



# First case in China of vaccine-associated poliomyelitis after sequential Inactivated and bivalent oral polio vaccination



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## ABSTRACT

A 16 week newborn vaccinated with bOPV 4 weeks after his first routine IPV vaccination. Nineteen days later, asymmetrical paralysis was developed on his legs, and it was diagnosed to be VAPP. Perianal abscess is suspected to be a risk factor based on some limited results of retrospective studies in China. This is a risk factor similar to the multiple intramuscular injections found by researchers in last century. The two risk factors remind us that, apart from the routine infection route of the fecal to mouth and intestinal tract, skin injury (ulceration) exposure pathway should not be ignored as another possible way of causing polio, for the local injury and lesions of the skin may increase the possibility of oral poliovirus vaccine's entry into the body. As a result, to further reduce the incidence of VAPP, bOPV should be avoided for perianal abscess. If there is perianal abscess, skin injury, or if injection is unavoidable after bOPV vaccination of an infant, much attention should be paid to the treatment and cleaning of infant feces.

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It is recognized internationally that oral polio vaccine (OPV) entails a risk of vaccine associated poliomyelitis (VAPP) around 2–4 cases per million children [1]. Such risk is the highest at the first dose of OPV. Inactivated polio vaccine (IPV) will not have such a risk but not all countries can provide children with 4 doses of IPV due to high price and limited production. Therefore, WHO recommended a sequential schedule (1–2 doses of IPV be given first then followed by OPV) for countries with high vaccination coverage and low importation risk [2,3]. Such sequential schedule is expected to reduce the VAPP risk to extremely low [4], but it does not mean VAPP will disappear [5]. Here we report a VAPP case after an IPV-bOPV sequential vaccination in China. It is believed to be the first VAPP case after the new sequence in China.

## 1. Case presentation

The boy was born in December 2016. At 6 months of age in the routine monthly physical development examination in a county level Maternal and Child Health Hospital, his feet were found to have varus. The left foot more obvious than the right, muscle strength of his left lower limbs was weak, and knee reflex was

weakened. The next day, he was transferred to the neurology department of a large-scale General Hospital for a further diagnosis. Examinations showed that his left lower limb activity was less flexible, his muscle strength level was III-IV (Lovett muscle strength test), left knee jerk reflex could be elicited but weaker than the right, Brudzinski sign was negative, weak of supportive standing force on left lower limb, his left foot was varus and poor response to stimulation, and a perianal fistula was visible around the anal skin. Electromyography (EMG) suggested wide neuronal damage of bilateral lower extremities (more serious on the left). Further investigations at the time of presentation included routine blood tests with white blood cell  $11.03 \times 10^9/L$ ; neuter cell rate 21.3%; lymphocyte ratio 71%; hemoglobin 123.00 g/L; blood platelet  $584.00 \times 109/L$ ; total protein 59.6 g/L; albumin 45.4 g/L; globulin 14.2 g/L. Immunoglobulin: IgG 3.5 g/L; IgA 0.2 g/L; IgM 0.3 g/L; IgE 0.4 IU/mL. Complement C3 0.86 g/L; C4 0.26 g/L. Myocardial enzyme spectrum: creatine kinase 276U/L; creatine kinase isoenzyme 32U/L; lactate dehydrogenase 370U/L;  $\alpha$ -hydroxybutyrate 320U/L; Liver function test: ALT 69U/L, AST 88U/L. Renal function and stool routine were normal.

