

Vital Surveillances

Vaccine-Associated Paralytic Poliomyelitis — 8 PLADs, China, October 2012–March 2014

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ABSTRACT

Introduction: Poliomyelitis is a highly contagious, seasonal viral disease caused by any of three poliovirus (PV) serotypes (types 1, 2, or 3). Oral poliovirus vaccine (OPV) on rare occasions causes vaccine-associated paralytic poliomyelitis (VAPP) in recipients of OPV and close contacts of recently vaccinated individuals. This study describes the epidemiology of VAPP when an all OPV schedule was used in the Expanded Program on Immunization (EPI).

Methods: VAPP cases were identified using standardized diagnostic criteria from data reported by 8 provincial-level administrative divisions (PLADs) to the National Acute Flaccid Paralysis (AFP) Surveillance System in an 18-month period between October 2012 and March 2014.

Results: During this period, 28 VAPP cases were reported. Using the number of births as a denominator, the estimated incidence of VAPP was 2.47 cases per million births. Using the number of OPV doses administered through routine immunization, the VAPP incidence was 0.55 cases per million doses. Among vaccine-recipient VAPP cases, 22 (85%) were associated with the first dose of OPV; 3 were associated with the second OPV dose. The relative risk of VAPP following the first dose compared with the second dose was 7.07.

Conclusions and Implications for Public Health Practice: The per-dose and per-child incidences of VAPP were consistent with incidence estimates by the World Health Organization (WHO). The vast majority (85%) of VAPP in China was associated with the first dose of OPV in an all-OPV schedule. Because inactivated polio vaccine (IPV) is known to prevent VAPP from subsequent doses of OPV in immunocompetent children, this association provided strong evidence for using an IPV-first, sequential IPV-OPV polio vaccination schedule in China during the

globally-synchronized cessation of type 2 OPV and introduction of IPV in 2016.

INTRODUCTION

Poliomyelitis is a highly contagious, seasonal viral disease caused by any of 3 poliovirus (PV) serotypes (types 1, 2, or 3). Paralysis is an uncommon (<1%) but possibly lifelong outcome of poliovirus infection (1). A key component for the control and prevention of polio has been the use of the poliomyelitis vaccine. Administration of oral live-attenuated poliomyelitis vaccine (OPV) initiates a complex process that results in humoral (systemic) and mucosal (local) immunity following replication in the gut (1). Since the start of the polio eradication program in 1988, an estimated 10 million cases of paralysis have been prevented (2).

OPV has been used in China since the early 1960s, and by using only OPV, China interrupted indigenous transmission of wild poliovirus in 1995. In 2000, the Western Pacific Region of the World Health Organization (WHO), which includes China, was certified to be free of polio. OPV, on rare occasions, causes vaccine-associated paralytic poliomyelitis (VAPP) in recipients of OPV and close contacts of recently vaccinated individuals. VAPP is clinically indistinguishable from poliomyelitis caused by wild poliovirus (WPV) and can cause lifelong paralysis. The estimated incidence of VAPP is 2–4 cases per million births per year in countries using only OPV (3). This is a study that estimated the incidence of VAPP and the association of VAPP with OPV dose number in 8 provincial-level administrative divisions (PLADs) of China.

METHODS

Eight out of China's 31 PLADs were selected to

achieve a balance of geographic locations (eastern, central, and western China) and socioeconomic status. Acute flaccid paralysis (AFP) surveillance was used to identify cases of polio among children. China established AFP surveillance in 1991 and consistently met or exceeded WHO AFP surveillance quality criteria for more than 20 years. Selected PLADs had to have met WHO AFP surveillance quality criteria during the 18-month study period of October 2012 to March 2014.

VAPP cases and related epidemiological data were obtained from the AFP surveillance system. AFP cases received final classifications and diagnoses by provincial-level diagnostic committees of experts. Highly-suspected AFP cases that were clinically compatible with polio were reviewed by the “Expert panel and working groups for the strengthening of poliomyelitis surveillance project”. A national-level diagnostic committee used standardized VAPP diagnostic criteria for identification and classification of VAPP.

For calculating incidence rates, we used data from 2013 from the Bureau of Statistics in each PLAD. The number of OPV doses administered through routine immunization and through supplementary immunization activities (SIA) in each PLAD was obtained from provincial-level Expanded program on Immunization (EPI) departments.

