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Immunization Program in China

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Preface

Immunization is one of the most effective and cost-effective means to prevent infectious diseases. The Chinese Government has long attached great importance to immunization, and with several generations of effort, China has made great achievements through its immunization program. Major accomplishments include elimination of smallpox and polio, near elimination of measles, a greater than 90% decrease of chronic hepatitis B infection among children, and substantial declines of the incidences of hepatitis A, meningococcal meningitis, and Japanese encephalitis. Incidences of vaccine preventable diseases covered by the National Immunization Program fell 99% after implementation of China's Expanded Program of Immunization (EPI) in 1978. China's EPI system plays invaluable roles protecting people's health, increasing life expectancy, and providing huge and persistent economic and social benefits.

China is the most populous country in the world, but its rapid development over the last four decades has been somewhat unbalanced. Remote and poor areas can be difficult to reach, and provision of immunization services to the floating population and left-behind children continues to be barriers to immunization. With declines in incidence, and therefore visibility of vaccine preventable diseases, and with increased public concern about adverse events following immunization (AEFI), including their investigation and adjudication, communication with the public and the media also pose a great challenge.

Using a combination of narrative and storytelling, this book describes a few of the many touching stories that happened in China's immunization effort during the last 60 years. The stories demonstrate some of the hardships and difficulties behind the immunization achievements and introduce the effort of EPI staff and the support and assistance from the international community.

The book consists of nine easy-to-understand chapters, starting with an introduction of vaccination and immunization policy before the 1970s by the former director of the National Immunization Program (NIP) of the Chinese Center for Disease Control and Prevention's (China CDC). This chapter describes how China's government gradually brought immunization into legal management and explores selected achievements and challenges faced by the immunization program. The next chapter introduces immunization services in China, including vaccine management, human resource capacity building, patterns of vaccination, and China's integrated disease surveillance system.

Starting in 2001, China began to improve AEFI surveillance and management as part of a program to strengthen the National Regulatory Authorities (NRA) for vaccines. In March of 2011, the World Health Organization (WHO) announced that China passed its formal NRA assessment, indicating that vaccine regulation and safety monitoring had achieved WHO/international standards. The chapter on management of AEFI is a compelling read, with several typical AEFI events presented from beginning to end. The stories about AEFI management show the professionalism of vaccination staff and experts and provide experience for similar events in China and other countries.

The chapter on innovative vaccines introduces China's independent research and development, describing the professionalism and selfless dedication of Chinese vaccine scientists. The chapter on the "journey of a vaccine" describes the entire process of vaccine production, storage and transportation, and procurement and distribution of vaccines. To help readers understand the current situation of vaccination in China, the workflow of grassroots vaccination staff is described through the story of a township health center doctor's work week. A later chapter describes China's largest measles supplementary immunization activity and its related social advocacy campaign.

One of the book's highlights is a chapter of memories of working in China by experts from WHO, GAVI, JICA, and other international organizations. We appreciate the great contributions made to China's EPI by our international friends.

We are pleased to share these experiences of Chinese immunization with peers around the world and to provide references and evidence for immunization program policy-makers for controlling vaccine preventable diseases and protecting more children! We hope that China's National Immunization Program is elevated to a level high enough to achieve universal access to immunization services, and we hope the future of prevention and control of infectious diseases becomes even more vibrant. We also hope that China's vaccines are introduced to Asia and to the world adding great new chapters for global immunization.

Beijing, China Xiaofeng Liang

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Acronym

AEFI	Adverse Event Following Immunization
AFP	Acute Flaccid Paralysis
ALT	Alanine Aminotransferase
BCG	Bacillus Calmette–Guérin
BMGF	Bill and Melinda Gates Foundation
CDC	Center for Disease Control and Prevention
CDE	Center for Drug Evaluation
CFDA	China Food and Drug Administration
CNBG	China National Biotec Group Company Limited
CoV	Clinic of Vaccination
DIP	Department of Immunization Programme
DTaP	Diphtheria, Tetanus, and Acellular Pertussis Vaccine
DTP	Diphtheria, Tetanus, and Pertussis Vaccine
EPI	Expanded Program on Immunization
EPS	Epidemic Prevention Station
EV71	Enterovirus Type 71
GMP	Good Manufacturing Practice
GPS	Global Positioning System
HAV	Hepatitis A Virus
HDC	Human Diploid Cell
HepA-I	Inactivated Hepatitis A Vaccine
HepA-L	Live Attenuated Hepatitis A Vaccine
HEV	Hepatitis E Virus
HFMD	Hand, Foot, and Mouth Disease
HSP	Henoch-Schönlein Purpura
IBPC	The Institute for Biological Product Control
IIMS	Immunization Information Management System
IPV	Inactivated Poliovirus Vaccine
JE	Japanese Encephalitis
JEV-L	Japanese Encephalitis Live-Attenuated Vaccine
JICA	Japan International Cooperation Agency
MCV	Measles-Containing Vaccine
MMR	Measles, Mumps, and Rubella Vaccine
MoH	Ministry of Health

MPSV-AC	Group A and C Meningococcal Polysaccharide Vaccine
MR	Measles, Rubella Vaccine
NHFPC	The National Health and Family Planning Commission
NICPBP	National Institute for the Control of Pharmaceutical and Biological Products
NIFDC	National Institutes for Food and Drug Control
NIP	National Immunization Programme
NNDRS	National Notifiable Disease Reporting System
NRA	National Regulatory Authority
OPV	Oral Poliovirus Vaccine
PATH	The Program on Appropriate Technology in Health (American)
PoV	Point of Vaccination
QA	Quality Assurance
QMS	Quality Management System
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	Supplementary Immunization Activity
SPF	Specific Pathogen Free
STDs	Sexually Transmitted Diseases
UNICEF	United Nations International Children's Emergency Fund
VAPP	Vaccine-Associated Paralytic Poliomyelitis
VDPV	Vaccine-Derived Poliovirus
VPD	Vaccine Preventable Disease
VVM	Vaccine Vial Monitor
WHD	World Hepatitis Day
WHO	World Health Organization

1 My Experience as Director of the National Immunization Program (Historical Review)

Xiaofeng Liang and Yanmin Liu

I (Xiaofeng Liang) graduated from the Public Health Department, Shanxi Medical College University, in 1984 and was assigned to the Department of Epidemic Prevention, Gansu Provincial Health Bureau. My responsibility was for tuberculosis control and for managing the immunization program. It was from that time forward that I was bound inextricably with vaccination. It was also the beginning of my understanding that measles, polio, and other infectious diseases could be controlled by vaccination and that vaccination was critically important to the health of children.

In the 1980s, polio, measles, and other vaccine-preventable diseases were prevalent in rural China; reducing the incidence of and mortality from these infectious diseases was a priority for protecting health and preventing epidemics. Most of the Health and Epidemic Prevention Stations (EPS) had not yet established a special department of the Expanded Program on Immunization (EPI), even though more and more people were engaged in the work of immunization. With China's reform and opening-up policies, international organizations and friendly countries began to support China on immunization, and terms like "immunization" and "cold chain" were gradually coming into common use in professional departments and the medical community. I was involved in immunization activities, and the work was new to me. I eagerly anticipated the work and planned to devote myself fully to immunization!

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1.1 Vaccination Before the 1970s

After becoming responsible for immunization, I often consulted experts in the Department of Epidemic Prevention and the Provincial EPS to better understand the history of vaccination. Director Chuanzhen Zhang and Vice Director Mingguang Tian helped me very much, and Director Guangxun Wang and Vice Director Zengrong Liu of the EPI Department in Gansu province EPS worked with me almost every day. They told me that in the early days of New China, infectious diseases, such as smallpox, were very serious and difficult to control. For example, with limited production capacity and supply of smallpox vaccine, the incidence and mortality rates of smallpox were very high among children. Fortunately, the new government placed prevention and control of infectious diseases in a very important position. On October 7, 1950, the Government Administration Council issued "Guidelines for Smallpox Vaccination Campaigns in Autumn" [1], which required implementation of a nationwide, free smallpox vaccination campaign. The campaign ultimately achieved coverage levels greater than 90% in most regions, with more than 500 million people vaccinated against smallpox in China between 1949 and 1952. As a result of this campaign, the incidence of smallpox decreased greatly – from 43,286 cases in 1950 to 847 in 1954. Smallpox was eradicated in China by 1961 – just 7 years later.

The Ministry of Health (MoH) established a BCG Promotion Committee at about the same time, with a charge to implement BCG vaccination to prevent serious tuberculosis. Annual vaccination during winter and spring against cholera, plague, typhus, typhoid, diphtheria, Japanese encephalitis, and pertussis was also implemented in some high-risk areas, effectively controlling epidemics of these infectious diseases. MoH issued a "Manual for Implementation of Vaccination" [1] for the first time in 1963 – the year I was born – and vaccination was gradually incorporated into the planned immunization program in each region, especially in urban areas. Universal children immunization was gradually improving.

The EPS system was abnormal during the "Cultural Revolution" period of 1965–1975. Health technical personnel were seriously depleted, and no one was responsible for the vaccination; management became poor, vaccination was sometimes disrupted, and immunization lagged. As a result, several infectious diseases that had previously been controlled re-emerged. Meningococcal meningitis was widely transmitted in the spring of 1967 due to the migration of a large number of people, to low vaccine coverage rates, and to the use of low-quality vaccines. Nationally, 3.044 million cases of meningococcal disease were reported in 1967 [1], which was the largest number of cases reported since the founding of the PRC. Poliomyelitis was a serious disease that caused a large number of deaths and disabilities among children. According to a survey in one province, between 1970 and 1972 coverage of polio vaccine hovered between 32% and 51.4% among children under the age of 7 years of age. A survey of 1281 polio cases in Jiangsu, Zhejiang, and Guangdong provinces found that none of the children who got polio had completed the polio vaccination schedule. The incidence of polio remained high, with a national annual incidence of greater than 2/100,000 in 1970–1973.

The State Council approved a document, "Report on Strengthening the Prevention and Treatment of Infectious Diseases," which was written by MoH in the mid-1970s [1]. With the acceptance of that report, important attention was again paid to vaccination work. Special staff members were designated in EPSs at all levels to be responsible for vaccination, and vaccination services at the grassroots level developed and matured rapidly. A system of citizens' vaccination cards was established; simple equipment for cold storage and transportation of vaccine was obtained; and the expanded program on immunization was implemented in many regions.

The cold chain is composed of cold rooms, refrigerated vehicles, freezers, refrigerators, cold boxes, and vaccine carriers that are collectively used for storage and transportation of vaccines. MoH issued "Notice of a Cooperative Project on Cold Chain between China and United Nations International Children's Emergency Fund (UNICEF)" in December of 1981 [1], and this notice opened the door for cooperation with UNICEF, WHO, Japan International Cooperation Agency (JICA), and other international organizations. It was at this time that China's government and UNICEF started their cooperative project on vaccine cold chain. First, a pilot project was initiated in Hubei, Guangxi, Fujian, Yunnan, and Sichuan provinces, where the climate is hot. Central and local governments actively cooperated by providing supplementary funding, and cold chain coverage increased rapidly. From 1996 to 2004, the China government used a World Bank loan to provide ten provinces, including Gansu province, with cold chain equipment. At that time, most families in China didn't have refrigerators and refrigerated vehicles were rare. In general, health centers were not equipped with refrigerators, and no refrigerated equipment was available in village clinics for storage of vaccines and biological products. Construction and wide availability of the cold chain played an important role in improving the quality and effectiveness of vaccines.

I began my work in October 1984 as a new "recruit," and in 1985 I participated in a national vaccination workshop in Changsha, Hunan Province. In the meeting an inscription by President Li Xiannian was shown: "Universal children's immunization, promoting the healthy growth of offspring." I also saw a number of domestic leaders who were responsible for the organization of immunization programs, including Wang Jian and Cao Qing from the MoH Department of Health and Epidemic Prevention, along with experts like Kai Zhao, Wenyuan Ze, Yongge He, Kaihua Sun, and Liandong Diao.

In 1986, Gansu province received funding from UNICEF to provide cold chain equipment for the 2.5-million-person Tianshui Prefecture. With the aid of international organizations like UNICEF and friendly countries, refrigerated vehicles, refrigerators, cold boxes, and cold carriers were gradually procured to establish a vaccine "cold chain" that went continuously from manufacturers to point of vaccination (PoV) clinics. Between 1986 and 1993, I visited the "Cold Chain Project Office" in Beijing's EPS, which had been established by MoH and drivers from county EPSs, and drove vaccine transport vehicles assigned to each county in my province for the long journey back to the counties. It was at that time I began to

know many colleagues, such as Qiyi Xie, Biao Guo, and Yanmin Liu. By the end of the last century, China had built a "cold chain" system for vaccine delivery and transportation across the entire country.

1.2 Vaccination Rates: Achieving the 3 "85% Goals"

The time I began work was the so-called golden era of EPI. The central and local governments attached great importance to EPI work. Mobilizing the public, increasing vaccination rates, and reducing the incidences of vaccine-preventable infectious diseases were the primary works of the Department of Health at each level. On August 15, 1985, on behalf of the Chinese government, President Li Xiannian committed to the goal of universal children immunization by 1990. The goal was to be achieved in two steps: first, vaccination rates should reach 85% in each province by 1988, and second, coverage should reach 85% in each county by 1990. These objectives were included in the 7th Five-Year Plan of the National Economic and Social Development. A National Immunization Coordination Committee was established in 1986, with members from MoH, the State Education Commission, China Women's Federation, the Ministry of Broadcast and Television, the Ministry of Foreign Trade and Economic Cooperation, and the State Ethnic Affairs Committee. April 25 was designated as "National Children's Immunization Day" [1].

In March 1989 and 1991, MOH, WHO, and UNICEF jointly reviewed and confirmed that the BCG, oral poliovirus, DTP, and live, attenuated measles vaccination rates among 1-year-old children reached 85% by provincial and county levels, respectively, achieving the goal of universal access to childhood immunization. Incidence rates of infectious, vaccine-preventable diseases had also been significantly reduced.

The pilot evaluation for the first 85% goal was conducted in Gansu province. Longde Wang, Deputy Director of Gansu Health Bureau, who later became the Vice Health Minister, was in charge of health protection and epidemic prevention in Gansu. Zhao Wang, Deputy Director of the MoH Department of Health and Epidemic Prevention; Baoping Yang, Director of the Immunization Program Division; and Jingjin Yu organized the evaluation. The pilot evaluation greatly promoted immunization in Gansu province. As a scientific researcher in the Gansu Health Bureau's Department of Health and Epidemic Prevention, I was responsible for the logistics of the pilot evaluation, along with support to leaders and experts from MoH.

In 1992, hepatitis B vaccine began to be managed by the children's immunization program. BCG vaccine, oral poliovirus vaccine, DTP vaccine, and live, attenuated measles vaccination rates had attained 85% at the township level among 1-year-old children by 1996. China had made great progress in the work of immunization and was highly praised by the international community. MoH won a Silver Medal for Children's Survival, awarded by UNICEF [1].

Once vaccine development, production, and supply issues were addressed, the priority of the universal immunization turned to management. That immunization in children in China achieved impressive results was due in part to the strong support from health administration departments at all levels. Immunization was the priority of public health and health sectors at all levels. In 1986, a special division of immunization was established in MoH that was responsible for managing the National Immunization Program (NIP). Since the beginning of the immunization division, a total of six people have served as director. I have had the honor to work with all of them, promoting together immunization in China. They are Baoping Yang, Jingjin Yu, Jun Zhou, Gang Cui, Quanle Li, and Ming Lu. Mr. Baoping Yang served as Director of the Department of Immunization, WHO Western Pacific Regional Office, and is now retired. Mr. Jingjin Yu is now the Director of the Department of Disease Control and Prevention, National Health and Family Planning Commission, still covering immunization. When I was the Director of NIP, China CDC, Jun Zhou was the Director, and certification of polio-free status after the importation of wild poliovirus in Qinghai was the priority. During this time we were planning a project with GAVI on hepatitis B vaccination and a measles control project in Guizhou. Mr. Gang Cui worked with me for the longest time, and together with provincial colleagues, we completed the hepatitis B vaccine GAVI project. We participated in the expansion of NIP to include more vaccines into the EPI system, promoted the use of auto-disposal syringes, established a surveillance system for adverse events following immunization (AEFI), and assisted with the prequalification of a Chinese JE vaccine. We properly addressed the Shanxi vaccine incident together with Director Jingjin Yu. We also took part in two events that could have had an important impact on the history of vaccination in China: the development of influenza A vaccine in 2009 and a national measles vaccine supplementary immunization activity in 2010.

1.3 A Series of Policies Developed to Promote Vaccination

Health services in rural China developed rapidly in the mid-1970s, with cooperative medical systems established in more than 70% of large cohort areas (administrative village, citizenship committees, hereinafter referred to as villages) across China. A team composed of 1.3 million barefoot doctors (village doctors) and 3.6 million health workers and midwives was established that provided medical and vaccination services. In 1978, the “Notice on the Strengthening of Immunization” was issued by MoH which required that “corresponding personnel must be designated in EPS to be responsible for immunization in all provinces, municipalities, and autonomous regions.” In 1982, MoH issued “National Immunization Regulations,” further requiring that teams should be constructed at EPSs to be responsible for EPI services. The vast cadre of rural doctors played a crucial role in improving vaccination rates as they went street by street and house by house to provide vaccinations. Because the cold chain system was not perfect, most vaccination was carried out in

the cold winter season when the ground was full of ice and snow and mountain roads were slippery – to the point that some CDC staff and clinic doctors lost their lives. In Gansu, where I worked, there were several rural doctors who lost their lives because of traffic accidents during polio vaccination.

Since then, EPI departments have been set up in EPSs in all provinces, autonomous regions, and municipalities (hereinafter referred to as provinces) and in all prefectures and cities (hereinafter referred to as prefectures); an EPI group was set up in departments of epidemic prevention in EPSs in all counties, districts (hereinafter referred to as counties), and specialized personnel were designated to be responsible for immunization programs in township hospitals. In the early 1990s, the Division of Immunization Management was set up in the MoH Department of Primary Health and Epidemic Prevention, and in 1989, the Immunization Technical Guidance Center was set up in the former Chinese Preventive Medicine Academy (CPMA), with Ke'an Wang acting as Director. The EPI office was placed in the Institute of Epidemiology and Microbiology. Experts, such as Rongzhen Zhang, Libi Zhang, Xia Liu, Mu Liu, Xu Zhu, Xiaojun Wang, Lixia Wang, Feng Chai, and Wenbo Xu, worked hard and played an important role in the construction of the technical platform for immunization, the development of technical guidance, and the work on international cooperation.

In 1995, I went to Beijing to pursue my master's degree in "Social Medicine and Health Management" in CPMA. This major was later changed to the In-service Masters in Public Health, which was included in the In-service Masters Education program. While I was studying in Beijing, I participated in routine activities with the EPI Division in MoH. At this time, the focus of immunization was to eradicate polio. The Japan International Cooperation Agency (JICA) played a significant role through a number of senior experts to assist the construction of a national and provincial polio laboratory surveillance network in China, to provide kits and equipment, and to train, hand in hand, CDC staff in China with a group of young experts, including Li Li and Jie Lei. Long-term and short-term experts, such as Yuanren, Chiba, Tiezuo, Rushan, and Qingshui, devoted themselves to this work in China. Through their work, they also established deep friendships with Chinese experts.

In 2000, together with other countries in the Western Pacific Region, China achieved polio-free status, and Health Minister Wenkang Zhang attended the certification conference in Tokyo.

In June 2000, MoH held a "Seminar on Strategies for Hepatitis Control" that resulted in the development of a National Proposal on Hepatitis Control, which was submitted to the State Council. During this time, the GAVI China project was started, with the central government and GAVI providing half of the funding necessary to provide free hepatitis B vaccine for newborn infants in the western provinces. An immunization strategy was gradually formed that combined routine immunization, supplementary immunization activities, and emergency vaccination. Vaccination service frequencies increased in most areas, with the interservice period shortened.

1.4 Vaccination Management by Law

After I obtained my master's degree, I had an opportunity to study at the medical school in the University of Miami in 1996. After returning to Gansu, I served as Deputy Director of Gansu province EPS, in charge of immunization. At that time, I worked with Hui Li, Director of the Department of Immunization, and Fuqiang Cui, Deputy Director of the Department of Immunization. Measles outbreaks were frequent in Gansu and other provinces, and together with Hui Li, I went to Wudu County to investigate and handle a measles outbreak. Due to the lower economic level in Longnan County, Gansu, the awareness of immunization among the general public was very weak. The POV workforce was lacking, and no funding was provided by the government to the township healthcare centers – almost leading to their closure. The majority of children living near hospitals developed measles; there were also many adult cases. In total, 12 patients died during the outbreak, which shocked me and gave us a profound lesson. I was transferred to work in the Chinese Academy of Preventive Medicine in 2000, and replaced Xinglu Zhang in 2001, serving as the Director of National Immunization Program (NIP), China CDC.

On the basis of the previous work in the National EPI Technical Guidance Center in CPMA, China CDC introduced professionals from provinces to expand the "national team." Huaqing Wang, Li Li, Fuqiang Cui, Jingshan Zheng, and Dawei Liu – all excellent – were transferred from the province level. Zijian Feng, Deputy Director of China CDC, was transferred from Henan Province CDC. He and I were the leaders of NIP for more than a year. He is now the Deputy Director of China CDC in charge of vaccination. Biao Guo translated materials on immunization from WHO and other organizations and accumulated professional knowledge for EPI work in China. In December 2004 [1], the "Law on Infectious Disease Prevention and Control" was implemented, in which the vaccination card system was required and free EPI vaccines begun.

In 2005 the State Council developed and issued the "Regulations on Vaccine Distribution and Vaccination Management" [1], with a principle of "person-oriented" services. The government provides "public products" to the people so that the general public has full access to services for the prevention and control of vaccine-preventable diseases (VPD) and is protected with public health rights. Vaccines were divided into two categories. The first category referred to free vaccines provided by government to citizens, which should be administered in accordance with the requirements of government. The first category of vaccines includes vaccines in the NIP, Provincial Immunization Programs, and vaccines for emergency or campaign use, as determined by government or health administrative departments at the county level and above. The second category of vaccines refers to other vaccines voluntarily received by citizens, with payment out-of-pocket. After the "regulations" were issued, a system to qualify vaccinators was inaugurated which required that only individuals (medical practitioners, physician assistants, nurses, or village doctors) who participated in a training course and passed a test organized by the county-level health administrative departments were qualified

to provide vaccination services. To further develop the immunization program, in 2007 the State Council decided to include more vaccines into NIP, with an ultimate total of 14 different vaccines, including hepatitis B vaccine, BCG, and many others. The number of NIP vaccines was expanded from 6 to 14, for provision at no charge to age-eligible individuals. The number of NIP vaccine-preventable disease increased from 7 to 15. Expansion of NIP vaccines was notable for its inclusion of meningococcal vaccine and Japanese encephalitis vaccine. After several years of immunization, with an increase in vaccination coverage, the incidences of meningococcal meningitis and Japanese encephalitis were reduced to below a hundred.

1.5 NIP Vaccine-Preventable Infectious Diseases: Transitioning from Common to Rare

It is the 30th year since I graduated from the university, and I deeply appreciate that the NIP vaccine-preventable diseases have decreased from common to rare, dropping to the historically lowest level. Thanks to the effort of several generations of immunization staff, transmission of these diseases has been effectively controlled.

1.5.1 Achievements in Polio Control

Reporting of polio cases began in 1953, with annual reports of 20,000–43,000 cases in the early 1960s. Since 1965, the use of oral poliovirus vaccine (OPV) manufactured in China has been promoted nationwide, with vaccination rates increasing with time and resulting in substantial decreases in the incidence of and death from polio. The incidence of polio decreased by 37% from the 1970s compared with the 1960s [1].

In the 1990s, polio eradication activities were carried out all over China. On top of routine immunization, mass catch-up immunization campaigns were conducted that rapidly improved population immunity levels. An effective immunity barrier against the spread of poliovirus was established in China that blocked the spread of native, wild poliovirus and decreased the incidence of polio year by year [1]. Since 1994, when the last polio case caused by wild poliovirus was reported, China has continuously maintained polio-free status. In 2000, China was certified as polio-free, which was confirmed by WHO.

In 2011, just as I left the position of NIP Director, a polio outbreak due to an imported poliovirus occurred in southern Xinjiang. Through virological analysis, it was confirmed that the outbreak was caused by a virus imported from Pakistan. In total, 21 cases were confirmed, and about half the cases were among adults, with a maximum age of 51 years. At that time, as an expert, I went to the site with Health Minister Zhu Chen and Vice Minister Li Yin. Looking at the serious faces of the two ministers, I really felt deep remorse. Tears came down especially hard when Director Yu Wang and I saw a 26-year-old Uighur male patient infected with polio who was paralyzed in both legs. I couldn't tell whether to feel guilt, sympathy, or something else.

Just 1 year before the outbreak, we sent a supervision group led by Jingui Chu to southern Xinjiang to monitor the polio vaccine supplementary immunization. They found that immunization in southern Xinjiang was weak and reported this finding to MoH. The newly appointed Deputy Director, Zhenglong Lei, and Quanle Li, Director of Division of Immunization, went to Xinjiang to supervise immunization. However, their finding didn't arouse enough attention by local leaders and professional department staff, and so this disaster occurred. More than 430 staff members from CDCs of other provinces were deployed to Xinjiang to assist in the response to the outbreak. The WHO office also sent staff to participate in the response; MoH and China CDC sent a long-term expert team to Xinjiang. The central government used the Air Force to transport the vaccines from Beijing to southern Xinjiang. A year later, WHO evaluated and confirmed that China had remained polio-free, and praised China's emergency response, which had set an example for the world.

It is really true that immunization cannot be slackened!

1.5.2 Implementation of Measles Elimination

In the 1960s, during the pre-measles vaccine era, there were measles epidemics every 2–3 years. Almost everyone was infected during childhood – in fact, it was difficult to avoid the infection [1]. In 1965, a measles vaccine was used in China for the first time, resulting in a continuous drop in incidence and mortality of measles since that time. The incidence and mortality of measles had decreased by more than 95% in 1990 compared with 1978. In 1998, China MoH proposed to accelerate measles control and developed a "Measles Control Action Plan" with an objective to lower the incidence below 8/100,000 total population. All provinces responded positively to the plan and took action to control measles.

A national measles vaccine supplementary immunization activity (SIA) was conducted in 2010 with more than 100 million age-eligible children immunized during two rounds of measles vaccination. There are many stories to tell when speaking of the SIA. In retrospect, the greatest barrier was communication and publicity. It was the first time that 100 million children under the age of 4 years were vaccinated against measles within 1 week. We thought that the measles vaccine was a commonly used NIP vaccine, with many sub-national SIAs conducted in the provinces, causing few problems. We subsequently found out that our social mobilization was not sufficient, and we didn't report this clearly to the leadership team. In the preparatory stage, Dr. Yu Wang, Director of China CDC, discussed the SIA twice with me and Huiming Luo, Deputy Director of NIP. Dr. Wang was concerned that the general public and the media might have a strong reaction. Full of confidence, I said, "no problem!" But later wide doubts appeared, especially through Internet rumors. The leadership team felt under a great deal of pressure, and the SIA was almost stopped before it started. Finally, MoH decided to carry out the SIA on time, with WHO officials providing answers to questions by mainstream media. Minister Zhu Chen and Vice Minister Li Yin personally took me to explain the SIA to influential

leaders and media opinion leaders. I also asked an expert on immunization from Peking University Health Science Center to come to the NIP office to discuss the rationale for this campaign and to resolve his doubts. In the end, everyone agreed to take their children to receive measles vaccine.

I still remember when the first dose of measles vaccine was administered in Sanjianfang community in Beijing Institute of Biological Products, with two ministers personally supervising the vaccination, with rescue equipment and emergency medicines on hand, and with an ambulance in the community health center prepared for anything. The scene is still vivid before my eyes.

1.5.3 Hepatitis B

Hepatitis B virus is highly epidemic in China. According to a national serological epidemiology survey for viral hepatitis in 1992, HBsAg carriers accounted for 9.8% of the total population [1]. In 2002, hepatitis B vaccine was included in NIP with a focus on improving the vaccination rate among children in rural areas of middle and western China. A national serological survey in 2006 showed that the HBsAg carriage rate was 7.2% (0.96% among children 1–4 years old), having decreased by 26.4% compared with 1992. Through hepatitis B vaccination of newborns in China, the current generation of children has been effectively protected against hepatitis B. The progress of hepatitis B prevention and control is significant. An objective to reduce HBsAg rate to less than 2% in children under the age of 5 by 2012 that was proposed by WHO was achieved in advance in China. In 2014, the HBsAg prevalence remained below 2% in children under 5 years of age according to a national serological survey of viral hepatitis.

Here, thanks to the support by national major special funding, I took the lead, while Fuqiang Cui and Li Li were responsible for the implementation of two national serological surveys on hepatitis B to understand the epidemiology of hepatitis B. In particular, hepatitis B vaccine was demonstrated to have protected children. Thinking of this, I am full of pride and honor simultaneously!

1.5.4 Hepatitis A

The reported incidence of hepatitis A has been on the decline since the 1990s, and the number and size of public health emergency events have decreased year by year and to a record been low in year 2012 [1].

In 2007, hepatitis A vaccine was integrated into the immunization program for 18-month-old children for routine vaccination. With emergency vaccination in flooded areas, earthquake-hit areas, and areas with high incidences, vaccination reduced the number of cases of hepatitis A [1].

1.5.5 Meningococcal Meningitis

There were many epidemics of meningococcal meningitis (MM) (referred to as epidemic meningitis, mainly caused by serogroup A) with variable intensity in China. Five national epidemics were recorded – in 1938, 1949, 1959, 1967, and 1977. The most serious epidemic was in 1967 with an incidence of 403/100,000, with more than 3.044 million cases across rural and urban China [1]. In 1980, China began to use a meningococcal polysaccharide vaccine, and outbreaks of meningococcal meningitis were effectively controlled. In 1984 a comprehensive prevention and control strategy with universal immunization using meningococcal polysaccharide vaccine was implemented as a priority which resulted in a continuous decrease in incidence. The incidence of MM was maintained at less than 10/100,000 through the 1990s and less than 0.1/100,000 since 2000. China-produced meningococcal conjugate vaccine A + C was initially marketed in 2007, and the disease incidence dropped to 0.09/100,000 that year. In 2007, MM vaccines were integrated into NIP, which further reduced the incidence of MM [1].

When it comes to meningococcal meningitis, an outbreak by serogroup C in Anhui province in the beginning of 2004 should be mentioned. In Hefei city, an outbreak of meningococcal meningitis occurred among primary school students. The outbreak was confirmed by academician Jianguo Xu to be caused by serogroup C. Dr. Xu's paper was published in *The Lancet*. This was the first serogroup C outbreak in China. I was in Anhui to organize the vaccine supply for supplementary immunization and lead the investigation. It was a thrilling war.

1.5.6 Japanese Encephalitis

The incidence of Japanese encephalitis (JE) increased since the early 1950s in China, reaching its first peak in 1966 and second peak in 1971, with more than 150,000 (incidence of 20.6/100,000) cases and 170,000 cases (incidence of 20.9/100,000) reported, respectively. The epidemics spread to the northeast and northwest of China. Starting in the 1980s, the incidence began to decrease significantly and dropped to less than 1/100,000 after 1998. The incidence showed a continuous decline after 2000 and has been maintained at historic lower levels [1].

When I worked in Gansu, I had never seen JE. But when I moved to Beijing, together with Feng Yang (Deputy Director of the Office of Emergency Response, National Health and Family Planning Commission) and Rongmeng Jiang (a famous expert at Beijing Ditan Hospital, with whom I worked on Ebola in Sierra Leone in 2014 for 2 months), I went to Xishuangbanna, Yunnan province, to handle a JE outbreak. There, I witnessed a 19-year-old stiffly lying in his father's arms, who could not speak and who could only pray from his eyes. The reason he developed JE was easy to understand – he had no money for vaccination, and he lived with his father in a sugarcane field that was full of mosquitoes.