On history, he was breastfed and in good health condition after a birth of full-term normal delivery. Redness and swelling was found on the skin around the anus on 15th days of age, and it became an abscess gradually within 3–4 days. Twenty days after birth, a perianal abscess drainage operation was performed for

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him in a county hospital. The perianal abscess disappeared after the drainage, but a small fistula was formed. Although this caused about one month's delay of the national immunization program, he received all of the required vaccinations of his age, including: hepatitis B vaccine (HBV) and Bacillus Calmette-Guerin (BCG) in the hospital within 24 h after birth; the second HBV on 30 days; the first dose IPV in 3 months; bOPV and diphtheria, tetanus and acellular pertussis (DTP) administered simultaneously in 4 months. The places of vaccination after discharging from the delivery hospital were a regular vaccination clinic of a township hospital. 13 days after the bOPV and DTP vaccination, he presented in a community clinic with diarrhea and indigestion, where he was administered oral probiotics and a drug named 'Erxieting' (a kind of Chinese medicine granules for pediatric diarrhea). Then 2 days later, he had a fever (39.3 degrees Celsius or 102.7 degrees Fahrenheit) and was presented in the pediatrics outpatient department of the county Hospital, where he was prescribed two drugs (oseltamivir granules, and a compound of pediatric paracetamol, artificial cow-bezoar and chlorphenamine maleate granules) and a symptomatic antipyretic treatment. The fever was gone in 4 days; he looked weak particularly in his lower limbs. But this symptom was thought by his family as just frailty after a disease, because they found that his limbs were gradually recovering strength. Then he was vaccinated with a second DTP 13 days later after the fever was gone, which was in 5 months after birth. He has no history of convulsion, injury, intramuscular injections, blood transfusion, allergic, hepatitis or tuberculosis, and an HIV test was negative.

He was diagnosed with "peripheral neuropathy" and was reported as an acute flaccid paralysis (AFP) case to the national monitoring system 3 days after admission to the hospital. Stool samples were collected on the 3rd and 5th day after admission and were sent to provincial CDC on the 6th and 7th day respectively. The first sampling time was 52 days after the bOPV vaccination. The result of the stool culture was: no nonpolio enteroviral growth and no presence of polio virus. He was treated with cardiac nutrition, neurotrophic and hepatoprotective drugs, rehabilitation exercises on limb functions. Having experienced improvement in his limbs, he was discharged from hospital within one month, when his right lower extremity was almost normal but left limb paralysis remained. About one week later he was back for a twenty-day second stage rehabilitation exercises; and a third stage rehabilitation for twenty days another week later. During the interval, he was presented to two hospitals in Beijing: the 301 Hospital of the People's Liberation Army and the Affiliated Hospital of National Rehabilitation Research Center, and was suspected to be a case of VAPP. And finally he was diagnosed by a local county expert panel for Abnormal Reaction Following Immunization of

vaccination to be 'clinically conforms to VAPP'. There had been no other VAPP case or contact infection reported in the county before. By the time of this report (18 months after first signs of paralysis), follow-up shows his left limb has not improved (see Fig. 1).

## 2. Discussion

This is believed to be the first VAPP related with bOPV after vaccination of IPV since the adoption of sequential schedule in May 1st, 2016. Before this case, a case of VAPP was reported after two doses of IPV in Canada and one tOPV [6]. The cases remind us that, although the risk of VAPP will be largely reduced after the introduction of IPV-bOPV sequential schedule, it still can happen, and attention should be paid to risks related with bOPV. And although the reasons of VAPP are complex, the history of perianal abscess stands out.

### 1. Evidences for perianal abscess as a risk factor of VAPP.

Perianal abscess is a common and sometimes trivial condition for children, in particular for male infants under 6 months of age [7]. Recent research suggests that increased androgen may play a role in the pathogenesis of the perianal abscess in infants [8]. There is a number of evidence in China that VAPP is associated with a higher proportion of perianal abscesses, especially in male infants. (1) The proportion of children with perianal abscess in VAPP patients is higher. Wu et al. (1999) reported that 33.3% (3/9) VAPP cases had perianal abscess in Shanghai [9]. Similar results were found in Beijing (30%) [10] and Henan province (34.6%, 9/26) [11]. And Wang et al. (2013) found that 44.4% (4/9) VAPP cases reported in Xicheng district of Beijing had perianal abscesses [12]. And Wendi et al (2018) reported that perianal abscesses cases were all male (24.8%, 39/157) in recipient VAPP cases in China, 2010–2015. [13] (2) Higher proportion of VAPP cases were seen in perianal abscess children. According to investigation of Wang et al. (2013) in 8346 hospitalized children of 0~ year old group in a Children's Hospital in Beijing, there were 2 VAPP cases in 16 cases (all of them were male) which had perianal abscess [12]. (3) Perianal abscess history appeared certain 'specificity' for VAPP in reported AFP cases. Liu et al. (2003) found that in reported AFP cases, only in VAPP cases were found to have had perianal abscess [10]. And Wang et al. (2013) found that no perianal abscess were reported in 267 non-VAPPs AFP cases [12]. (4) Besides the above findings, two researches in Japan reported 1 of 9 VAPP cases between 2003 and 2008 [14], and 2 of 10 VAPP cases between 2000 and 2008 [15] had a perianal

