Adverse Events Following Immunization

4

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4.1 An Anxious Mother in the PoV

Scenario One

"Wa, Wa,…." The silence in a CoV (clinic of vaccination) is broken by a child's piercing cry….

"Your vaccine seems to be problematic, my child is suffering such a high fever; you have to be responsible," the mother cried with anxiety….

"Madam, please calm down," the CoV doctor tried to comfort….

The child's crying and mother's concern came from a CoV clinic in Township A Hospital. Yesterday morning the mother took her baby to the clinic and received meningococcal polysaccharide A vaccine after she signed an informed consent form. Dr. Zhang (a new doctor) informed her that the child might develop a fever, redness at the injection site, and possibly other reactions after vaccination. After the injection, the mother and her child stayed in the observation room for 30 min in accordance with Dr. Zhang's request, and then they went home. That afternoon the child did not stop crying, with his temperature increased to 38 °C and redness and swelling appeared at the injection site. The mother thought that these were caused by the vaccine, so she took her child back to the CoV to let the clinic know.

The doctor believed that he administered the vaccination in accordance with the standards and that the clinic operations were also done properly. He told the mother: "Madam, please calm down; let me have a look at the child." Dr. Zhang provided a rapid physical examination of the child, finding a temperature of 38 °C

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X. Liang (ed.), *Immunization Program in China*, Public Health in China 3,
https://doi.org/10.1007/978-981-13-2438-3_4

and redness of approximately 1 cm in diameter at the injection site. No lymphadenopathy, no redness of the throat, and no rashes were observed. Dr. Zhang asked the mother whether the child had other recent illnesses, such as a cold; the mother said no. The doctor drew a preliminary conclusion that the child developed fever and local reactions due to the vaccination. He explained to the mother that "the vaccine can induce antibodies to protect the children, but some of the ingredients contained in the vaccine may cause fever, redness, and other symptoms at injection site. Generally, these reactions don't require treatment. Most children recover fully after appropriate rest. However, if a high fever persists, I recommend that you take the child to a hospital for treatment." "Oh, if that is the case, perhaps I was too worried," and then the mother was no longer so anxious and agreed to go home to continue observation.

Later, Dr. Zhang filed an AEFI case report about the details of the child's vaccination and symptoms. According to the requirements by the "National Guideline for the Surveillance of Adverse Events Following Immunization" [1], because the adverse event was mild, it was not necessary to report it to the national AEFI information management system.

Scenario Two

Today is the vaccination day in Township B. Inside the CoV clinic, there are many parents with children ready for vaccination; the day's work is orderly, although many people are waiting in line. Suddenly, a mother found that her child began to cry 20 min after vaccination and a rash appeared on the child's abdomen and then spread to her whole body. She hurries to find the doctor. Dr. Liu talks with the parents and asks whether the child had an allergic reaction to any vaccine, and he asks whether the child had contact with other potential allergens. The parents said no both questions. Then Dr. Liu examines the child and takes the child's temperature; no abnormities are found other than the rash. His preliminary conclusion is that the child is having an acute allergic reaction. About taking antiallergic drug 10 min later, the rash subsides, and the mother feels a bit more relaxed, but she has a doubtful expression on her face. She says that "in the informed consent form, it is indeed stated that the child may develop fever, rash, and other mild symptoms after vaccination, but why is my child's condition so serious, and why did this happen so fast?"

Dr. Liu explains: "most serious AEFIs are acute allergic reactions to a vaccine, among which the most common is allergic rash. There are several types of rashes that may be caused by allergies, and some have rapid onset. Generally, the onset of an allergic reaction is acute with rapid resolution. During an acute reaction, no lasting damage occurs. Allergic reactions differ widely dependent on individual differences and genetic makeup. Children may differ in terms of onset (acute, subacute) and severity of the disease. In general, the prognosis is good, assuming no complications." "In that case, I am relieved," the mother says. Dr. Liu also asks the mother to observe the child closely and should return if new symptoms develop.

In accordance with requirements, Dr. Liu filed an AEFI form with detailed information regarding the vaccination and symptoms. Township B's hospital can

use its VPN to log into the national AEFI information management system, and so Dr. Liu submitted the AEFI case report online to the AEFI information management system.