1.5.7 Pertussis and Diphtheria

Pertussis: the incidence of pertussis in China ranged between 100/100,000 and 200/100,000 in the pre-vaccine era, with epidemics every 3–5 years. The pertussis incidence decreased substantially during the EPI era. However, an "underestimate" of incidence has been controversial in recent years due to antibiotic overuse. Prevention and control of bacterial diseases have again received attention by relevant disease control departments [1].

Diphtheria: the morbidity and mortality from diphtheria have been greatly reduced during the EPI era, and the incidence in recent years has been reduced to a surprisingly low level. Between 2003 and 2006, only ten cases were reported in China, and no cases have been reported since 2007 [1].

1.5.8 Development and Vaccination of Influenza A (H1N1) Vaccine

A pandemic caused by influenza A (H1N1) occurred in 2009. In early June, China established a coordination mechanism for development and research and production of influenza A (H1N1) vaccine composed of the National Development and Reform Commission, MoH, the Ministry of Industry, China FDA, China CDC, the Chinese Institute of Control Pharmaceutical and Biological Products, and ten influenza vaccine manufacturers. China CDC organized and implemented a clinical trial of influenza A (H1N1) vaccine. More than 13,000 volunteers were vaccinated with the vaccine. All NIP staff went to the sites for implementation of this trial. Thanks to the support by colleagues of the provincial CDC, this historically largest vaccine clinical trial in China was successfully completed. Huaqing Wang and I witnessed the first dose injected to Minister Zhu Chen in his office, after he volunteered to receive the vaccine.

At the beginning of June, China's H1N1 influenza vaccine production companies obtained vaccine seed virus from WHO and developed/produced the vaccine according to the production process of seasonal influenza vaccine for clinical trials. The clinical trial began on July 22, and applications for licensure by eight producers were submitted starting in early September after on-site inspection, registration inspection, review, and evaluation.

On September 8, 2009, Health Minister Zhu Chen said China was the first country in the world with an H1N1 influenza vaccine. Zhu Chen said at a press release that China successfully conducted a clinical trial of the vaccine and demonstrated the safety and effectiveness of H1N1 influenza vaccine on September 7. After licensure, the State Food and Drug Administration released the first batch of qualified vaccine, and China became the first country with an H1N1 influenza vaccine.

Subsequently, high-quality AEFI surveillance was conducted; AEFIs were reported daily. A study to determine whether there was a relationship between acute

flaccid paralysis and the H1N1 vaccine was published in the *New England Journal of Medicine*; the study provided strong evidence that the H1N1 vaccine would not cause GBS.

1.6 The Future of Immunization Program

I left NIP, China CDC, after working there for 10 years. My mind is still attached to NIP. China's EPI has achieved fruitful outcomes. Through the effort of several generations of EPI staff, smallpox and polio were eradicated; China has moved solidly toward the goal of measles elimination; the HBsAg prevalence declined greatly; incidences of hepatitis A, meningococcal disease, and Japanese encephalitis have decreased continuously. Especially since 1978, when EPI was implemented, the incidence of NIP vaccine-preventable infectious disease has decreased by 99%. NIP has played an invaluable role in the protection of people's health, increasing life expectancy, resulting in huge economic benefits and persistent social benefits.

However, with the progress and expanding of immunization program, China's NIP faces an unprecedented opportunity for development and at the same time faces many difficulties.

When the essay was close to being completed, the "illegal sales of vaccine in Ji'nan Shandong" occurred. The impact of the event on vaccination was unprecedented in terms of the scale and significance. Its conclusion will reveal itself later.

Due to an imbalance of economic development in China, neither a long-term financing-guaranteed mechanism for vaccination nor policies for financing the immunization program were established in some areas – especially in remote and poor areas. Financing challenges affect equity of EPI services. Major barriers to further development of NIP include the following: (1) inclusion of vaccination into the primary public health services, (2) funding for expansion of cold chain equipment, (3) subsidies for immunization services and emergency vaccination at the grassroots level, and (4) funding for NIP team construction. At the same time, we have to (1) prevent and block the transmission of imported poliovirus and maintain polio-free status, (2) rapidly control intermittent measles epidemics, (3) provide immunization services for migrant populations, (4) develop new vaccines and combination vaccines, (5) reduce vaccine wastage, (6) eliminate unsafe injection during vaccination, and (7) improve the sub-optimal AEFI compensation mechanism. The above issues may impede achievement of equity for the children's access to immunization services.

With the progress of China EPI, we need to (1) accelerate financing mechanisms for immunization; (2) strengthen the NIP team and manage the migrant population; (3) learn from international experiences to develop a reasonable vaccine evaluation mechanism; (4) fully utilize expert consultation to develop technical guidance and fully use the information management system; (5) develop new vaccines and combination vaccine by thorough integration of research, academia, and industry; and (6) continue maintaining "polio-free" status, eliminate measles, and control hepatitis B – all these to contribute to disease prevention and control in China.

China's immunization program will be upgraded to a new level with its brilliant future and with universal access to immunization services. At the same time, China's vaccines will be exported to Asia and to the world to make new contributions to global immunization efforts. We believe that vaccination will continue to benefit children and make contributions to achieving the goals in Healthy China 2030.

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Immunization Services in China

2

Jingshan Zheng and Huaqing Wang

2.1 Immunization Management System

2.1.1 My Story with the Immunization Program

In July 1989, I (Jingshan Zheng) graduated from the Department of Public Health, School of Public Health, Tongji Medical University and was assigned to work at Jianli County Epidemic Prevention Station (EPS) in Hubei province. I worked in the Department of Epidemiology and was responsible for infectious disease surveillance and epidemic response, immunization services surveillance and management, prevention and control of parasitic diseases, disinfection, elimination of insects and mice, and prevention and control of sexually transmitted diseases (STDs).

When I began working, two important events took place in the history of China's disease prevention and control. The first event was that the "Law on Infectious Disease Prevention and Control in the Peoples Republic of China" was issued in 1989. The law required implementation of "a planned vaccination system" (similar to EPI) and a "vaccination card system" for children. The second event was that a goal to achieve vaccination coverage rates of more than 85% in every county was reviewed and agreed with by WHO China in 1990. The county I worked in was selected for review. I was placed in charge of the immunization program and was also responsible for assisting with surveillance, notifiable infectious diseases reports, and response to epidemics.

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In 1997 I moved to the provincial EPS (later renamed to CDC) to undertake the responsibility of surveillance and management of the immunization program. In the years following, I was responsible for routine immunization coverage surveillance (1998), acute flaccid paralysis (AFP) surveillance (1999), preparation of documents for certification of polio-free status (2000), measles case-based surveillance (2001), integration of hepatitis B vaccine into the immunization program (2002), immunization information management system and pilot project for adverse events following immunization (AEFI) surveillance (2005), and implementation of expanding the national immunization program's work (2007).

My understanding of EPI gradually deepened through personal engagement in the immunization program's work and by guiding grassroots-level staff to improve vaccination coverage rates and improve quality of immunization information management, learning from experienced leaders and experts, participating in professional conferences and training courses organized by higher levels, and learning from grassroots EPI staff.

2.1.2 The Network for Immunization Services and Management [1]

After the implementation of EPI in China in 1978, a network of immunization services and management was established that consisted of a specialized department in all four levels of disease prevention and control institutions – national, provincial, prefecture, and county levels. Points of vaccination (PoV) were established at township (town, street, community) and village levels.

In the early days of EPI, the work of vaccination was largely undertaken by village doctors. The facilities were quite poor, and village clinics often had no specific vaccination room or vaccination space. In many clinics, vaccination and treatment were done in the same room. Immunization services were usually provided once every 2 months and once a month if conditions allowed. Management of vaccination information was relatively backward, and vaccination cards for children 0–7 years of age were usually written by village doctors. Every time a vaccination round was conducted, village doctors had to look through every vaccination card to find children targeted for vaccination. Parents were informed by house-to-house visits, by village staff, or by public broadcasts to bring their children to the clinic for vaccination. In many areas, village doctors carried vaccine carriers containing ice packages on their backs to travel house to house and vaccinate. Because vaccination was provided by the village, the number of PoV was huge. According to the National Immunization Review, there were more than 360,000 PoVs across China [2].

In 2005, the State Council issued a document called "Regulations on Vaccine Distribution and Vaccination Management" [3] (hereinafter referred to regulations). Subsequently, county health administrative departments began to manage the PoVs according to a strict qualification system. The eighth provision in the regulations stipulated that only health sector PoVs designated by the county health administrative departments were qualified to vaccinate. When county health departments

designate PoVs, the geographical locations for which PoVs were responsible had to be made clear. The 21st provision in the regulations required that PoVs should meet the following criteria: (1) the PoV must have a license to practice; (2) the PoV must have qualified medical practitioners, physician assistants, nurses, or village doctors who were trained by county-level health administrative departments; (3) the PoV must have refrigeration facilities and equipment that meet requirements for vaccine storage and transportation and cold chain management.

After implementation of the regulations, standardized PoVs and fixed PoVs in villages and in hospital obstetric departments were further strengthened throughout China. More stringent PoV hardware and software requirements were put forward by health administrative departments, resulting in improved conditions of PoVs. In some areas, so-called qualified PoVs, model PoVs, standardized PoVs, digital PoVs, star PoVs, and warm PoVs were constructed to provide standardized, comfortable, and safe vaccination environments for children. Specifications for these clinics were indicated clearly in terms of area, functional zoning (generally including waiting, registration, vaccination, observation, cold chain, and data management), use of different rooms or tables for vaccination, frequency of immunization service provision (according to daily, weekly, or 10-day schedules), immunization information management, and vaccination publicity, among other things.

2.1.2.1 Vaccination Services Sites

According to the 2013 National Immunization Program Review, there were 216,269 PoVs in China in 2013. Among these, 50,859 (23.5%) provided centralized vaccination services at town or township levels, 131,642 (60.9%) were fixed-point clinics at the village level, 20,536 (9.5%) provided home-based vaccination, and 13,232 (6.1%) were located in obstetric departments or other facilities. Other than the PoVs in obstetric departments and other facilities, the remaining 203,037 PoVs provided services for an average population size of 6604 persons per PoV (30,648 per urban PoV, 19,551 per rural PoV, 1743 people per fixed, village-level PoV).

Compared with a survey conducted in 2004 [2], the total number of PoVs had been reduced by 41.1% by 2013, mainly through decreases in house-to-house PoVs (an 82.5% reduction) and village-level PoVs (a 31% reduction). The percent of the population served in urban area and township PoVs increased from 62.6% to 80.5%, while the population served by house-to-house PoVs decreased from 12.3% to 3.5% (Fig. 2.1).

2.1.2.2 Vaccination Service Frequency

According to the 2013 National Immunization Program Review, among 81,819 POVs studied (excluding PoVs in obstetrics departments), 14,847 (18.1%) provided daily vaccination and covered 45% of the population; 8565 (10.5%) provided weekly vaccination and covered 30.3% of the population; 6682 (8.2%) PoVs provided vaccination services once every 10 days and covered 7.5% of the population; 51,709 (63.2%) provided monthly services and covered 17.1% of the population; and 16 (0.02%) provided bimonthly vaccination services and covered 0.1% of the population.

According to the 2004 evaluation [2], the proportion of PoVs providing daily, weekly or 10-day, monthly, and bimonthly vaccination were 2%, 5.6%, 42.8%, and

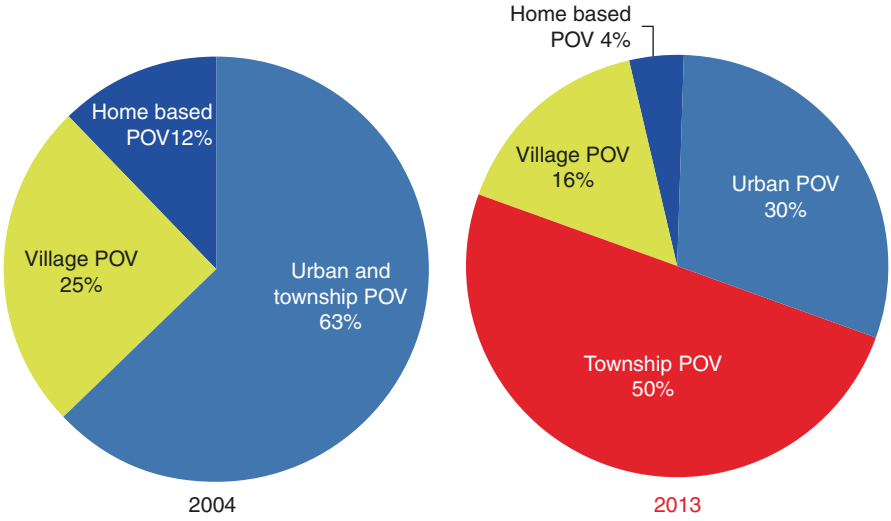

Fig. 2.1 Proportion of population by PoV types. Comparison between 2004 and 2013

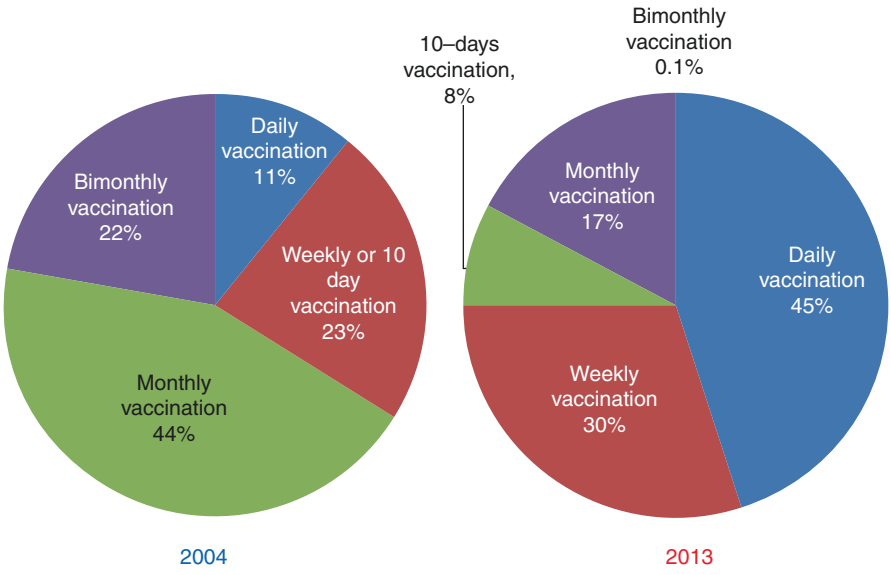

Fig. 2.2 Population covered by PoV service type. Comparison between 2004 and 2013

46.8%, respectively, and covered 10.4%, 22.6%, 43.2%, and 22.1% of the population, respectively. Compared with 2004, POVs providing daily and weekly (or 10-day) vaccination services had increased significantly by 2013, with a larger population covered and a decrease in PoVs providing only bimonthly vaccination services. PoVs providing monthly vaccination increased, but the population they covered declined (Fig. 2.2).

2.1.2.3 Standardization of PoVs

Standardized PoVs refer to PoVs at the township level that are approved by the health administrative department and trained and qualified professional and technical personnel with fixed vaccination spaces and equipment and provide vaccination services at set times and sites in accordance with the "Working Standards on Immunization." A project on standardized PoV construction was initiated in Jiangsu in 1988 and expanded to the whole of China by 2000.

The construction of standardized PoVs was an innovative activity that upgraded traditional PoVs to a standardized, information-rich, scientific management system. This effort was a "people-oriented, high-quality service" project that represents an important strategy to improve the quality of immunization services and support a sustainable national immunization program. This work also demonstrated an important guarantee to carry out a "prevention first" policy and to strengthen grassroots capacity – especially construction of healthcare systems in rural areas that serve to prevent and control infectious diseases.

Through the construction of standardized PoVs, the quality and level of vaccination was greatly improved, and the prevention and control of infectious diseases was improved in the following ways:

Development of a primary healthcare (PHC) network at the grassroots level to meet the public health demand. According to the requirements for PoV construction, qualified professional and technical personnel should be allocated appropriately for duties and responsibilities, with consideration of the population size and the area and geographical conditions of the administrative region. Thus, PHC services are to be undertaken by qualified staff in an improved service environment to satisfy the health needs of the public.

Standardization of vaccination practices. Centralized service delivery, a high technical level of vaccinators, and a clean environment improved the quality of vaccination services while preventing loss of vaccine potency. Standardized vaccination practices reduced cross infection and vaccination accidents, facilitated timely treatment of adverse events following immunization (AEFI), and ensured the safety of vaccination.

More vaccination opportunities improved vaccination coverage. Standardized POVs provided more vaccination services per month and longer vaccination sessions, increasing opportunities for vaccination and increasing vaccination coverage levels. At the same time, development of the immunization program was promoted by the improvement of the working environment and the skills and professionalization of the vaccinators, leading to greater trust in vaccination by the general public.

Improvement of PoV efficiency. Standardized PoVs facilitated immunization information management and solved management problems with vaccination of migrant children. Vaccination cards, certificates, and records were improved. Statistical data were more accurate and reliable, and efficiency was greatly improved.

Reduction of vaccine wastage. Standardized PoVs provide services for more people per session, which may reduce vaccine wastage.

Development of technologies for communication and information management enabled automatic short message service notifications to be used through the immunization information system, QQ, WeChat, and other social media channels to

inform parents of upcoming vaccination visits and make the visits more timely and efficient. Information sent to parents included the vaccines to be administered, the appointment time and location, and any precautions for the vaccines.

2.1.2.4 Management System and Coordination of the Immunization Program

The Chinese government has always attached great importance to immunization, giving strong support through laws, regulations, policies, personnel, and funding.

In 2005 the State Council issued the regulations, and then the Ministry of Health issued "Standards for Vaccination" (2005), "Vaccine Storage and Transportation Management Standards" (2006), and "Identification of AEFI" (2008) to standardize technology, terminology, and performance management of the immunization program.

A national immunization coordination committee was established in 1996 after being approved by the State Council. It consisted of the MoH, the Ministry of Education (MoE), the National Women's Federation, the Ministry of Broadcast and Television, the Ministry of Foreign Trade and Economic Cooperation, and the National Ethnic Affairs Commission, among other organizations.

After expanding the national immunization program in 2007 through the addition of new EPI vaccines, the State Council established an immunization coordination mechanism. In this mechanism, MoH is responsible for development and implementation of the national immunization program and for conducting its annual planning process. The Ministry of Finance (MoF) is responsible for immunization program fiscal policy. The National Development and Reform Commission is responsible for storage and distribution of NIP vaccines and for confirming prices of the vaccines. MoE is responsible for checking vaccination cards when children enter kindergarten and primary school – a strategy that has been included into the management system for infectious disease prevention and control. The Chinese Food and Drug Administration (CFDA) is responsible for monitoring and management of production and distribution of NIP vaccines. Local institutions of health, finance, development and reform, education, food, and drug administration are to establish appropriate coordination mechanisms under the leadership of local governments. Local governments are charged with strengthening organization and leadership, clarifying responsibilities, strengthening coordination and cooperation, and improving implementation and management of EPI.

2.1.2.5 Government Increased Investment in Vaccination

After expanding NIP in 2007, the central government increased the program's budget from 210 million yuan in 2006 to 2.7 billion yuan – primarily for the purchase of vaccines and syringes and for subsidies for middle and western underdeveloped areas. In 2008, an additional 374 million yuan were allocated as supplementary funds for cold chain improvement in western provinces. Local governments included NIP-related indicators into their social development indicator system, enhancing policy support and funding for NIP. After 2010, vaccination services

were included into the integrated management system for the primary public health services, with vaccination subsidies covered by primary public health services funding.

2.1.2.6 Establish and Improve the Vaccine Cold Chain System

China began to work with UNICEF on cold chain projects in 1981. By the mid-1980s, more than 90% of the population was covered by an improved cold chain management system. From 1996 to 2004, China used a loan of 716 million yuan from the World Bank (Health VII Project) to supplement cold chain equipment in ten provinces in the middle provinces of China, including Gansu, Guangxi, Guizhou, and other provinces. After the expansion of NIP, the investment in cold chain infrastructure was increased in parallel. The central government invested 374 million yuan in the middle and western provinces for cold chain development in 2009, addressing needs for their cold chain operations.

2.1.2.7 Establish and Improve Surveillance Systems

Beginning in 1991, China gradually established surveillance systems for the immunization program, including a system for measuring routine immunization coverage (1991), vaccine management (2007), cold chain management (2010), AEFI (2005), AFP(1991), measles (2002), hepatitis B (2002), Japanese encephalitis (2007), and meningococcal meningitis (MM) (2008). Several of these were integrated with the laboratory surveillance network, for example, the polio, measles, JE, and MM laboratories. Establishment and optimization of surveillance systems played a critical role for evaluation of progress of the immunization program, timely detection of epidemics and epidemic risk, control and elimination of vaccine preventable diseases, and enhancement of the capacities for surveillance and management of the immunization program.

2.1.2.8 Professional Advisory Groups for Immunization

A National Immunization Technical Advisory Group (NITAG) was established for EPI under the Ministry of Health. As a technical advisory group, the NITAG plays an important role in development of policy and technical guidance for China's immunization program.

NITAG had its origins as the EPI committee under the Medical Sciences Committee of MoH, which had been established in October 1982 along with six regional coordination committees for EPI. In June 1988, the EPI committee was placed under MoH and consisted of 26 members. In October 1992, the membership partially changed and the committee was increased to 28. In March 1997, the composition of the committee was changed to be 27 members with 3 consultants. In October 2004, the EPI committee was renamed to the "NITAG of MoH" and consisted of 30 members: 1 chairman, 3 vice chairmen, and 26 members. In 2010, MoH established a subcommittee for the immunization program consisting of 29 members, under the Expert Committee for Disease Prevention and Control. The subcommittee for the immunization program included experts in vaccine development,

vaccine identification, pediatrics, infectious diseases, immunology, health policy and management, public health, epidemiology, and health statistics.

2.2 Human Resource for Immunization Program

2.2.1 Personnel for Surveillance and Management in China CDC [4]

According to the "standards of immunization," relevant professional and technical personnel should be allocated based on responsibilities and duties, taking into account population size, service area, and geographical conditions in the administrative regions at CDCs. Personnel in immunization program at CDCs are mainly responsible for surveillance and management of the immunization program.

2.2.1.1 Provincial-Level Immunization Program Staff

There were 453 provincial immunization staff members in 2004, with an average of 14.5 staff members per province. The technical/professional titles of provincial immunization staff were usually intermediate and junior, accounting for 33.55% and 30.02% of staff, respectively (Table 2.1). Their educational levels were most commonly university and college, accounting for 50.55% and 24.06% of staff (Table 2.2).

2.2.1.2 Prefecture-Level Immunization Program Staff

A comprehensive review in 2004 showed that there were 518 prefecture-level immunization staff, with an average of 6.5 staff members per prefecture. The number of staff differed widely among prefectures – for example, there were 26 staff in Qingyuan, Guangdong province, and only 1 staff person in Haidong, Qinghai province. Technical titles of prefecture-level staff were generally intermediate and junior level, accounting for 41.70% and 38.03% of staff members. Their educational levels were generally university and secondary technical school, accounting for 31.21% and 34.30% of staff.

2.2.1.3 County-Level Immunization Program Staff

In 2004, there were 596 immunization staff members, with an average of 6.4 staff per county. The number of professional staff varied widely among counties – for example, there were 23 staff in Ulanhot County in Inner Mongolia, but no

Table 2.1 Technical title of immunization staff at provincial, prefecture, and county level in 2004

	Staff	Title of professional staff								
Level	Total	Average	Senior	%	Intermediate	%	Junior	%	No title	%
Provincial	453	14.6	123	27.15	152	33.55	136	30.02	42	9.27
Prefecture	518	6.6	79	15.25	216	41.70	197	38.03	26	5.02
County	596	6.4	18	3.02	168	28.19	335	56.21	75	12.58

Table 2.2 Educational level of immunization staff at provincial, prefecture, and county level in 2004

	Staff	Education										
Level	Total	Average	Postgraduate	%	University	%	Junior college	%	Secondary technical school	%	No	%
Provincial	453	14.6	35	7.73	229	50.55	109	24.06	63	13.91	17	3.75
Prefecture	518	6.6	9	1.73	162	31.21	143	27.55	178	34.30	27	5.20
County	596	6.4	2	0.34	65	10.92	191	32.10	275	46.22	62	10.42

immunization staff in Rongjiang County, Guizhou province. Technical titles of these staff were usually junior level, accounting for 56.21% of staff. Education levels were mainly junior college and technical secondary school, accounting for 32.10% and 46.22% of staff.

2.2.1.4 Immunization Program Staff in 2013

According to a review in 2013, there were 568 province-level immunization staff members, for an average of 17.8 staff per province. Beijing had the largest number of EPI staff (33), and Xinjiang Constructive Military Corps had the fewest (4). Among the 310 sampled prefectures, there were 1987 prefecture-level immunization staff members, for an average of 6.4 staff per prefecture, similar to results in 2006. Among the 947 counties studied, there were 4486 county-level immunization staff – an average of 4.74 per county.

2.2.2 Township and Village Immunization Program Staff

Township and village immunization staff are mainly responsible for basic immunization services, although some staff members also conduct surveillance and management for the local immunization program.

In accordance with the regulations, vaccinators should have a valid certificate as a practicing physician or as an assistant practicing doctor, nurses, or village doctors. He or she should be trained by country health administrative departments and must have passed relevant examinations.

In 2004, there were 9683 staff in 186 township hospitals that were studied, among whom included 1111 healthcare and prevention staff, accounting for 11.47% of the total staff. Among the healthcare and prevention staff, there were 855 immunization staff, accounting for 76.96% of this group of professionals; 475 were full-time staff, accounting for 4.9% of total staff at the township hospital.

A comprehensive evaluation showed that there were 4761 village doctors, among whom 1807 engaged in the immunization program, accounting for 37.96% in total village doctors, an average of 1 staff per village. The difference in number of immunization staff was related to the types of vaccination services provided.

In 2013 an NIP evaluation showed that there were 65,709 township immunization staff in 947 counties surveyed, an average of 69.4 staff per county. Compared with 2004, the average number of immunization staff per county increased by 13.9 (27.2%). There were 108,068 village-level vaccination staff, an average of 114.1 per county, and a decrease of 6.3% compared to 2004.

2.2.3 Training of Immunization Program Staff

In the early days of EPI, China established a cascade training system for immunization staff in order to improve operational and management quality.

2.2.3.1 Training Models

In addition to a traditional training model in which the national level trains the provincial level, the provincial level trains the prefecture level, the prefecture level trains the county level, and the county level trains the township level; higher levels can train more than the level immediately below them. For example, the province level trains the county level, and the county level trains the village level to reduce the number of levels of training and to improve the training outcomes.

In addition to conventional lectures in training courses and routine meetings, a "participatory (interactive) training method" was introduced in China to train immunization staff. The new training methods include small-scale lectures, group discussion, case studies, role play, debate, games, skill demonstration and practice, and interpersonal communication skills.

2.2.3.2 Training of Staff

According to an NIP review in 2004, provinces conducted two to seven training courses each between 2002 and 2003, with various types of training conducted in most of the prefectures, counties, and townships (Table 2.3). Townships trained village staff in meetings. In the townships evaluated, 66.9% of the village doctors were trained by higher levels. Detailed information is presented in the table below.

After adding new vaccines to the routine immunization schedule in 2007, all provinces conducted training for the expanded schedule. According to preliminary results, all 31 provinces and Xinjiang Construction Military Corps conducted training on the expanded NIP in 2007–2008, with a total of 421,984 individuals trained.

2.3 Vaccination Service Model at Grassroots Level

2.3.1 Grassroots Vaccination Service Patterns

Vaccination service delivery is divided into routine immunization and vaccination campaigns.

Table 2.3 Training of immunization program staff in 2002 to 2003

Level	No. investigated	No. providing training	Training number	Average days per training	Number of persons trained	Average persons trained per time
Provincial	31	31	151	3.6	12,145	80.4
Prefecture	79	67	207	1.9	15,004	72.3
County	93	78	261	1.5	14,041	53.8
Township	187	175	2885	89.9	61,221	21.2

2.3.1.1 Routine Immunization [5]

Routine immunization implies that PoVs routinely provide vaccination service to age-eligible persons to prevent and control infectious diseases, in accordance with the current schedule of NIP vaccines, the "China Pharmacopoeia (3rd edition, 2005)," or the vaccine label, which is developed based on the epidemiology of the disease and the local vaccination plan.

2.3.1.2 Vaccination Campaigns

Vaccination campaigns are centralized vaccination services provided at certain locations and time, targeting specific populations for one or more infectious diseases. Vaccination campaigns are divided into three categories – supplemental, emergency, and concentrated.

Supplementary immunization activities (SIAs) A SIA is a mass vaccination campaign targeting certain populations within a short time period, based on the epidemiology characteristics of infectious diseases, herd immunity, and objectives for control of the disease. SIAs are conducted regardless of the vaccine history and have a purpose to rapidly increase the vaccination rate to establish an effective immunity barrier and protect the susceptible population.

Currently, the vaccines most commonly used in SIAs are oral poliovirus vaccine (OPV) and measles vaccine. Polio vaccine SIAs are divided into national SIAs and local SIAs according to geographical scope, while measles SIAs are generally divided into initial SIAs and follow-up SIAs. Follow-up SIAs are conducted periodically (such as every 3–5 years) after the initial SIA in order to accelerate control of measles.

Emergency response vaccination Emergency response vaccination means vaccination targeting a susceptible population in order to control an outbreak or when there is an epidemic trend.

Emergency response vaccination during outbreaks and epidemics of infectious diseases should be approved by the governments or the public health administrative institutions at county level or above, in accordance with the law and the "Regulations on Response to Public Health Emergency." Emergency vaccination should follow the "regulations." Emergency response vaccination action plans are developed by CDCs, and the appropriate vaccination patterns are selected and conducted as soon as possible.

Concentrated vaccination Routine immunization services are generally provided one to three times every year for eligible children in remote areas, such as islands, plateau pastoral, and other inaccessible areas, often through a house-to-house approach. This model of vaccination is also referred to as concentrated vaccination.

Concentrated vaccination was widely used in China before expanding NIP. After China expanded NIP, there is a requirement that at least six rounds of vaccination should be provided every year. Concentrated vaccination is being used less often, but it is still used in isolated, remote areas with poor transportation and adverse climate. The NIP review in 2004 showed that in some areas of Tibet, concentrated vaccination was still used quarterly or semiannually to provide vaccination services.

2.3.2 Grassroots Vaccination Service Pattern and Frequency

Grassroots vaccination service patterns and frequencies can be divided into several common types, such as fixed PoV, home-based PoV, and temporary PoV.

2.3.2.1 Fixed PoV

Fixed PoV refers to the PoVs that have been established by health administrative departments at the county level or above that provide immunization services for those visiting the PoV. Fixed PoVs are at healthcare institutions at the township level or above or are at village clinics. Fixed PoVs can be divided into vaccination outpatients, village PoV, and PoV at birth.

Vaccination Outpatient Services

According to the regulations, health institutions in urban areas and towns should establish vaccination outpatient services based on population density, age-eligible population size, and service radius. Vaccination can be provided on a daily, weekly, or every 10-day basis. Township hospitals establish vaccination outpatient services in rural areas when appropriate and provide centralized vaccination for the township on a periodic basis.

In general there are strict requirements for vaccination outpatient services in terms of room area, function partitioning, arrangement of vaccination room/table, vaccination personnel, vaccine refrigeration conditions, safety injection, publicity on vaccination, and room temperature, in order to provide children with a relatively warm, friendly vaccination environment with standardized vaccination services that facilitate the improvement of the quality of vaccination services.

