no poliovirus was detected, no further comparisons were necessary.
§ Two negative results indicated that no further specimens and testing were needed.

him. Among 160 healthy children investigated, specimens from 2 children who lived 4 kilometers from the residence of the AFP case were positive for VDPV2s—one with 27 nucleotide changes and the other with 33 changes. We detected another VDPV2, with 27 nucleotide changes, in a healthy child in Leibo county who lived 5.5 kilometers from the initial child during investigation of 300 other healthy children (Table 1).

We assessed polio vaccine coverage in the village and surrounding townships among 88 children 1–5 years old in the village and 164 children <6 years old in 4 surrounding townships. In the village, 53.4% (47/88) had no history of polio vaccination, 35.2% (31/88) received 1 dose, 6.8% (6/88) received 2 doses, 3.4% (3/88) received 3 doses, and 1.1% (1/88) received 4 doses. In the surrounding townships, 65.0% (106/164) received 3 or more doses of polio vaccine.

We conducted retrospective searches for AFP cases in Liangshan on June 12 and five surrounding prefectures on June 17. The provincial medical investigation team reviewed 31,631,487 in-patient and out-patient records from 778 hospitals, going back to May 1, 2016. Among the 279 AFP cases found, 10 had not been reported previously. These newly-identified AFP cases were reviewed by provincial polio experts, and polio was diagnostically excluded from all 10. AFP "zero case reporting", which is requiring absence of cases to be reported every day to ensure complete reporting of any cases, was started on June 21 (August 19 in Aba) to enhance sensitivity of surveillance in Liangshan and its 6 surrounding prefectures.

Response and Further Search

Two non-selective Supplementary Immunization Activities (SIAs) with Sabin-strain IPV (sIPV) were conducted in Liangshan Prefecture—one in June and a second in August of 2019—targeting children 2 months to 5 years old (born between 1 July 2013 and 30 April 2019). SIA vaccination rates were 95.6% (30,424/31,812, first SIA) and 98.3% (30,751/31,283, second SIA) in Leibo County. In Liangshan Prefecture, over 450 thousand children received sIPV in each SIA, with vaccination rates of 97.4% (457,719/469,964) and 98.8% (488,803/494,920).

In the six surrounding prefectures (Panzhihua, Leshan, Yibin, Ya'an, Aba, and Ganzi), we conducted one selective sIPV SIA (June–October) for children 2 months to 5 years old without documentary proof of any type 2 polio vaccination. We conducted one non-selective sIPV SIA in December, similar to the Liangshan Prefecture SIA. In total, 34,000 children were vaccinated in the selective sIPV SIAs and 780,000 children were vaccinated in the non-selective sIPV SIAs.

After testing stool samples from close contacts, 300 additional stool samples were collected between August 13 and 21 from 6 sites—3 counties bordering Leibo county and 3 townships bordering the index patient's township. Each site collected 50 samples (from 1 to 5-year-olds; 10 samples from each year cohort), and one VDPV2 was found.

We conducted environmental surveillance (ES) for poliovirus in four prefectures (Liangshan, Yibin, Aba, and Chengdu—guided by risk assessments), and 2 samples were collected in each site every month. ES has been consistently negative through December 2019, and from August 2019 to date, no type 2 polioviruses have been detected in any surveillance. We conducted serological surveys for poliovirus immunity prior to the SIAs, and the results are pending.

Discussion

According to WHO (*4*), there have been 47 cVDPV2 outbreaks in 20 countries since the switch from tOPV to bOPV in April 2016. Some of these outbreaks involve more than one country. On average, 2–3 VDPV events happen in China every year (*5*). The Sichuan VDPV2 is the first VDPV2 that has been discovered in an AFP case since the polio vaccination switch on May 1, 2016. One VDPV2 was isolated from environmental samples in Xinjiang (April 2018) (*3*), but no VDPV2s were found among AFP cases in Xinjiang.