Having worked in the immunization program for more than 10 years, Dr. Liu has a deep scientific understanding and intuitive sense about AEFI. Prevention and treatment of acute AEFI has become his top priority. He knows that the most common AEFI are local reactions and are generally not serious and that the most serious type of allergic reaction is very rare. Anaphylactic shock and other hypersensitivity are life-threatening, and therefore they must be treated on-site as medical emergencies. In preparation for allergic emergencies, Dr. Liu always prepares the "life-saving medicine," adrenaline, and often teaches young doctors how to identify vaccine reactions and how to treat them. In line with the National Guideline for the Surveillance of AEFI [1], he strictly requires that all relevant information be reported in a timely manner. Small CoVs care for thousands of families; careless cannot be allowed. In such a way, Dr. Liu leads young doctors to work together, day after day, carefully and seriously administering each dose of vaccine. His happiest moments are when he sees children successfully vaccinated, because he does know that vaccine not only minimizes risk of disease but also makes infectious diseases gradually disappear. Isn't it a great profession? He always looks forward to his work day….

4.2 Not All AEFIs Are Caused by Vaccination

At 8:30 every morning, Dr. Zhang, who works at Department of Immunization Program (DIP), County M CDC, signs into the Chinese AEFI information management system to check the work to be done that day. During the 5 years since she moved from the Township POV to the County CDC, Dr. Zhang reviews, day by day and item by item, all AEFI cases reported to the information system. With many years of experience in a POV clinic, 5 years of experience in AEFI surveillance and management, and her sensitivities as a mother, she is not only able to accurately find subtle errors in AEFI case report but is also able to reach preliminary conclusions for AEFI classifications to guide subsequent action.

On Monday morning, when Dr. Zhang opened the surveillance system, the phone rang. It was director Liang of Township A Health Center. Liang told Dr. Zhang that Grandpa Zhao, who was from a village, came to the health center to report that his 3-year-old granddaughter received Group A and C meningococcal polysaccharide vaccine MPSV-AC on last Thursday. On the weekend the girl went out to play but fell and broke her knee, resulting in continual bleeding with leg pain. A red rash appeared on her body. The day before, his son and daughter-in-law sent the girl to the hospital and Grandpa Zhao came to seek help because it was he who took the child in for vaccination. Doubting a relationship with the vaccination, Nurse Sun in the hospital had already entered the basic information about the child, the vaccine, and the current medical conditions into the system. Dr. Zhang opened the to-do list to find the child's report which showed more serious symptoms for

the child, unlike the fever and redness commonly reported. Dr. Zhang responded quickly, by reporting to the Chief Wang of the DIP.

Chief Wang, together with Dr. Zhang and Dr. Li, the pediatrician from the county hospital, rushed to Township A Hospital to investigate the case. Just then, Liang called to say that the family called again. Tiantian (the girl) was diagnosed with Henoch-Schonlein purpura (HSP) and a blood clotting dysfunction, hence, the serious bleeding. Tiantian was referred emergently to the Prefectural Children's Hospital. The parents were beginning to suspect that the vaccination caused the girl's HSP.

Chief Wang immediately called Dr. Song, a DIP staff member in the Prefectural CDC, to explain the situation. The four professionals were divided into two groups, one to go to the township hospital under Wang's leadership and another to go to the children's hospital under Dr. Zhang's leadership to learn the current conditions and contact Song at the Prefectural CDC. HSP is a serious disease but is relatively rare. However, the child is currently in critical condition, beyond the normal situation seen in HSP. Chief Wang has prepared to ask the Prefectural CDC to participate in the investigation.

Unfortunately, when Dr. Zhang arrived at the Prefectural Children's Hospital, the emergency treatment of Tiantian has failed, and she passed away because of excessive bleeding. The Prefectural CDC DIP took over the case and organized an expert committee to conduct a causality assessment of this AEFI case.

Dr. Zhang followed the progress of the case investigation every day. The case report form had been entered into the surveillance system on time. Dr. Song occasionally called to request additional data, and twice he brought staff from the drug administration department to collect relevant information on the vaccine cold chain and transportation system. Dr. Zhang developed a summary report and updated the information in the surveillance system according to the investigation progressed. As time went on and more information became available, Dr. Zhang believed that the root cause became clearer. But Dr. Zhang's heart felt heavy when seeing the sad eyes of Tiantian's mother. Dr. Zhang took the mother's hand and comforted her, knowing that she had to persuade her to have an autopsy to determine the cause of death.

A month later, Dr. Zhang received the conclusion of the expert committee on causality assessment from Song. Per the medical history in the two hospitals, vaccination data and autopsy results, the expert group, consisting of experts in epidemiology, clinical medicine, forensics, and other relevant fields, drew its conclusions after the evaluation and discussion. The experts concluded that the coagulation dysfunction was related to brodifacoum, a powerful anticoagulant chemical used in pest control, which was detected in Tiantian's blood; there was no evidence of allergy. A causal relation with the vaccine was excluded – this was not vaccine reaction.