In accordance with the regulations, standards and management of vaccination outpatient should be developed by provincial health administrative departments.

Village PoV

In rural areas, based on population density, traffic patterns, and service radius, one or several village PoVs are set up to provide fixed vaccination services on a 10-day, monthly, or bimonthly basis, with at least six rounds of services provided every year. Fixed PoVs are generally set in the village clinics.

Village PoVs can provide standardized vaccination services, with key characteristics.

Convenient The fixed PoV is usually set in appropriate geographic locations with convenient transportation, with services provided at fixed times. Village POVs generally have a service radius of less than 2 km. Some PoVs can provide comfortable conditions, providing heating in winter and cooling in summer.

Capable vaccine management Village PoVs make full use of modern cold chain equipment, such as purpose-built vaccine carriers and refrigerators, to ensure storage and transportation under temperature-controlled conditions to ensure vaccine potency.

Educational Village PoVs educate the general public on vaccination using posters and other teaching materials.

Combined with medical services Village PoVs can be combined with medical services in village clinics because regular emergency medicine is available. The capacity for observation after vaccination is also available in PoVs, providing ready access to medical equipment and trained staff for timely response to adverse reactions.

Designed for vaccination Fixed PoVs can be divided into appropriate functional areas that have different tables for different vaccines, in order to prevent administration of an incorrect vaccine and to ensure the safety of vaccination.

PoV at Birthing Facilities

In accordance with the principle of "the person who assists in the delivery should be responsible for vaccination," obstetrics departments of medical institutions are responsible for hepatitis B and BCG vaccine administration. Hepatitis B vaccination must be accomplished within 24 h of birth to prevent vertical transmission of hepatitis B.

In order to improve the timely hepatitis B vaccine vaccination rate, healthcare personnel at the hospital regularly go to obstetric departments to determine the condition of newborns and to prepare vaccines, equipment, and registration materials in advance. They provide the first dose of hepatitis B vaccine for the neonates within 24 h after birth. PoVs in obstetric departments of hospitals must have trained obstetric staff; have appropriate vaccine storage equipment; have sufficient hepatitis B vaccine, vaccination equipment, and registration materials in hand; and have a specialized vaccination room and table available for use. After childbirth, the first dose of hepatitis B vaccine and BCG is administered directly to the newborn by obstetric staff.

2.3.2.2 Home-Based Vaccination

In remote mountainous areas, islands, pastoral areas, and other inaccessible areas, home-based vaccination is used to provide convenient and timely services to children. Home-based vaccination has the following requirements:

- Vaccination services should be provided at a frequency of no less than six times per year.

- Vaccination dates should be set for a time that is convenient for most people.
- Information about the vaccination should be sent to the child's guardian prior to visit so that during the vaccination visit, the child and guardian will remain at home, prepared with the child's vaccination card.
- The vaccines must be stored in the specified temperature conditions in vaccine carriers in order to ensure potency. In cold areas, when removing vaccines from a vaccine carrier, it is also necessary to take measures to prevent hepatitis B, DPT, and DT vaccines from freezing.
- For home-based vaccination, special attention should be paid to multidose vaccines, such as BCG, DPT, DT, and measles vaccines to ensure sterile conditions for the vaccine and use of the vaccine within a specified time period.
- Safe injection practices and proper waste disposal must be used at all times.

2.3.2.3 Temporary PoV

When a mass vaccination campaign or an emergency vaccination is conducted in gathering areas of certain populations, such as migrant communities, temporary PoVs can be used to provide vaccination services to supplement fixed PoVs and home-based PoVs. The following requirements apply to temporary PoVs:

- Temporary PoVs should be fixed PoVs when possible. This can help ensure appropriate cold chain and safe injection practices. Informed consent before vaccination, observation after vaccination, and timely treatment of adverse reactions must be strictly observed.
- Temporary PoVs can be set up in school medical facilities, meeting rooms or offices in some institutions, and health rooms or clinics. Eye-catching signs should be used. A temperature-controlled environment is preferred for the comfort of those being vaccinated.
- Temporary PoV should supplement fixed PoVs and home-based PoVs. Age-eligible children who lack cards and records should still be vaccinated to avoid missed opportunities. Vaccinations performed in temporary vaccination PoVs should be included in the local children's routine immunization management system. Immunization cards and records should be obtained as soon as possible, and missed NIP vaccines should be provided in accordance with the vaccine schedule.

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Establishment and Development of the Disease Surveillance System

3

Ning Wen

3.1 Basics of Disease Surveillance

3.1.1 Definition of Disease Surveillance

Disease surveillance is the long-term, continuous, systematic collection of information about diseases and their relevant influencing factors, followed by analysis of the data in a timely manner to guide intervention measures and evaluate their effectiveness. This definition reflects the three basic characteristics of disease surveillance: (1) distributions and trends of diseases can be evaluated only through long-term, continuous, systematic collection of data; (2) original data can be translated to valuable information only through analysis and interpretation of the data; and (3) results can be fully utilized in the real world only after information is provided back to the relevant departments and personnel – hence the importance of timely feedback.

3.1.2 Classification of Disease Surveillance

3.1.2.1 Passive Surveillance and Active Surveillance

Passive surveillance is when lower level units routinely report surveillance data that the higher level units passively accept. In contrast, active surveillance involves higher level units conducting specialized investigations or requiring lower level

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units to collect and report data in strict accordance with requirements. Notifiable infectious disease reporting that is used in most countries is passive surveillance. Special surveys, such as those conducted by CDCs in China to assess underreporting of infectious disease, and monitoring of certain diseases in accordance with standard requirements are examples of active surveillance. In general, active surveillance data quality is better than passive surveillance data quality.

3.1.2.2 Routine Reporting and Sentinel Surveillance

Routine reporting involves regular disease reports, which are used to understand the epidemiology of the disease. Routine surveillance collects data from all reporting resources (e.g., hospitals, institutions, or healthcare personnel). Examples are the notifiable infectious disease reporting system in all countries. The diseases covered vary by country. Sentinel surveillance refers to regular, quantitative monitoring of certain diseases in high-risk populations in well-described areas, depending on the epidemiological characteristics of the disease, with a purpose to understand more fully the epidemiology of the disease. Sentinel surveillance may require more time and resources than routine surveillance but generally provides more detailed information about the disease. An example is when nasopharyngeal swab samples are collected from each patient in selected areas where influenza sentinel surveillance sites are established to identify the type of influenza viruses circulating. The data collection method is not likely to be applicable to all patients but must be done systematically in sentinel surveillance.

3.1.2.3 Surveillance Cases and Actual Cases

Because there is no clear distinction between disease and health, when using clinical diagnostic criteria to detect cases, there will be a number of missed diagnoses and misdiagnoses. In public health surveillance, it is preferable to pay less attention to the accuracy of a diagnosis in an individual case but to emphasize unified, standard clinical diagnostic criteria with good potential for operationalization. Cases detected using the diagnostic criteria are called surveillance cases. The proportion of actual cases to surveillance cases should be as high as possible, and the relevant proportions and their variation should be estimated.

3.2 China's Notifiable Infectious Disease System

3.2.1 Diseases Included in Notifiable Infectious Disease System

The list of notifiable diseases differs in different countries. "Notifiable infectious disease" refers to an infectious disease that should be reported and for which patients should be treated and possibly isolated according to the law. Notifiable infectious diseases are often ones that spread fast and have severe outcomes and high fatality rates. According to the Chinese law, the notifiable infectious diseases in China are divided into categories A, B, and C, with different reporting requirements for each

category. There are 39 notifiable infectious diseases in China, including 2 category A diseases, 26 category B diseases, and 11 category C diseases.

3.2.2 History of Notifiable Infectious Disease Surveillance in China

Disease surveillance was initially established in the 1930s in China, when Keqian Chen conducted a small-scale epidemiological surveillance project in Ding county, Hebei province. After 1950, New China established an epidemic reporting system and began to monitor epidemics.

In June 1955, China MoH issued the first "Law on Infectious Disease Management" and established the national epidemic reporting system, in which the 18 notifiable infectious diseases were divided into category A or B. Three diseases belonged to category A: plague, cholera, and smallpox; 15 belonged to category B: Japanese encephalitis, diphtheria, typhus, relapsing fever, dysentery (bacterial and amebic), typhoid and paratyphoid, scarlet fever, meningococcal meningitis, measles, poliomyelitis, pertussis, anthrax, brucellosis, tick-borne encephalitis, and rabies.

In September 1978, there were 25 notifiable diseases, still divided into two categories. Starting September 1, 1989, the list of notifiable diseases was expanded to 35 diseases in three categories – A, B, and C. Two diseases were category A, plague and cholera; 22 were category B, viral hepatitis, bacillary and amebic dysentery, typhoid and paratyphoid, AIDS, gonorrhea, syphilis, poliomyelitis, measles, pertussis, diphtheria, meningococcal meningitis, scarlet fever, epidemic hemorrhagic fever, rabies, leptospirosis, brucellosis, anthrax, epidemic and endemic typhus, JE, malaria, dengue fever, and Kala-azar; and 11 were category C, tuberculosis, schistosomiasis, filariasis, echinococcosis, leprosy, influenza, mumps, measles, neonatal tetanus, acute hemorrhagic conjunctivitis, and infectious diarrhea other than cholera, dysentery, and typhoid and paratyphoid.

In December 2004, SARS and human infection from highly pathogenic avian influenza were included into category B reportable diseases, and some diseases were moved between categories B and C. In May 2008, hand, foot, and mouth disease was included into category C, and on April 30, 2009, influenza A/H1N1 (formerly called swine flu) was included into category B.

In October 2013, avian influenza H7N9 infection was included into category B; influenza A/H1N1 was moved from category B to category C and was incorporated into the management system for seasonal influenza; human infection with highly pathogenic avian will no longer be prevented and controlled as category A.

3.2.3 Noncommunicable Disease Surveillance

With the changing spectrum of human morbidity and mortality, the diseases covered by surveillance were expanded to noninfectious diseases, such as malignant tumors,

cardiovascular and cerebrovascular diseases, occupational diseases, birth defects, and other noncommunicable diseases.

3.2.4 Other Public Health Surveillance

In order to achieve specific public health goals, various surveillance activities are conducted, including environmental surveillance, nutrition surveillance, infant and maternal mortality surveillance, adverse drug reaction surveillance, family planning surveillance, and other conditions or events as needed to assess progress toward goals.

3.3 Surveillance of Vaccine-Preventable Infectious Disease in China

The ultimate goal of the immunization program is to control and eliminate infectious diseases.

In addition to routine surveillance of infectious diseases, some diseases targeted by the immunization program required specific surveillance. Poliomyelitis serves as a good example. The acute flaccid paralysis (AFP) surveillance system was established in 1991, in which all acute flaccid paralysis cases of unknown cause among children under 15 years old were identified and evaluated. The AFP surveillance system has played a critically important role in the polio eradication program.

3.3.1 Acute Flaccid Paralysis (AFP) Surveillance System

3.3.1.1 Establishment of the AFP Surveillance System in China

The AFP surveillance system was established in the context of polio eradication: The WHO region of the Americas (PAHO) adopted a goal in 1985 to eradicate wild poliovirus by 1990, and in 1988, the WHO Western Pacific Region (WPRO) adopted a goal to eradicate poliomyelitis by 1995. As a member of WPRO, China committed to eradication of poliomyelitis in 1991. Jiangsu, Shandong, Henan, Hebei, and Anhui provinces set up AFP surveillance systems that year, and the system was called the polio special reporting system. MoH issued the "polio special reporting standard" in 1992, and the system was renamed as the AFP surveillance system in 1994. The polio special reporting system included a computerized database for AFP cases: a zero-case reporting database and a polio laboratory database at provincial Epidemic Prevention Stations (EPS, subsequently renamed to CDC). In 1993, except for Tibet, all provinces in China established AFP surveillance systems. AFP cases were reported by hospitals and by personnel at the county level CDC through active surveillance. Surveillance data were collected and summarized level by level. Since 1995, the AFP surveillance system has become better and better, and surveillance quality has been gradually improved. More than 5000 AFP cases have been

reported annually with an AFP rate of more than 1/100,000 in China among children under 15 years old.

3.3.1.2 Definition for AFP Surveillance

The AFP surveillance system reports all cases with acute flaccid paralysis symptoms in children aged less than 15 years and all clinical polio cases regardless of age.

The clinical features of AFP are acute onset, decreased muscle tone, decreased muscle strength, and decreased or nonexistent tendon reflexes. Because several diseases have similar clinical features, AFP is monitored in order to detect possible polio cases.

The most common diseases diagnosed among AFP cases in China are (1) poliomyelitis; (2) Guillain-Barre syndrome (infectious polyradiculitis, GBS); (3) transverse myelitis, myelitis, encephalomyelitis, and nerve root acute myelitis; (4) polyneuropathy (multi polyneuropathy due to drug, toxic substances, and unexplained reasons); (5) nerve root inflammation; (6) traumatic neuritis (including neuritis due to injection in gluteal muscle); (7) single neuritis; (8) plexus neuritis; (9) periodic paralysis (including low potassium paralysis, high potassium paralysis, and normal potassium paralysis); (10) myopathy (including myasthenia gravis, poisoning, and unexplained myopathy); (11) acute polymyositis; (12) botulism; (13) quadriplegia, paraplegia, and monoplegia (unknown cause); and (14) transient limb paralysis.

3.3.1.3 Change of Reporting Patterns

The reporting pattern in China experienced four stages: in the first stage, paper-based reports were used; in the second stage, paper reports were augmented with computer-disk reporting; in the third stage (2004–2011), internet browser reporting was used; and in the fourth stage, beginning in 2012, direct reporting through the Internet was integrated into the notifiable infectious disease reporting system.

From 2004 to 2011, a client-server system was used for China's AFP surveillance. The "clients" were at provincial, prefecture, and county levels; they used software to download data from the national server and used analysis functions in the client software to identify and characterize AFP surveillance indicators. This client-server system made it easier to collect AFP surveillance data with automatic analyses, although some disadvantages continued to exist. First, the client software needed to be upgraded to keep pace with surveillance standards. However, each time the client software was upgraded or personal computers were upgraded or reinstalled, the client software need to also be reinstalled, making maintenance of client software burdensome. Second, AFP data need to be uploaded to the national server through the clients' software without real-time uploading and updating of the data between the client software and server.

To further improve the sensitivity of the surveillance system and learn the features of AFP cases in a timely manner, a direct reporting system through the Internet was implemented in 2012. It was called the "acute flaccid paralysis surveillance information report and management system" (hereinafter refer to real-time online

AFP surveillance system). The system, which uses Internet browsers, is considered a real-time surveillance system. Data entry is performed through a personal computer using web browsers to log on to the national server. The system has been improved and upgraded continuously to meet the needs of AFP surveillance; however, most upgrades need to be done only on the server side. All case information is transferred to the server on a real-time basis. Persons with access authority can obtain access to the real-time data and can conduct analyses to determine results in real time. This system is divided into three modules: case reporting, case information management, and data analysis. Specific administrative rights are allocated to staff commensurate with their roles in AFP surveillance.

The process of AFP reporting and management is as follows. Medical institutions and county CDCs with reporting permission report AFP cases by completing an "infectious disease reporting card" in the "real-time online AFP surveillance system." Epidemiologists at county CDCs conduct epidemiological investigations of AFP cases after receiving AFP reports; they collect stool samples during this time. The CDC with proper authority enters data in the "real-time online AFP surveillance system," including epidemiological information and stool sample collection dates. Stool samples are sent by county CDCs to province CDC laboratories, and staff at provincial laboratories enter the "real-time online AFP surveillance system" to indicate receipt of stools and results of laboratory tests when they are available. If the laboratory result is positive for poliomyelitis, samples are sent to the national laboratory for detailed characterization. Provincial laboratories enter the "real-time online AFP surveillance system" to complete the feedback loop from the national laboratory. County CDCs conduct follow-up investigations of AFP cases and enter investigation information into the system. A provincial expert group makes the final diagnosis and classification of AFP cases to determine whether polio is excluded or not. After final diagnosis and classification, staff at provincial CDC enter the final diagnostic classification into the "real-time online AFP surveillance system" (Fig. 3.1).

The polio laboratory network is an integral component of AFP surveillance. Established in 1992, China's polio laboratory network consists of polio laboratories at China CDC (certificated as Western Pacific Region's reference laboratory by the WHO in 1995) and 31 provincial CDCs.

Cell culture, virus isolation, and serological identification are performed at the provincial polio laboratories using reagents, cell lines, and procedures recommended by the WHO. All polioviruses isolated by provincial polio laboratories are sent to the national polio laboratory for type identification, sequencing, and other analyses. The responsibilities of national polio reference laboratory include type identification and distinguishing vaccine strains from vaccine-derived polioviruses (VDPVs) and wild polioviruses. Differences from vaccine strains are determined using polymerase chain reaction – restriction fragment length polymorphism (PCR-RFLP) or enzyme-linked immunosorbent assay (ELISA).

The national polio reference laboratory is one of the three WHO-certified reference laboratories in the Western Pacific Region. In accordance with WHO certification standards, China's provincial polio laboratories have also been certificated as national level polio laboratories.

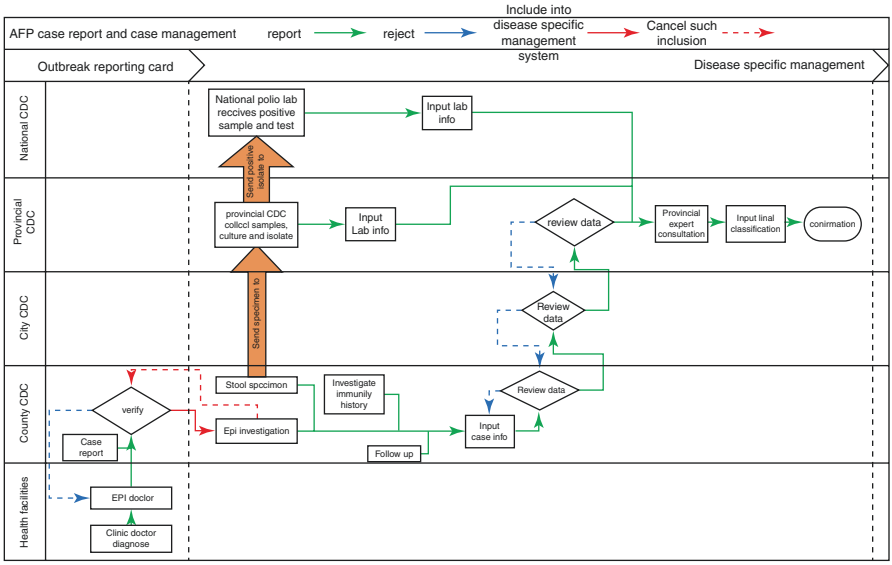

Fig. 3.1 Procedure of the Real-time Online AFP Surveillance System

As a reference laboratory in the Western Pacific Region, on-site certification and performance assessment of China's national polio laboratory has been conducted by WHO experts every year since 1996. On-site certification and performance assessment of provincial polio laboratories are conducted every 1–3 years, depending on the laboratory's most recent assessment result.

3.3.2 Other Disease-Specific Surveillance Systems

In addition to the AFP surveillance system, there are three other surveillance systems: measles, meningococcal meningitis, and Japanese encephalitis.

Measles surveillance data aggregated by province has been reported through the national notifiable disease reporting system (NNDRS) since 1959. In 1998 a standard NNDRS-based measles surveillance program was developed. The current real-time dynamic measles surveillance system (MSS) combined epidemiological and laboratory surveillance. From 2004, each province began to report measles cases through the "China Immunization Program and Surveillance Information Management System."

China established JE surveillance in 2007 and meningococcal meningitis in 2008. Surveillance systems play an important role in the control of diseases.

Adverse Events Following Immunization

4

Keli Li, Wendi Wu, Jiakai Ye, Disha Xu, and Dawei Liu

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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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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Innovative Vaccines in China

5

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5.1 Japanese Encephalitis Live Attenuated Vaccine

- The first vaccine in China prequalified by the WHO

Yongxin Yu is an academician at the Chinese Academy of Engineering and a highly respected person when it comes to Japanese encephalitis (JE) live attenuated vaccine (Fig. 5.1). After the JE vaccine he developed was approved and marketed in 1989, hundreds of million doses have been used, demonstrating the safety and effectiveness of this vaccine under large-scale use. The effectiveness of this vaccine is over 95%, as recognized by the WHO and other international organizations.

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Fig. 5.1 Academician Yongxin Yu

Academician Yu is one of China's most famous virologists and experts in biological products; he has received an outstanding contribution award by improving China's medical health. He is also a renowned scientist in China and in the world with his great contributions. His science is rigorous and realistic; pays attention to the accuracy, reliability, and integrity of the experimental data; and is loved by scientific and technological personnel.

5.1.1 The Severe Burden of JE

In 2014, Xu Bai, a Xinhua Net reporter, interviewed Yongxin Yu, who was then 85 years old, and still wore a white coat. Bai said, "he still cannot forget the epidemic of JE in the middle of the last century in China. At that time JE epidemics were very serious. According to Yu, the fatality rate was as high as 30% among children and usually followed by serious sequelae, including development of paralysis from brain damage in 10% of the individuals. There were many JE

patients in hospitals. In children's hospitals, the wards and the aisles were full of pediatric JE patients."

JE, also called Japanese encephalitis, is an acute infectious disease transmitted by mosquitoes with a high mortality and morbidity rate among its victims. JE is caused by the JE virus and is one of the most serious threats to the population, especially to children. With an acute onset, the disease presents with varying severity, ranging from latent infection to mild and to severe encephalitis. Severe cases always involve invasion of the central nervous system with high fever, convulsions, coma, spastic paralysis, and even death. Obvious complications nearly always occur in survivors, including persistent confusion and paralysis. Epidemics of JE occurred in the 1960s and early 1970s across China. There were different intensities of epidemics in China (including Hong Kong, Macao, and Taiwan) except for Qinghai, Tibet, and Xinjiang where JE is rare.

About 30,000–50,000 cases are reported globally every year with 15,000 deaths annually [1]. The actual number of patients is far higher than the reported figures due to lack of diagnostic capacity and reliable data. JE is highly endemic in Southeast Asia and the Western Pacific Region and is endemic in the coastal areas of Russia, Japan, North Korea, South Korea, Vietnam, Laos, Cambodia, Burma, Thailand, India, Indonesia, Sri Lanka, the Philippines, Malaysia, Nepal, Pakistan, and other places [2]. In the most recent 25 years, the spread of JE has increased in some countries, while the endemic range has increased globally, with the disease extending to regions of Asia that were not affected previously and even to northern Australia [3, 4].

5.1.2 The Development of JE Attenuated Vaccine

There is no effective treatment for JE; therefore prevention and control of JE are critically important work of disease prevention and control institutions in epidemic areas. It is not currently feasible to control infected mosquitoes because they multiply in the natural environment. Given that 70% of JE cases are children, most experts advocate universal immunization for children in endemic areas to prevent JE. Many years of experience from China and other countries has shown that JE vaccination is the most economic and effective way to control JE [5].

There are two types of JE vaccines – inactivated vaccine and live attenuated vaccine. Historically, Japanese scholars developed a mouse brain-based, purified inactivated JE vaccine, which became widely used in epidemic areas. In China, an inactivated JE vaccine produced in primary hamster kidney (PHK) cells was widely used. Japan's mouse brain inactivated JE vaccine caused a few serious and even fatal allergic reactions due to residual brain tissue in the vaccine – events that were reported in Japan and South Korea. As with China's PHK JE vaccine, the primary schedule for Japan's mouse brain vaccine included two or three doses – burdensome to deliver and therefore difficult to complete the full immunization schedule to obtain adequate immunity.

Not long after he began to work, Yongxin Yu received a task: improve the JE vaccine. “There were lots of quality problems in the domestic JE vaccine,” he recalled. Hemin Li, director of a Department in the Institute of Control Biological Products, asked Yongxin Yu whether a better vaccine could be developed. “I didn’t know how difficult it would be,” Yu said lightly. He had no idea that his promise to develop an improved JE vaccine would occupy his entire life.

His first task was to find a suitable JE virus strain for producing a virus vaccine. It was not until 1967 that Yu’s team identified a potential vaccine strain that could be used as a live, attenuated vaccine – a strain that was demonstrated to be safe, stable, and effective in an animal model. However, experts did not reach agreement about testing the vaccine candidate in humans, so Yu and five colleagues made a bold decision: to vaccinate themselves. “It is impossible to say not to worry, but according to our own experimental data and study results, there should be no major problems,” he said. After 2 weeks of observation, they were free from infection with the vaccine virus. Yu became more confident. They decided to vaccinate their own children. “My daughter was six years old, and the kindergarten-age children of 5 other colleagues participated in this experiment. Everything went well; we were very happy and felt that we had achieved an initial success,” he said. However, their work was far from over, as more subjects were needed to prove the safety of the vaccine candidate.

In 1988, after more than 20 years of hard work, an expert group led by Yu in the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) finished the development of a strain for a live attenuated vaccine, SA14-14-2. This JE live attenuated vaccine (JEV-L) was produced successfully by Chengdu Institute of Biological Products. The vaccine, which had been independently developed in China with independent intellectual property rights, was included by the World Health Organization in its list of prequalified vaccines. The vaccine won first prize for Technological Progress in the Ministry of Health (MoH) in 1989 and won the National Science and Technology Progress award in 1990. The vaccine is now indicated for children above 8 months old and for adults who move from non-endemic areas to endemic areas. Vaccination has significantly reduced the incidence and fatality rate of JE in endemic areas, effectively protecting hundreds of millions of children.

Since the approval in 1989, JEV-L has been proven to be safe and effective through several large-scale clinical trials, serological studies, and field observational studies. This vaccine is now the most widely used JE vaccine in the world.

Yu’s JE vaccine has a very good safety profile. Through several clinical studies organized by Chinese and foreign experts, JEV-L has been demonstrated to be safe and effective, with no serious adverse reactions related to the vaccine. Compared with inactivated JE vaccine, local and systemic reactions are significantly fewer [6, 7]. In 2006 JEV-L was used widely in India for the first time, with more than 9 million children vaccinated and with the adverse reaction closely monitored by the India MoH. The WHO also conducted safety assessments during this mass vaccination effort and showed that the vaccine had a good safety profile [8].

Clinical studies showed that JEV-L was immunogenic, not only in a Chinese population but also in other Asian populations. A study in South Korea showed that the neutralizing antibody conversion rate was as high as 96% after a single dose of JEV-L [9] and that average neutralizing antibody GMT was significantly higher than among those who previously received JE mouse brain inactivated vaccine, suggesting that JEV-L could induce memory response [10]. A study conducted in Thailand showed that the seroconversion rate for developing neutralizing antibodies was 95% after a single dose of JEV-L and 100% after two doses [11]. Under the support of the Rockefeller Foundation, a joint clinical study by West China School of Medicine, Sichuan University, and the University of Pennsylvania was conducted in Chengdu, Sichuan Province. The study showed that the effectiveness of two doses of the vaccine was 97.5% (95% CI, 86–99.6%) [12]. According to clinical observations in Nepal in July 1999, the effectiveness of one dose of JEV-L was 99.3% (95% CI, 94.9–100%) [13].

Compared with the inactivated vaccine, the JEV-L is easier to administer, requiring only a single primary dose. A study of concomitant administration of JEV-L and measles vaccine in the Philippines showed that JEV-L can be co-administered with measles vaccine with no influence on the immunogenicity and safety of either vaccine, facilitating the introduction of JEV-L into national immunization programs [14].

5.1.3 Prequalification of JE Vaccine by WHO

In May 2013, Chengdu Institute of Biological Products Ltd. (Chengdu Institute), a subsidiary of China National Biotec Group Company Limited (CNBG), was inspected on-site by the WHO for prequalification of JEV-L. On October 9th, JEV-L was officially prequalified by WHO – an event that was widely reported in the media. This is the first time that a Chinese vaccine was prequalified by WHO, obtaining the first "ticket" for a Chinese vaccine to reach the international market. Prequalification means that JEV-L is qualified for procurement by the United Nations (UN), which contracts for vaccines for more than 120 developing and middle-income countries.

"This is a welcome development both in the fight to protect children in developing countries from JE and in the future availability of vaccines more generally, as China is now producing vaccines up to WHO standards," says WHO Director General Dr. Margaret Chan. "There is a huge potential for vaccine manufacturing in China and we hope to see more and more Chinese vaccines become WHO prequalified. The whole world will benefit."

Co-chair of the Bill and Melinda Gates Foundation (BMGF), Bill Gates, said that "vaccines can save lives, and can protect children's lives. China joins the global vaccine supply chain, and can provide high quality and inexpensive vaccines for many developing countries. This is a great boon for the millions of Asian children whose lives and health suffer from the threat of Japanese encephalitis."

The WHO representative in China Dr. Bernhard Schwartländer said, "JE vaccine is a start. The gate is opened, and more Chinese vaccines will go to the world."

5.1.3.1 The Road to Prequalification: China's JEV-L

Chengdu Institute's JEV-L prequalification effort started from its own internationalization.

After the successful development of JEV-L in 1989, it aroused the attention and interest of experts in the United States, South Korea, Japan, and the WHO. In 1992, Dr. Scott B. Halstead, deputy director of the Health Sciences Department in Rockefeller Foundation, learned of the development and production of JEV-L in Chengdu Institute by Yongxin Yu and showed great interest to make a site visit to the production facilities and meet the personnel involved with JEV-L. In order to enhance international confidence in the vaccine, experts from the United States and the West China School of Medicine, Sichuan University, vaccinated children aged 1 and 6 years old in Chengdu in 1995 and showed a seroconversion rate of 97.5%. The research also pointed out that "if the new vaccine, which is safe, reliable and affordable, is promoted widely, millions of Asian children will be protected from death or lifelong disability every year." Mark Steinhoff, from the School of Public Health in Johns Hopkins University, wrote: "health institutions and vaccine manufactures in Asia and the world should adopt best practices to produce and distribute this inexpensive vaccine that effectively prevents Japanese encephalitis." At about the same time, the Rockefeller Foundation funded experts from the United States and Chengdu Institute to design a modern production plant for JEV-L that would be consistent with current good manufacturing practices (cGMP). Due to limits on the level of economic development, the GMP production facility was not used.

The Lancet published a scientific article on the study conducted jointly by Chinese and foreign experts that showed satisfactory safety and effectiveness of JEV-L [13]. Once again, the safety and effectiveness had been demonstrated in clinical research, and this augmented the scientific and business rationale to enter the international market and to attract attention from investors.

The publication in *The Lancet* attracted attention and interest by Korean experts. Since 1996, the Chengdu Institute has cooperated with South Korea's Glovax company, striving to internationalize JEV-L. The joint preclinical and clinical research by China and South Korea once again demonstrated the safety and effectiveness of JEV-L. The seed viruses, PHK sera, PHK cell line, and vaccine samples were tested by the British authorities' laboratory (Q-One Biotech Ltd.) to determine whether there could be virus contamination. They searched for 10 mouse viruses, 18 viruses of rat mouse, and 2 bovine viruses, finding no contaminants and meeting international standards. Additionally, no retrovirus was detected. The safety of the vaccine had been demonstrated again.

On October 13, 1998, the Conference for Vaccination Control of JE was jointly held by WHO and CVI in Thailand. The participants agreed that Chengdu's JEV-L was stable and that its virulence was shown to be attenuated by tests in sensitive animals (such as rhesus monkey and mouse). There had been more than 100 million people vaccinated with JEV-L, demonstrating that the vaccine was not only safe but

also effective. JEV-L was a new safe and effective vaccine against JE, requiring fewer injections, and was relatively inexpensive.

In early 2000, WHO held an expert committee meeting on JE and dengue fever, during which it was clarified that JEV-L would be the direction for development of JE vaccine, with its fewer doses and lower cost. WHO adopted TRS-980 based on Chengdu's "production and specifications for freeze-dried live attenuated JE vaccine." The adoption of this document paved the way for China's JEV-L to enter the international market and improved reputation of vaccines throughout the world.