The case definitions were established based on types of VAPP. Laboratory-confirmed VAPP: AFP cases were individuals with clinical manifestations compatible with polio and from whom a vaccine-strain poliovirus was isolated; vaccine-strain polioviruses had to have ≤ 9 nucleotide (nt) changes in the VP1 coding region for type-1 PV (PV1) and PV3, and ≤ 5 nt changes in VP1 for PV2. Recipient VAPP: a laboratory-confirmed VAPP case in which fever occurred 4–35 days following OPV administration, and onset of paralysis occurred in 6–40 days following OPV administration with no further OPV administration after paralysis. Contact VAPP: a laboratory-confirmed VAPP case without OPV administration during the 40 days prior to onset of paralysis occurring and no further OPV administration after paralysis. Clinically-compatible VAPP: AFP cases with clinical manifestations compatible with polio, without PV isolation, but with fever occurring 4–35 days following OPV administration, and an onset of paralysis occurring 6–40 days following OPV administration, and no further OPV administration. Residual paralysis: paralysis compatible with

poliomyelitis with a duration of at least 60 days.

Descriptive statistics were then used to describe the epidemiology of VAPP; the Poisson distribution was used in estimates of confidence intervals (CI); and single-factor logistic regression was used for risk analyses.

The incidence of VAPP per OPV doses administered and per child were estimated. When estimating VAPP based on doses administered, we made two estimates: one with only routinely administered doses in the denominator and a second that included the SIA campaign.

VAPP incidence (per million births) = No. of VAPP cases during the study period in the 8 PLADs / Birth cohort population in the same period in the 8 PLADs \times 1 million

VAPP incidence (per million doses administered) = No. of VAPP cases during the study period in the 8 PLADs / OPV doses administered in the same period in the 8 PLADs \times 1 million.

RESULTS

From October 2012 through March 2014, 28 cases of VAPP were reported in the 8 PLADs. Of the 28 cases, 12 were laboratory-confirmed VAPP — 10 recipient cases and 2 contact cases — and the remaining 16 cases were recipient, clinically-compatible cases (Table 1). Figure 1 showed the distribution of VAPP cases by time and laboratory confirmation status.

All VAPP cases were among children less than 2 years of age. The other 26 cases were among infants, including 8 cases at 2 months, 14 at 3 months, 1 at 4 months, and 1 at 5 months of age (Figure 2).

Of the 28 cases, 27 were among males ($\chi^2=15.7464$, $p<0.0001$). Single-factor logistic regression analysis showed that the male:female ratio was significantly greater than one (male:female odds ratio=18.97, 95%CI: 2.56–140.78).

Of the 28 cases, 26 were among OPV recipients with 10 being laboratory-confirmed and 16 being clinically-compatible cases. Among OPV-recipient cases, 22 (84.6%) occurred following the first dose of OPV, and the median length of time between receiving the OPV and onset of paralysis was 21.5 days (range: 12–32 days). Furthermore, 3 (11.5%) cases occurred following the second dose of OPV, with onsets of paralysis at 17, 31, and 35 days after receiving the OPV. The other recipient VAPP case had a history of previous vaccination with 2 doses of OPV, with time

TABLE 1. Vaccine-associated paralytic poliomyelitis (VAPP) cases in 8 provincial-level administrative divisions (PLADs) of China between October 2012 and March 2014.

PLAD	No. of cases	Laboratory-confirmed VAPP			Clinically-compatible VAPP		
		Recipient	Contact	Subtotal	Recipient	Contact	Subtotal
Hebei	4	2	0	2	2	0	2
Jiangsu	2	0	0	0	2	0	2
Shandong	8	4	0	4	4	0	4
Henan	6	2	0	2	4	0	4
Hubei	1	1	0	1	0	0	0
Guangdong	3	0	1	1	2	0	2
Guangxi	2	1	1	2	0	0	0
Sichuan	2	0	0	0	2	0	2
Total	28	10	2	12	16	0	16

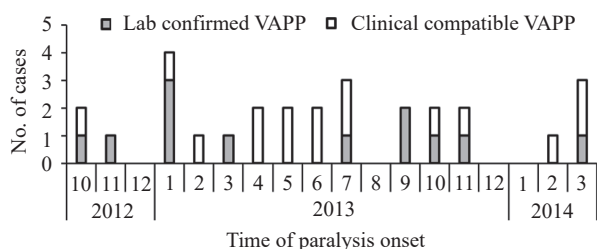


FIGURE 1. Time distribution of paralysis onset for the 28 Vaccine-associated paralytic poliomyelitis (VAPP) cases.

windows of 10 days from the second dose and 38 days from the first dose, both doses being within the interval of 6–40 days.