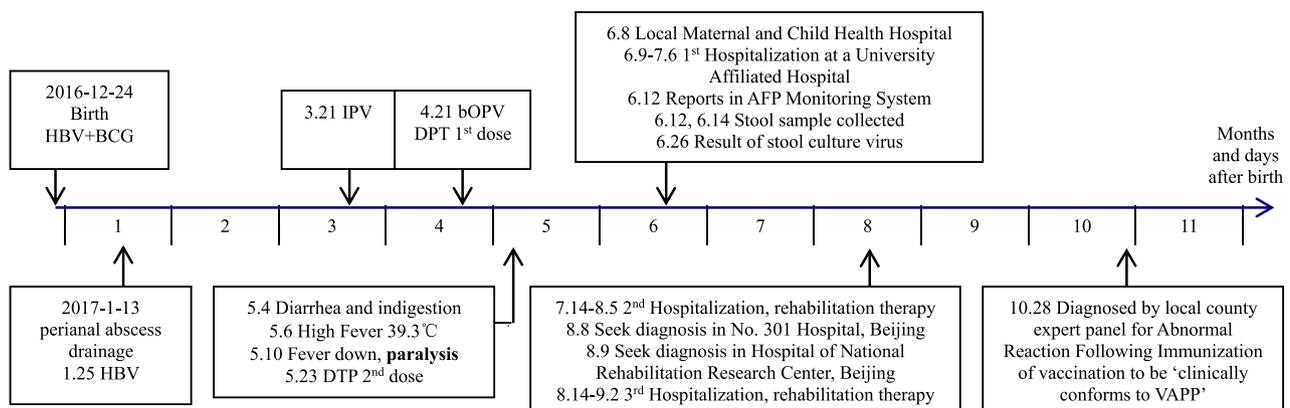


Fig. 1. Process from birth to the diagnosis of the First VAPP case after IPV-bOPV Sequential Vaccination in China.

abscess; several case reports in China [16–22], a case report in Japan [14] and in the United Kingdom [23] also reported to have had perianal abscess. Although there is no more strictly designed epidemiological evidence, much attention still should be paid to these findings. We suggest finding more evidence from VAPP cases in more countries.

Several researchers in China have suggested that perianal abscess be as a contraindication for bOPV or for a delay of bOPV vaccination [9–13,24,25]. This suggestion has been taken in immunization clinics of some provinces in China. In this case, the bOPV vaccination was more than three months after the perianal abscess drainage operation, and when there were no redness and swollen but a small hole with a little damage remained in local skin. The immunization staff was reminded of this symptom by the parents while doing physical examination, and it was believed that bOPV could be administrated. Unfortunately the small hole was later confirmed to be an anal fistula, and remained until 7 months later.

**2. Possible explanations on causes of perianal abscess as a risk factor of VAPP.** The causes of the association between perianal abscess and VAPP are not clear. Although there was a doubt that it is related with the immunity decline associated with perianal abscess, and research showed that development of immune function of perianal abscess infants were delayed to reach the normal level [26], no evidence showed that VAPP cases with perianal abscess have immune deficiency [15].