According to the requirements of the WHO, as one of the most important raw materials for vaccine production, the hamsters used for cell lines should be specific pathogen-free (SPF). To this end, the Chengdu Institute established the first SPF hamster in China. The SPF hamster was verified by NICPBP and the UK Q-One laboratory. The establishment of SPF hamster raised the quality of experimental animals to a higher level.

However, prequalification by WHO was the necessary route for JEV-L to enter the international market and for widespread use by countries around the world.

The Program on Appropriate Technology in Health (American) (PATH) established a JE Project Team at the end of 2003. The team was funded by BMGF to promote the use of safe, effective, and inexpensive JE vaccine in Asian endemic countries and to control and reduce the burden of Japanese encephalitis. To achieve these objectives, the PATH JE Project Team searched for the most suitable JE vaccine in the world. PATH organized two evaluations in August 2004 and February 2005 by well-known, international experts in GMP and vaccine to assess in detail clinical studies and Chengdu JEV-L manufacturing facilities. After receiving the evaluation report on vaccine safety and effectiveness, PATH compared JE vaccines in the global market and in the developmental stage and ultimately selected Chengdu Institute as its partner. JEV-L (SA14-14-2) was selected as the target vaccine. Starting at that point, Chengdu Institute's JEV-L was on the road to prequalification.

5.1.3.2 The Process of Prequalification for China's Vaccine

According to the WHO vaccine prequalification procedure, a complex process must be completed for prequalification of vaccine:

- First, the country in which vaccine is produced must have a National Regulatory Authority for Vaccines that has been verified by the WHO to be functional – this is a prerequisite for the manufacturer to submit a prequalification application for a vaccine.
- Second, manufacturers must submit a vaccine product summary file (PSF) to WHO, and then WHO organizes experts to evaluate the PSF and clinical data about the vaccine.
- Third, after the PSF document is reviewed, manufacturers submit vaccine samples for laboratory testing by a WHO-designated independent laboratory.
- Fourth, WHO sends an on-site inspection team to evaluate the production of the vaccine, its quality, and cGMP compliance.

- Fifth, if the on-site inspection meets the relevant regulatory requirements of WHO, the inspection report and the manufacturer's reply will be submitted to a WHO Special Committee for a decision whether the vaccine can be prequalified.

Chengdu Institute began international cooperation in the mid-1990s to conduct assessments of the safety of JEV-L, to optimize the production processes, and to facilitate international market registration. Before prequalification, JEV-L had been registered in many countries, including South Korea, Thailand, India, Nepal, Sri Lanka, Kampuchea, and Laos, and these national registrations facilitated the prequalification process. To introduce the vaccine into the UN Procurement Catalog and make the vaccine available to more children globally, in 2006, Chengdu Institute began a cooperative agreement with PATH that was funded by BMGF and conducted with the guidance of China Food and Drug Administration (CFDA), initiating the process of the WHO prequalification for JEV-L vaccine.

Chengdu Institute decided to establish a quality management system in accordance with WHO GMP, the Pharmaceutical Inspection Co-operation Scheme (PIC/s) GMP, and the European Union GMP at the beginning of the program, before Chengdu Institute was about what a huge undertaking this would be. For example, Chengdu Institute originally planned to only build a JEV-L production plant and an SPF hamster plant but later found these were far from adequate. At that time, Chengdu Institute analyzed all plants involved with JEV-L production and identified gaps between current practices and the WHO GMP standard. Finally, new warehouses for raw materials, hazardous goods, and finished products were established, and the SPF experimental animal breeding plant, animal experiment room, medium building, QA/QC building, and central control building were renovated. All plants and facilities had to have complete validation data.

In addition to the "hardware," Chengdu Institute improved the management system in accordance with ISO guidelines, WHO GMP, TRS910 (WHO live attenuated JE vaccine production and quality control guidelines), and other regulatory documents, including the file management system, a verification management system, a measurement management system, a maintenance system, a raw material and supplier management system, compliance management, prevention and correction, modification control, risk management, trend analysis, product quality review, environmental monitoring, and deviation management.

In March 2011, CFDA passed NRA evaluation by WHO. In November 2012 National Institutes for Food and Drug Control (NIFDC) became a contract Inspection Laboratory for prequalification, and in January 2013 WHO designated the Institute for Biological Product Control (IBPC) of NIFDC as a WHO Reference and Evaluation Collaborating Center (WHO CC) for biological products. These achievements provided technical support for JEV-L prequalification.

Chengdu Institute raised funding to invest in JEV-L-related hardware facilities and management systems, with ten plants constructed or renovated; domestic and international clinical research conducted; a comprehensive quality management system (QMS) completed; staff trained; operations and management of QMS

Fig. 5.2 Japanese encephalitis live attenuated vaccine

enhanced; more than 10,000 new standard operating procedures and records drafted, issued, and implemented; and more than 300,000 person-time of training completed. After an almost 7-year effort, JEV-L was prequalified and production capacity expanded.

Prequalification of JEV-L (Fig. 5.2) was not only a ticket to the international vaccine market for Chengdu Institute but also was a means to build a new platform for internationalization of vaccines. The international standards of the new quality management system make Chengdu Institute and China National Biotec Group Company Limited (CNBG) leaders among the Chinese vaccine manufacturers, providing a distinct advantage for future domestic and international competition. With such an advanced platform, one can anticipate that more vaccines from CNBG and from other Chinese companies will be prequalified! Chinese vaccines are entering the world market to benefit the world population!

5.2 Hepatitis A Vaccine

5.2.1 Hepatitis A: A Highly Endemic Disease in China

Viral hepatitis is caused by five different viruses, A, B, C, D, and E, with hepatitis A ranking the first in terms of incidence. Hepatitis A is a usually self-limited disease with serious public health impact that is caused by the hepatitis A virus (HAV), which is transmitted by the fecal-oral route. HAV may survive in the natural world outside of the body for months. Dr. Fuqiang Cui, an expert in the National Immunization Program of China CDC, said that a seroepidemiological survey of viral hepatitis in 1992 in China showed that the average prevalence of antibodies against hepatitis A was 80.9% in the Chinese population with an annual incidence as high as 60 per 100,000 in the early 1990s. Thus, China was a highly endemic country.

Hepatitis A is prevalent throughout the world. According to the WHO, the global incidence of acute hepatitis A increased from 177 million in 1990 to 212 million in 2005 and deaths due to hepatitis A increased from 30,283 in 1990 to 35,245 in 2005. The majority of the increase was among children 2–14 years of age and adults over 30 years of age [15].

Most human infections with HAV are subclinical or asymptomatic, with only a small proportion of human infections manifesting symptoms. Generally, patients fully recover, and do not develop chronic hepatitis or become carriers; death is a rare outcome of HAV infection. However, in patients with chronic liver diseases for whom the threshold of new diseases is decreased – especially for viral superinfection – hepatitis A is the leading cause of exacerbations and death. During a hepatitis A pandemic in 1988 in Shanghai, the fatality rate among 27,346 people who were HBsAg-positive was 5.6 times [16] higher compared with HAV infection alone. HAV infection may cause heavy economic loss in developed and developing countries. For example, the annual average economic cost due to treatment and productivity loss from hepatitis A in the most recent 10 years was $200 million in the United States [17].

5.2.2 Development of Hepatitis A Vaccine

The best way to prevent hepatitis A is hepatitis A vaccination, and the main way to prevent hepatitis A for those at risk of infection or travelling to endemic areas on short notice is intravenous immunoglobulin. With the successful development of vaccines, hepatitis A vaccine has become the preferred means of prevention of hepatitis A, except in special groups and special circumstances (elderly people, immunocompromised patients, patients with chronic liver disease, or people who travel to high incidence areas with less than 2 weeks of advanced notice).

Before 2008, hepatitis A vaccination strategies varied by province according to local epidemiology and economic development. From 1992 to 2007, 156 million doses of hepatitis A vaccine were used, with most use among children and students. In 2007 hepatitis A vaccine was introduced into the National Immunization Program, and after that, vaccine coverage among age-eligible children increased to >90%.

With development of the economy, improvements in health, and widespread use of hepatitis A vaccine, the incidence of hepatitis A showed a declining trend in the past 10 years in China. Introduction of hepatitis A vaccine into NIP in 2007 reduced the incidence of hepatitis A among young children.

There are two kinds of hepatitis A vaccine: inactivated hepatitis A vaccine (HepA-I) and live attenuated hepatitis A vaccine (HepA-L). Because hepatitis A virus has only a single serotype, the vaccines made from any HAV in the world are suitable for the entire world. Breakthrough progress was made in China and abroad by the development of hepatitis A vaccine. In foreign countries, GlaxoSmithKline Co. Ltd. and Merck Co. Ltd. successfully developed HepA-I at the end of the 1980s and early 1990s. Chinese experts began to conduct related research, focusing on the development of HepA-L. China preferentially developed HepA-L for several reasons. First, humans develop immunity following vaccination through two mechanisms, humoral and cellular immunity. Inactivated vaccines only induce humoral immunity, but live attenuated vaccine can induce both humoral and cellular immunity, similar to natural infection. Second, live attenuated vaccine is relatively inexpensive to produce, which was suitable for China's economic condition. The key

was to select and culture a suitable virus strain for live attenuated vaccine. Serious problems could follow if the virulence of the virus is not well controlled. The selected vaccine strain should maintain a certain amount of activity, but not cause disease. Chinese researchers finally developed two vaccine strains – H2 and L-A-1 – through unremitting efforts of screening and cultivation of the virus strains to identify candidates suitable for production of live attenuated vaccines.

H2 was developed by Chinese Academy of Sciences academician, Jiangsen Mao, and his research team after 10 years of hard research. Mao went to Zhejiang Province to investigate viral diseases in 1978 and found that hepatitis A ranked first, from which farmers suffer seriously. That year saw a hepatitis A pandemic in rural with up to 41% of people suffering from jaundice hepatitis in Yuan Pu Cun on the outskirts of Hangzhou. He saw one family of five in which all had been infected with hepatitis A virus. Mao and his colleague Nianliang Chen conducted a house to house survey of hepatitis patients. His work of stool collection is unforgettable: every morning, the first thing he did was to go to rural farmers and hospitals to collect stool specimens from jaundiced hepatitis patients; each pack of stools was put in a plastic bag and brought back to the lab, with a hope of isolating HAV. He collected enough stool samples to fill two large refrigerators. Finally, in 1982, he isolated HAV from stool samples from a 12-year-old boy living in the outskirts of Hangzhou. The virus was initially cultured in a primary monkey kidney cell line (NMK) for 20 passages (15 passages at 35 °C followed by 5 passages at 32 °C), followed by 5 passages in human embryo lung diploid cell KMB-17 at 32 °C to attenuate the HAV. In 1988, a live attenuated hepatitis A vaccine strain was successfully developed. The strain is now owned by Zhejiang Pukang Biotechnology Co. Ltd.

The L-A-1 strain was developed by Professor Mengdong Hu and her team in Shanghai CDC from HAV that was isolated in December 1980 from a 2-year-old boy with hepatitis A in Harbin, Heilongjiang Province. Shanghai CDC and Changchun Institute of Biological Products cooperated in the development of the vaccine strain, which went through 7 passages in human diploid lung cells SL7, followed by 4 passages in human embryo lung diploid cell line 2BS at 32 °C and 7–14 passages at 35 °C. The final strain was obtained after a successful marmoset monkey infection and challenge trial. The strain is now owned by Changchun Biological Products Ltd. Co. (formerly Changchun Institute of Biological Products).

The two manufacturers carried out the necessary research on the strains, including stability testing and nucleotide sequencing after passages, entered the strains into the three-tier seed banks, and obtained national approval for their use.

The H2 strain of Zhejiang Academy of Medical Sciences (now Zhejiang Pukang Biotechnology Ltd. Co.) is stable after passages in the human diploid cell line KMB17 and is in large-scale production. A liquid presentation of live attenuated hepatitis A vaccine made from the H2 strain obtained licensure in 1992. Zhejiang Academy of Medical Sciences assessed the duration of immunity and showed that seropositive rates were 98.6% and 81.3% at 2 months and 15 years after vaccination with the H2 strain, HepA-L, and concluded that the vaccine has a good immunogenicity and persistence. However, there is a serious weakness for the liquid

attenuated hepatitis A vaccine, as it must be transported in low-temperature conditions (under −20 °C), and the shelf life is very short – only 5 months when stored at 2–8 °C. This disadvantage is not favorable for large-scale use and leads to waste and inefficiency. Therefore, researchers aimed to develop a freeze-dried formulation that would make the vaccine more useful in China and globally. Following unremitting efforts, in 2000, a freeze-dried live attenuated hepatitis A vaccine obtained licensure and market authorization. The new-generation vaccine has been demonstrated to be safe and immunogenic through more than 10 years of use. In 2005, the vaccine received an import drug license and market authorization from the India Drug Administration and was exported to India in January 2006.

The L-A-1 strain is owned by Changchun Institute of Biological Products, is stable during passage, and can be produced in large scale in 2BS cells. In 1996, L-A-1 HepA-L received a formal production license from the national regulatory authority. The vaccine had been demonstrated to be safe in preclinical trials in monkeys, which showed no elevation of alanine aminotransferase (ALT). A large-scale epidemiological study with more than 500,000 participants showed that most subjects responded well to vaccination, with no serious adverse events being observed. The study showed that the immune response persisted 4 years after immunization, with a protection rate of 96.8% [18]. After 3 years of follow-up, the vaccine protection rate was 96.85%, with a disease incidence of only 1.99/100,000 [19]. Because the shelf life for liquid vaccine is short and liquid vaccine is less stable, researchers successfully developed a freeze-dried formulation and obtained a national patent (Patent No.: ZL 98120633.6)/international patent (South Korea) (10-0702086) and the second award of National Technology Invention in 2001 (the first award being vacant). The freeze-dried vaccine (trade name: Haiweike) received new drug certificate and production approval in 2000. Vaccine stability tests showed that vaccine virus titers remain unchanged for 18 months at 2–8 °C and for 28 months at −20 °C. Decreases in virus titer were less than 0.5 log when stored at 2–8 °C for 22 months and −20 °C for 30 months. The serum antibody conversion rate reached 98% by 1 month after vaccination and 100% [20] by 2 months. The vaccine has now been in use for 15 years, with nearly 50 million doses used, and its safety and effectiveness has been demonstrated.

China's independently developed HepA-I vaccine has also showed good results. In 1984, NICPBP and Tangshan Yi An Biotechnology isolated virus from the stools of a patient during a hepatitis A outbreak in rural Hebei Province. The extracted virus-containing liquid was inoculated into 2BS cells for three passages. With continued passage in 2BS cells, the replication period of the virus was gradually shortened. After ten passages, the replication was peaking at 14 days and was showing high ELISA titers with increasing HAV yields. At that time, the vaccine candidate virus was established with a name of TZ84 in a virus seed bank. By the end of 1999, Beijing Sinovac Biotech Ltd. (former Tangshan Yi An Biotechnology company) successfully produced HepA-I vaccine from this strain, retaining independent intellectual property rights and receiving new drug certificate and production approval from the regulators. The vaccine was made using human diploid cell and was marketed with the brand name of Healife.

NICPBP and the Biological Research Branch of the Institute of Chinese Medical Science isolated hepatitis A virus from stools from a Nantong patient during the 1988 Shanghai hepatitis A epidemic. The virus was cultured for 6 passages in KMB-17 cell lines, followed by an additional 20 passages. During these passages, the viral replication cycle was shortened from 35 days to 12–16 days and was shown to yield high antigen and infectious particle titers. The Biological Research Branch of the Institute Chinese Medical Science established a virus seed bank for this vaccine candidate with the strain name of Lu 8. HepA-I vaccine produced using this strain was made in a human diploid cell line by the Biological Research Branch; the vaccine obtained new drug certificate and production approval in 2003 and is still marketed today in China under that trade name of Weisairuian.

5.2.3 Strict Quality Control of Hepatitis A Vaccine Production in China

Currently, there are four manufacturers producing freeze-dried HepA-L; all use similar production technology but use different vaccine strains, cell lines, freeze-dry processes, stabilizers, and vaccine specifications. Two manufacturers produce HepA-I, with vaccine strains and cell lines developed in China; aluminum hydroxide is used as an adjuvant, and the production technology is similar to the international vaccine production technology. Milestones of hepatitis A vaccine development and production in China are presented in Table 5.1.

Freeze-dried HepA-L uses an attenuated virus strain that is inoculated into human diploid cells for incubation, followed by harvesting, extraction, stabilizing, and lyophilizing to a final formulation of loose material that is white or cream colored. After reconstitution, the vaccine is a clear liquid. For HepA-I with an alum adjuvant, the virus is inoculated into human diploid cells, followed by culture, harvest, purification, inactivation, and adsorption onto aluminum. This product is a white liquid suspension and can be divided into layers but is easily mixed by shaking. The product, consisting mainly of inactivated HAV, may contain preservatives and other materials, including aluminum hydroxide, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, and sterile water for injection.

The manufacturing process for freeze-dried HepA-L is relatively simple compared to HepA-I. A key difference between the two manufacturing processes is after harvesting the virus. HepA-I must go through multiple purifications, a formaldehyde inactivation, and adjuvant adsorption. HepA-I, therefore, has greater purity compared with HepA-L. The freeze-dried HepA-L is processed with chloroform and then stabilized and lyophilized. HepA-I requires more preparation processing than does freeze-dried HepA-L.

Strict quality control in the production of hepatitis A vaccine is implemented in China:

(a) Virus seeds for production must be ensured to have had appropriate attenuation while retaining adequate immunogenicity.

Table 5.1 Hepatitis A vaccines in China

Vaccine type	Manufacturer	Brand name	Vaccine strain	Cell medium	Components	Specification	Antigen or virus content	Preservative
Freeze-dried live attenuated vaccine	Zhejiang Pukang Biotechnology Ltd. Co.	No	H2	KMB17	Live virus+ stabilizer	After reconstitution 0.5 ml per dose	Live hepatitis A virus no less than 6.50 lg CCID50/dose	No
	Institute of Medical Biology, Chinese Academy of Medical Science	Weisairuiji	H2	KMB17		After reconstitution 1.0 ml per dose		
	Changchun Institute of Biological Products	Haiweike	L-A-1	2BS		After reconstitution 1.0 ml per dose		
	Changchun changsheng Institute of Biological Products	Wanxin	L-A-1	2BS		After reconstitution 1.0 ml per dose		
Inactivated hepatitis A vaccine	Beijing Sinovac Biotech Ltd.	Healife	TZ84	2BS	HAVAG + aluminum adjuvant	Pediatric: 0.5 ml/dose	250 U	No
						Adult: 1.0 ml/dose	500 U	
	Institute of Medical Biology, Chinese Academy of Medical Science	Weisairuian	Lu 8	KMB17	HAVAG + aluminum adjuvant	Pediatric: 0.5 ml/dose	320 EU	2-Phenoxyethanol
						Adult: 1.0 ml/dose	640 EU	

Sources, histories, and biological characteristics of virus seeds must be clearly documented, and the relevant documents should be complete and approved by CFDA. Virus seeds are managed based on three batches, including the original seeds, the master seeds, and the working seeds. The genetic characteristics of viruses used in live attenuated vaccines must be consistent with the original seed and/or the master seed. Virus seeds used for production should be identified completely according to regulatory requirements, including identification testing, virus titer assays, serialization, *Mycoplasma* and exogenous virus test, and immunogenicity testing. Virus seeds are stored at −60 °C at specific sites in which other viruses cannot be stored. Because only primates can be used as testing animal models, the safety and immunogenicity of the master virus seeds have to be evaluated in monkeys.

In the *Chinese Pharmacopoeia* (2010 edition), passages for vaccine viruses are clearly defined, and the range of multiplicity of infection (MOI) in inoculation and culture is clearly defined to ensure stability and consistency during the production process. In the *Chinese Pharmacopoeia* (2015 edition), it is required that the background information of the whole genetic sequence for master virus seeds should be established and master seed of live attenuated vaccine should be sequenced completely.

(b) Establishment of cell line bank and conduction of comprehensive testing.

Cell lines are essential raw materials for virus vaccine production, and the quality of the cell line directly affects the quality and yields of the vaccine, including the safety profile [21]. The current hepatitis A vaccines on the market are all made from human diploid cell (HDC) which ensures cell line safety. In the production process, the sources of cell lines should be very clear and must correspond to the appropriate cell bank. The HDC age is estimated according to reproduction times, which double the cell population in one generation. The age of the cells used for vaccine production is limited to the first two thirds of the cell life expectancy. Quality control for the cell line is concerned primarily with the potential presence of exogenous factors and the biological characteristics of the cells [22]. HDCs must be identified comprehensively according to the current pharmacopoeia, including identification, serialization, *Mycoplasma* test, exogenous factor test, specific virus test, chromosome test, and cell tumorigenicity.

(c) Strict standards for final product testing.

In the *Chinese Pharmacopoeia* 2010 edition, the HepA-L final product must be tested for the following items: identification, appearance, water, chloroform residues, virus titration, thermal stability test, bovine serum albumin residues, antibiotic residues, sterility, abnormal toxicity test, and bacterial endotoxin test. In addition to the above items, the *Chinese Pharmacopoeia* 2015 edition requires pH and concentration of osmotic pressure testing.

The *Chinese Pharmacopoeia* 2010 version required that final product of HepA-I must be tested for the following items: identification, appearance, volume, pH, aluminum contents, free formaldehyde contents, chloroform residues, 2-phenoxyethanol contents and relative potency test in vitro, antibiotic residues, sterility, bacterial endotoxin, and abnormal toxicity. In addition to the above items, the 2015 edition of *Chinese Pharmacopoeia* included concentration of osmotic pressure testing.

Fig. 5.3 Live attenuated hepatitis A vaccine

5.2.4 Prospects

China independently developed HepA-L (Fig. 5.3) and HepA-I vaccines, which have been marketed for many years and have made great contributions to the control of hepatitis A endemics. With rapid progress in biotechnology, many researchers are focused on the development of new types of hepatitis A vaccine – for example, a combination vaccine or a genetically engineered vaccine. At least one of these innovative vaccines has been marketed – a hepatitis A and B combination vaccine.

5.3 Inactivated Enterovirus Type 71 Vaccine

5.3.1 Enterovirus Type 71 (EV71) and Hand, Foot, and Mouth Disease

In March 2008, Fuyang People's Hospital, Anhui Province, China, admitted and treated numerous pediatric patients with hand, foot, and mouth disease (HFMD); many were critically sick, and some died. The epidemic caused widespread concern by the public and the media [23].

HFMD is a common infectious disease caused by several human enteroviruses. Most patients present with mild symptoms – fever and rash and herpes-like lesions on the hands, feet, or mouth [24]. A small number of patients develop aseptic meningitis, encephalitis, acute flaccid paralysis, neurogenic pulmonary edema, and myocarditis, with a rapid progression that can lead to death [25–27]. Viruses causing HFMDs include EV71, coxsackievirus group A type 16 (CV-A16), and ECHO virus. Of these, EV71 is, arguably, the most important HFMD pathogen [28].

From 2008 to 2015, a total of about 13.8 million HFMD cases were reported in China, with an average annual incidence of 147/100,000. Among these, approximately 130,000 cases were severe and more than 3300 patients died. HFMD represents a serious threat to the health of children in China [28]. According to Yu Hongjie's study of the epidemiology of HFMD in China from 2008 to 2012, published in January 2014 in *The Lancet*, EV71 accounted for 41% of all laboratory-confirmed cases, 81% of severe cases, and 93% of deaths [29].

During the past 20 years, HFMD was widely prevalent in the Asia Pacific region, including in Malaysia, Japan, Singapore, Vietnam, China (Mainland, Hong Kong and Taiwan), South Korea, and Cambodia [30–33]. The largest outbreak of HFMD in recorded history happened in 2000 in Singapore, in which 3790 cases were reported, with 73% being caused by EV71 [33]. In 2012, at least 54 Cambodian children died of EV71 infection [34]. EV71-related HFMD has long been prevalent in many countries and regions in Asia and is considered an important public health problem.

5.3.2 EV71 Vaccine: Research and Development

To reduce the incidence and mortality of HFMD, the World Health Organization and disease control departments in several countries have adopted measures such as surveillance, disinfection, isolation, and education to identify and control HFMD epidemics. EV71 virus spreads through direct contact; virtually all children are susceptible, and after infection, most are asymptomatic. Given these characteristics, it is difficult to prevent and control HFMD with hygiene, alone [28].

To prevent and control HFMD epidemic caused by EV71 infection, many countries or regions have begun to develop EV71 vaccines, including inactivated vaccines, live attenuated vaccines, subunit vaccines, DNA vaccines, peptide vaccines, and recombinant virus-like particle (VLP) vaccines [28].

Research on whole-virus inactivated vaccine has been the fastest, as there are five manufacturers or institutes whose EV71 vaccine has entered into clinical trials. A vaccine developed in Singapore completed its Phase I trial in Taiwan and then entered a Phase II trial. The Institute of Medical Biology, China Academy of Medical Sciences (Kunming Institute), Beijing Sinovac Biotech Co. Ltd. (Beijing Sinovac), Biological Technology Research Co. Ltd., and Wuhan Institute of Biological Products (CNBG) completed Phase III trials in 2013. These three EV71 vaccines by Chinese manufacturers received new drug certificate in 2015 and 2016 from CFDA [28].

The Chinese government gave strong support to development and clinical research on EV71 vaccine, through the National Major New Drug Development in the "11th Five-Year Plan," the "12th Five-Year Plan," and other projects.

EV71 vaccine from Beijing Sinovac has obtained several patents in China, including "HFMD vaccine and its preparation and application" and "EV71 virus neutralization epitope assay kit and preparation method." The next section will introduce research and development of EV71 vaccine by Beijing Sinovac.

5.3.2.1 Selection of Virus Seed

There is only one serotype of EV71. From 1999 to 2008, all EV71 strains isolated from mainland China were C4 subtype, providing a basis for selection of candidate virus genotypes for EV71 vaccine [35–38]. Through several years of cooperation with China CDC, Beijing Sinovac isolated 20 strains of EV71 that varied by patient symptoms, genotype, and region of isolation. To identify EV71 strains for vaccine development, candidate viruses were screened for the ability to generate high titers after culture, ability to induce immunity with cross-protection, and protection against death in animals. Genetic stability of selected strains was demonstrated by comparison of whole genome sequences with the original virus.

5.3.2.2 Evaluation of Protection in Animals

The traditional mouse model was not suitable for evaluation of EV71 vaccine. Beijing Sinovac created a new animal model through collaboration with the Laboratory of Infectious Diseases and Immunology Research, Australia University of Sydney. Two doses of vaccine were administered parentally to female rats. After conception, the suckling mouse obtains maternal EV71 antibody. Challenged by a lethal dose of EV71 (mouse-adapted strain) on suckling rats, morbidity and mortality were able to be monitored to evaluate protection by EV71 antibody induced by the candidate vaccine.

To evaluate immunogenicity and effectiveness, Beijing Sinovac manufactured EV71 vaccine in different dose amounts and commissioned Peter McMinn, professor of Medicine of Infectious Diseases and Immunology, Medical School University of Sydney, to conduct challenge trials in mice. The results showed that after two doses of vaccine given to maternal mice, the morbidity and mortality of suckling mice were significantly lower than a control group, suggesting that EV71 vaccine can produce effective neutralizing antibodies to protect a sensitive animal from infection. EV71 vaccine was also demonstrated to provide cross-protection against a challenge by other gene subtype of EV71 [39].

5.3.2.3 Evaluation of Protection Efficacy in Large-Scale Clinical Trial

Beijing Sinovac began to develop EV71 vaccine in 2008 and completed a preclinical study in December 2009. After the clinical trial approval was obtained in December 2010, their EV71 vaccine became one of the first EV71 vaccines to enter a clinical trial in China. The clinical trial showed that EV71 inactivated vaccine was safe and effective, using a schedule of two doses – day 0 and day 28. The vaccine is indicated for prevention of HFMD, herpangina, encephalitis, and other diseases caused by EV71 infection. EV71 vaccination can effectively reduce hospitalization due to HFMD and severe HFMD. On December 30, 2015, Beijing Sinovac's EV71 vaccine (brand name, Evlife) was approved by CFDA.

The results of Phase I–III trials and three consecutive clinical trials showed that EV71 inactivated vaccine had good safety and immunogenicity. The overall adverse reaction rate of the experimental vaccine was 52.52%, but there was no significant difference in the incidence of adverse reactions between the vaccine group and the control group. In Phase III clinical trials, the subjects were followed for 14 months,

with no severe HFMD cases in the experimental vaccine group or EV71-associated severe disease or pathological immune response. Following completion of the schedule, efficacy was 94.6% against HFMD of any severity within 1-year period (95% CI, 86.6–97.8) and 100% against severe HFMD. In the 2nd year, EV71 vaccine showed an efficacy of 95.1% (95% CI, 63.6–99.3) against HFMD by EV71 infection. The immunogenicity against different genotypes indicated that the candidate vaccine induced cross-protection against different genotypes and subtypes [40]. Relevant results were published in international journals, including the *New England Journal of Medicine*, *Vaccine*, and *The Journal of Infectious Diseases* [41–43].

In addition, an immunological surrogate endpoint was assessed in the Phase III trial. The threshold of neutralizing antibody correlated with protection against diseases was 1:16 [43].

Three consecutive clinical trials showed that 95% CI of GMT log difference between three batches of vaccines was in the expected range (−0.176 to 0.176), suggesting that three consecutive batches of vaccine were consistent. Phase III clinical trial of four batches of 400 U vaccine showed that, 56 days after immunization, the coefficient of variation of GMT was 7.97%. These results showed that the vaccine was stable, with excellent consistency between the batches and production process [44].

5.3.2.4 Vaccine Evaluation Criteria and Standards

EV71 vaccine is a new vaccine developed in China, for which there is no global reference for development processes, no global standards, and no reference vaccine. The Center for Drug Evaluation (CDE), CFDA, and NIFDC developed standards for EV71 vaccine manufacturing and testing. In order to ensure safety, CFDA strengthened the criteria for purity of inactivated EV71 vaccine, requiring that purity should be no less than 95% by a HPLC detection method, a similar standard used for recombinant genetically engineered vaccines. Residual DNA and Vero cell host proteins are controlled according to the most stringent international standards.

In 2010, NIFDC worked with the manufacturer to jointly develop a standard vaccine for potency testing and to establish a standard assay for EV71 vaccine neutralizing antibody and antigen content (2010 National Biological Standard 0023; 0024). In addition, in order to meet the anticipated demand for EV71 vaccine in other countries or regions, NIFDC worked with the British National Institute for Drug Control to develop a WHO reference assay for EV71 neutralizing antibody. This was the first time that China undertook the development of a vaccine reference for WHO [45].

5.3.3 Prospect of EV71 Vaccine

EV71 vaccine is a Class 1 new biological product developed independently by China (Fig. 5.4). Registration of EV71 vaccine suggests that China's biological product industry is becoming advanced in the world. The EV71 vaccine and antibody reference developed by China provide a "reference" for the research and development of EV71 vaccine globally.