Among the 12 laboratory-confirmed cases, PV1 was isolated from 2 cases, PV2 from 3 cases, PV3 from 2 cases, PV1+3 from 2 cases, PV2+3 from 1 case, and all three types from 2 cases. PV2 and PV2+3 polioviruses were isolated from the 2 contact laboratory-confirmed

VAPP cases.

The 8 PLADs had a 11.36 million births during the study period yielding an estimated incidence of 2.47 cases per million (95%CI: 1.64–3.56 per million) from the 28 cases. The estimated incidence of VAPP per PLAD ranged from 1.05 to 4.74 cases per million births (Figure 3), with Shandong having the highest incidence and Hubei having the lowest incidence. Differences by PLAD were not statistically significant.

A total of 50.52 million doses of OPV were administered from October 2012 to March 2014, yielding an estimated VAPP incidence of 0.55 cases per million routine OPV doses (95%CI: 0.37–0.80 cases per million doses) due to the 28 cases. The estimated incidence for each of the 8 PLADs ranged from 0.26 to 1.35 cases per million (Figure 4), with Shandong ranking the highest and Hubei the lowest among the 8 PLADs. Differences by PLAD were not statistically

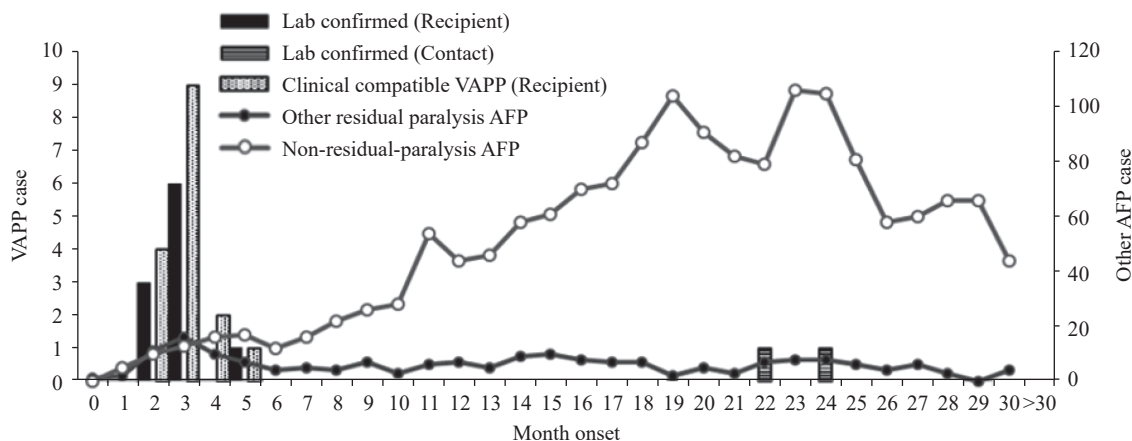


FIGURE 2. Age distribution of the 28 VAPP cases and other AFP cases with and without residual paralysis with onset by 30 months of age. Abbreviations: VAPP=Vaccine-associated paralytic poliomyelitis; AFP=Acute flaccid paralysis.