A week after hearing the causality assessment conclusion, Liang came to the County CDC in person. Grandpa Zhao refused to accept the experts' conclusion; he believed that the child was not poisoned and asked Liang to explain further. Because they refused to accept the conclusion of the causality assessment experts, Tiantian's

parents applied to the Prefectural Medical Association for the identification; the application was granted. As the vaccinator, Liang needed to submit relevant information and make statements during the identification meeting, and Liang needed support from the county. Together with Liang, Dr. Zhang went through the confirmation and investigation information of the event, and investigation information was provided by Dr. Song in supplement to Liang's statement at the meeting.

Another busy week passed, and on a Monday morning, Nurse Sun from Township A and who is responsible for information technology came to the County CDC for training. During break time, Sun informed Song about the AEFI identification, which she had attended with Liang the previous Friday. The Prefecture Medical Association organized five experts to conduct the causality assessment. Because the previous conclusion of the expert group was sound and reasonable and because the documents Dr. Song helped to prepare were clear and orderly, Liang's statement and defense went smoothly. Nurse Sun said that the results may be available this week and that a copy will be sent to the County CDC.

Before closing the office on Friday, Dr. Song received a copy of Tiantian's identification report. The medical identification expert group confirmed the previous conclusion that MPSV-AC had no causal association with Tiantian's death. The medical experts based their conclusions on the AEFI expert group's investigation and on the clinical manifestations, the autopsy, the vaccination history, the blood coagulation dysfunction, and, critically, the detection of brodifacoum in Tiantian's blood. Dr. Song scanned the report and uploaded it to the surveillance system, hoping to close this very sad case. It should be noted that the report mentioned that any party can apply to provincial medical identification group within 15 days of receiving the report if the party refuses to accept the conclusion.

4.3 Extremely Rare Catastrophic Disability (VAPP)

At 11 o'clock am, Dr. Wang from District S CDC received a call from the Provincial People's Hospital. The hospital's pediatrician-in-chief had reported an AFP case suspected to be related with receipt of oral trivalent poliovirus vaccine (tOPV). The hospital called to explain the event's details. Dr. Wang asked some basic information about the case and immediately reported via phone to the next higher level – the immunization program at Prefecture T CDC. Dr. Zhang, from Prefecture T CDC, provided some guidance on the phone to Dr. Wang, advising Wang to report the case as soon as possible through the AFP surveillance information management system and the AEFI surveillance information system, while investigating the case. Next, Dr. Wang called the child's father to make an appointment that afternoon in the hospital to start the epidemiological investigation. Dr. Wang and Dr. Li from the Prefectural CDC investigated the case together. Because this case was suspected to be vaccine-associated paralytic poliomyelitis (VAPP), in accordance with the National Guideline for the Surveillance of AEFI [1], it should be investigated and diagnosed by a prefecture or provincial AEFI expert group, and the Prefecture T CDC should participate in the epidemiological investigation [1].

At about 2 o'clock in the afternoon, Drs. Wang and Li went to the pediatric ward of the Provincial People's Hospital to check on the patient's condition and his diagnosis. The boy's name was Xiao Hui; he was 3-month-old and had a birth weight of 4 kg; he was previously healthy. On the day of his birth, he received BCG and his first dose of hepatitis B vaccine; he received his second dose of hepatitis B vaccine at the age of 1 month, with no adverse reactions. At 2 months of age, he was brought to the township health center for tOPV, which was given without any problems. Two weeks ago, Xiao Hui developed fever, drowsiness, and decreased activities of his legs – symptoms which didn't resolve after 2 days of IV infusion at the village clinic. His parents then brought him to the city hospital for treatment. City hospital admitted him with a diagnosis of "virus infection and central nervous system infection." After treatment in the inpatient department, no obvious improvement was observed. The boy was referred to the Provincial People's Hospital the day before yesterday. The admission examination found normal temperature, irritability, lethargy, unwilling to cuddle, crying, nervous and stiff neck, not able to suckle, positive Kernig and Brudzinski signs, cerebrospinal fluid with increased leukocyte count, and normal glucose and chloride but negative Pandy test. Medical examination showed that strength and tone were decreased in both lower limbs, and tendon reflexes were absent. Because Xiao Hui needed to be hospitalized for treatment, diagnosis was to be further clarified.

Drs. Wang and Li went to the ward to ask about vaccination. Xiao Hui's father mentioned that the child had been breastfed and healthy. There had been no reaction to the vaccines given at birth. When the child received tOPV at 2 months of age, he stayed at the township hospitals for 30 min and then went home, apparently healthy. After 10 days, the child was ill and was taken to see a doctor. Dr. Wang briefly recorded diagnostic and vaccination information and asked the doctor to help collect two stool samples for isolation of intestinal virus.