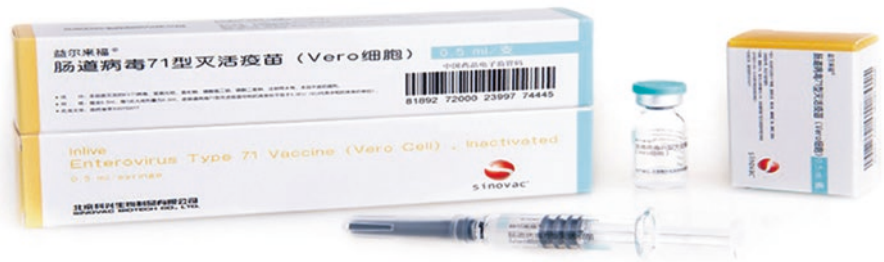

Fig. 5.4 Enterovirus type 71 vaccine

The successful development of EV71 vaccine will play an important role in the control of HFMD outbreak and epidemics related caused by EV71 globally. Peter C. McMinn, professor of the Institute of Infectious Diseases and Immunology, Medical School, University of Sydney, wrote a commentary in the *New England Journal of Medicine*: "… if these vaccines prove to be effective in preventing EV71-associated neurologic disease, an important tool for controlling, or even eradicating, EV71 infection in regions where it is endemic may have been developed. If its promise is realized, a priceless gift will have been given to the children of the Asia–Pacific region and to the rest of the world" [46].

5.4 Hepatitis E Vaccine

On March 5, 2015, a study was published in the *New England Journal of Medicine*, showing that the world's first hepatitis E vaccine (Fig. 5.5) developed by Professor Ningshao Xia from Life Sciences, Xiamen College, provides protection for at least 4.5 years [47].

5.4.1 Background of Development of Hepatitis E Vaccine

Hepatitis E, caused by a RNA virus, is an acute viral hepatitis that has sudden onset following an incubation period of 4–9 weeks. The clinical symptoms are similar to hepatitis A but present with greater severity [48], usually with manifestations of jaundice, fever, fatigue, loss of appetite, extreme fatigue, unconsciousness, liver failure, and sometimes death. In childbearing age women, patients with chronic liver disease, the elderly, and infants, the manifestations tend to be more serious; for example, hepatitis E infection in pregnant women may lead to miscarriage, premature birth, stillbirth, neonatal hepatitis by vertical transmission, or death. Infection will cause severe hepatitis in one third of pregnant women, with a fatality rate of up to 20% [49, 50]. Approximately 44–83% of patients with chronic liver disease are at risk of superinfection with hepatitis E, with fatality rate as high as 75% [51, 52]. Hepatitis E virus (HEV) is spread primarily through the fecal-oral route, with two

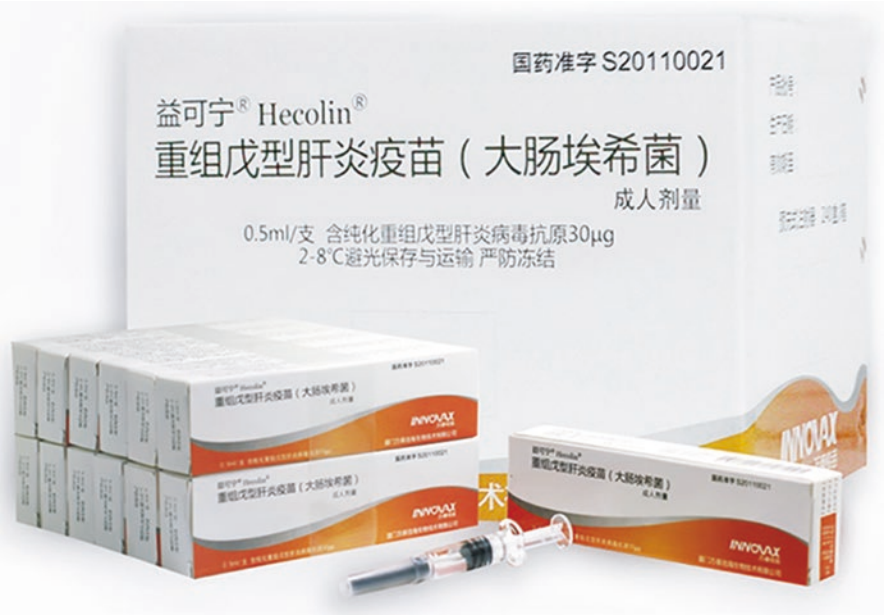

Fig. 5.5 Hepatitis E vaccine

common models [53]: spread by water polluted with feces causing large-scale outbreaks occurring mainly in underdeveloped countries and regions or spread by poor personal or public hygiene conditions, prevalent throughout the world.

Since the 1980s, hepatitis E has been prevalent in India and other developing countries in Asia, Africa, and Latin America. There was a big outbreak in Kitgum in northern Uganda in Africa in October 2007 [54] that had a cumulative number of cases of 10,196 and caused the death of 160 people. In the most serious involved areas of Madi Opei and Paloga, the incidence rates were 30.9% and 19.2%, respectively. The most affected populations are pregnant women and children aged 0 to 2-year-olds, having mortality rates of 8.2% and 8.7%, respectively.

Since 1982, hepatitis E has been notifiable in China, and thus far, there have been several outbreaks reported. The largest outbreak occurred from September 1986 to April 1988 in three prefectures, Hotan, Kashi, and Kezilesu in southern Xinjiang, covering 23 counties and lasting more than 20 months [55]. The epidemic had two peaks, a total of 119,280 cases, and caused serious harm and widespread concern in the community. In almost all provinces and autonomous regions of China, there are sporadic hepatitis E cases reported. Hepatitis E ranks first in acute sporadic viral hepatitis. A seroepidemiological survey in 63 disease surveillance sites in 13 provinces and autonomous regions in China showed that out of 31,120 people aged from 1 to 59 years old surveyed, the anti-HEV antibody prevalence was 17.2% [56], suggesting that HEV infection in Chinese is prevalent. The incidence of hepatitis E has increased year by year, from 9655 in 2003 to 29,202 in 2011 – an increase of 202% [57].

Hepatitis E is not only prevalent in developing countries with poor hygiene conditions; in the most recent 10 years, sporadic hepatitis E cases have been reported in developed countries in Europe and in the United States, Japan, and Australia, with most cases being indigenous. In immunocompromised groups such as those with HIV infection, organ transplant recipients, and others, chronic hepatitis E infection is common.

5.4.2 Hepatitis E Vaccine: Development

As early as the 1990s, GlaxoSmithKline, the University of Oxford, and other institutions invested in research and development of hepatitis E vaccine. However the first approved was a hepatitis E vaccine (Yikening), developed by Professor Xia in Xiamen University.

Starting in 1998, Professor Xia led his team to develop hepatitis E vaccine. In December 2004, Yikening received clinical trial approval, and in 2005 a clinical trial was started. By October 2012, Yikening was officially approved [58].

Because HEV is difficult to culture in large scale in vitro, it is difficult to use the traditional inactivated approach and live attenuated approach to create a vaccine. A subunit vaccine or DNA vaccine made by a genetic engineering approach could be more appropriate. Xia's team adopted a genetic engineering approach to develop a recombinant subunit vaccine. Through a series of experiments, they found that VLPs can be expressed by *Escherichia coli* bacteria. This VLP antigen is immunogenic and able to induce high titers of neutralizing antibodies, potentially serving as a candidate antigen for a hepatitis E vaccine. On this basis, Xiamen University and Xiamen Innovax Biotech Corp (Xiamen Wantai) worked together to develop a vaccine and established an HEV vaccine production process using HEV VLPs in a series of preclinical and clinical research studies. They broke the long-standing concept that an *Escherichia coli* expression system is not appropriate for complex antigen production and thus laid the foundation for large-scale production of hepatitis E vaccine. Their new technology was later applied by Xiamen University and Xiamen Wantai to develop a human papillomavirus vaccine.

During the development of hepatitis E vaccine, governments at all levels provided support through the 863 plan science and technology funding, such as the National Tech Program, to ensure that the vaccine could successfully overcome development barriers. The traditional view that "a prokaryotic system does not express virus like particles" was debunked by the success of this product. Previous genetic engineering approach used yeast, insect, or mammalian cells, all of which are eukaryotic.

Between 2005 and 2007, Phase I and II clinical trials were completed [59], and they showed that hepatitis E vaccine had good safety and immunogenicity profiles: 505 volunteers received 1279 doses of HEV, with no serious adverse reactions observed. Fever (4.2%) and fatigue (2.7%) were the most common systemic reactions, and itching (4.1%) and redness (2.3%) were the most common local reactions.

From 2007 to 2009, Xiamen University, Xiamen Wantai, and Jiangsu CDC jointly completed a Phase III clinical trial that had 120,000 subjects, confirming the safety and efficacy of the vaccine [60]. During the clinical trial, adverse reactions were mild, and no vaccine-related serious adverse events were observed, again showing that the vaccine had a good safety profile. One month after completing the vaccination schedule, the seroconversion rate (IgG) was 98.69% (95% CI, 98.35–98.97%), with antibody titers increasing 139.27-fold (95% CI, 134.01–144.74), confirming that the vaccine was highly immunogenic. One year after vaccination, no hepatitis E cases were observed in the hepatitis E vaccine group, and 15 hepatitis E cases were observed in the hepatitis B vaccine group (control group), yielding a protection rate of 100% (95% CI, 72.1–100.0%). In 2010, Xia published the Phase III trial in *The Lancet* with Dr. Holmberg, of the US CDC Division of Viral Hepatitis, commenting that "the clinical trial convincingly confirmed the safety and efficacy of the hepatitis E vaccine, and is a major breakthrough in the prevention of hepatitis E in the world."

To further determine the duration of protection, Xia's team conducted a 4.5-year follow-up study and found that among 60 subjects infected with HEV, 7 were from the study group and 53 were from the control group, for a protection rate of 93.3% (95% CI, 78.6–97.9%) [47]. In the study group, HEV IgG antibody was positive in nearly 90% subjects 4.5 years after immunization, while only 9% of the control group were positive. These data confirmed that the hepatitis E vaccine can induce excellent and persistent immunity, significantly reducing the risk of hepatitis E. The results were published in the *New England Journal of Medicine*. Dr. Eyasu Teshale from US CDC said: "A hepatitis E vaccine could become a powerful new tool in the prevention and control of HEV transmission and disease" and suggested "now is the time to answer these remaining questions and establish the public health applications of a hepatitis E vaccine."

5.4.3 Significance of Hepatitis E Vaccine

After 14 years of efforts and more than 500 million yuan invested, hepatitis E vaccine, "Yikening," was officially approved in October 2012. This is the first approved hepatitis E vaccine in the world and so far the only hepatitis E vaccine with regulatory approval for market authorization. Hepatitis E vaccine is a major, innovative scientific achievement in China – a breakthrough in genetically engineered vaccines. The approval of hepatitis E vaccine changed the unfortunate situation that no vaccines were available against hepatitis E. Now hepatitis E is a vaccine-preventable disease, paving the way to prevention and control of hepatitis E.

The success of Yikening is a major breakthrough in the field of biomedical innovation. Through the research on Yikening, Xiamen University and the Xiamen Innovax Biotech established a vaccine development platform that will make an important contribution to increase the availability of vaccines in the world, especially in developing countries. We believe that in the future there will be more Chinese new and innovative drugs approved to the benefit of human beings.

5.5 Inactivated Polio Vaccine from Sabin Strains

On January 14, 2015, the CFDA website announced the "approval of the first Sabin inactivated poliovirus vaccine (IPV) in the world," announcing that after 30 years of research and development, the innovative Sabin-IPV, which is made from the attenuated Sabin strains of poliovirus, was formally approved. The successful development of this innovative vaccine will play a vital role in ensuring the eradication of polio in China. As a product with major significance, it not only fills a gap in the field of IPV production in China but also improves eradication of polio in China and in the world – especially in developing countries.

Sabin-IPV, a national Class 1 new drug, was independently developed by the Institute of Medicine and Biology, China Academy of Medical Sciences, retaining complete intellectual property rights. There was no Sabin-IPV in China prior to this development, and there was no stand-alone Sabin-IPV licensed anywhere in the world. The development of this vaccine demonstrated advanced vaccine development capacity in China. Sabin-IPV is one of the best choices for use in the final stages of polio eradication.

5.5.1 The Eradication of Diseases

Polio is a disease that is as old as smallpox that has been observed since the beginning of recorded human history. The earliest known image of polio is possibly the portray in an Egyptian Stele between 1300 and 1500 BC, depicting a young priest with one atrophic leg, an image consistent with polio.

Polio is a highly infectious disease caused by poliovirus serotypes I, II, or III, mainly affecting the gray and white matter in the anterior horns of the spinal cord. Poliovirus infections can cause permanent damage to the gray matter, with subsequent weakness of the muscles innervated by affected nerves and flaccid paralysis of the limbs. Polioviruses historically typically infect children under the age of 5 years; it has a clinic presentation of fever, followed by stiff neck and vomiting. About 1 out of every 200 people infected with polio become paralyzed, with respiratory muscle paralysis and death in severe cases. Because the disease is common in infants and young children, it is also called infantile paralysis. The disease is preventable but has no effective treatment. Once limb paralysis occurs, lifelong disability and even death follow. Humans are the only natural host of the poliovirus. Poliovirus spreads primarily by the fecal-oral route but also by nasopharyngeal droplets.

In 1916, an outbreak of polio occurred in New York resulting in more than 9000 cases and 2343 deaths. During the same year, a total of 27,000 cases and 6000 deaths occurred in the United States, most cases being among children. Since then, outbreaks became more frequent in the twentieth century. The most serious epidemic in the United States was in 1952. Polio had also been endemic in China, and there were polio case records as far back as 1882. By 1938 there were 14 provinces and municipalities that reported sporadic cases. In 1955, China's MoH included

polio into the list of notifiable infectious diseases, and as surveillance improved it became clear that outbreaks were increasing and that endemic areas were expanding. In 1955, the first large-scale polio outbreaks in China were reported in Nantong, Jiangsu Province, and Qingdao, with incidence rates of 32.1/100,000 and 50/100,000, respectively. The annual number of cases ranged from 20,000 to 43,000, with a peak in 1964 when 43,156 cases were reported, for an incidence of 6.21/100,000. The majority of children who got polio suffered lifelong disability. People lived in extreme fear – the common disease known as "polio" made children suffer seriously [61].

5.5.2 Emergence of Vaccines

Because of fear of polio and the significant threat of outbreaks, many scientists work on the prevention and treatment of polio. Microbiologist Jonas Salk isolated the virus in 1952 in the University of Pittsburgh and developed the first injectable vaccine containing three serotypes (IPV), which was approved in the United States in 1955. After the vaccine was in use, the number of cases in the United States declined from 35,000 in 1953 to 5300 in 1957. For several years Dr. Salk's IPV was the standard polio prevention measure; indeed, in Finland, Iceland, Holland, and Sweden, IPV vaccination successfully blocked the spread of wild poliovirus. At about the same time, Albert Sabin, a virologist at the University of Cincinnati, worked to develop a polio vaccine and ultimately successfully developed oral polio live attenuated vaccine (OPV). Because OPV was simpler to administer, less expensive, and more convenient to transport compared with IPV, most countries replaced IPV with trivalent OPV (Sabin strain) in 1963 as the main polio preventive measure [62].

The Chinese government has long attached great importance to the prevention and control of polio. In 1959, according to an agreement on science and technology between China and the former Soviet Union, China MoH sent Fangzhou Gu and Dexiang Dong from the China Academy of Medical Sciences, Zhongquan Wen from Beijing Institute of Biological Products, and Jingwu Jiang from Chengdu Institute of Biological Products to the Soviet Union to study polio vaccine manufacturing technology (Fig. 5.6). The Institute of Medical Biology of the Chinese Academy of Medical Sciences was approved to produce polio vaccine in Kunming and to conduct research on enteroviruses. The project team recommended the use of OPV based on the pros and cons of OPV and IPV, China's large population, and China's developing economic condition. This pioneering work represented key steps for the later control and eradication of polio in China. In March 1960, the first lot of 5 million doses of monovalent OPV for type I, type II, and type III was produced in pilot batches, and the vaccine was demonstrated to be effective after evaluation in about 4 million children in a clinical trial. In 1963, to promote the use of poliovirus vaccine in rural areas, the Institute and Shanghai Xinyi Pharmaceuticals jointly developed OPV in pill formulations. In 1965, China began to gradually promote the use of OPV in China, leading to decreases in the number of cases by 60%

Fig. 5.6 Fangzhou Gu and other comrades learning in the Soviet Union

in the 1970s compared with the 1960s. In the 1980s, China strengthened EPI, further reducing the incidence of poliomyelitis. Since October 1994, no cases caused by indigenous wild polio have been reported in China.

On very rare occasion, OPV can cause vaccine-associated paralytic poliomyelitis (VAPP) and can mutate into vaccine-derived polio viruses (VDPVs) that can circulate in nature and cause polio. In addition, although also rare, patients with primary immune deficiencies can become long-term excretors of VDPVs leading to prolonged spread of polioviruses. The last case of wild type II polio was seen in 1999, and the disease caused by the type II OPV strain has exceeded the amount of disease caused by wild poliovirus. Because IPV cannot cause VAPP and VDPVs, IPV has become an essential weapon to finally eradicate polio.

5.5.3 Development of IPV in China

Research and development of IPV from Sabin strains began in the last century in China. Sabin-IPV development received support from the National 863 Plan, major new drug development major science and technology projects, the Bill and Melinda Gates Foundation (BMGF), and the Special Major Science and Technology Funding of Yunnan Province Biological Vaccine. This support effectively promoted Sabin-IPV development. Sabin-IPV is represented in two national patents, "culture method for attenuated strain IPV" (Patent No.: ZL2004 10040721.1) and "post-processing method of IPV production from attenuated strains" (Patent No.: ZL2004 10040720.7), retaining independent intellectual property rights.

While studying in the Commonwealth Serum Laboratory (CSL) of Australia in 1983–1984, Shude Jiang, who was among the first generation of biology scientists

in the Institute and who had been engaged in OPV research for more than 20 years, began the development of IPV using Sabin strains. In 1987–1990, Jiang guided the graduate student Liang Nong to conduct a study called "comparison of IPV from attenuated and virulent viruses," which showed that the seroconversion rates in rabbits were both 100% whether vaccinated with IPV from Sabin strain or IPV made from wild (Salk) strains. In 1988–1989, Jiang explored the production processes for Sabin-IPV that used a micro-carrier technology and Vero cell lines from the National Institute of Health and Environmental Protection in Holland.

In 1990–1999, the Institute of Medical Biology obtained a loan from the World Bank to build a modern OPV production line. The OPV production line was developed in compliance with European good manufacturing practice (GMP) standards. As the responsible technical lead, Jiang used the production line to conduct research on Sabin-IPV. In 2000, the research project received its first support from a special science and technology project funding source, "Yunnan province new drug research special fund," which provided a valuable 1.3 million yuan to open the door for Sabin-IPV development. By 2005, the production technology of Sabin-IPV had matured, and a Sabin-IPV that is stable, safe, and consistent was developed. That year, the Institute submitted an application to the CFDA for a clinical trial.

In May 2007, CFDA approved the clinical trial application. A total of 1830 subjects participated in the Phase I, II, and III trials, which showed that the vaccine had good safety and immunogenicity, inducing immunity against infection by all serotypes of poliovirus. The Phase III clinical trial showed that positive antibody rates for type I were 100% and 95.87% after vaccination with Sabin-IPV and Salk-IPV, respectively; for type II were 96.09% and 92.46%; and for type III were 99.30% and 98.40%, respectively.

During the development of Sabin-IPV, the Institute received great support from international experts. After completing Phase II clinical trials, in order to select an appropriate vaccine dose, neutralization tests were conducted to determine the level of neutralizing antibodies against Sabin strains (attenuated strain), pre- and postvaccination, by NIFDC. Because polio type II has been eradicated, it is impossible to use wild virus to carry out neutralization testing. CFDA commented in the clinical trial application approval letter (2011 L01484) for the Phase III clinical trial: "the applicant should be aware of the importance of cross neutralization (against wild virus) to the evaluation of vaccine effectiveness." After receiving that feedback, the Institute went to Geneva to participate in a polio virus research meeting, and during the meeting the Institute communicated with coordinator Dr. Roland Sutter, an expert from WHO on polio vaccine development and immunization strategies. With Dr. Sutter's coordination, testing was completed by the US CDC with support from Dr. Mark Pallansch. The results showed that serum antibody induced by Sabin-IPV had a good protective effect on different strains, could prevent infections by different polio viruses, and had immunogenicity no less than the imported Salk-IPV. This international cooperation effectively promoted the development of Sabin-IPV, and the results were recognized by scientists worldwide.

NIFDC further cooperated with WHO and the British NIBSC to establish a standard Sabin-IPV vaccine D antigen assay method. The Institute is actively involved in the process. Each year, the WHO invites experts from the Institute to Geneva to participate in an annual meeting about global polio vaccine development and uses and to present at the meeting.

On January 14, 2015, after 30 years of extremely hard and challenging work, Sabin-IPV obtained new drug certificate and was the world's first stand-alone Sabin-IPV produced on an industrial production scale. On June 30, 2015, Sabin-IPV was launched, and on July 1, the world's first dose of China's Sabin-IPV was administered to a 2-month-old baby as the first polio dose in Daguan Community Health Service Center in Kunming City in Yunnan Province.

5.5.4 Significance of Sabin-IPV

A small volume of 0.5 ml vaccine represents the heroic efforts of 30 years of hard work by several generations of biologists, all with a common goal of "making polio into history" (Fig. 5.7). Sabin-IPV changed the concept of "made in China" to "developed in China" in the vaccine field and represents a Chinese dream for the Chinese vaccine industry. Sabin-IPV fills a gap in the field of attenuated IPV in China, with the research achieving an advanced global level. Sabin-IPV will have a huge impact on polio eradication in China and the world, especially in developing countries. The successful licensure of Sabin-IPV demonstrated that China, with one-fourth of the world's population, is able to rely on its own technical capacity to eradicate polio and to contribute to the final eradication of polio worldwide.

Sabin-IPV is safe to produce, and its price has been lessened by using a large-scale micro-carrier fermentation technology that lowers production costs and is especially suitable for developing countries. The successful licensure of Sabin-IPV will also bring great economic benefits to developing countries.

Fig. 5.7 Sabin-inactivated poliovirus vaccine

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The Journey of Vaccines

6

Lingsheng Cao and Lei Cao

China, as country with the largest population in the world, is now becoming one of the largest producers and users of vaccines. Hundreds of millions of doses of vaccines are produced annually in China – not only to meet the needs in China but also to export to other countries [1, 2]. How are these "magic weapons" against infectious diseases produced? We know that vaccines are sensitive to heat and light, and therefore, how are these vaccines stored and transported? Here we introduce the journey of a vaccine, from production, storage, and transportation to finally being administered to an individual.

6.1 Production, Storage, and Transportation of Vaccines

6.1.1 How Are Vaccines Produced?

We introduce the process of vaccine production using influenza vaccine as an example.

"I," an influenza virus with diameter of only 80–120 nm, am the vaccine strain recommended by the World Health Organization and by the China Food and Drug Administration to be used to produce the current season's influenza vaccine. The vaccine made from "I" can protect about 70–90% of healthy people from the influenza. How am "I" transformed into a vaccine? Only after nine strictly regulated production and testing procedures, including obtaining embryonated eggs,

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inspection by light (candling), inoculation, inactivation, purification, sub-packaging, packaging, cold storage, and sample inspection.

First, "I" need to be transformed to grow rapidly in an embryonated chicken egg – a fertilized egg containing a living embryo. To produce a large amount of influenza vaccine, "I" must be duplicated in large numbers. After nearly a century of research, scientists determined that "I" grow well in chicken embryos' allantoic cavities (equivalent to a human amniotic sac), with the growing embryo giving me cells to infect so that "I" can replicate. To be suitable for making vaccine, the requirements of chicken embryos are very high, including that their environment, food, vaccines administered, etc. are serum pathogen-free to minimize exogenous pathogens in the vaccine. On a daily basis, qualified chicken egg suppliers send tens of thousands of eggs that have hatched for 10 days to the vaccine production plant. In the candling room, staffs conduct as many as 13 inspections of the chicken embryo; only qualified chicken embryos can be used to culture "I." "I" am inoculated into the allantoic cavities of qualified eggs after the shells are disinfected. The embryo is then placed in a sterile incubation room with a constant temperature where "I" will quietly but rapidly replicate. Three days later, "I" become a huge number of viruses. After reinspection, unqualified and dead embryos are discarded, with the rest of the chicken embryos moved to a harvest plant. A shell cutting machine quickly cuts the eggs, and a probe is used to draw "I" and the liquid part of the eggs, such as ovalbumin, into a closed container. After that, large numbers of "I" are combined and transferred to an inactivation plant where an inactivating agent is added. In the process of continuously stirring, "I" slowly lose consciousness and fall asleep. After about a week, I wake up to find that I have lost all activity and can neither grow nor make people sick! I am surrounded by a variety of substances from the egg and the inactivation agent. In the purification plant, "I" go through a sieve and enter a centrifuge rotating at high speed for a long time. The many "I" become concentrated, and impurities like the inactivated agent are removed. At this time, "I" am added with a special substance called a splitting agent, and "I" am changed from a whole virus into fragments from which nucleic acid and macromolecular proteins, which may cause adverse reactions, are removed. The main antigens and internal antigen proteins that induce immune responses are retained. After filtering and sterilization, "I" receive a new name, "virus bulk," and "I" am diluted with saline to form a semifinished product. From the inoculation of eggs to this stage takes about 20 days. After inspection, the qualified "I" enter the next process.

The next step is sub-packaging and packaging. "I" am first divided into small bottles in a sterile work area, each bottle having been washed three times by the injection of water and high-pressure steam, dried and sterilized at 350 °C. Rubber plugs seal the vials. Then "I" go through a packaging line and am inspected visually. The first step is light inspection: "I" am checked by comparing photos taken by seven cameras using a variety of background lighting and angles to ensure that no visible impurities are in the vial, the packing volumes are accurate, and the cap is installed correctly. After being labeled with the production date and lot number, "I" am put into a small box together with instructions for proper use (the package insert). "I" then go through a sophisticated machine that measures the box weight to

an accuracy of 0.01 g. Each box is printed with a drug electronic supervision code – the identification number for "I." My "birthdate" and where I am sent can be tracked by scanning this number. Because "I" am sensitive to heat, I need to be stored at 2–8 °C and protected from light with several layers of coating: ten small packages of "I" are placed into a medium-sized package to which a thin film is attached; four cold boxes are put into a moisture-proof, light-proof silver box; and finally, all of "I" are put into a high-density foam box. Ice packs are placed at the top and bottom of this box, so even if the outside conditions are poor, "I" will be maintained at 2–8 °C for a safe period of time. In the next 2 or 3 weeks, random samples of "I" will go through two inspections by manufacturers and NICPBP. Only by passing the manufacturer's and the national regulator's tests, which include potency, pH, inactivation agent residue, bacterial contamination, and other tests, can each batch of "I" obtain lot release approval by NICPBP. That is to say, only at this time "I" really received my legitimate "identity" and am officially a vaccine that can be used to fight influenza [3, 4].

6.1.2 How Is the Vaccine Stored and Transported?

After "I," in vaccine form, am produced, how am "I" transported and stored? We know that "I" originated from microorganisms and their metabolites, which am composed of proteins, polysaccharides, lipid polysaccharides, and protein complexes, are very sensitive to heat and light. During transportation and storage, "I" need to be protected from high temperature, sunlight, and freezing and thawing. Different "I" have different requirements for temperature, but most of the vaccines are stable at 2–8 °C and cannot be frozen except for OPV. Repeated freeze-thaw cycles can damage proteins and render "I" unable to induce immunity [5].

6.1.2.1 Vaccine Storage and Transportation in the Early Days of Vaccination

Before the 1980s, due to limited refrigerating equipment and power supplies in China, "I" was only vaccinated at low-temperature seasons – winter or spring – in annual vaccination campaigns. This immunization strategy left many children unvaccinated due to being age-ineligible, not at home, or having a febrile illness during the campaign, and these children had to wait until the next season's campaign. Such a strategy negatively impacted vaccination rates and led to an accumulation of susceptible children, increasing risk of exposure and causing frequent epidemics. Due to a lack of refrigerating equipment, "I" could not be supplied in a timely manner, so emergency vaccination to control outbreaks was nearly impossible. Due to a lack of funding, an "EPI" insurance system was implemented in some areas, charging service fees to families to provide funds to purchase storage and transportation equipment for "I" and to consolidate into a three-tiered rural health services network [6].

Let me introduce how "I" was stored and transported in 1958 in Xuzhou. "I" was stored in a refrigerated warehouse at city and county EPSs. The lack of reliable

electrical power required creative solutions to maintain the necessary 2–10 °C environment in PoVs [7]. PoVs are stirred 400–500 g of crude ammonium chloride for 2 min in 1500 ml widemouthed thermoses filled with cold water to serve as a cooling system. At the bottom PoV storage equipment, "I" was placed on top of a 4 ft by 4 ft plate. Alternatively, "I" was stored in a kerosene-powered refrigerator.

Vaccine storage and transportation also required creative solutions. Transportation of live, liquid measles vaccine from Lanzhou Institute of Biological Products to rural areas in Xinyang Prefecture of Henan Province during the winter of 1976 serves as an example. At that time, China's measles vaccine was a liquid presentation. Because the stability of the liquid measles live vaccine was felt to be poor, in order to assess the ability to maintain potency during transportation to rural and remote areas without refrigeration equipment, Lanzhou Institute of Biological Products conducted a study to evaluate the cold chain from Lanzhou to Xinyang in January 1976. Due to inadequate transportation, it took nearly 12 days to bring the vaccine 1495 km to the most remote rural areas in Xinyang. Vaccines were transported by train from Lanzhou to Xinyang, by bus from Xinyang to a public community facility, and by bicycle or by foot to the village. The evaluation showed the temperature fluctuation to be large, but the investigators also observed that during a winter without cold storage conditions, high-titer liquid vaccine remained acceptably potent as long as the vaccine was administered in a timely manner. Even after storing the vaccine at room temperature, adequate vaccine virus titers remained at the end of shelf life and with no significant difference in titers from vaccines stored in cold rooms. This observation also supported to the feasibility of vaccination during cold seasons [8].

Beginning in the early 1980s, China began to implement EPI in accordance with WHO initiative and actively built an effective vaccination system; transportation and storage conditions gradually improved. In 1980, MoH made a clear request to the vaccine storage and transportation at first time: "Cold chain equipment should be provided at all levels of EPS and community health centers. Ice bottles should be available at the PoVs. Storage and transportation of biological products had to be in accordance with the requirements of the specification. Vaccines that expire, become discolored, clump or coagulate, or vaccines with foreign bodies visible after shaking, that have no label or an unclear label, or that have cracked ampoules, must not be used. After opening an ampoule, live bacterial vaccines must be used within two hours, and inactivated bacterial vaccines must be used within four hours. Vials not used within the time limit have to be discarded." Furthermore, "National EPI plan from 1982 to 1990" established even stricter requirements so that all levels actively improved storage conditions for biological products. "Provinces, municipalities and autonomous regions lacking of cold rooms should establish them as soon as possible. By 1985, all county EPS had to be equipped with special refrigerators or freezers; village clinics had to be equipped with vaccine carriers or ice bottles. By 1990, township hospitals had to be equipped with special refrigerators, and provincial, municipality-level, and autonomous region-levels had to be equipped with refrigerated vaccine vehicles. Manufacturers of biological products had to be properly equipped with an appropriate cold chain from the production line to end user."

6.1.2.2 How Are Vaccines Stored and Transported Now?

Currently, the storage and transportation of vaccines generally flow from producers to provincial CDCs, to prefecture CDCs, to county CDCs, to township hospitals and community health centers, and finally to PoVs. CDCs (called EPSs before 2003) at all levels purchase, store, and transport vaccines according to the national requirements of EPI, adjusted to local vaccination service mode and cold chain storage conditions. The vaccine transportation cascade went from community health centers or township hospitals to village clinics for administration to vaccines. Governments at all levels in China use their funding to purchase cold chain equipment, including vaccine vehicles, cold rooms, refrigerators, etc. With living conditions greatly improved, "I" do not have to worry about the safety, even in the hot summer.