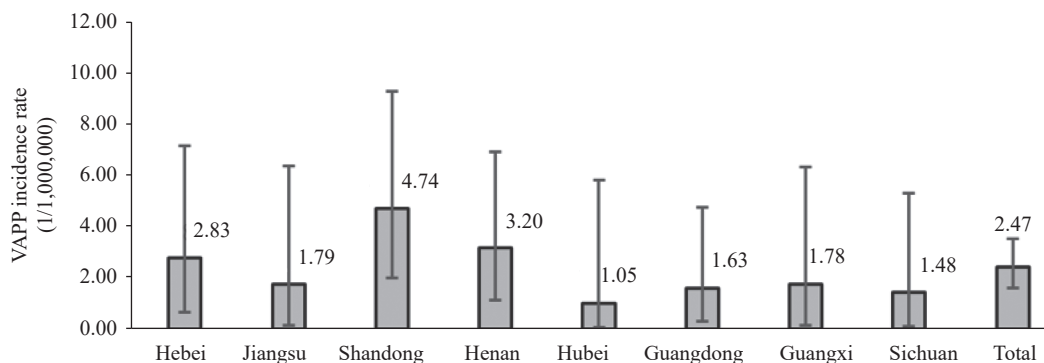


FIGURE 3. Estimated incidence of VAPP in 8 PLADs using numbers of births between October 2012 and March 2014 as denominators. Abbreviations: VAPP=Vaccine-associated paralytic poliomyelitis; PLADs=provincial-level administrative divisions.

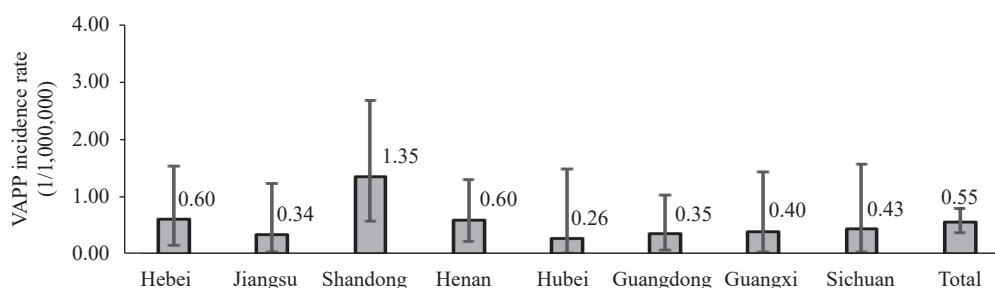


FIGURE 4. Estimated incidences of VAPP per routinely-administered dose of OPV in 8 PLADs during the study period. Abbreviations: VAPP=Vaccine-associated paralytic poliomyelitis; PLADs=provincial-level administrative divisions.

significantly different. When OPV administered during SIAs was included in the denominator, the overall incidence of VAPP was 0.28 cases per million doses (Table 2).

Using the number of routine OPV1 doses administered as the denominator, the VAPP incidence following the first dose was 1.61 cases per million (95%CI: 1.01–2.43 cases per million). Using the number of routine OPV2 doses administered as a denominator, the VAPP incidence following the second dose was 0.23 cases per million (95%CI: 0.05–0.67 cases per million) (Table 3). The relative risk of VAPP following the first OPV dose compared with the second OPV dose was 7.07 (95%CI: 2.12–23.62).

DISCUSSION

As paralysis from wild poliovirus is eliminated, VAPP becomes more prominent in countries that used only OPV. VAPP and paralytic polio caused by vaccine-derived polioviruses (VDPVs) are receiving increased attention as important risks from OPV (4) because as long as OPV is used, VAPP will remain a

risk. However, the inactivated poliovirus vaccine (IPV) does not cause VAPP and is able to prevent paralysis from all types of poliovirus, including the Sabin strains of OPV that can cause VAPP. Switching from an all-OPV schedule to an IPV-OPV sequential schedule can prevent VAPP from occurring from an OPV dose given after an IPV dose. Because the vast majority of VAPP in China is associated with the first OPV dose in the all-OPV schedule, substituting IPV for the initial dose of a sequential IPV-OPV schedule should prevent VAPP in immunocompetent children.

VAPP and VDPVs can lead to questions of the safety of vaccines and pose a challenge to the whole immunization program. IPV can work effectively to control and eradicate polio without the risk of VAPP and VDPVs. Results of this study were used to change the polio immunization schedule in China from an all-OPV schedule to an IPV-first sequential IPV-OPV schedule. Based on the progress of polio eradication, we will ultimately need to stop using OPV routinely after interrupting all wild poliovirus transmission (5). The sequential, IPV-first polio vaccination schedule was a major step towards an all-IPV polio schedule.

The incidence of VAPP in these 8 PLADs was 2.47

TABLE 2. Estimated incidences of VAPP, lab confirmed VAPP, and clinically-compatible VAPP (using number of births and number of routine OPV doses administered as denominators).