Two weeks later, Xiao Hui was discharged from the hospital with both legs still weak and in need of rehabilitation treatment in the community hospital.

Dr. Wang went to the hospital after Xiao Hui's discharge and collected his medical records. During this time, the provincial CDC tested the paired stool samples to try to isolate poliovirus.

Two months later, after compiling the data available, Prefecture T CDC organized an AEFI expert group to make causality assessment of the case. The panel included experts from the Prefectural Hospital, the Maternal and Child Health Hospital, the Provincial People's Hospital, the provincial and Prefectural CDC, pediatricians, and experts in neurology, radiology, immunization, and epidemiology. The experts were briefed by the town health center and parents about the vaccination and the disease; they reviewed the materials provided by both parties and determined that the information was credible. Experts examined Xiao Hui on the spot and found that his both upper limbs were normal in strength, tone, and tendon reflexes, with a varus foot ptosis, muscle strength of proximal lower limbs grade II and distal grade I, muscular tone normal, no knee tendon reflex or Achilles tendon reflex, and with no sensation disorder of the lower limbs. The experts looked at the MR images and other auxiliary data and discussed the case. The immunization experts concluded that the tOPV was managed in compliance with requirements of

vaccine procurement, supply, storage, and transportation. They concluded that the vaccination was administered properly and in accordance with the routine immunization schedule and that there was no evidence of problem with vaccine quality. The clinical experts concluded that according to the symptoms and signs, combined with the physical examination and other clinical data, other diseases, such as encephalitis and spinal meningitis, can be ruled out and that the diagnosis of clinical polio was suspected. Epidemiological experts said that the child's fever, reduced activities of both lower limbs, and other symptoms 2 weeks after being given tOPV were consistent with the temporal pattern of polio. Both stool specimens were positive for poliovirus, also supporting the diagnosis of VAPP. The expert group ultimately agreed that Xiao Hui had VAPP, a known, rare adverse reaction caused by tOPV.

After the experts meeting, Dr. Wang contacted Xiao Hui's father and told him the conclusion of the experts meeting. He explained the compensation policies for VAPP. Xiao Hui's father had no disagreement to the conclusion and wished to apply for compensation necessary for follow-up treatment on rehabilitation. Doctor Wang explained how to apply for compensation.

In accordance with national policies, compensation in a one-time payment should be given if the vaccinated person dies or suffers from severe disability or organ damage due to a vaccine reaction. According to the policies in Shandong Province where Xiao Hui lives, he needs to be assessed and graded by the Medical Association for his disability, which in turn determines the amount of compensation. Facing the sad father, Dr. Wang again consoled him. About two to four cases in a million birth cohort will develop VAPP following tOPV per year [2]. Even though it is so rare, VAPP is a catastrophic blow to the family. Dr. Wang said: "our province issued a series of new policies in 2012 in order to provide better care and assistance to families with vaccine reactions, which can help you solve some practical difficulties. I will give you a document to study." The document Dr. Wang provided was "On Improving AEFI Compensation, Care and Assistance," issued in 2012 by the office of the provincial government. The document had been jointly developed by eight institutions including the provincial health department. Xiao Hui would obtain a higher amount of compensation after the disability was graded. In addition, Shandong included AEFI cases into the Hui Min Medical Services that will provide "six exemptions and two reductions" in medical treatment costs, free expert registration fees, emergency registration fees, general outpatient medical fees, emergency bed fee, and air conditioning and heating fee for above bed. Some examination and treatment fees will be reduced by 30%, and drug fees will be reduced by 10%. In establishing and improving the mechanism for care and assistance of AEFI cases, Shandong also issued specific policies on Medicare reimbursement, schooling, employment, allowance for low income, and other aspects of disability assistance [3].

One year later, Dr. Wang went to the Xiao Hui's home to pay a visit. Xiao Hui had been receiving rehabilitation treatment for more than half a year at a designated rehabilitation hospital. He could stand with the support of his parents and could walk on his own for one or two steps. The government had provided them a minimum living allowance every month, which eased the financial burden. Xiao Hui's mother was ready to have another child, adding new hope for the family.

Leaving Xiao Hui's home, Dr. Wang felt sad and happy. The sad side was that Xiao Hui suffered so much at such a young age. The happy side was that his family received certain guarantees according to government policies. With emotion, Dr. Wang also thought "after replacing the first dose of tOPV with inactivated polio vaccine (IPV) across the nation, there may be not any more paralysis due to tOPV. This will be another milestone in the history of China's immunization program!"