After 2008, China gradually conducted the National Immunization Program (NIP) through replenishing and renewing the equipment of the storage and transportation for vaccines. The living conditions of "I" were further improved. Currently all NIP vaccines should be stored and transported at 2–8 °C in dark conditions, with the lone exception that OPV must be stored and transported at −20 °C [9]. An example how vaccines are stored and transported in urban areas is shown below.

"I," as one of the NIP vaccines, funded by the central government of China, am procured by provincial CDCs and transported to PoVs. Because "I" must be stored at temperatures between 2 and 8 °C from production to the child, the cold chain is critically important. Transportation equipment includes special-purpose refrigerated trucks, refrigerated containers, and refrigerated vaccine carriers. The main storage facility is the cold room. The entire process from production to PoV is tightly regulated. Vaccines are transported by the manufacturer via refrigerated trucks to provincial cold rooms, then transported from provincial to prefecture cold rooms or refrigerators via refrigerated trucks, then to counties via refrigerated trucks or cold-box vehicles, then to township hospitals or community health centers, and then finally to refrigerators at PoVs.

"In fact, the entire cold chain can be seen as a giant mobile refrigerator that continuously maintains vaccines between 2 to 8°C," Director Li, chief of EPI in a city CDC said. "In refrigerated trucks, a cold chain manager accompanies the vehicle to continuously monitor its refrigeration equipment. In real-time, the system automatically sends warning messages to the terminal of the refrigerated vehicle to alert us for any temperature excursions."

Li also explained that when problems happened with refrigeration equipment, the refrigerated truck is immediately sent back, if the truck has not gone too far, to bring the vaccines back to the CDC cold room. If the truck is too far away from the CDC, the vaccines can be brought to the closest cold storage facility.

"After vaccines reach PoVs, they are stored in PoV refrigerators. Vaccine temperatures are required to be recorded twice a day," said Dr. Li. To ensure the quality of the vaccines, the prefecture and county CDCs and the PoVs must store vaccines according to the National Vaccine Storage and Transportation Management Regulation and record each input and output of vaccines correctly and secure vaccines in cold chain conditions at all times. One person is designated to manage the vaccines and ensure that the relevant policies are upheld.

In recent years, with the emergence of professional logistics companies, the CDC transportation model is gradually changing. In developed areas like Beijing, Shanghai, and Tianjin City, transportation and storage of vaccines are serviced by the professional logistics companies funded by government procurement [10–12]. Let us take Beijing as an example to explain how a third-party company is used to transport and store vaccines.

Transportation and storage of vaccines in Beijing is managed by three logistics companies that won government contracts. First, a manufacturer transports vaccines to the appropriate logistics company's storage facility in accordance with the Beijing's vaccination program. PoVs and county CDCs report vaccine demand monthly to Beijing CDC, and Beijing CDC then informs the logistics company of the PoV and county demand projections. Beijing has established an "inventory management information system for vaccine procurement in Beijing," in which information about NIP vaccines and non-NIP vaccines is recorded, including vaccine type, formulation, presentation, specification, quantity, and shelf life. An electronic information management system is used to obtain and store vaccine manufacturer and CFDA lot release documents and certificates. Transportation and storage must comply with cold chain requirements, including documentation of temperatures all along the way. We went to one of the three logistics companies – China Pharmaceutical Logistics Co., Ltd. – to conduct an on-site investigation. This company is responsible a portion of Beijing's vaccine storage and transportation. A transportation temperature monitoring record will be uploaded and filed in the system. Vaccines are inspected in the waiting areas to ensure accurate documentation of manufacturer, vaccine name, quantity, batch, and shelf life. Quality control personnel check the boxes one by one in accordance with the CDC delivery list; a probe is put into the box to measure the temperature; vaccines will be accepted only if everything checks out as normal. A logistics company will transport vaccines to the designated PoVs in cold chain trucks. PoVs receive and store vaccines to immunize age-eligible children.

China's Food and Drug Administration (CFDA) regulates the storage and transportation of vaccines. Effective management is strictly implemented through a series of laws and regulations including "Management Regulations for Vaccine Storage and Transportation," which specifies vaccine distribution oversight in detail. In China, only provincial FDA-accredited distributors can handle vaccines. Accreditation implies having sufficient trained professional and technical personnel and validated cold storage and transportation equipment. With few exceptions, vaccines are not to be sold by pharmacies. CDCs and PoVs that provide vaccination services must also comply with the cold chain. FDA, MoH, CDCs, and PoVs supervise storage and transportation to ensure requirements are met [13].

6.2 Establishment and Operation of the Vaccine Cold Chain System

In October 2014, CCTV launched a special project called "Going to the Grassroots Level – the Immunization Program" in southern Xinjiang Province. On October 22, EPI staffs accompanied reporters along the Xinjiang-Tibet Highway south line for

180 km. The journey took them across two mountains more than 3000 m above sea level to Xihexiu Township in Yecheng County, deep in the heart of Karakoram Mountain. After a night of rest and adjustment to the high altitude, the group went to the Xihexiu Village Clinic to interview a fixed PoV and a household immunization. The group walked with two local village doctors for over an hour at an altitude of more than 3300 m before arriving at some nomadic family homes to administer OPV, DTap, and measles, mumps, and rubella (MMR) vaccine. The village doctors rode a motorcycle with a vaccine carrier, but soon the highway became a small road that was traversable only by donkey. Near the edge of the cliff, even the donkey could not fit, and the doctors and reporters had to climb the mountain by foot. The reporters videoed the exceptional route of the village doctors, revealing the incredible hard work of grassroots staffs. On October 24, the group went to Shache County and Yinjisha County and interviewed two families that had suffered from polio during the 2011 outbreak of imported wild virus into Xinjiang. With these families' stories, they aimed to educate the entire society on the importance of vaccination and the seriousness of vaccine-preventable diseases [14].

The CCTV project showed many cold chain difficulties – something unimaginable to ordinary people. But what is the cold chain? It is the supply chain that ensures the quality of vaccines from their production to the PoVs, regardless of season and external temperature. Infectious disease can be controlled and even eliminated through an adequate supply of vaccines that are stored and transported in an effective cold chain system (combined with high population uptake, of course). The cold chain system requires professional management, a sound infrastructure, and standard operating procedures. A cold chain system enables routine immunization at health centers year round, which greatly increases vaccination opportunities and improves vaccination rates. How was the vaccine cold chain system in China established?

In the 1980s, vaccination was accomplished by campaigns that could be conducted during lower temperature seasons not requiring a functional cold chain, as one did not exist at that time in China. Since 1982, with technical and financial support from UNICEF, a cold chain system has been pilot tested in the hot climate areas of Yunnan, Guangxi, Sichuan, Hubei, and Fujian provinces. The project was expanded to 18 provinces in 1985 and to 30 provinces in 1989. By 1993, China had established a vaccine cold chain system that covered more than 90% of the population. By the end of 1995, the joint UNICEF/China project had invested about 35 million dollars to establish the cold chain, train personnel, and conduct social mobilization and advocacy for polio eradication. China's governments at all four levels financed education and project management. With the establishment of a cold chain, the traditional rhythm of winter and spring campaigns was able to be changed to a daily, weekly, or monthly vaccination service in urban areas and to monthly or more frequently in rural areas. Regions with difficult terrain and climate were able to be provided with immunization services at least six times a year. The vaccine cold chain system was not only useful for storage and transportation of vaccines, but it also promoted development of the immunization program. The vaccine cold chain system now covers all levels, strongly supporting routine immunization across all of China [15–16].

The essence of an effective cold chain is equipment and facilities that maintain specified temperature ranges, coupled with temperature monitoring to detect temperature excursions that can be addressed before the vaccine loses potency or has to be discarded. Since 2000, China has issued a series of rules and regulations that place stringent requirements on the vaccine cold chain, including "Vaccine Storage and Transportation Management Regulations," "Immunization Practice Regulations," and "Good Supply Practice." If temperatures in cold chain vehicles or facilities exceed the allowable range, remedial action should be taken and the incident recorded. Vaccine manufacturers, distributor, and PoVs are required to monitor and record temperatures using automatic temperature recorders in cold rooms and freezers and using thermometers in refrigerators.

Innovations in communications and information technology are now being applied to monitor the vaccine cold chain. In Wuxi, Jiangsu Province, medical refrigerators that have Global Positioning System (GPS) wireless temperature monitors are provided as standard issue for PoVs. Three types of early warning modes are used as the system automatically sends warning messages to managers as needed [17]. Tianjin developed an automatic temperature monitoring system that detects and locates cold chain problems [18].

A more direct tool for monitoring the temperature of the vaccine is also used in China. Vaccine vial monitors (VVM) have labels onto which is printed a special temperature-sensitive material that changes color when exposed to too much heat. VVMs are the only available tool that can track the temperature of a vial from the factory to the end user. The VVM ensures that vaccine is not subject to excessive heat, helping to ensure potency and reduce waste. WHO and UNICEF recommend that Member States use VVMs. In 2006 a VVM was prequalified by WHO, and in 2010 VVM use was a critical element in the revised prequalification application by WHO [19]. VVMs have been used in some kinds of vaccines in some provinces, such as hepatitis A vaccine by Beijing, Sinovac by Shanghai, pneumococcal polysaccharide vaccine by Chengdu Institute of Biological Products, and varicella vaccine by Changchun Baike [20].

Independent supply and distribution are a trend in modern logistics. There is a strict requirement for vaccine cold chain system regarding transportation, temperature control, and timely distribution. Because vaccine supply demand are from wide geographical areas, some with small amounts of vaccines needed, distribution of vaccine can be characterized as having low volume, multiple batches, multiple frequencies, and multiple regions. Distribution by the manufacturer or end user is always expensive. Third-party distribution can reduce logistics costs and improve coverage, efficiency, and service level while ensuring vaccine potency. There is a trend in China to purchase vaccine storage and transportation services from the third party. Cold chain distribution began in China in the 1950s, and following years of development, cold chain has reached a certain stature, although there remains a gap between China and developed countries in Europe and the United States. According to the Chinese cold chain logistics industry in 2014, 500 companies planned to purchase 1244 refrigerated vehicles, accounting for 44% of the total number planned; 121 companies planned to build 13.57 million tons of cold rooms, accounting for

72% of the total number of cold rooms planned, and among these, 0.8 million tons (6%) are planned to be built by third parties [21]. Thus, we can say that China's cold chain logistics has entered a stage of rapid development. The proportion of pharmaceutical products transported by cold chain is increasing due to increasing intensity of regulation and stricter requirements on businesses. Among the top 100 best-selling drugs, 45% are required to be stored in cold temperatures. Uneven development is a barrier to purchase cold chain services from society. At present, all vaccine distribution works through third-party logistics services in Beijing, Shanghai, and Tianjin, and some eastern developed regions are exploring purchase of third-party services for vaccine cold chain distribution.

6.3 Vaccine Procurement and Distribution

6.3.1 How Are Vaccines Purchased and Distributed?

Vaccines are made by manufacturers, such as the Institute of Biological Products, company of biological products, and then sent to the NICPBP for "quality inspection." After 52 days of evaluation, vaccine lots passing all tests are released, which means they can enter the market for distribution and administration. Vaccines belong to "big families" and include many "brothers and sisters," such as BCG, hepatitis B, DPT, OPV, measles-rubella (MR), MMR, DT, Japanese encephalitis, hepatitis A, influenza, rabies, varicella, Hib, oral rotavirus, and 23 valent pneumococcal vaccines. Available vaccines include those "born" in China and abroad and can be divided into live attenuated, inactivated, polysaccharide, conjugated, and recombinant vaccines according to the nature of the vaccine. Vaccines are further divided into Type 1 and Type 2 vaccines according to who purchases the vaccine [22]. Type 1 vaccines are those procured and purchased by the government and that are provided free to citizens, who should be vaccinated in accordance with the requirements of the government. Type 1 vaccines are hepatitis B, BCG, OPV, DPT, MR, MMR, DT, JE, and hepatitis A vaccines. The government requires that age-eligible children complete the immunization schedule for Type 1 vaccines, which consists of 22 doses per child. Type 2 vaccines are voluntarily paid for by citizens themselves; they include influenza, rabies, varicella, Hib, oral rotavirus, and 23 valent pneumococcal vaccines.

At the end of each month, Dr. Z, who is responsible for the daily log, determining vaccine needs at a rural hospital, and children's physical examinations, checks the daily immunization log and vaccination information system. He will summarize the vaccines administered, doses in storage, and doses needed next month according to demands and wastage (including BCG, hepatitis B, DPT vaccine, OPV, MR, MMR, DT, JE, hepatitis A vaccines). A vaccine procurement plan is developed to fit the projected vaccine needs and submitted to the county CDC.

The county CDC will aggregate township hospital and PoV plans and submit the aggregate plans to prefecture and provincial CDCs. Type 1 vaccines will be procured by provincial governments through a bidding process; the Provincial Health Department commissions the provincial CDCs to distribute vaccine. Provincial CDCs

distribute Type 1 vaccines every 2 months according to the prefecture plans. Prefecture CDCs distribute Type 1 vaccines to county CDCs, and county CDCs distribute Type 1 vaccines to township health centers and PoVs according to demand. CDCs at all levels must store and transport the vaccines in accordance with requirements in the "Pharmacopoeia of PR China," "Standards for Vaccine Storage and Transportation," and "EPI Operational Standards." Temperature records are kept 2 years for auditing purposes. Type 2 vaccine storage and transportation uses the same requirements as Type 1 vaccines.

Type 2 vaccines are procured by provinces through bidding. Market entrée permission has been used since 2008, with provincial or prefectural procurement from distributors. Every year, EPI experts and epidemiologists at the province and/or prefecture levels review Type 2 vaccines and manufacturers/distributors based on the applications by the manufacturers, company qualifications, product quality, supply management practices, price, reputation, and customer service records. Recommendations for Type 2 vaccines are developed based on the current immunization and disease control needs and are used by provinces for procurement of vaccines. An open tender procurement is used to ensure vaccine quality. To better supply vaccines, each unit should submit the plan of need before procurement. Provincial CDCs distribute vaccines to prefectures by refrigerated trucks, with temperature records and lot release reports containing the provincial CDC seal. The major distribution routes for vaccines are standardized to ensure that the vaccines are from qualified manufacturers and ensure maintenance of cold chain during storage and transportation. Fixed PoVs at the township level with qualified vaccination staff are responsible to ensure that the vaccination services are adequate.

The vaccine supply plan is developed as follows. The provincial CDC estimates the number of children targeted by Type 1 vaccines based on the number of newborns the previous year according to the county health department's statistics department, deducting the number of children who emigrated, adding the number of children who immigrated, and using the "Immunization Information Management System." The target number of children is multiplied by the number of doses needed per child for each vaccine, and these results are multiplied by a wastage coefficient to obtain the number of vaccine doses required for each vaccine in the province. The province will also store a certain amount of vaccine for emergency use. Type 2 vaccine need is based on demand and is also reported from lower levels to higher levels (PoVs, township, county, prefecture, and province) according to the local economic level, the number of infants, and other vaccination program characteristics. Vaccines are supplied from province to prefecture and to the county CDC via cold chain. County CDC distributes vaccines to the township level and PoVs every 2 months [23].

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Weekly Work by a Township Hospital Vaccinator

7

Zundong Yin, Yixing Li, Junhong Li, Guijun Ning, Dan Wu, Zhenlong Zhang, Zhigang Zuo, and Bin Zhang

Chairman Mao Zedong said, "It is difficult for a person to do something well for their whole life, while it is not difficult for a person to do only one thing well." It is not simple to do simple things perfectly; it is not ordinary to do ordinary things perfectly. Grassroots-level immunization staff are ever mindful to "let every child have access to vaccine and become protected," with dedication and responsibility, with enthusiasm and effort, while doing an extraordinary job from an ordinary position.

District Z is the central district of a city that has 6 towns, 6 offices, and more than 800,000 residents. There are 10 obstetrics hospitals delivering 20,000 newborns each year; some hospitals provide delivery services and vaccination services for migrant families. To facilitate informed consent for vaccination, Z District CDC designed and printed, "Understanding Neonatal Vaccination," which is a booklet provided by obstetric hospitals to parents, along with an immunization card recording the first dose of hepatitis B vaccine and bacillus Calmette-Guérin (BCG). The locations and telephone numbers of points of vaccination (PoVs) are provided in the booklet to remind parents or guardians to continue vaccination when the child is 1 month old. This approach ensures that each child will receive information and reminders about upcoming vaccination starting the day they are born.

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Dr. Sun is a staff member at a township hospital and is responsible for vaccination. She graduated from the provincial health care school in 1990. Majoring in epidemic prevention, she did not realize that the year she graduated was a milestone year in the history of China's epidemic prevention. In 1985, President Li Xiannian, on behalf of China, committed "by 1990 to achieve universal childhood immunization." The year 1990 was also the deadline for vaccine coverage to be over 85% measured at the county level, and 1990 was the first year of implementation of the "Law of the People's Republic of China on Prevention and Treatment of Infectious Diseases." As a beginner, she didn't fully understand the burden on her shoulders, and she felt that she had many things to learn that were not covered in books or lectures. The time was a transition period for local vaccination service practices – from monthly vaccination sessions in village clinics to weekly vaccination sessions at township hospitals. Village doctors were responsible for informing parents about the vaccination needs of their children.

The township hospital fixed-site PoVs greatly shortened inter-vaccination intervals and improved timely vaccination and vaccination quality. However, the vaccination workload was greatly increased. Dr. Sun and her colleagues focused their effort on children's vaccination. With the inclusion of new vaccines into the national immunization program (NIP), such as hepatitis B vaccine; Japanese encephalitis (JE) live attenuated vaccine; measles and rubella (MR) vaccine; measles, mumps, and rubella (MMR) vaccine; and hepatitis A vaccines, NIP was on a developmental fast track. Dr. Sun and her colleagues were "pathfinders." By now, engaged in vaccination for more than 20 years, her daily work remains providing vaccinations on vaccination days, data management on non-vaccination days, baseline surveys of children, and making appointments for children having missed opportunities for vaccination. This seemingly simple work is not simple to complete!"

Dr. Sun works in N town, located in the southern suburbs of Z District. N town has 15 villages, 2 citizen committees, and a new community center. There are more than 20,000 people engaged in agricultural in the town. N town is also an important industrial center in Z District because it has a large state-owned enterprise and some small- and mid-sized factories. N town attracted a large number of migrant workers and now boasts more than 70,000 migrants. In recent years, the number of newborns having local citizenship is similar to the number of nonlocal, migrant newborns. It is a challenging task for Dr. Sun and other immunization staff to vaccinate migrant children. Dr. Sun has no fear of difficulties, though, and she has developed a set of effective solutions through her nearly 20 years of experience. Each of the 17 villages in N Town has a clinic. On non-vaccination days at the beginning of each month, Dr. Sun visits each clinic and collects data on babies born during the previous month and on migrant children new to the area. She also goes to the town's birth registration department to obtain birth data. She reconciles these data with information system data to identify children with immunization cards and certificates in each village. For children without cards or certificates or who have not been coming in for vaccination, she will inform parents and make appointments by telephone or through village doctors. Dr. Sun and her colleagues also conduct quarterly surveys of migrant children, focusing on the farmers' market, shopping malls, supermarkets, and factories where

there are more migrants. They make an active search for children aged 0–6 years old and notify parents, indicating the importance of vaccination, the vaccination schedule, and addresses of PoVs with their telephone numbers. It is because of her and her colleagues' diligent "multisource, active search" that ensures timely vaccination for migrant children and avoids under-vaccinated areas.

Most of the PoVs in Z district provide immunization services at least 3 days each week, generally on Tuesday, Thursday, and Saturday. PoVs affiliated with N town hospitals usually provide vaccination services for 100–300 children a day. Dr. Sun is responsible for the first step: preregistration. She needs to verify carefully the vaccination record of each child, register the child, and make an appointment for the next vaccination. She will patiently answer questions from parents. She knows that every link of vaccination is seemingly ordinary but is related to healthy growth of children. Patience and carefulness of PoV staff are strictly evaluated, with not the slightest carelessness allowed. At the end of each vaccination day, she and her colleagues need to collect and summarize vaccination data, check the inventory of vaccines, clean the PoV, and record the corresponding disinfection information. At the end of each month, inventory has to be taken to develop a vaccine procurement plan for the next month. Each month, vaccinations given must be summarized, non-vaccinated children must be identified, and their parents contacted and reminded. Information is summarized and reported monthly to the district CDC.

In addition, N town has 4 schools and 7 kindergartens, with a total of over 8000 students. Every year, the PoV staff go to schools and kindergartens to check students' vaccination certificates and provide missing vaccinations. To avoid eroding students' learning time, Dr. Sun uses Saturdays to immunize students who missed one or more doses of vaccine. If there is an ongoing supplementary immunization activity or other emergency vaccination campaign, they will work on Sunday. It is their strong sense of professionalism and great sense of responsibility that ensure the healthy growth of children!

7.1 Participation in Regular Meetings, Receipt of Vaccines (Monday)

In order to avoid busy vaccination days, Z District CDC convenes routine immunization program meetings at the end of each month. PoV heads and the district PoV leader must attend the meeting. Dr. Sun attends all routine meetings, whether in summer or winter. She rides an e-bike, which replaced her regular bicycle last year, traversing the district's familiar streets for nearly 30 min before arriving at the district CDC. In the meeting, she sees familiar faces from other townships, and they discuss recent work. In the meeting, she listens carefully and makes notes in the "regular meeting book" issued by the district CDC.

The meeting begins at 9 a.m. and ends at noon. Staff from six township hospitals and six urban hospitals participate in the meeting. Usually, meetings include three topics: the first topic is a summary of recent work, including the distribution of immunization cards and certificates, vaccination rates, missed vaccinations, supplementary

vaccination, surveillance of vaccine-preventable disease, adverse events following immunization (AEFI) reports, and timely and accurate reporting, followed by a discussion on how to solve problems. The second topic is to arrange follow-up steps in accordance with higher-level requirements, considering the local situation. The third topic is training of PoV staff on policy, theory, and skills (such as how to freeze ice packs, how to conduct a vaccine shake test) in accordance with the requirements by higher level, considering the local situation.

Dr. Sun is responsible for the coordination of N township hospital's vaccination effort and for updating policy information and technology. After she returns to the clinic, she will organize PoV staff to meet in the township hospital. She will review the district meeting notes and provide some training to ensure that all policies, technologies, and measures of the immunization program are implemented in a timely manner.

In addition to regular district CDC meetings, the township hospital established a routine PoV meeting. Today, being Monday, is the date of the routine meeting, and Dr. Sun has invited leaders in charge of vaccination and PoV staff to participate. All village doctors have come; she announces that the meeting has begun.

"Hello, let's start today's meeting. The meeting includes the following topics. First, I'd like to discuss the upcoming measles supplementary immunization activity (SIA) with record checking for missed vaccination. Second, I will discuss verification of vaccination certificates for school and kindergarten enterers. And finally, I'll ask you to report your progress from last week."

"The measles SIA is nonselective; all children under the age of 15 years should be vaccinated regardless of doses received previously and measles disease history. Regardless whether the child is local or migrant, domestic or foreign, the child should be vaccinated according to the principle of 'management by residence.' Children who received measles vaccine within one month should not be vaccinated. Prior to the meeting, each attendee received a set of questions and answers about the measles SIA as a reference for parents' questions. The SIA has to be completed within 10 days. Time is short, and the workload is huge. When you go back, please inform the parents with eligible children about the SIA micro plan so they take their children to PoVs for vaccination. Our PoV will arrange for vaccines, personnel, and other preparatory work."

"Of course, we have conducted this kind work before; are there any questions?" Dr. Sun asked.

Village Dr. Ma asked: "If parents don't give consent, or it is they are not present for the vaccination, what should we do?"

Dr. Sun said: "First of all, it is not a mandatory SIA. For parents who don't give consent, we need to talk with them and explain with patience and in detail the rationale for the SIA. International experience shows that not all children are protected after measles vaccination due to a variety of factors. About 5–10% of children may develop the diseases after exposure due to primary vaccine failure. Considering China's policy to eliminate measles, the SIA is necessary. If parents decline, we respect their choice. Specific information is included in the Quality Assurance manual for your reference."

"Our second topic is verification of vaccination certificates. School will be in session soon; when you go back please find out when kindergartens and primary schools open. Please inform kindergartens and schools to collect every child's vaccination certificate. The district CDC has issued the relevant documents. Please verify the information in the vaccination certificates against the NIP schedule. If some doses or vaccines are missed, the parents should be informed to take the child to the PoV for make-up vaccination. Again, please take verification of certificates seriously, especially including those of new students and migrant children."

"Next, let's talk about this week's progress."

Village doctor K said: "I would like to go to speak first. I heard that a middle-school child from our village developed meningococcal meningitis this week that was diagnosed at the county hospital, and that the child is in quite serious condition. Should we consider emergency vaccination in our village?"

"This is an urgent issue. The District CDC knew of this case from the direct network reporting system, and recently made arrangements. Because the case happened in a school, there is no need for the entire village to have emergency vaccination. At present, we have obtained prophylactic medicines from the district hospital, and contacted the school principal. Contacts of the case need to take prophylactic antibiotics. We also require the contacts to be monitored closely. We are prepared for emergency meningococcal vaccination in the school, if needed, so that it can be implemented quickly. In addition, we conduct daily morning checks, disinfection of school classrooms and dormitories, and publicity on prevention and control of meningococcal meningitis," Dr. Sun says.

All participants presented and exchanged information about their activities of the week, including problems and the approach to solving the problems. Dr. Sun wrote the minutes and summarized the meeting. Dr. Sun learned the needs of village doctors, solved the problems she was able to solve, and reported to higher levels for support for problems she was unable to resolve.

7.2 Obtaining and Transporting Vaccines

Obtaining vaccines is an important task for each PoV. There is a designated person who is in charge of PoV vaccine management. Dr. Sun's colleague, Dr. Li is one such person. Dr. Li, who has a strong sense of responsibility, will draft a vaccine plan for the next month and submit the plan to Z district CDC before the fifth of every month. She carefully calculates the doses needed for routine vaccination and combined these doses with the monthly and quarterly doses needed for supplementary vaccination. Vaccine transportation under cold-chain conditions is essential to ensure potency of the vaccine. No vaccines can withstand long-term exposure to high temperature, as they lose potency. To strengthen vaccine management and cold chain, Z district CDC always includes management into routine supervision. Every quarter and at year's end, the district Health and Family Planning Commission will assess vaccine management. The district CDC

distributes vaccines to township hospitals at least once a quarter. Dr. Li reviews the various vaccines, syringes, emergency medicine, vaccination equipment, and other supplies every week to ensure that they are in proper condition and functioning well. All relevant documents are kept in the archives for at least 2 years after the vaccine expiration dates.

A school-based emergency vaccination turned out to be necessary, but it would be some time before the district CDC could distribute the necessary vaccines. To avoid a wait, Dr. Li rode her electric bicycle to the CDC to supply a portable cold box with vaccine. In accordance with the "Emergency Vaccination Plan," Dr. Li counted the number of doses and then put ice packs neatly in the sides and bottom of the box, placing the vaccine in the center under icepacks. She paid special attention to avoid direct contact between the vaccine and the icepacks to avoid freezing the vaccine or breaking vials (Fig. 7.1). The road to the township hospital was undergoing maintenance, making the road bumpy, so Dr. Li puts plastic foam in the cold box to cushion the vaccine.

With the vaccine neatly packed in a cold box, Dr. Li rode her bike to the township hospital. On the way, she took a sharp turn and didn't see a fast-moving oncoming vehicle. Dr. Li had to take evasive action and fell, hitting the ground hard. Her first instinct, though, was to check the cold box, without even a thought of herself. To her pleasant surprise, the cold box was intact, and her bike still worked, so she continued her trip to the township hospital, despite discomfort from road rash. When she arrived at the hospital, she verified that the vaccines were ok and at the proper temperature. She felt relieved; road rash heals, but lifesaving vaccine in cracked vials can't be used.

When storing vaccines, Dr. Li always follows the "Vaccination Management Standards," accurately recording the doses in the vaccine storage registry and vaccine transportation records. Before she puts the vaccines in the refrigerator, Dr. Li checks the lot numbers and places the vaccines in lot number sequence (Fig. 7.2). The distribution of vaccines will follow the order of arrival and the expiration dates – first in, first out.

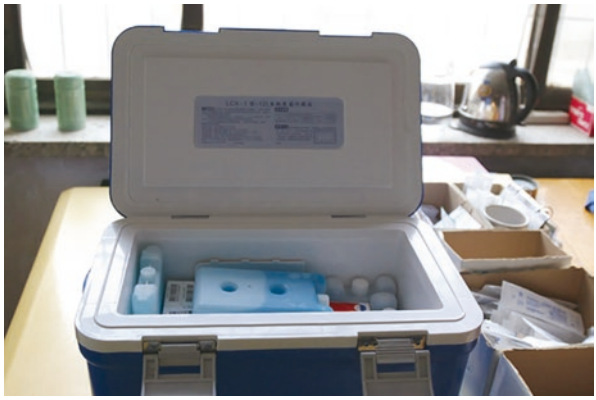

Fig. 7.1 Placing vaccines in a vaccine carriage

Fig. 7.2 Neatly placed vaccines in a refrigerator

7.3 Vaccination Days (Tuesday, Thursday, and Saturday)

The PoV where Dr. Sun worked provides vaccination services every Tuesday and Thursday. For the convenience of children in kindergarten and the school, vaccination services are also provided on Saturdays in accordance with the requirements by the district CDC, ensuring that vaccination is provided at least 3 days a week with service times from 8:00 to 11:30. Today is Tuesday, and parents holding a child are patiently waiting in the PoV for vaccination. The PoV is divided into a cold chain room, a preexamination room, an injection room, an observation room, and a children's play room, with beautiful and neatly lettered signs to distinguish the rooms from each other. On service days, there should be at least five staff members in the PoV, engaged in preexamination and registration, vaccination, and on-site organization, with responsibilities for each of the five staff members standardized.

The vaccination procedures are as follows:

- Preexamination to determine whether the child can be vaccinated that day
- Registration to record the vaccine to be administered and, if the vaccine is a type 2 vaccine, to collect money from the parents for the vaccine
- Vaccination
- Observation for 30 min in case the child has an allergic reaction or faints.

Little Lingling is a 2-year-old, and today she is brought to the PoV by her mother for JE vaccination. Dr. Sun performs a preexamination and checks Lingling's "child vaccination notice" for completeness.

To Lingling's mom: "Has Lingling ever had an allergic reaction? Has she had fever, or other problems after a vaccination? Has she been ill recently?"

"She has been healthy recently and she has never had fever or an allergic after a vaccination." Dr. Sun checked Lingling's vaccination certificate, letting Lingling's mother know that Lingling will be given a JE vaccine, which prevents Japanese encephalitis. Dr. Sun documents the preexamination and history.

After the preexamination, Lingling's mother brings Lingling to the registration area. The registration personnel check Lingling's vaccination certificate again and make an appointment in the IIMS for the next vaccination.

After registration, Lingling is brought to the injection room. A specialized vaccinator, Dr. Cao is responsible for vaccination. Dr. Cao completes "three checks and seven verifications" before vaccinating. "Three checks" means to check health status and contraindications, vaccine appearance and batch number, and vaccine expiration date. "Seven verifications" means to verify the child's name, age, vaccine to be administered, specifications, vaccine dose, and vaccination route. The vaccination site fills out the immunization card and certificate.

Dr. Cao asks Lingling's mom "Is this child Wang Lingling?" as she opens the child's vaccination certificate and checks.

"Yes, doctor."

"This time she needs JE vaccine."

Lingling's mom rolls up Lingling's sleeve. Lingling begins to cry when she realizes that she will get a shot: "Mom, no shot, let's go home, let's go home."

"Please hold Lingling tightly. Lingling is such a brave girl. Don't be afraid, I'll be quick."