This VDPV2 outbreak followed cessation of OPV2, but despite careful investigation, we were unable to identify the source of transmission. Similarly, a putative epidemiological link between the Sichuan and Xinjiang viruses has not been established. We believe that the VDPV2 likely circulated for three years in Liangshan enabled by weak routine immunization in this remote county, which is evidenced by the vaccination coverage survey described above.

Using sIPV or requesting monovalent mOPV2 from the WHO to attempt to stop the outbreak was a difficult choice. Most countries with cVDPV2 outbreaks used mOPV2 to control their outbreaks. However, the relative low gut immunity to type 2 poliovirus following the cessation of OPV2 vaccination

carries the implicit risk that Sabin-strain lineages can survive to become cVDPV2s in the future, necessitating outbreak response with monovalent OPV2 and thereby potentially seeding new lineages (*6*). Based on current evidence, the sIPV campaigns in Sichuan Province appear to have prevented further VDPV2 spread; however, it is still uncertain whether this IPV-only strategy will completely stop transmission. We must sustain intensive AFP and environmental surveillance to guide any possible further response to this event. Experience and data from this outbreak and our use of an sIPV response can augment the growing evidence base of the Global Polio Eradication Initiative for managing VDPV2 outbreaks.

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Perspectives

Why Have cVDPV2 Outbreaks Increased Globally After the Polio Immunization Strategy Switch: Challenges for the Polio Eradication Endgame

Huaqing Wang[1,#]

Since the World Health Assembly (WHA) set the goal of polio eradication in 1988, the Global Polio Eradication Initiative (GPEI) has reduced the global incidence of polio by more than 99%, and the number of countries with endemic polio decreased from 125 countries to 3. Except for Afghanistan, Pakistan, and Nigeria, wild poliovirus (WPV) transmission has been confirmed to have been interrupted globally. Thanks to the polio eradication program, more than 10 million people are able to walk today who would have been paralyzed by polio had the initiative not been undertaken (*1*–*2*). In September 2015, WHO declared eradication of polio caused by the wild poliovirus type 2 (WPV2) (*3*–*5*), and in October 2019, WHO announced the eradication of polio caused by wild poliovirus type 3 (*6*). After 40 years of effort, polio eradication has made great progress; we are in the final stage towards a polio-free world (*7*–*8*).

However, eradication of polio means eradication of all polioviruses—not only wild poliovirus, but also vaccine-derived polioviruses (VDPV) and the occurrence of vaccine-associated paralytic poliomyelitis (VAPP). In 1999–2000, GPEI realized that VDPVs could cause outbreaks of polio, similar to wild virus outbreaks (*1*). Although the last WPV2 had been seen in 1999, more than 90% of outbreaks that were caused by circulating VDPVs (cVDPV) were caused by type 2 vaccine-derived polioviruses (*1*) and 40% of VAPP was caused by type 2 oral poliovirus vaccine (OPV2) (*3*).

Because wild type 2 poliovirus had apparently been eradicated globally, but OPV2 was causing polio, in October 2015, the WHO Strategic Advisory Group of Experts on Immunization (SAGE), reviewed the epidemiology of type 2 vaccine-derived polioviruses (VDPV2) against the criteria of OPV cessation and recommended a globally-coordinated withdrawal of OPV2 among all OPV-using countries in 2016. SAGE recommended switching from the use of trivalent OPV (tOPV) to a type 1 and type 3 bivalent OPV (bOPV) and introducing at least one dose of inactivated polio vaccine (IPV) into routine immunization schedules (*4*) to reduce the occurrence and ultimately eliminate all VDPV2s.