VAPP is an extremely rare AEFI, and the causality assessment is complex. Because of the presence of limb paralysis and other symptoms, suspected cases need to be investigated and diagnosed by AEFI expert group organized by provincial or Prefectural CDCs. Xiao Hui's investigation and diagnosis were made by the prefectural AEFI expert group. According to the criteria for polio, laboratory testing is critical to the diagnosis of VAPP. District S CDC successfully collected two qualified stool samples with the cooperation of the Provincial People's Hospital, and the Province CDC isolated the virus. This careful preparation was critical to the diagnosis of VAPP and avoided challenges to the investigation and diagnosis that can happen when negative results are obtained due to unqualified specimens.

VAPP is a rare reaction following tOPV administration – especially the first dose. Although oral poliovirus vaccine plays an important role in eradication of polio, it can cause serious adverse reactions. Therefore the polio vaccination strategy for eradication needed to be adjusted, that is, to substitute tOPV with IPV partially or completely. The components in IPV are inactivated polio virus, which cannot cause paralysis. There are many countries using IPV alone for childhood immunization. China is working with other countries to switch polio vaccines. One day in the future, VAPP will become history, and disability from VAPP will no longer be a nightmare.

The Chinese government has been committed to addressing AEFI cases and providing assistance as needed. In April 2014, the National Health and Family Planning Commission, the Ministry of Education, the Ministry of Civil Affairs, the Ministry of Finance, the Ministry of Human Resources and Social Security, China FDA, China Disabled Persons' Federation, and the Red Cross Society of China developed and issued a "Guideline on Further Addressing serious vaccine reaction," in which higher requirements were put forward with treatment, rehabilitation, investigation and diagnosis, identification, compensation, and follow-up care and assistance. It was further required that policies should be developed to encourage and promote compensation through commercial insurance [4]. Pilot projects on compensation for serious vaccine reaction by commercial insurance have been carried out in some areas of Beijing and Jiangsu, with the purpose of exploring new mechanisms for compensation. We anticipate that in the near future, compensation procedure for serious vaccine reaction in China will be more efficient, in order to improve compensation and assistance to those suffering vaccine injuries.

4.4 An Event That Should Have Been Avoided

On May 10, 1990, routine vaccination was going smoothly at the Township X POV clinic. Suddenly, a panicked shout from a parent, "Oh, my God! My child is going to faint," and the atmosphere became intense. The shout was from a parent of a

9-year-old girl who received influenza vaccine a few minutes previously and who became uncomfortable in the observation area. “Don’t panic, let me have a look” said Dr. Li, who had been providing vaccinations for 5 years and had a wealth of experience. The girl came to the clinic healthy; she had no fever when examined before being vaccinated or discomfort after vaccination, but shortly thereafter, she turned pale and had cold sweats. She was nauseous; her hands and feet were cold; and she was somewhat unconscious. Dr. Li immediately placed the girl in a quiet emergency room and let the girl lie supine, with her head lower than her feet, and loosened her collar. A quick investigation showed HR, 105 bpm; BP, normal; and no rash or redness suggestive of allergy. Based on these results and the history, Dr. Li thought this was not an allergic reaction, but rather was syncope, probably psychogenic. Dr. Li immediately asked the nurse to provide a cup of hot water for the girl, and about 4 min later, she was fully conscious, with a ruddy face and no nausea, although she felt slightly tired. She was observed for half an hour, after which the doctor allowed her to go home with her mother, as the girl continued to have no discomfort.

After the so-called panic, the nurses said that Dr. Li was experienced and calm. Of course, treatment of a psychogenic reaction itself is not complex. Psychogenic reactions are caused by psychological factors, which can be isolated or clustered during or after vaccination. The reaction generally includes syncope and hysteria. Syncope is not uncommon and usually affects children over the age of 5 years. For syncope, no specific treatment is indicated and lying in a supine position is all that is needed. But do you know what could happen with an inappropriate or delayed response to a psychogenic reaction to a vaccination? In June 2005, in Anhui Province, such an event took place. What follows is the story of an actual event [5].

4.4.1 A Fierce and Sudden Onset

On June 16–17, 2005, the healthcare team of Township D, County J, Prefecture H, Anhui Province, organized a Hepatitis A vaccination campaign for primary and high school students. On the morning of June 17th, the vaccination team was at primary school S to provide hepatitis A vaccine to a wide age range of children – preschool to higher grade students. Vaccination activities were started in the teachers’ offices but were moved to a classroom because the office was too chaotic.