While speaking calmly, the doctor checks the child's arm and identifies the lower edge of the lateral upper arm deltoid muscle. She uses a sterile cotton swab dipped in 75% ethanol and disinfects the injection site from inside to outside via a neat spiral. After disinfection, she opens a bag and takes a syringe, drawing up the JE vaccine and administering it subcutaneously. Completing the injection, she puts the syringe directly into a sharps box (Fig. 7.3).

The child is still crying, but the mom says: "Lingling, darling, we're all done, no need to cry."

Dr. Cao records the vaccine, formulation, lot number, and administration time in Lingling's vaccination certificate. "Lingling's mom, here is the vaccination certificate. Please keep it carefully. Please bring Lingling to the observation room for 30 minutes; come back to me if she is uncomfortable. When you are home, please look for redness and swelling at the injection site; if you see this and it is severe – such as having a diameter of more than 1 dime (>1.5 cm) – please call me, and I'll tell you what to do. In addition, Lingling needs to receive measles vaccine next month; here is a 'child vaccination notice.' Please fill in your phone number here, and please come back in 1 month for the measles vaccine. Any Tuesday, Thursday, or Saturday mornings will be fine."

Fig. 7.3 Vaccinating a child by POV staff

"Well, thank you, doctor!" says Lingling's mother.

At the end of the morning's vaccination session, Drs. Cao and Du disposed of the used auto-disable syringes and other medical waste in accordance with the "Regulations on the Administration of Medical Wastes." Some treatment equipment, such as forceps, is disinfected and sterilized for reuse. PoV staff check vaccination notices, vaccination cards, and personal information of the children and cross-check with vaccine doses used. The doses administered are recorded immediately in the vaccine storage form along with a daily inventory calculation and monthly inventory summarization to ensure a match between usage and inventory.

For local children, PoV staff will issue a "Notice of Child Vaccination" to parents when providing vaccination services, make an appointment for the next vaccination, and provide parents with the PoV telephone number, asking them to carefully observe the child. Parents are also asked to complete the parent section in the "Notice of Child Vaccination" and to sign and provide a contact phone number. For those failing to come back for a scheduled vaccination, every Monday, PoV staff will send reminder SMS messages from the information system and export a name list of children who are not up-to-date and who will be prioritized for vaccination. PoV staff will arrange for a person to call parents, make appointments, learn why the child missed a vaccination opportunity, and inform parents of the standard vaccination recommendations if the child doesn't come in for vaccination within 2 weeks of receiving an SMS message. If the calls fail to connect with parents, PoV staff will contact the village doctors or community service provider to pay a visit to

the parents. PoV staff will make a note in the vaccination registry and information system if the child moves out of the PoV jurisdiction or is otherwise lost to follow-up.

Patient and careful baseline surveys and appointments by PoV staff, close collaboration with village doctors, and comprehensive and accurate information on births and migrant children provide a foundation for ensuring timely completion of vaccinations for age-eligible children.

7.4 Tracking Missed Vaccinations (Wednesday)

There are always some children who don't receive their vaccines on time. Possible reasons include "the child is new to the area," "I do not know where the PoV is," "my child is sick or not feeling well or has a cold with fever," "the child moved to another area with her parents," or "I forget about the vaccination visit." To ensure that every child completes their vaccinations, checking missed vaccination and providing makeup vaccinations are a necessary job for each PoV.

In accordance with NIP requirements, Drs. Cao and Du went through the IIMS to make a list of children who didn't come to the PoV for vaccination. They determined which vaccines were needed, recorded the relevant information on the missed vaccination form, and sent SMS messages to the parents. They then downloaded and filed the list of names, planning to call the family if they don't bring their child to the PoV within 2 weeks.

Dr. Cao patiently called families one by one. The first call was to Cao Haiyang's parents; Dr. Cao asked, "Hello, are you the parents of Cao Haiyang?" "Yes, who are you?" "I am Dr. Cao from the township hospital, and I'd like to ask you about Cao Haiyang's vaccinations. We checked the vaccination system and found that he should have come for his Hepatitis A vaccination two weeks ago, but he did not come. Can you tell me why?"

"Oh, I recently heard that a child developed fever after vaccination, and I hesitate to take him for the vaccination."

Dr. Cao replied: "The China NIP vaccines are safe and effective. Some children will develop fever, local swelling, pain and other common reactions after vaccination, but the incidence of serious reactions is very, very low. To keep Cao Haiying safe from hepatitis A, we recommend that he gets vaccinated with Hepatitis A vaccine. Please be assured that this is a very safe vaccine."

"OK, I'll take him to the clinic when I am free."

"We provide vaccination on service Tuesday, Thursday and Saturday morning. You can bring your child to our clinic; we are responsible keeping your child's vaccinations up-to-date."

The second call was to the parents of a child who was ill during his scheduled vaccination period and still had a fever. Dr. Cao made a note in the vaccination information management system and told the parents to bring the child to the PoV for vaccination until he recovered from illness.

During the telephone call, Dr. Cao was patient and explained his reasoning in detail and in a way that was understandable to the parents. The doctors make appointments for all types of vaccinations, provide information about the diseases and the vaccines, and obtain consent from the parents for the vaccination after answering their questions. In the PoV system, responsibility for make-up vaccination is allocated to individual staff members to ensure the quality of the vaccination and appropriate follow-through.

For PoV doctors, the most frustrating issue is an inability to contact parents who stop phone service, change phone number, or are otherwise inaccessible. In such cases, Dr. Cao and Dr. Du will check the most recent vaccination date through the IIMS and find a Notice of Vaccination for Children that has an updated phone number. If the parents are still inaccessible, Dr. Sun will use the address to ask local village doctors or village administrative officials to help contact the parents. For those who have moved out of the area or are lost to follow-up for more than 1 year, Dr. Cao and Dr. Du will indicate this information in the management system and the vaccination registry.

For children not vaccinated, the PoV will repeatedly remind the parents or provide at-home vaccination to ensure that the eligible child is registered and vaccinated. Information about make-up vaccinations will be recorded in the child's vaccination certificate and the vaccine registry. It is the doctors' feelings of responsibility and their attitudes to do excellent work that enable timely vaccination and ensure accurate record keeping.

In addition to checking missed vaccination and supplementary vaccination every week, at the end of each month, PoVs will recheck missed vaccinations and make-up vaccination, targeting migrant children by focusing on villages and communities with a migrant population. Outreach to migrant children is complicated but necessary to achieve full coverage of all children.

According to the "Program for Checking Missed Vaccinations and Make-up vaccination" issued by the district CDC, publicity, coordination, preparation of materials, and hiring sufficient personnel are necessary actions. Staff at township hospitals and village doctors conduct public outreach with a survey of kindergartens and primary schools to register eligible children, obtain telephone numbers, and check vaccination cards. PoVs prepare vaccines, replenish emergency medicines, check cold chain equipment, and post vaccination notices to ensure the successful vaccination. To ensure high quality of services, PoV and village doctors received training about the vaccines, their contraindications, surveillance, and management of AEFI related to the vaccines.

Dr. Cao looked for children near the farmer's market with some village doctors. Inside farmer-market shops, the shop owner's child can often be found. In a hardware store, they found a mother holding her little boy (Fig. 7.4).

"How old is your child?"

"3 years old."

"I believe that you know me. I am from the township hospital. We need to determine your child's vaccination status. May we have a look at the vaccination certificate – the green booklet?"

Fig. 7.4 Doctors carrying out on-site publicity

"Ok, just a moment."

"Has your child received any injections recently?"

"His mother just brought him back from a visit, so I don't know." the child's grandmother said.

Dr. Cao checked the vaccination certificate, finding that the child was not yet vaccinated against invasive meningococcal disease.

"It is time for the child to receive meningococcal vaccine. Does the child have a cold or a fever?" asked the village doctor.

"No."

"Please take this certificate with the child to the village clinic to get him vaccinated. There is a doctor providing the service of vaccination. This is important because without the vaccine, he is susceptible to a serious disease called meningococcal disease."

"OK, thank you, we'll go," said the child's grandmother.

Dr. Cao recorded the information on the registration form, Name: Liu Lei, Birth date: August 31, 2012.

Dr. Du was in the village clinic. Liu Lei's grandmother and mother held the child and came into the village clinic. "Hello Doctor, we were notified for the vaccination."

"Come and sit down here," Dr. Du said, "please give me the vaccination certificate." (Fig. 7.5).

The mother took out the vaccination certificate.

"Are you Liu Lei?"

Fig. 7.5 A child is holding his vaccination certificate

"Yes."

"It is time for the meningococcal vaccine."

Dr. Du asked about the child's health and then provided meningococcal polysaccharide group A and C vaccine. Dr. Du asked the parents to stay for 30 min for observation. The relevant information was recorded in the registration form for the missed vaccination and supplementary vaccination. Once they vaccinate a child, vaccination staff feel responsible to protect the child. They go through the streets looking for children; they skip meals and take no rest, but they are unaware of being tired.

Checking for missed vaccinations and providing makeup vaccination imply providing vaccination while simultaneously conducting a baseline survey. Vaccination cards and certificates will be provided for children who don't have them. Information about the make-up vaccination will be recorded in the registry form. All activities of checking for missed vaccinations and providing make-up vaccination will be evaluated so that every child will ultimately be protected.

7.5 Handling Adverse Events Following Immunization

China is a major vaccine-producing country, making 61 different vaccine kinds of against 33 infectious diseases. The annual production of vaccines is over one billion doses, and China's regulatory oversight of vaccines meets or exceeds WHO requirements – China's National Regulatory Authority for vaccines has passed WHO assessments in 2010 and 2014. Immunization of healthy children, adolescents, and adults with Chinese vaccines is safe and effective.

Because of individual biological variability and coincidence, some children will have an AEFI. Some of these AEFI are purely coincidental and would have happened whether the child was vaccinated or not, and some are caused by the vaccine. Z District CDC has established AEFI reporting and management procedures and plans; vaccination staff members are trained every year on the identification, reporting, and managing AEFI. To help parents, a contact telephone number is printed in the first page of the vaccination certificate booklet along with information about how to report concerns or obtain medical care for an AEFI. During vaccination procedures in the PoV, prior to giving the vaccine, the PoV nurses and doctors will discuss common adverse reactions and their treatment with parents, and they will remind parents to inform PoV staff if they suspect any adverse reactions to the vaccine.

Dr. Ma specializes in consulting, registration, and answering questions about AEFI. The vast majority of the events that Dr. Ma has observed and handled over the years are common, minor reactions. Most reactions are reported by parents through a telephone call for consultation; serious AEFIs are rare, and so are rarely reported.

One morning, a mother rushed her 2-year-old child to the PoV. She hurriedly said that the child was vaccinated yesterday but developed a low-grade fever in the evening and then the injection site became red. Dr. Ma came to the office to check the child.

Dr. Ma gave the mom a glass of hot water and let her take a rest. Dr. Ma asked questions about yesterday's vaccination and how the child was doing after getting home. Dr. Ma touched the child's forehead and took his temperature – it was 37.8 °C. There was no fever and the child was wide awake. Dr. Ma asked the mom to remove the child's coat, exposing the left arm; the vaccination site had a nontender red area of 0.5 cm. Dr. Ma's professional knowledge and experience and the history and physical examination told him that this was a common mild reaction.

Dr. Ma explained to the mother that, like all drugs, vaccines are foreign to the human body and that the majority of healthy people will not develop any adverse reaction after vaccination but that a few people will develop an adverse reaction due to their individual biological variability. An example is the MMR. According to the WHO, pain, swelling, and redness at the injection site are seen in about 10% of recipients, and a temperature of more than 38 °C is seen in 5–15% of recipients. This child had a low-grade fever with mild redness and swelling at the injection site with no obvious tenderness; therefore, this was a common mild reaction with no impact on the child's health. This reaction will likely resolve in 2–3 days with no complications. The mother was advised to allow the child to rest and drink water and to observe the child closely. Dr. Ma said that no treatment is indicated, except for applying a compress a few times a day for 10–15 min for each time.

Even though the fever and redness experienced by the child didn't need to be reported to the AEFI surveillance system, Dr. Ma recorded the information from vaccination certificate into the AEFI registration system and reported the event to

the prefecture CDC. He knew that the prefecture CDC will summarize AEFIs and prepare an AEFI monthly report that will go to all the PoVs and improve awareness of vaccine safety and the capacity to deal with AEFI.

7.6 Tending the Vaccination Information System and Disposing of Medical Waste (Friday)

The immunization information management system (IIMS) in Z District is based on the framework, "Information Management of Infectious Diseases for Better Public Health." IIMS has two platforms: service and management; it enables parents to make appointments with a mobile-phone app, with WeChat, and via the Internet on a home computer or laptop.

Mrs. Lee has two children and she knows that vaccinations help keep babies healthy. Her first baby had been vaccinated in the township hospital. But when she thought of the vaccination experience for her first baby, she was a bit afraid, because every time she went to the PoV, there was a huge line. After waiting outside the POV for over an hour, she was finally able to register her baby. Inside, the PoV was full of people queueing; the air was musty, and she was afraid that the baby might catch a contagious disease.

Mrs. Lee went to the PoV early today to obtain a vaccination certificate and to make an appointment for the next vaccination. When she arrived at the PoV, she was surprised about the big change. A few years ago, the PoV was renovated, giving it spacious and bright rooms. Services were being managed smoothly – no more lines! Dr. Sun looked at the materials submitted by Mrs. Lee, quickly completed the vaccination certificate, and gave her some informational materials about IIMS. Looking at Mrs. Lee's happy expression, Dr. Sun mentioned the PoV improvements and the implementation of IIMS and how it has transformed the vaccination experience. Dr. Sun showed Mrs. Lee how to scan the two-dimensional code with the smartphone app and that she can now see the vaccines that her child received, the vaccines to be administered next, and the time recommended by the PoV for the next visit. The app will send a reminder a few days before the appointment that includes information about the vaccines to be given and tips for ensuring a smooth visit. The app also serves as a platform for professional parenting, with an encyclopedia of vaccine and health-care knowledge. The app helps doctors and pediatricians answer their questions about vaccination, and the app can be used to provide online consulting services about child care and to share parenting tips.

Mrs. Lee downloaded the app, entered the baby's information, and made an appointment for next vaccination. Since she was new to the app, she was still somewhat worried, so she confirmed the next vaccination appointment with Dr. Sun just to be sure. Before she left the PoV, she met a friend, Doudou's mom, who also uses the same PoV. Mrs. Lee asked her about the app. Doudou's mom said that the app was convenient and eliminates the need to queue for vaccination. The vaccination time can be arranged according to the PoV's and parents' schedules. The app produces a

sequential number, and vaccination will be in the order of that number. Last time, she made an appointment for Tuesday afternoon, but that morning, an emergency happened, so she used the app to change the appointment to today.

The information system also lightened Dr. Sun's workload significantly. Previously, she wasn't able to make appointments for her patients, and she needed to remind parents by phone that a vaccine was due or past due. There were long lines of children waiting for vaccination, and there were many missed vaccinations. Now, through the "Internet+" mode, appointments are sent directly to parents' mobile phones, and parents are able to select a convenient time to come to the clinic. The PoV uses the information system to manage vaccination. Each child and each dose will be scanned into the system to ensure the integrity and accuracy of the information. The information system automatically analyzes vaccination data to develop reports, manage vaccine storage, and upload a list of vaccines needed to the prefecture CDC. The information system covers the entire city, and, importantly, vaccines administered to migrant children in other areas of the province can be shared through the information system. Dr. Ma uploads information on vaccine precautions, contraindications, and common AEFI, to the system. Very convenient for parents and for the PoVs!

Of course, some children's parents work out of the area while their children are cared for by grandparents. Elderly people in China rarely use the Internet or smartphones to make appointments. Therefore, in order not to miss a child, Dr. Sun makes phone calls to the grandparents who have never used the app to let them know about missing vaccinations. For those she is unable to contact, she asked the village doctors to visit the family.

There is much medical wastage on vaccination day that has to be handled properly before the PoV closes (Fig. 7.6). Sharps boxes and other medical waste items are stored temporarily in the township hospital. A vehicle from the medical waste treatment facility picks up medical waste at 4:00 p.m. every day to transport it safely to the disposal facility. Sharp needles and syringes are incinerated by a low-pollution incinerator.

Fig. 7.6 Safety box and package bag for medical waste

7.7 A Sudden Emergency Job

Dr. Sun finished work at 5:00 p.m. one Friday afternoon. After five busy work days, she could have a rest. When she left the PoV, it was snowing and only a few vehicles and people were in the street. Some students in school uniforms were walking along the road; others were riding their e-bikes.

After 6:00 p.m., Dr. Sun arrived at her nice warm home and was looking forward to preparing a delicious meal to share with her husband. After dinner, she watched the second episode of the TV series "Empresses in the Palace" and made plans to go skiing in the suburbs with friends the next day.

On the TV show, Huan Zhen was imprisoned in Yuxuan Cui for offending the Yuan Chun Queen, when, suddenly, a phone call came from an unknown woman.

"Hello, is this Dr. Sun?" said the voice on the phone, sounding anxious.

"Yes. Who is this?" Dr. Sun asked carefully.

"It's, I… I… dog bite…… my child, what do I do now……?" The voice on the phone was a little incoherent and full of worry.

"Don't worry, please calm down. Is it you or the child who was bitten by a dog?" Dr. Sun patiently inquired.

"It is my son, what do I do? I heard that he has to get a rabies shot, but his dad is not home. My leg is injured, and it is snowing. No buses are available in Dangou village at this time of day; can you please come to give my son a shot?" Dr. Sun could hear the pleading tone of the child's parent. Dangou village is a small village close to the border. Although 10 km is not very far away, but in such a snowy condition, the road can be slippery. Rural roads are always difficult to traverse, and in a snowy weather, driving is quite dangerous. Considering the special situation of the child's parents and that rabies vaccine should be administered as early as possible, she couldn't delay.

Dr. Sun told the child's mother to wash the wound with tap water for 5 min, then to wash the wound with soapy water for 10 min, and finally to rinse the wound with tap water and dry the area with cotton swabs or a paper towel. When she gives the vaccine, she will disinfect the area again.

Dr. Sun told her husband about the event – he is used to the emergencies in her line of work. In the dark and snowy night, without reconsidering for even a minute, he drove Dr. Sun to the township hospital so she could prepare a cold box with rabies vaccine and then drive to Dangou village.

The road was slow going after the snow; the car would slide if he drove faster than a crawl. The best he could do was only 20 km/h. The road was empty, but they occasionally saw an empty truck or two groaning past, leaving deep ruts in the snow. Along the way, Dr. Sun's husband clenched the steering wheel with both hands, staring tensely ahead. Dr. Sun was eager to provide rabies vaccine to the child so that the parent would not worry.

After nearly an hour of hard driving, Dr. Sun finally arrived. The parents enthusiastically thanked Dr. Sun and her husband and gave them hot water to drink. The mother had an apologetic smile, but Dr. Sun was all business and rushed to tend the

child's injury. Fortunately, the 4-year old was bitten by his own dog; therefore, vaccine alone would be sufficient. Dr. Sun treated the wound properly and then gave the child a rabies vaccination. The little boy was a real man; he did not cry and smiled after receiving the vaccine saying, "thank your auntie, you are very good, it didn't even hurt." After the vaccination, the mother gave some money to Dr. Sun for the rabies vaccine and another 50 yuan for Dr. Sun's time and travel, thanking her profusely. But how could Dr. Sun accept her money? Finally, Dr. Sun pushed the money back into the mother's pocket and explained that she would come back to administer the remaining doses of vaccine if it is not convenient for them to go to the POV.

The night was late and the road was slippery; the trip back was not so easy. Dr. Sun felt a kind of subconscious pleasure when she thought of the grateful expression on the faces of the mother and her son.

8 The 2010 Nationwide Measles Supplementary Immunization Activity (SIA): China's Largest Vaccination Campaign Ever

Lixin Hao, Yuqing Zhou, and Chao Ma

8.1 A Difficult Decision: Nationwide Measles Vaccine SIA

"MoH issued an action plan for a nationwide measles vaccine SIA!" This news made Dr. Xiaofeng Liang, China CDC NIP director, very excited, but then he felt the burden on his shoulders increase. Given that China is the world's largest country, having a population of 1.3 billion people, it was not so easy to make a decision to conduct a nationwide SIA.

Measles is an acute respiratory infectious disease caused by measles virus. Measles is highly infectious, most commonly affecting children; severe cases can result in death. Measles has long been considered a significant disease in China. For example, nearly 10 million cases and nearly 300,000 deaths due to measles were reported in China in 1959, before the vaccine had been invented [1]. In 1965, China began to vaccinate against measles, and in 1978, measles vaccine was included into EPI, becoming free for all age-eligible children. With vaccination rates increasing, the incidence of measles decreased gradually and remained at about 100 per million total population after 1987, with approximately 100,000 cases reported annually [2, 3].

Vaccination is the most economical and effective public health intervention to prevent and control infectious diseases. Elimination of measles is technically feasible and achievable. In 2005, the WHO Regional Office for the Western Pacific proposed a goal to eliminate measles in 2012; China's government responded enthusiastically, and MoH developed and issued "The Action Plan of National Measles Elimination: 2006–2012" [4].

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One of the important strategies to eliminate measles is a measles vaccine SIA. Measles vaccine SIAs can rapidly improve population immunity in a geographic area in a short period of time, building an immunity barrier and blocking spread of measles virus [5]. However, due to limited vaccine production and financial constraints, before 2009 China could only conduct SIAs in a few key areas and to variable degrees. Although measles vaccine SIAs showed good results, establishing effective long-term, nationwide population immunity was nearly impossible because of variable timing of SIAs in different areas and China's large migrant population.

From 2009 to 2010, MoH organized expert evaluations and concluded that a nationwide measles vaccine SIA could establish high-level population immunity in a short time, protecting children's health, accelerating measles elimination, and promoting the development of EPI. Conducting SIAs is an important strategy to prevent the spread of measles virus, eliminate measles epidemics, and protect people's health.

In July 2010, MoH, the National Development and Reform Commission, Ministry of Finance (MoF), Ministry of Education (MoE), and the China Food and Drug Administration (CFDA) jointly issued a "National Action Plan for Elimination of Measles, 2010–2012," which required that "in the fall of 2010, a nationwide measles SIA is conducted covering children aged 8 months to 4 years of age in order to maximize population immunity and block the spread of measles virus" [6]. China's national measles vaccine SIA was officially announced.

8.2 Food and Fodder Go Ahead of Troops and Horses (Better Safe than Sorry): Detailed Preparation

Conducting a national SIA is a huge project, involving tight organization and mobilization, cooperation, logistics, vaccine, and many other considerations. The target population of the SIA was going to vary by province and geographical area. Throughout the SIA, Leader Xiaofeng Liang had attached importance to early preparation: adequate preparation means half way to success. The most important activities included:

8.2.1 Government Attaching Importance, Organizational Committee Established

In January 2010, Health Minister Zhu Chen mobilized the measles vaccine SIA at the National Health Conference and the National Disease Control Workshop. On April 7, 2010, Vice Premier Li Keqiang pointed out in a plenary session of the National Patriotic Health Campaign Committee that "governments at all levels should take the elimination of measles as an important task, and implement according to objective management, careful organization, and implementation quality."

To strengthen the leadership of measles elimination, MoH established a national leadership group for the elimination of measles in June 2010, with Minister Chen as

its head. It included several departments of MoH, including the Office of Administrative Affairs, the Department of Planning and Finance, the Department of Policy and Legal Affairs, the Department of Rural Health, the Department of Maternal and Social Security, and the Department of Medical Administration. A National Office of Measles Elimination and Expert Advisory Group was established in China CDC that was primarily responsible for undertaking activities for eliminating measles. To support the nationwide SIA, several teams were set up under the National Office, including a measles vaccine SIA comprehensive team, a vaccine supply coordination team, a technical guidance team, an AEFI surveillance and management team, a supervision team, and a publicity and risk communication team. A regular meeting mechanism was established to systematically arrange activities and facilitate communication.

8.2.2 Close Cooperation Among Various Departments and Ensuring Funding

During preparation, MoH, the National Development and Reform Commission, the MoE, MoF, and CFDA jointly issued a "National Measles Elimination Action Plan: 2010 – 2012" in which the responsibilities of various departments were clarified and coordination and collaboration among departments was strengthened. Human resources, financing, and other resources were to be ensured. The activities of 2010–2012 were planned year by year to strengthen implementation. The immunization program clearly stated that the SIA should be conducted in 2010. Because the activities needed cooperation of several departments, the National Publicity Department, the Ministry of Broadcast, CFDA, and MoE issued specific documents or held meetings to arrange for the activities of the departments.

After several rounds of discussion and consultation, in 2009, the central government provided 157 million yuan to purchase sufficient vaccines and syringes to reach a projected target of 96 million children. To ensure smooth progress of the SIA, local financial departments tried to secure additional, necessary SIA funding. Health departments at all levels were actively raising funds for the SIA. SIA financing was ensured through various mechanisms, such as financial funding, self-financing, self-payment in advance, and advance loans. Provincial and lower level governments invested 174.71 million yuan into operations and 236.21 million yuan for additional subsidies.

8.2.3 Seeking Comments, Carefully Developing a Program

Commissioned by MoH, China CDC organized experts to discuss and develop national measles vaccine SIA plan from March 2010. The experts determined that a nonselective immunization strategy should be used, based on the WHO headquarter suggestions and combined with the actual situation in China. During that time, China CDC held many meetings and workshops to develop documents about measles vaccine SIAs and measles elimination strategy. After combining the suggestions and

comments from domestic and foreign experts, the National Measles Vaccine SIA Guideline was issued by MoH at the end of July.

In 2010, the National Measles Elimination Office organized experts to develop a "Working Manual on Measles Vaccine SIAs" [7] and printed 120,000 copies to distribute free to field staff. Focusing on parental and media concerns, the office developed a Q&A document for the SIA that included 83 questions. A deep but simple introduction was provided that described the epidemic situation of measles, basic knowledge of measles vaccine, the rationale for conducting the SIA in 2010, the main activities of measles vaccine SIA, and precautions for vaccination. Relevant experts were organized to develop a "National AEFI Surveillance and Management Plan for the Measles Vaccine SIA" and a "Risk Communication Program for the National Measles Vaccine SIA," which provided technical support for a successful SIA.

8.2.4 Training of Staff, Strengthening Technical Guidance

China CDC held workshops to "Training of Trainers (ToT) on SIAs" and held trainings on risk communication for a measles vaccine SIA; more than 80 people from the provincial CDC participated. In mid-August, China CDC and the National Adverse Drug Reaction Center held a training workshop on AEFI surveillance during an SIA. At the end of August, in order to improve risk communication capacity and answer relevant questions by 12,320 hotline staff during the measles vaccine SIA, the 12,320 leading group from MoH (12,320 National Management Center) held a national training on the measles vaccine SIA for 12,320 hotline staff in Beijing, with more than 60 staff from 30 provinces, autonomous regions, and municipalities participating in the training.

In August 2010, MoH conducted supervisory visits to Jiangsu, Hebei, Inner Mongolia, Guangdong, Xinjiang, Henan, Heilongjiang, Chongqing, and Sichuan to learn the readiness for SIA and to strengthen technical guidance in key areas.

In accordance with the requirements of the national level, a cascaded training was carried out. According to documented records, a total of 1.62 million staff was trained. After the training, temporary vaccination staff, who were scheduled to participate in the SIA, were also trained and provided temporary certificates for vaccination, helping to ensure the safety of SIA and use of standardized vaccination practices.

8.2.5 The Vaccine in Place on Time, the Cold Chain Ensured

In December 2009, MoH wrote a letter to the China National Biotec Group (CNBG) Company Limited to coordinate the measles vaccine production and supply. China CDC, commissioned by MoH, organized an investigation of the procurement and supply of SIA measles vaccine in each province in March, June, and August 2010. In March, China CDC went to CNBG to learn about the production and supply of measles vaccine, batch release procedures, and local procurement practices in preparation for the arrival of vaccine on August 3 and 5. In August 2010, MoH, CFDA, China CDC, and NICPBP held a coordination meeting about the measles vaccine

supply in Beijing, with a measles vaccine supply coordination group that consisted of relevant staff. From August 12 on, the measles vaccine supply coordination group collected SIA vaccine inventory data from each province on a daily basis. The measles vaccine supply report was developed and submitted to MoH and submitted as a "briefing on measles vaccine SIA." CNBG actively cooperated on the SIA planning efforts, supporting the information system, and designating people to be responsible for some geographical areas to ensure adequate supply of vaccine.

CDCs at province, prefecture, and county levels distributed measles vaccine and syringes to townships and PoVs in advance of the SIA. The transportation and storage cold chain was in strict accordance with "Regulations on Vaccine Distribution," "EPI Operational Standards," and "Standards on Vaccine Storage and Transportation." Cold chain records and vaccine and syringe records were in place. Materials for addressing AEFI, such as the required emergency medicine, equipment, facilities, and vehicles were in place or equipped before the SIA.

8.2.6 Careful Arrangements, Thorough Baseline Survey

Before the SIA, a baseline survey was conducted by every region to measure the target population size according to geography. Most of the baseline survey and registry for migrant children was conducted by street offices and township governments; baseline surveys and registries for children in kindergarten and school were conducted by county bureaus of education. At the time of the baseline survey, a "letter to parents" was delivered to parents. During the baseline survey, special attention was paid to migrant children and out-of-family plan children. Vaccination cards and certificates were printed for children not having cards or certificates. All of these newly found children were included in the routine immunization management system. When investigators filled in the "Registry form of baseline survey for measles vaccine SIA and vaccination," a "notice to parents" was issued to the parents to let them know the address of their child's PoV and the date of SIA and to let them know that vaccination certificate should be brought to the site of vaccination.

8.3 No Rule No Outcome: The Orderly Implementation of SIA

On September 11, 2010, the national measles vaccine SIA was officially kicked off!

8.3.1 Establishment of an Efficient and Smooth Central Information and Communication System

General headquarters – there were people on duty in the National Office for the Elimination of Measles all day long to keep information flowing. Daily progress was reported according to requirements, and surveillance of AEFI and public opinion was strengthened. The National Office communicated with provincial health

administrative departments – the provincial CDCs. A contact book of staff responsible for reporting was developed; procedures for SIA data collection were also developed. During September 12–21, according to the MoH-issued "Notice on Measles Vaccine SIA," the number of children vaccinated and AEFIs reported by 18:00 of the previous day in each province should be collected by noon by fax every day. In total, 17 issues of "Progress on the National Measles Vaccines SIA" were published.

On September 13, MoH held a national telephone conference on the measles vaccine SIA, summarizing progress of the SIA in the first 2 days and putting forward additional implementation requirements for the SIA. MoH and MoE jointly issued "Emergency Notice on Further Improving the SIA" on September 16, and a daily reporting system was implemented during vaccination times, which required that the actual number of children vaccinated, the doses used, and AEFI reported during the previous day be aggregated by county and province and/or prefecture and sent to China CDC every day.

8.3.2 PoV Practices, Clarification of Responsibilities, Developing Scientific and Standardized Vaccination Procedures, and Ensuring the Safety of Vaccination

To ensure that the SIA was safe and orderly, PoVs were set up scientifically and reasonably with standardized vaccination procedures in all regions and in accordance with the distribution and size of the target population. A total of 571,471 PoVs, including 223,101 fixed PoVs, 303,512 temporary PoVs, and 44,858 mobile PoVs, participated in the SIA. All PoVs were accredited by the local health administrative departments, with obvious signs and posters displayed with information about precautions and reminders to stay for observation following vaccination. There were partitions for fixed PoVs and temporary PoVs that divided the space into pre-registration rooms, inoculation rooms, observation rooms, AEFI rooms, and disposal rooms, with emergency facilities and drugs in place. Staff responsible for on-site organization, pre-registration, vaccination, providing assistance, and treating AEFI were allocated to appropriate rooms; pre-registration and AEFI treatment staff were experienced as pediatricians or physicians.