Unfortunately, rather than decreasing, the number of cVDPV2 outbreaks increased significantly after the tOPV-to-bOPV switch. Although there were only two countries with cVDPV2 outbreaks in 2017, 96 cases were reported—the largest number since 2010 (excluding 2019) (*9*–*10*). The number of countries with cVDPV2 outbreaks increased to 5 in 2018 with 71 cases reported and to 15 countries with 251 reported cases in 2019 (reported by January 14, 2020). The number of reported cases and the number of cVDPV2 virus strains isolated from people and from the environment reached the highest level in history (*10*). The 2017 cVDPV2 outbreak in Syria lasted for more than half a year with 74 cases reported (*11*); a cVDPV2 outbreak in the Democratic Republic of the Congo (DRC) was discovered in 2017 and has continued to date with 105 cases reported—63 of them in 2019 (*10*,*12*). A large outbreak in 2019 in Angola comprised 88 cVDPV2 cases (*10*).

In short, after the tOPV to bOPV switch, the unanticipated increase in cVDPV2 outbreaks and positive environmental samples has made the VDPV2 situation significantly more challenging than the expectation prior to OPV2 cessation.

Why is that? Based on analysis of existing data, I believe that there are seven reasons.

First, the risk of cVDPV2 outbreaks after the switch was underestimated. In October 2015, SAGE confirmed the switch date as all readiness criteria had been met. Risk assessments showed that continued use of type-2-containing tOPV posed a greater risk to public health than withdrawal of OPV2, even though introduction of a dose of IPV would be delayed in some OPV-using countries due to supply constraints (*4*). Although risk of cVDPV2 transmission after the tOPV-to-bOPV switch was anticipated, it was believed that this risk was greatest during the first six months

after the switch. Since 2014, risk of cVDPV2 transmission was believed to be greatest in Nigeria and Pakistan, while risk in other parts of the world was considered to be of lesser magnitude (*4*,*13*). According to one modelling study, cVDPV2s were predicted to be gone within a year and a half of OPV2 cessation and the number of cVDPV2 transmissions would be limited (*14*). Having to rely on underestimated modelling shows limitations and challenges for polio eradication strategy decision making.

Second, Supplementary Immunization Activities (SIAs) were not conducted in some areas that had low routine vaccination coverage before the tOPV-to-bOPV switch. Two mathematical modelling studies demonstrated that in order to reduce risk of cVDPV2 outbreaks in low-vaccine-coverage regions, it was important to establish high population immunity against type 2 polio virus through high quality tOPV SIAs conducted before the switch (*14*–*15*). However, pre-switch tOPV coverage in Syria was reported to be about 65% (*16*), and actual coverage before the Syrian cVDPV2 outbreak was less than 50% (*11*). Similar low-coverage situations occurred in Nigeria (*17*), Central Africa, and Somalia, where coverage ranged from 30% to 60% and cVDPV2 outbreaks occurred after the switch (*16*). Although DR Congo reported high tOPV coverage of 90% (*16*), a 2017-2018 cVDPV2 outbreak showed that children living in affected areas had not received good routine immunization services or supplementary vaccination with tOPV before switching OPVs (*18*).

Third, OPV2 cessation from the switch weakened population immunity against type 2 poliovirus, in part because of a global shortage of IPV, but also because of the different abilities of OPV and IPV to induce intestinal immunity. In countries that had cVDPV2 outbreaks after the switch— especially countries with many cases—preexisting type 2 poliovirus population susceptibility due to low coverage, augmented with new birth cohorts that received bOPV rather than tOPV, has resulted in sizeable populations with little intestinal immunity to stop type 2 virus transmission, leading to cVDPV2 circulation. Since IPV produces little intestinal immunity, children born after OPV2 cessation who receive all of their type 2 protection from IPV may not have sufficient intestinal mucosal immunity (*19*–*20*) to interrupt transmission of type 2 poliovirus (*17*,*21*).

Although one dose of IPV is unable to establish an effective intestinal immunity barrier to prevent the spread of cVDPV2s, it can mitigate the risk of cVDPV infection and prevent paralysis from the poliovirus vaccine. However, a global shortage of IPV after the switch worsened the situation. WHO data show low coverage globally with one dose of IPV—about 50% in 2016, 60% in 2017, and only 72% in 2018 (*22*). Prior to the tOPV-to-bOPV switch in April 2016, only 94 of the 126 tOPV-using countries had introduced IPV. Rapidly increasing demand for IPV, with lower-than-anticipated supply, led to global shortages (*23*) to the extent that UNICEF was able to supply less than 50% of the IPV demand in 2016 and 2017 and some countries had no IPV available at all after the switch (*24*–*25*). At the end of 2018, there were still countries that lacked IPV (*22*).