Fourth grade children were being vaccinated at 10 a.m. A 12-year-old girl developed dizziness, chest tightness, nausea, pallor, cold sweats, and numbness a couple of minutes after vaccination. The vaccination staff gave her epinephrine but saw no improvement. The girl was sent to a hospital for treatment and she vomited once on the way. She had been healthy before the vaccination without fever, acute infectious diseases, or contraindications to hepatitis A vaccine. After the girl was taken to the hospital, the vaccination staff explained to other students, teachers, and parents that this was a common response and not to worry; they continued vaccination. Soon five more vaccinated students developed similar symptoms – four girls and one boy – and this caused some nervousness among the teachers. The school told

parents to take their children to the hospital if they have a reaction after being vaccinated. That day, and through that evening, Township D hospital treated 23 students from primary school S who had similar symptoms. The treated students' ages ranged from 7 to 12 years; 12 were boys and 11 were girls; 2 student patients were referred to the county hospital for further treatment. The school had a total of 263 students, and of these, 110 were vaccinated. Fifteen preschool students were vaccinated without event. Two similar events occurred among 21 vaccinated in grade 1, none among the 20 vaccinated in grade 2, 8 among the 27 vaccinated in grade 3, 9 of the 16 vaccinated in grade 4, and 4 of the 11 vaccinated in grade 5.

The news spread rapidly, and on June 18 and 19 other schools were reporting similar events. In addition to Town D hospital, County J hospital, a Chinese traditional medicine hospital, and other hospitals began to see and treat vaccinated children. Common symptoms were headache, dizziness, nausea, vomiting, palpitations, being out-of-breath, and numbness of the limbs. Among some patients, there was decreased HR, convulsions of the limbs, and increase in myocardial enzymes. Because of the abnormal myocardial enzymes, on June 19th, the Prefecture H Health Bureau organized a panel of experts from the prefecture hospital, a hospital affiliated with B Medical College, and N hospital to discuss the events having a diagnosis of allergic reaction following hepatitis A vaccination. By June 20, the cumulative number of hospitalized children had increased to 78. Local media reported the event on June 21st, and by the next day, the cumulative number of hospitalized patients increased to 119. Many parents called the 120 hotline or sent their children to the county hospital or Chinese medicine hospital directly for investigation and treatment regardless of whether symptoms developed after hepatitis A vaccination. Treatment was often chaotic in the two hospitals because parents were worried and concerned and because there were too few beds.

A 6-year-old girl died from a serious disease on June 23rd despite attempts at treatment. She was a preschool student from primary school S at Township D. She had developed dizziness and chest tightness after hepatitis A vaccination in the morning of June 17th. She had been sent to J County traditional Chinese medicine hospital for treatment on the 20th. Her clinical investigation showed temperature, 37.5 °C; HR, 84 bpm; WBC 7.3*109 with N, 68% and L, 32%; myocardial enzyme CK, 214.8 IU/L; and a sinus arrhythmia with left ventricular false tendons on color Doppler ultrasound. On June 22nd, reexamination showed a CK-MB of 27.89 IU/L and a CK of 342.65 IU/L. Parents took the girl to buy some food that afternoon. At 4:30 on the 23rd, she developed fever with a temperature of 39.3 °C; at 11:00 she developed diarrhea with yellow, watery stools. Stool examination was positive for WBCs and RBCs. She developed convulsions and a high fever and was diagnosed with "acute severe dysentery." At 13:00 she was referred to county hospital and died at 14:00 despite treatment. Analysis on June 26th by a provincial expert group concluded that the direct cause of her death was systemic inflammatory response syndrome, which led to multiple organ system failure and finally led to death due to respiratory and circulatory failure. The panel said that the cause of death may have been related to a reaction to the hepatitis A vaccination, but severe infectious diseases could not be ruled out. The family refused an autopsy.

Her death caused strong emotional responses among the public. J County Government expressed condolences to her parents and relatives and provided the family with some financial compensation. Addressing the aftermath, the government explained and clarified the circumstances to the public. Because many of the hospitalized children were discovered to have abnormal myocardial enzymes, the county government decided to provide free myocardial enzyme tests for all children. On June 26th, under the arrangement of H Prefecture Health Bureau, J County CDC organized 68 people into 15 teams to collect blood samples and screen for elevated myocardial enzymes among non-hospitalized students, vaccinated and unvaccinated. Students without reactions after vaccination were also included.

After June 23rd more media reported the event – including CCTV – causing widespread concern by the entire society. On June 27th, up to 70 people were hospitalized; 3 days later, 311 patients had been hospitalized.