Province	VAPP		Lab confirmed VAPP		Clinical compatible VAPP	
	No. of cases	Estimated incidence (95%CI)	No. of cases	Estimated incidence (95%CI)	No. of cases	Estimated incidence (95%CI)
Using number of births as the denominator						
Hebei	4	2.83(0.71–7.21)	2	1.41(0.14–5.09)	2	1.41(0.14–5.09)
Jiangsu	2	1.79(0.18–6.43)	0	0.00(0.00–3.30)	2	1.79(0.18–6.43)
Shandong	8	4.74(2.01–9.36)	4	2.37(0.59–6.04)	4	2.37(0.59–6.04)
Henan	6	3.20(1.17–6.99)	2	1.07(0.11–3.84)	4	2.13(0.53–5.44)
Hubei	1	1.05(0.11–5.88)	1	1.05(0.11–5.88)	0	0.00(0.00–3.89)
Guangdong	3	1.63(0.33–4.79)	1	0.54(0.05–3.00)	2	1.09(0.11–3.92)
Guangxi	2	1.78(0.18–6.40)	2	1.78(0.18–6.40)	0	0.00(0.00–3.29)
Sichuan	2	1.62(0.15–5.34)	0	0.00(0.00–2.74)	2	1.48(0.15–5.34)
Total	28	2.47(1.64–3.56)	12	1.06(0.55–1.85)	16	1.41(0.83–2.99)
Using number of routine OPV doses administered as the denominator						
Hebei	4	0.60(0.15–1.54)	2	0.30(0.03–1.08)	2	0.30(0.03–1.08)
Jiangsu	2	0.34(0.03–1.23)	0	0.00(0.00–0.63)	2	0.34(0.03–1.23)
Shandong	8	1.35(0.57–2.67)	4	0.68(0.17–1.72)	4	0.68(0.17–1.72)
Henan	6	0.60(0.22–1.30)	2	0.20(0.02–0.72)	4	0.40(0.10–1.01)
Hubei	1	0.26(0.03–1.48)	1	0.26(0.03–1.48)	0	0.00(0.00–0.97)
Guangdong	3	0.35(0.07–1.02)	1	0.12(0.01–0.65)	2	0.23(0.02–0.84)
Guangxi	2	0.40(0.04–1.43)	2	0.40(0.04–1.43)	0	0.00(0.00–0.73)
Sichuan	2	0.43(0.04–1.56)	0	0.00(0.00–0.80)	2	0.43(0.04–1.56)
Total	28	0.55(0.37–0.80)	12	0.24(0.12–0.42)	16	0.32(0.19–0.51)
Using number of routine and SIA campaigns OPV doses administered as the denominator						
Hebei	4	0.19(0.05–0.47)	2	0.09(0.01–0.33)	2	0.09(0.04–0.33)
Jiangsu	2	0.32(0.03–1.14)	0	0.00(0.00–0.58)	2	0.32(0.03–1.14)
Shandong	8	0.46(0.2–0.91)	4	0.23(0.06–0.59)	4	0.23(0.06–0.59)
Henan	6	0.29(0.11–0.64)	2	0.10(0.01–0.35)	4	0.19(0.05–0.50)
Hubei	1	0.18(0.02–0.99)	1	0.18(0.02–0.99)	0	0.00(0.00–0.65)
Guangdong	3	0.22(0.04–0.65)	1	0.07(0.01–0.41)	2	0.15(0.01–0.53)
Guangxi	2	0.24(0.02–0.88)	2	0.01(0.02–0.88)	0	0.00(0.00–0.45)
Sichuan	2	0.27(0.03–0.95)	0	0.00(0.00–0.49)	2	0.27(0.03–0.95)
Total	28	0.28(0.18–0.40)	12	0.12(0.06–0.21)	16	0.16(0.09–0.26)

Abbreviations: VAPP=vaccine-associated paralytic poliomyelitis; OPV=oral poliovirus vaccine; SIA=supplementary immunization activities.

cases per million birth cohort, which was consistent with the estimate from the WHO of 2 to 4 cases per million births. The incidence of VAPP on a per-dose basis of 0.55 cases per million routine OPV doses was also consistent with the WHO estimate. The vast majority of the cases were among OPV recipients, and among these cases, 85% were associated with the first dose of OPV.