Furthermore, one dose of IPV, either Sabin IPV or Salk IPV, produces limited immune protection. A domestic study showed that seroconversion after one dose of Sabin IPV was 62% (93% for 2 doses and 99% for 3 doses) (*26*). Similar results were also found for Salk IPV (*27*–*29*). OPV-only countries that introduce a single dose of IPV at 14 or 16 weeks may protect only about half of the population from type 2 polio (*29*).

Fourth, emergency use of monovalent OPV2 (mOPV2) to stop cVDPV2 outbreaks can seed type 2 virus and increase risk of transmission of VDPV2 and future resource needs. When a large cVDPV2 outbreak occurs, an mOPV2 campaign is a critical intervention to interrupt transmission. Such vaccination campaigns must be of high quality, with several rounds that yield high vaccination coverage. Low-coverage campaigns or campaign with fewer rounds may neither stop cVDPV2 transmission nor interrupt transmission of mOPV2 itself, potentially seeding additional cVDPV2 outbreaks (*15*,*30*). Genetic sequence analyses showed related VDPV2s occurred 1–2 years after the tOPV/bOPV switch, indicating that these VDPV2s probably came from mOPV emergency campaigns responding to VDPV2 outbreaks (*12*,*30*–*31*).

Fifth, VDPV2s can have a long-term existence and sustain transmission silently. The possibility of long-term replication and silent transmission VDPV2s after the switch has been demonstrated through genetic sequence analysis (*31*). Most have sustained transmission for 1–2 years, and a few for more than five years based on epidemiological data and laboratory evidence. Such sustained transmission raises the importance of timely identification of cVDPVs and initiation of outbreak control (*12*,*30*).

Sixth, the widespread existence and spread of VDPV2s have increased the difficulty of control

measures. The latest cVDPV2 outbreaks showed that VDPV2s were not only found in paralyzed patients, but were also isolated from healthy people and the environment (*10*). In addition, studies have shown that while the severity of VDPV2 paralysis is similar to that of the wild virus, the case∶infection ratio appears to be lower, so that one VDPV2 patient may indicate the presence of more than a thousand infected people in the community maintaining VDPV2 transmission (*31–32*).

Seventh, before the switch, compared with type 1 and 3 VDPVs, type 2 VDPVs caused the majority of VDPV outbreaks and those with the largest scale—an observation that suggests this virus might transmit more readily and be more difficult to control and stop.

Polio eradication has a long way to go, and the increasing number of cVDPV2 outbreaks poses a great challenge to polio eradication. It is worth further reflection on the tOPV/bOPV switch to re-evaluate cVDPV2 risk and determine the effectiveness, the scientific basis, and the feasibility of the current polio eradication strategy.

Key questions are how to safely terminate existing outbreaks and how to prevent future cVDPV2 outbreaks. Regions or countries with existing VDPV2 outbreaks can introduce two doses of IPV in high-quality campaigns of emergency vaccination to increase type 2 immunity and help reduce cVDPV2 transmission. Monovalent OPV2 should be used very carefully as it increases risk of future VDPV2 outbreaks. Novel OPV2, a genetically more stable vaccine, appears to be a safer alternative to mOPV2 for stopping cVDPV2 transmission and should be considered for emergency use authorization once available later this year, as endorsed by SAGE (*33–34*). Countries and regions using bOPV, should accelerate introduction of 2 doses of IPV and catch up children who lack 2–dose protection from type 2 polioviruses. When epidemiological conditions permit, a 4-dose IPV schedule will prevent generation of cVDPVs and eliminate VAPP.

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Conflicts of Interest

No conflicts of interest were reported.

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