4.4.2 Clarification by Investigation and Diagnosis

Between June 27th and July 2nd, the Ministry of Health sent three groups of experts to investigate and address the event. After their arrival in J County, some experts went to the hospital to investigate, and other experts went to S primary school to talk with teachers and parents. Dr. Feng Zijian, the expert team leader and former deputy director of China CDC's National Immunization Program, thought it was necessary to further discuss the events with the doctors and to consider carefully the situation. Focusing on the preliminary conclusion of the local expert team (allergic reaction to the vaccine), he first tried to determine the answer to the following question: if it was an allergic reaction, what type of allergic reaction was it? This question challenged the local doctors because the symptoms and onset were not consistent with any known allergic reaction. The second question Dr. Feng raised concerned the diagnosis of the serious disease. What, exactly, was the specific clinical diagnosis? Doctors were asked to clarify the diagnosis and etiology without considering the vaccination – without the influence of the vaccination. These questions, having been raised at a critical moment, calmed down the clinical experts and epidemiologists. Subsequently, the onset and diagnosis were analyzed in a scientific, in-depth, and detailed way.

The expert group studied the children who had been admitted to hospitals, and they found that 11 children had obvious clinical symptoms – some with underlying medical conditions, such as measles, acute bronchitis, premature ventricular contraction, tonsillitis, sinusitis, viral infection, and other diagnosable illnesses. These diseases appeared to be coincidental with the vaccinations. The first case they discussed was a 12-year-old girl who had been diagnosed with suspected myocarditis and a psychogenic reaction. The national expert group repeatedly evaluated and discussed the girl who had died, drawing a unanimous and consistent conclusion: she died of respiratory and circulatory failure because of a severe infection; the infection was probably toxic dysentery, which was consistent with the clinical data; and there was no causal relation with the hepatitis A vaccination.

The epidemiological investigation of 292 cases found that patients mainly presented with chest tightness, dizziness, headache, weakness, numbness of limbs, and fever. Except for fever, most patients had nearly identical symptoms, with no pathognomonic signs having been observed. Doctors from Beijing Anzhen Hospital and Beijing Union Medical College Hospital concluded that the levels of myocardial enzymes seen in these patients were within the range of normal according to Japanese and Danish criteria for myocardial enzyme levels in children. Combined with results of a case-control study, it was clear that the notion of hepatitis A vaccination leading to cardiac myositis was wrong. The experts emphasized that high myocardial enzymes must be interpreted in the context of the clinical presentations and other laboratory results in order to reach valid clinical diagnoses.

Between June 17 and 30, 2005, 311 children were hospitalized following hepatitis A vaccination. The peak incidences of hospitalization were June 20th to 22nd and June 24th to 27th. These hospitalizations were ultimately caused by incorrect preliminary conclusions of the event, media reports, a coincidental death, uncontrollable emotions of parents, incorrectly diagnosed increases in myocardial enzymes, and, perhaps, overreporting by the major media. After careful discussion and analysis, on June 28th, the expert group reached a conclusion that it was a mass psychogenic reaction. On that day, they explained their conclusion to parents, the media, and medical personnel. After the expert panel's explanation, the number of newly admitted patients decreased rapidly; no new patients were hospitalized after June 30th, and by July 10th all children hospitalized in this event were discharged.

During the event, Gao Qiang, the former Minister of Health, led a working group to the hospitals to visit the students and to console parents, teachers, and students associated with the school. The working group reviewed the conclusions and causality analyses of the expert group and province, prefecture, and county government staff. Minister Gao held a press conference stating that it was a mass psychogenic reaction following an illegal mass vaccination campaign. He described response measures and investigations. Following the press conference, he was interviewed by CCTV, Hong Kong Oriental TV, Phoenix TV, and other media.

This mass psychogenic reaction event received wide publicity throughout the country and raised the question – what is a mass psychogenic reaction? Mass psychogenic reaction refers to hysteria with identical or similar manifestations in most patients, happening simultaneously with or immediately after vaccination. Symptoms can vary, although most individuals show manifestations of autonomic nerve dysfunction, possibly with symptoms of multiple systems, but with no positive signs during physical examination. Specific symptoms (mild headache, dizziness, and mouth and hand tingling) may develop from hyperventilation due to anxiety – something relatively common in mass vaccination campaigns. This type of reaction has no relationship with the vaccine but rather related to the injection. Some people have needle phobia, which can increase the severity of response. During a mass vaccination campaign, mass hysteria may occur, especially when children see other children faint.