OPV has been essential to the elimination and eventual eradication of poliomyelitis. Although OPV is

safe, on rare occasions OPV can also lead to VDPV, which are able to act like wild poliovirus and cause VAPP. The WHO has estimated the global burden of VAPP in countries using OPV to be 250–500 cases annually (6), with an incidence of VAPP of 1 case per 2–4 million births per year (3). Our 28 cases yielded an estimated incidence of 2.47 cases per million births.

Per-dose estimates of VAPP risk were consistent with studies in other countries. Using the number of OPV doses administered as the denominator, the

TABLE 3. Estimated incidences of VAPP per million following the first and the second dose of oral poliovirus vaccine by provincial-level administrative division.

Province	Following first dose		Following second dose	
	No. of cases	Estimated incidence (95%CI)	No. of cases	Estimated incidence (95%CI)
Hebei	2	1.15(0.11–4.13)	2	1.13(0.11–4.06)
Jiangsu	1	0.65(0.07–3.66)	0	0.00(0.00–2.42)
Shandong	8	5.26(2.23–10.38)	0	0.00(0.00–2.39)
Henan	5	1.94(0.62–4.54)	1	0.39(0.04–2.21)
Hubei	1	0.85(0.09–4.77)	0	0.00(0.00–3.76)
Guangdong	2	0.73(0.07–2.63)	0	0.00(0.00–1.57)
Guangxi	1	0.75(0.08–4.22)	0	0.00(0.00–2.88)
Sichuan	2	1.87(0.19–6.75)	0	0.00(0.00–3.15)
Total	22	1.61(1.01–2.43)	3	0.23(0.05–0.67)

Abbreviations: VAPP=vaccine-associated paralytic poliomyelitis; CI=confidence intervals.

incidence of VAPP was estimate to be 0.71 cases per million in England and Wales (7) between 1985 and 1991, 0.45–0.67 cases per million in Latin America and the Caribbean (8) between 1989 and 1991, 0.09 cases per million in Brazil (9) between 1995 and 2001, 0.50 cases per million in Japan (10) between 1971 and 2000, and 0.25 cases per million in India (11) in 1999. We found an estimated risk of 0.55 cases per million routine OPV doses administered and 0.27 cases per million doses when SIA-administered doses are included.

The results on risk of VAPP due to which dose of OPV (e.g., first dose, second dose) were consistent with results in the United States (US). The vast majority (26 of 28) of VAPP cases in our study were recipient cases, and among these, 85% were among first-dose recipients and 15% were among second-dose recipients. We found the relative risk of VAPP following the first dose compared with the second dose to be 7.07. In the US (12) between 1990 and 1999, the incidence of VAPP following the first dose was 1 per 0.9 million vaccinees and was higher than for second and other doses. The risk of recipient and contact VAPP following the first dose of OPV was 6.6 times higher than that following second or third dose in the US. However, other countries have had different experiences with risk of VAPP by OPV dose rank. In Latin America, 49% of VAPP cases were associated with the first dose (13), and India has had more VAPP cases associated with third and subsequent doses of OPV(14).

The results of associating VAPP with specific types of poliovirus were consistent with other countries showing that VAPP can be associated with any of the 3 types of OPV virus. A survey by the WHO of 13

countries indicated that PV3 was the predominant serotype isolated from the recipient VAPP and PV2 from contact VAPP. In the US (12), PV3 was usually isolated in cases of VAPP among individuals with normal immune function, while PV2 was usually isolated from VAPP cases among immunodeficient individuals. Among 60 recipient VAPP cases reported in India (11), 41.7% were PV3, 31.7% were PV1, and 15.0% were PV2.

The Adverse Events Following Immunization (AEFI) surveillance system in China was capable of tracking adverse events following OPV administration, which implies that all cases of VAPP in the AEFI system were cases receiving OPV rather than contact cases. In addition, this system was further analyzed by national and provincial-level diagnostic committees to use standardized, consistent case definitions to categorize VAPP into 4 categories, which provided more detail on VAPP epidemiology.

This study was subject to some limitations. The study was only conducted using data from 8 PLADs in 3 regions (western, central, and eastern China) and results may differ in other PLADs. However, socioeconomic status was accounted for in the study design to help with generalizability of the data. Furthermore, contact VAPP is challenging to detect, leading to possible underestimation due to inability to characterize these cases. To address this, the AFP surveillance system was used to identify cases of VAPP to capture both recipient and contact VAPP.

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