There are some other risk factors for VAPP such as a history of tooth extraction, tonsillectomy, non-emergency surgery or frequent intramuscular injections within one month of administration of OPV [15]. In these risk factors, intramuscular injections within 30 days of the immunization of OPV has been obtained a relatively large number of studies. The discovery of intramuscular injection as a risk factor can be tracked back to the 1940–50s [27,28], and the reason has not been clear, but it was particularly prominent in developing countries [29,30]. There were two hypotheses, firstly, virus can enter into the peripheral nerve end by intramuscular injection, and then be transported into the anterior horn through retrograde axonal transport to cause nerve damage [31]; secondly, intramuscular injection plays a role of provocation, which greatly promotes the replication of viruses that have already entered the central nervous system [32].

Putting the risks together for a comprehensive analysis, we could see that the common point of them is the destruction of the skin and the lack of normal epithelial protection, which lead to the easy access of the virus to the body or the nerve end then to the central nerve system (CNS). Therefore, the understanding of the way of polio vaccine virus' invading to the body should not be limited to the traditional fecal-oral (i.e. stool-gut). The possibility of contact pathways for virus to invade into the body from skin injury or damage to cause rare VAPP cases should not be ignored. An explanation is that the feces of newborns often stay in diapers for a relatively long time, even if they are finally cleaned up, the skin will not be kept clean at all times. Thus the virus may intrude from the skin wound, epithelial infection and ulceration. When perianal abscesses or multiple intramuscular injection (especially buttocks and thigh injections) cause more skin ruptures, the polio vaccine virus live in the stool is easier to enter the nerve cells and the body through local skin. The reasons that these risk factors could not be found in the United States [33] may be mainly because the vaccination supervised by experienced pediatricians after checking and evaluation of the physical condition of children in the US, thus most OPV vaccinations at risks were avoided, and in the US there were much fewer intramuscular

injections. These were quite different from other less developed countries.

**3. Suggestions on perianal abscess as a contraindication of OPV.** Based on the above evidence and explanation, we suggest that perianal abscess be listed as a contraindication of OPV vaccination. To reduce the risk of VAPP, asking about the history of perianal abscess and the evaluation of perianal skin should be used as a routine workout before bOPV vaccination. For children with perianal abscess history, buttocks and thigh muscle injection, breakage or scratches, or epithelium infection of oral, esophagus and digestive tract, bOPV should be avoided, and an all-IPV schedule needs to be adopted. For those who have been vaccinated with bOPV, much attention should be paid to the cleaning of the stool, the cleaning and nursing of the buttocks, so as to prevent the cracked skin from being contaminated by bOPV virus feces.

In addition, local nomenclature that is easy for parents to understand should be used in communication. For example, in China, most people do not know what is “perianal abscess”, because they normally call it “fire knot”.

Another issue to be mentioned is that the child was delayed for about one month to present to the hospital after the initial paralysis. The delay caused that stool sampling was not taken until 52 days after the bOPV vaccination, which lead to incomplete laboratory results. Evidence showed that even within 30–45 days of OPV intake, polio vaccine virus shedding can only be detected in a small proportion (no higher than 35%) of children who was previously administrated IPV [34–36]. The reasons for the delay were (1) The family thought the weakness of the limbs was a normal part of “being weak after disease”; (2) The grandmother sought superstitious methods (to see a witch doctor) to deal with the problem, which is a common practice in rural and county-level cities in China, especially among the elderly population; (3) Parents are busy with work and have no time to take the child to the hospital earlier. The above reasons reflect three barriers for the utilization of the health care system in China, namely, the lack of cognition for the early atypical symptoms, the belief of superstition, and the neglect of parents due to constraints. Although the paralysis in this case is difficult to be avoided by early treatment, it still prompts us that, to enhance public awareness of health and improve the health environment and basic medical conditions is not just a health problem, it will be a long and complex social process, and it requires the joint efforts of the community, especially in the developing world.

This study had the following limitations: (1) Possibility of low immunity and congenital immunodeficiency, which may be an independent or joint risk factor other than perianal abscess, could not be excluded. (2) Other viruses and DTP vaccines as the reason for paralysis cannot be completely excluded. And this atypical complex case may be the most common situation in the practice of vaccine adverse events in developing countries.

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## Declaration of interest

None.

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