4.4.3 Lessons Learned and How to Avoid the Tragedy

The expert group summarized the event as follows: D township hospital of J County conducted an unapproved mass hepatitis A vaccination campaign, violating vaccination regulations. The vaccines used were purchased from an unqualified supplier and transported without proper cold chain. Parents of all students were charged too much for the vaccination. The vaccinators were not adequately trained. They did not quickly treat the student who had developed a psychogenic reaction, resulting in a panic among children and parents and initiating a mass psychogenic reaction. The initial, incorrect conclusion by local authorities that the event was an allergic reaction due to vaccine quality, coupled with media overreporting and exaggeration, worsens the event and increased the difficulty of bringing down the mass hysteria under control. After the event, the local government took timely measures to address the situation, but lack of experience had led to a large-scale negative event.

The national expert group recommended that lessons from this event should be learned by all other areas: PoV staff and vaccinators should be qualified in strict accordance with requirements; management of vaccine distribution and vaccination implementation should be standardized, and management of mass vaccination should be improved; training on AEFI should be enhanced, and coordination of AEFI management should be improved; health education should be strengthened to enhance public confidence in vaccination; and sufficient immunization financing should be secured by governments at all levels.

The news of this mass psychogenic reaction event was broadcast widely, causing considerable embarrassment despite the conclusion that there was no relation of the event with the quality of the vaccine. The event itself had a huge, negative impact on China's immunization program, resulting in concern about vaccination by the general public and raising doubts about vaccine safety. Vaccination coverage decreased significantly in some areas, thus increasing the risk of outbreaks or epidemics of infectious diseases and increasing the risk of infectious disease faced by children. This was a war with no guns. Let us remember the painful lessons of history and never fail to promote the public health benefits of vaccination while acknowledging correctly AEFI, actively communicating and addressing each AEFI, and providing the public with accurate information about the benefits and risks of vaccination. Let us not allow this tragedy to happen again.

4.5 The AEFI Surveillance System in China: Continuously Improving

Since 1999, China has been committed to improve vaccine safety monitoring through participation in the National Regulatory Authority (NRA) assessment of the World Health Organization. Between 2001 and 2005, WHO conducted three formal assessments on China's NRA, but China's AEFI surveillance as one of the functions of NRA passed none of these assessments, indicating the need to strengthen AEFI

surveillance in China. Then, with WHO support and guidance and 5 additional years of effort, MoH and CFDA jointly issued a national AEFI surveillance guideline in 2010. This guideline required the AEFI surveillance system with AEFI data to be shared among health departments and drug administration departments. After the issuance of this guideline, AEFI surveillance and response made great progress.

In December 2010, WHO assessed China's NRA once again. A WHO expert group went to China CDC, Shanghai CDC, Hebei CDC, and other institutions or CoV to conduct a formal field assessment of the AEFI monitoring and analytic systems. In March 2011, WHO announced officially that China passed the NRA assessment. WHO specifically praised the AEFI surveillance in China after the field evaluations of disease control institutions, adverse drug reaction surveillance institutions, and vaccine manufacturers. Passing the NRA assessment was a milestone with great significance for China's vaccine regulatory system. These demonstrated that regulatory oversight of each link in the vaccination system – from production to end user – met the WHO/international requirements, ensuring the safety and efficacy of vaccines and enabling vaccines produced in China to be considered for prequalification by WHO for the UNICEF procurement.

In 2014, WHO conducted a scheduled reassessment of China's NRA for vaccines. The WHO expert group evaluated AEFI surveillance at China CDC, Hubei CDC, Chongqing CDC, and other related institutions and CoVs. WHO announced that China passed the NRA evaluation in July 2014. In both the 2010 and the 2014 NRA assessments, the marks for AEFI surveillance were outstanding, suggesting that major progress had been made in AEFI surveillance and management, response, signal detection, and investigation capacity.

Of course, with the increasing concern about vaccine safety in a complex global situation, surveillance and response to AEFI in China still has a long way to go – challenges and opportunities coexist. China will continue to improve the sensitivity and timeliness of AEFI surveillance and will redouble efforts to improve the quality of surveillance in weak areas. China will conduct AEFI surveillance training to improve awareness of requirements to report AEFI among medical institutions and CDCs, to improve the capacity to investigate and address AEFIs, and to improve causality assessment capacities of AEFI expert groups. AEFI surveillance data analysis, signal detection, and early warning must be further strengthened, and AEFI surveillance information should be released in a standardized manner. The compensation mechanism for rare and serious vaccine-caused reactions should be refined. Communications among relevant institutions should be strengthened, and international exchanges and cooperation should be encouraged. Research on AEFI should be encouraged and supported. By ensuring high-quality vaccination and AEFI surveillance, China will become an important contributor to the global vaccine safety network.

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