During registration, PoVs checked and confirmed the children's identities carefully and discussed contraindications to vaccination. Children were screened for fever and other medical contraindications to determine whether to vaccinate or not. Vaccination was conducted in strict accordance with the "Rules of Vaccination," with vaccinees being observed for 30 min before being allowed to leave. After completing vaccination, the vaccination equipment was cleaned; auto-disposable syringes were disposed after use in strict accordance with the relevant provisions of "Regulations on Disposal of Medical Waste."

8.3.3 On-Site Supervision and Evaluation to Ensure the Quality of SIA

During the SIA, supervision was strengthened at all levels with a standard supervision plan and supervision manual. Supervisors completed daily supervision logs. MoH organized 16 supervisory groups (WHO, PAHO, UNICEF, and US CDC

experts invited for supervision in Henan, Shaanxi, and Shanghai) to supervise the SIA in all provinces (autonomous regions and municipalities). MoH mobilized personnel of MoH, CFDA, and other relevant departments to participate in on-site supervision and to find and solve problems, to ensure that the all SIA activities were implemented properly.

In total, 153,084 supervisors were used during the SIA, including 110,853 mobile supervisors. From top to bottom, all levels were supervised, with responsibilities and individual responsibility clarified and strict quality control conducted.

8.3.4 Surveillance and Addressing of AEFIs

Throughout the country, real-time surveillance for emergencies, AEFI, and public opinion was strengthened, and dynamic analyses were conducted to prepare responses. The number of vaccinated children and number of AEFIs were reported daily by PoVs. It was required that all AEFI should be treated first, followed by investigation of the AEFI. Each PoV had a fast track to ensure that an ambulance could be in place for transportation to designated hospitals if needed for treatment of children with an immediate AEFI. AEFI cases were to be treated in accordance with the principle of high-quality service, stable treatment, and quick treatment as priorities.

A total of 14,955 AEFI cases were reported during the SIA, for an incidence of 14.46/100,000. Among these cases, the incidence of AEFI related to vaccination was 2.39/100,000; and the incidence of serious vaccine reactions was 0.29/100,000 – in the expected range [8]. During the SIA, there were no deaths associated with measles vaccine, nor were there clusters of AEFI.

8.4 Social Mobilization: The Important Role of Publicity and Communication

The SIA in China vaccinated more than 100 million children in only 10 days – a huge challenge. China's unparalleled publicity and mobilization work played a major role in the success of the SIA.

8.4.1 A Special Working Group Was Set Up at the National Level that Was Responsible for Organization and Implementation of Publicity and Communication

The working group developed a "National Measles Vaccine SIA Plan" that required health administrative departments, CDCs, and health education centers to publicize the SIA and conduct risk communication using a systematic plan. The plan promoted the creation of good public opinion to improve the understanding of the SIA among parents, health workers, and the media.

The MoH News Office issued a press release and held a press conference. The "Q&A on the Action Plan of Elimination of Measles in China" document was issued. Promotional short videos (animated and documentary videos) to publicize

the SIA were developed and were issued through the SIA website at China CDC. Experts conducted online interviews; public opinion was monitored and analyzed, and promotional materials were prepared to guide the implementation of publicity and communication about the SIA. Consulting and Q&A were also provided through the 12,320 hotline.

8.4.2 Fully Prepared and Trained Staff Played Key Roles

In order to prepare for any potential risk during the SIA, in advance of the SIA, an on-site survey was conducted in Beijing, Jilin, Chongqing, and Guangdong to learn attitudes about the SIA and potential doubts and concerns among parents and first-line vaccination staff. The surveys showed that potential risks were predicted and that documents such as the "Plan for Risk Communication on the Measles Vaccine SIA," "Guidelines for Risk Communication on the Measles Vaccine SIA," "Q&A Manual on the Measles Vaccine SIA," and "Case Studies of Risk Communication on the Measles Vaccine SIA" were able to provide technical support for grassroots staff and appropriately answer questions by the media, the public, and the community.

In July 2010, MoH commissioned China CDC to organize a training course on risk communication of measles vaccine SIA. More than 80 staff from provincial CDCs attended the training. During the training, experts from China CDC, US CDC, WHO, Tsinghua University, Health News, and sohu.com introduced risks inherit in SIAs and appropriate response strategies, public opinion monitoring and risk communication skills, and concerns by the media.

On August 26, MoH issued "Notice on Strengthening Publicity of Measles Vaccine SIA." That day, a training course was held in Chengdu, Sichuan province on publicity and risk communication of measles vaccine SIA. Staff responsible for publicity from the health administrative departments of all provinces attended the course. In the course, it was required that publicity and risk communication of measles vaccine SIA should be carried out and attendees were trained on relevant knowledge and communication skills.

By the end of August, the national 12,320 management center held a workshop called "National 12320 Training Course on Hotline Q&A of the Measles Vaccine SIA," with more than 60 hotline staff from 30 provinces, autonomous regions, and municipalities attending. Materials, including "50 Q&A manual," were developed in all provinces, and special column was established on the 12,320 website. "Guidelines for Public Consultation" was released on schedule.

8.4.3 Monitoring and Guidance of Public Opinion

On September 11, 2010, the measles vaccine SIA was officially kicked off. MoH commissioned a team at Tsinghua University to monitor and analyze public opinion about the measles SIA from September 1 onward in news media, blogs, and

forums. Quantitative and qualitative analyses were conducted. Analysis showed that public opinion in the news media was mainly affected by the news released by MoH – the authority's news. Public opinion was also influenced by Internet opinion leaders. Monitoring data showed that the public interest peaked 2–3 days before the SIAs, with a large number of posts in forums spreading rumors, such as "one hundred million vaccines drop from heaven," "poisonous vaccine," and "foreign conspiracy." These rumors questioned whether this large-scale measles vaccine SIA would have a negative impact on children's health and whether the vaccines were safe and effective. Many of these questions came from the media, parents, social celebrities, and a few medical personnel from grassroots and scientific research institutions. They are challenging the SIA strongly, and the SIA was at risk of being "stopped."

The MoH News Office provided an unparalleled response. They combined questions from the daily mail to the minister, information from domestic and foreign media, public opinion monitoring, and the "12320 measles vaccine SIA public opinion monitoring daily" and wrote a measles vaccine SIA public opinion report every day, submitting it directly to the minister and all relevant personnel. Through monitoring of public opinion, the decision-makers could understand the public concerns and public opinion direction and made correct judgments.

On September 19, the MoH invited Kai Zhao, an academician from the Academy of Engineering Chinese, an influential medical virologist and epidemiologist, and UNICEF officials to communicate online with Internet friends on "The Forum on Strong China."

Xiaofeng Liang, the former director of NIP, China CDC, made appointments to talk with public opinion leaders in professional institutions to impress upon them the significance and importance of the measles vaccine SIA. He used his personal blog to strongly support the SIA, thus facilitating the SIA.

Relevant experts from China CDC developed a series of popular science articles, and CCTV produced a short video called "Free Measles Vaccination." China CDC and the China Health Education Center jointly developed leaflets, posters, and other promotional materials for the SIA (Figs. 8.1 and 8.2).

Through this comprehensive and strategic response, negative information in the media was well controlled. By September 18, negative public opinion decreased significantly, and SIAs in all regions went smoothly from that point onward, with even more people coming in for vaccination. By the end of the SIA, 103 million age-eligible children were vaccinated [9].

Rethinking the success of measles vaccine SIA, a few words can be offered: overall planning, overall arrangement, adequate preparation, timely response, and sincere communication. The SIA involved many departments and personnel, including those in health, education, and public security. Inside the health system, health bureaus, CDCs at all levels, community health service institutions, WHO, UNICEF, and other international organizations were involved. MoH led the SIA, including the provision of authoritative news releases by internationally famous experts and officials to educate the public about vaccine safety and the true incidence rates of adverse reaction – ultimately resulting in a good impact. The mainstream media and

Fig. 8.1 Folders on measles vaccine SIA

Fig. 8.2 Poster on measles vaccine SIA

opinion leaders effectively influenced the direction of public opinion. This was possible because of careful planning of an SIA that was conducted with a safe and effective vaccine.

8.5 The Largest Public Health Intervention in Recent Years in the World with Significant and Far-Reaching Impact

In just 3 weeks, more than 100 million age-eligible children were vaccinated against measles, with no vaccine-related deaths or clusters of AEFIs. China's measles vaccine SIA in 2010 was the largest public health intervention in the world; it stands as a milestone in China's immunization program and in the global elimination of measles, with obvious, far-reaching impact.

8.5.1 A Substantial Reduction of Immunization Gaps in the Target Population

Large-scale vaccination campaigns can immunize those who missed vaccination opportunities in the past, in part because of its great publicity and the "sensational" nature of such a large-scale, pulsed event. In poor rural areas and areas with

low-quality routine immunization, a vaccination campaign can quickly improve the rate of measles vaccination. In 2010 the national measles vaccine SIA provided one free dose of measles-containing vaccine (MCV) for all children born between 1995 and 2009 in every province and for children born between 1991 and 2009 in some provinces. The SIA bridged cumulative immunization gaps, improving herd immunity.

8.5.2 A Significant Reduction in Transmission Level and Incidence of Measles in SIA Covered and Uncovered Population

In the year after the SIA (Oct. 2010 to Sep. 2011), the incidence of measles in the whole population dropped significantly compared to the previous year – Oct. 2009 to Sep. 2010; the incidence decreased by 72.5%, with the largest reduction in the SIA-covered group (77.3%). Compared with the 5-year average from Oct. 2005 to Sep. 2010, the overall incidence declined by 88%, with the greatest reduction in the SIA covered group (91.7%). In addition, in the year following the SIA, the age-specific incidence for all age groups decreased significantly – compared with average of the previous 5 years, the biggest decrease in incidence was among 7–14-year-olds, followed by 1–6-year-olds. Compared with the Oct. 2009 to Sep. 2010 time frame, the largest decline was among those >35 years old, followed by 25–34 years old, suggesting that SIAs significantly decreased measles incidence rates, regardless of whether the age group was targeted by the SIA or not (e.g., <8-month-olds and adults).

After the national SIA, 2011 and 2012 saw a continuous decline in the incidence of measles in China. In 2012 the reported measles incidence was 0.46/100,000, with 6183 total cases and 8 deaths, a declined compared with 2011 that reached the lowest levels in history [9]. Although measles cases reported from 2013 to 2015 increased, the incidence was still far below the level prior to 2010 [10].

8.5.3 Lessons Learned

Children targeted by SIAs should be vaccinated for free, regardless of previous vaccination history, especially for poor, migrant, and out-of-family plan children. Most people benefited from free vaccination, experiencing the equity in primary public health services. The national measles vaccine SIA received great attention by government officials at all levels, including health administrative departments, disease control and medical institutions, and rural doctors. The publicity, strong organization, and ultimate success of the SIA allowed the program to gain experience for conducting similar, major public health activities. The SIA improved the ability of health department to coordinate, communicate with other departments and the media, and mobilize social resources. Measles vaccine SIAs that include a baseline survey and vaccination activities for target groups, especially among the poor,

migrants, and out-of-plan children, improve the capacity for advocacy, mobilization, coordination, and administration of vaccination services of public health institutions at all levels, potentially benefiting other public health efforts.

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Publicity and Communication of the Immunization Program

9

Wenzhou Yu, Guomin Zhang, and Fuqiang Cui

Since China implemented its Expanded Program on Immunization (EPI) in 1978, publicity and social mobilization have been one of the important activities of the program, from the central government to local health administrative departments and Centers for Disease Control and Prevention.

9.1 Routine Publicity on Immunization

China CDC built a website, "Chinese Vaccines and Immunization," through which information on vaccines and disease prevention is provided and questions about the immunization schedule, vaccine safety, and other common issues are answered. Promotional videos, advertisements, and posters from National Children's Immunization Day and World Hepatitis Day are made available to help parents and guardians obtain information about vaccines and immunization.

To improve the impact of publicity, in 2010, MoH and China CDC invited the famous CCTV host Ju Ping to be an ambassador for immunization. Several promotional videos were shot to advocate measles elimination, including "Vaccination to Eliminate Measles" and "Combating the Virus to Conquer Viral

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Diseases." The video "Immunization: Start with the Baby" was broadcast on the life program of CCTV1; other vaccine science videos were broadcast to publicize how to safely and effectively vaccinate, significantly improving coverage of the immunization program.

With the development of social media, immunization staff at all levels need to fully recognize the role of this new media for communication. Some provinces set up WeChat accounts to deliver information about vaccine-preventable diseases, progress in vaccine development, relevant policies, and to answer common questions. Some CDCs established official blogs to interact with the public and to release immunization program information. For areas with more advanced information systems, a mobile phone vaccination app was created to release information, send reminders for vaccination, and make PoV appointments, making it convenient for guardians to keep their children up-to-date on their immunizations.

In recent years, there has been much more questioning by the public of the safety of vaccines, some parents have become hesitant to vaccinate their children, and some parents even refuse to vaccinate their children [1, 2]. To facilitate routine publicity and serve as a reference for grassroots vaccination staff and improve their communication skills, China CDC's NIP, in cooperation with Tsinghua University, China Communication University, and other partners, developed a manual on communicating with the media and the public. Through this manual, grassroots vaccination staff can become the most trusted information source about vaccination and can learn how to use easy-to-understand language to deliver core information. The manual can also help develop skills for answering common immunization questions, laying a solid foundation of publicity for the immunization program.

In previous years, leaflets and brochures were used in publicity activities. Once distributed, these materials were seldom read and frequently discarded. New promotional materials with living features have been developed by the provinces to increase parents' exposure to immunization information and improve public awareness of the immunization program.

To further promote immunization, NIP worked with the Baidu Maps search engine. In 2015, a pilot vaccination clinic geographic information system that was developed in Anhui Province was extended to most provinces in China. This system can locate vaccination clinics for parents. In the future, this system may be able to help manage the location of vaccination clinics and can help access to vaccination services.

9.2 National Children's Immunization Day and World Hepatitis Day

9.2.1 National Children's Immunization Day: April 25

April 25 is National Children's Immunization Day in China. On June 20, 1986, the State Council approved the development of an immunization coordination committee, which was subsequently established by MoH, the National Education

Commission, the National Women's Federation, the Radio and Television Bureau, the Ministry of Foreign Trade, and the National Ethnic Affairs Commission. The charge to the committee was to promote universal childhood immunization, enhance publicity and education about the immunization program, and mobilize the entire society to create favorable conditions for vaccinating children. April 25 was designated as the National Children's Immunization Day. This day is not only a festival for children but also is a celebration for immunization program staff. Since the 1990s, a topical theme has been selected each year for the National Children's Immunization Day around which the communication messages are developed [1].

The central government leads the planning for the National Children's Immunization Day. Health departments and epidemic prevention institutions of all levels use the day to promote universal children's immunization, with goals of sustaining parental confidence in vaccines and improving vaccination coverage. Leaflets, posters, and videos are used to get the word out about the importance of immunization to children's health. One year, Ju Ping, a well-known CCTV host, became an ambassador for immunization. Promotional and educational programs about vaccines were broadcast on seven channels including CCTV2, CCTV6, CCTV7, etc. Science videos about safe and effective immunization were broadcast on CCTV1, and linked articles were published in *Guangming Daily*, *Health News*, *Life Times*, and *Public Medicine*, in addition to other newspapers and magazines. Internet outlets, including sohu.com, sina.com.cn, Tianya, and xinhuanet.com, held online interviews with vaccine experts. Other creative methods to raise interest in immunization include fun and educational quizzes about vaccines and artistic performances. Traditional media including radio, television, and newspaper, and some new media, such as the Internet, smartphone messages, public transportation videos, and outdoor electronic screen, played an important role in maximizing public exposure to the immunization messages (Table 9.1).

9.2.2 World Hepatitis Day: July 28

The World Health Assembly resolution on "World Hepatitis Day," "WHA63.R18," was adopted May 21, 2010, with key support from Brazil, Indonesia, Columbia, and China. The resolution designated July 28th (the birthday of US Dr. Baruch Blumberg, who discovered hepatitis B surface antigen) as World Hepatitis Day [2]. World Hepatitis Day (WHD) represents only the fourth disease associated with a day of recognition by WHO.

July 28, 2011, was the first WHD; its theme was "This is hepatitis" [3]. China's WHD theme was "Raise awareness of hepatitis, scientific prevention, and control of hepatitis," with a goal to make more people recognize the dangers of hepatitis.

The WHO theme of the 2012 WHD was a continuation of the 2011 theme, "This is hepatitis," coupled with a new message that "It's closer than you think" [4]. China's 2012 WHD theme was "Take active action, fight hepatitis together." The 2013 theme was "This is hepatitis, understand it, face it." China's theme that year was "Early

Table 9.1 Themes for "4.25," the National Children's Immunization Day

Year	Theme
1990	85%: the goal of national immunization coverage
1991	Children's rights and opportunities – immunization, eradication of polio
1992	Eradication of polio, vaccination with hepatitis B vaccine, protect children's health
1993	Social participation – the eradication of polio
1994	Eradication of polio in China
1995	A polio-free world
1996	Universal children's immunization, love for children
1997	Every child should have access to immunization
1998	Immunization – children's health and family's well-being
1999	Hepatitis B, enemy to health; vaccination, weapons for prevention
2000	Immunization – pay attention to migrant children
2001	Maintain polio-free status
2002	Hepatitis B vaccination, for children's health
2003	Hepatitis B vaccine – love to new life
2004	Immunization, prevention of hepatitis B
2005	Immunization program protects children's health
2006	Same rights, same health – attention to vaccination for migrant children
2007	Vaccinating every child on time is the responsibilities of government at all levels
2008	Vaccination, guarantee to health
2009	Timely vaccination, everyone enjoys health
2010	Eliminate measles, control of hepatitis B, you and I are involved
2011	Vaccination for children's health
2012	Vaccination, family's responsibility
2013	Baby's health start with vaccination
2014	Vaccination, protect health
2015	Vaccination, the right of children, the responsibility of society
2016	Have confidence in vaccination, enjoy a healthy life
2017	Standardize vaccination, build healthy China

prevention of hepatitis, health is in your hand." The fourth WHD theme was "Re-think hepatitis, a silent killer," and China's theme was "Fight hepatitis, start with yourself." The National Health and Family Planning Commission (NHFPC) was calling on the general public to pay attention to their own health and to overcome the viral hepatitis through vaccination, early screening, and standardized treatment. The fifth themes were "Fight hepatitis, start with yourself" and "Fight against hepatitis, prevention first," with a subtheme of "Vaccination benefits, paving the way to health." The sixth theme was "Know hepatitis, act now," and China's theme was "Love and protect liver, enjoy health." The seventh theme was "eliminate hepatitis," and China's theme was "Standardize test and treatment, stop hepatitis."

In order to publicize WHD, slogans and posters are collected every year in China. Promotional videos, posters, brochures, specific programs, online interviews, art shows, and quiz contests are developed at the local level to meet local needs. Information on viral hepatitis prevention and control is also disseminated through free diagnosis and treatment services for those infected. Awareness of viral hepatitis has been improved among the public, contributing to a more favorable environment

for prevention and control. Additionally, "fear" of viral hepatitis is receding, as is discrimination and stigmatization.

9.2.3 Geography-Specific and Group-Specific Publicity

There are vast territories in China with different cultures, practices, and languages. With the development of society and economic growth, the size of the migrant population has increased, bringing another challenge to public information campaigns. China CDC and medical and health institutions at the province, prefecture, and county levels have developed health education materials that are specific to ethnic, language, or other population groups.

Parents vary by educational achievement and therefore differ widely on their understanding of technical information about vaccines. China CDC's NIP developed the *Vaccination Handbook* that is easy for parents to understand and that uses illustrations to get messages about vaccines vividly. In combination with small group lectures, this handbook has improved parental knowledge about vaccines.

Peer education for guardians of special groups, such as left-behind children. The guardians of left-behind children are often grandparents, who may have little awareness about immunization. To improve their understanding and awareness, heath education is being conducted by some provinces using a peer education model. Families with higher educational achievement, strong communication skills, and prestige among the public hold discussion groups to discuss vaccines with other families.

Education for ethnic and religious minorities. Ethnic minority groups are sometimes unable to obtain timely, accurate information about vaccines due to a language barrier. Bilingual publicity materials can help address this problem. Bilingual vaccine information is used frequently in Tibet, Qinghai, Gansu, and Inner Mongolia. Religious leaders have been very helpful to reach out to religious minority groups such as those in Ningxia and Xinjiang. CDC staff explain the importance of immunization with religious leaders and provide the leaders with brochures about immunization. The religious leaders, in turn, bring information about vaccination to their followers.

Special publicity combined with local culture. Kangle County in Gansu Province is a Muslim settlement. Kangle County edited some local songs – *Hezhou Flowers* and *Lotus Flower* – and new Shaanxi modern opera, *Marriage medical check*, to educate the public of the dangers of hepatitis B and the importance of prevention. Huating County created an opera "Entering the door three times" in 2002 to promote awareness of hepatitis B prevention. This opera was performed more than ten times in Huating County, Zhuanglang County, and Tianshui Prefecture, with more than 67 thousand people attending.

Local folk songs were developed to promote EPI knowledge and hepatitis B control in Huzhu County, Haidong Prefecture, in Qinghai Province. County CDC staff went to the township during a health services campaign and a temple fair to promote vaccination with easy-to-understand content. CDCs in nomadic areas used temple fairs and religious events to invite Buddha to promote hepatitis B prevention.

The Northeast Local Opera (Er Ren Zhuan) was used in the farming off-season in Heilongjiang Province to promote immunization. In Yunnan Province, newspapers and online media were used to provide accurate information about hepatitis B to the public, with a goal of improving participation rates for prevention and treatment of hepatitis B virus infection.

9.3 Hepatitis B Vaccine Event and Response

Some parents and providers can become hesitant to vaccinate their baby out of concerns about the safety of vaccines. Often times, an event triggering concerns is purely coincidental to vaccination and not caused by a vaccine. However, as is illustrated below, parental concerns about vaccine safety can result in declines in vaccination coverage. Here is a well-documented event that serves as a good illustration of the phenomenon.

9.3.1 Overview of the Event

Three infants were reported to have had serious adverse events following hepatitis B vaccination in Changning County, Hengshan County, and Hanshou County, in Hunan Province on December 6 and 9, 2013. Infants in Hengshan and Changning Counties died after receiving hepatitis B vaccine. On the evening of December 11, 2013, Hunan television reported that "Three infants have suffered after receiving hepatitis B vaccine – 2 died and 1 is in the intensive care unit." Some media quickly picked up the Hunan television report, repeating some misleading information [1, 2].

On December 13, China CDC sent experts to Changsha to conduct an investigation into the deaths with experts and officials from other relevant departments. Later that day, CFDA suspended the use of two batches of hepatitis B vaccines by Shenzhen Kangtai Biological Products Co. Ltd. (Kangtai). On December 20, CFDA and NHFPC suspended the use of all hepatitis B vaccine by Kangtai and launched an in-depth investigation into the causes of the infant deaths.

The NHFPC responded rapidly with an investigation, increasing AEFI surveillance, ensuring a replacement supply of hepatitis B vaccines, interviewing providers and parents, and examining the medical records of the infants. Autopsies were reviewed and formal assessments of causality were conducted. NHFPC held a press conference to inform the public of the investigation. CFDA sent teams to the manufacturer to assess the production of the vaccine and the production history of the manufacturer. Vaccine from the withdrawn batches was evaluated for contamination. The World Health Organization was invited to review all data and information from the investigations.

On January 3 and 17, 2014, CFDA and NHFPC issued a joint report on the investigation results: Kangtai's hepatitis B vaccine were tested within specifications and had no chemical or biological contaminants. The 17 infants that died following vaccination died of causes bearing no relation to the vaccination. One infant, who had

allergic shock, was treated, and who recovered, may have had an allergic reaction to hepatitis B vaccine or to vitamin K. The investigation concluded that the deaths were coincidental to the vaccine but not caused by the vaccine. NHFPC and CFDA issued a notice that vaccines made by Kangtai could be used again [4, 5].

9.3.2 The Impacts of Event

Although lasting only 1 month, the hepatitis B vaccine event influenced strongly the vaccination program in China. After the event, public trust in immunization decreased, and many parents expressed hesitancy to vaccinate their children. Vaccine hesitancy and refusal led to a decrease in the use of hepatitis B and other NIP vaccines. Parents' confidence in vaccines went almost back to its baseline high level, but during the time of decreased confidence, the use of the timely birth dose of hepatitis B vaccine declined nearly 10% [4, 5].

9.3.3 Summary

There were several lessons learned from the hepatitis B vaccine event. Immediate official investigation and timely information sharing were essential. Monitoring in near real-time of the event's impact was also very important. NHFPC and FDA worked closely together in the investigation, and the two ministries conducted media briefings for the public. They explained the process of the investigation and the results and conclusions as they became available. Misunderstandings about the event and the vaccines were corrected. This information was received positively. The media briefing on January 3rd was particularly valuable because conclusions of the investigation were available for release. China CDC actively organized relevant technical experts providing leadership in the health investigation. China CDC conducted timely surveillance of awareness of the event, parent and provider confidence in the vaccine and immunization strategy, and utilization of hepatitis B and other NIP vaccines. China CDC also measured coverage with the birth dose of hepatitis B vaccine in hospitals. The data from these surveillance systems were important for gauging the impact of the event and shaping the response.

9.3.4 Insight

Given that coincidental vaccine events are unavoidable and happen frequently (due to the background neonatal mortality rate), how should the program prepare for the next "vaccine-causing death" event? Advanced preparation is important. A risk communization capacity should be established through (1) strengthening training of primary health and grassroots-level staff on risk communication skills; (2) developing a system to monitor parent and provider attitudes toward vaccines and immunization; (3) enhancing capacity to monitor real-time vaccine utilization and coverage;

and (4) developing a comprehensive communications strategic plan that anticipates coincidental vaccine events that occur frequently. A good communication mechanism with the mainstream media should be established to ensure that accurate information is provided to the media. The communications strategic plan should emphasize timely release of information, for example, when test results become available.

In addition to crisis management, routine information about vaccines and immunization, including successes of the immunization program, should be shared with the public and the media. For example, popular science articles can be developed with the public's need for vaccine knowledge in mind. Accurate information on hepatitis B prevention should be provided to the mainstream media. In the new (social) media era, it is important not to allow a wall to form between the government and the public, with information from the government accessible only by the media. Outreach from the government directly through social media can be a useful strategy for providing accurate information.

Concerns of parents and the media should be monitored so that their concerns are understood and can be addressed effectively. A lesson from the 2013 to 2014 hepatitis B event was that because two doses of hepatitis B vaccine are given in the first month of life – the age with the greatest background death rate – these coincidental events will continue to happen with hepatitis B vaccination. Thus, the importance and necessity of hepatitis B vaccination should be made evident to parents and the media. The scientific rationale for hepatitis B vaccination should be readily available to everyone in China.

Sentinel sites should be selected in some provinces to regularly monitor awareness, attitudes, and knowledge of parents and providers about vaccines and immunization. By understanding parental knowledge and specific concerns, the immunization program can be responsive to concerns and proactive to keep parents engaged with the program. Key opinion leaders may be able to serve as spokespersons about vaccines and immunization. With familiarity to mainstream and social media, opinion leaders may be very helpful in times of crisis. During normal, non-crisis times, key opinion leaders can help educate parents and the media about the importance of keeping their children fully vaccinated and protected from vaccine-preventable diseases.

9.4 Social Problems and the Improvement of Laws and Regulations Caused by Polio Vaccines

Polio is a severe acute intestinal infectious disease caused by the poliovirus that can cause lifelong disability or death. Polio was widely prevalent throughout the world in the past. Due to the widespread use of live attenuated oral poliovirus vaccine (OPV) in China in the 1960s, the incidence of polio dropped significantly, and polio-free status was certificated in 2000 [6, 7]. However, on very rare occasion, while replicating in a vaccine recipient, OPV can acquire mutations that cause neuro-virulence and result in paralysis of the person vaccinated (or a close contact),

a condition called vaccine-associated paralytic poliomyelitis (VAPP). Although the incidence of VAPP is very low, with about two to four cases/million birth cohort per year according to WHO, VAPP has a serious impact on the normal life of patients and families [8]. VAPP is a prototypical example of a serious, vaccine-caused AEFI. The diagnosis, identification, and compensation for AEFI can cause social conflicts and many societal problems, which has led to the establishment and optimization of relevant laws and regulations in China.

Determining whether there is a causal relationship between an AEFI and a vaccination is a prerequisite of compensation for AEFI. Causality assessment can be particularly challenging, and most countries rely on special committees of experts and physicians to ensure the accuracy of identification and diagnosis of AEFI. Globally, the identification of AEFI is divided into two parts. The first part is to determine the type of AEFI and time of onset in relation with a vaccination. For example, a "vaccine injury form" is used in the USA to gather key clinical and timing data that are known scientifically to be associated with certain AEFI [9]. The second part is the use of an expert committee to decide whether or not to compensate for an AEFI. Examples include an assistance group for vaccination victims in Taiwan and a subcommittee on vaccination for identification of AEFI in Japan [10, 11]. Members of the committees are experts in the relevant fields who are employed by the nation and who are responsible for providing detailed comments on the diagnosis and compensability of AEFI.

Because there are many kinds of diseases and complex etiologies associated with AEFIs and there is often no definitive diagnosis that can be made, AEFI identification should be made comprehensively by expert groups that include clinicians, immunologists, and epidemiologists. Diagnosis and identification of AEFI in China are the responsibility of an expert committee, consistent with the general practice of the world. In accordance with "Identification rules of AEFI," the investigation and diagnosis of AEFI should be conducted by an expert group consisting of epidemiologists, clinicians, pharmacists, and other experts. Identification should be conducted by a neutral third party – the medical association. Medical associations at the province level should establish a database of experts on AEFI identification to provide experts for medical associations at the province and prefecture levels. During selection to serve on a panel, the experts should be sampled from the database by families that had a history of an AEFI. In 2014, eight ministries including NHFPC, the Ministry of Finance, and the Ministry of Commerce jointly issued Guidelines on Further Addressing AEFIs (hereinafter referred to "Guideline"), which specified that uncertified medical institutions or individuals are not allowed to provide a diagnosis of an AEFI, mainly because such diagnoses need specific professional knowledge. Inexperienced or unqualified experts are not capable of conducting an investigation and making a diagnosis, and a third party with no specific professional knowledge does not have the capability to accurately diagnose AEFI.

From a practical and legal perspective, CDCs in China at all levels and medical associations are able to complete the duties authorized by laws and regulations and are capable to scientifically, fairly, and equitably conduct investigations, diagnoses, and identification of AEFI. However, according to the current management system

in China, CDCs manage vaccination services and develop technical guidance. If CDCs manage vaccination and organize investigations and diagnoses of AEFI, their neutrality may be doubted by families with regard to the diagnosis, identification, and conclusion of an AEFI investigation. In accordance with the "Guideline," China CDC developed a standardized "Survey Form for AEFI" in July 2014. China CDC also developed a "Reference Book for Evaluation of Causal Relation of AEFI," providing a scientific foundation for causality assessment and scientific investigation of AEFI that is used by the AEFI expert groups and CDCs. The purpose of the survey form and the reference book is to enhance the credibility of expert conclusions from AEFI investigations and identifications.

In accordance with the "Regulations of Vaccine Circulation and Vaccination Management" (hereinafter refer to "Regulations"), a specific compensation method shall be developed by the province government. Compensation liability and the mechanism for AEFI diagnosis were clarified by this document for type 1 and type 2 vaccines: compensation for AEFI due to type 1 vaccines should be covered by the provincial government through vaccination funds allocated by the province's finance department; compensation for AEFI due to type 2 vaccines should be covered by the vaccine manufacturer. In 2014, the guideline further required that the AEFI compensation budget should be in place and available at all times. Currently, most provinces have developed AEFI compensation methods based on local conditions. However, because of the imbalance in socioeconomic development by province, there are some differences in the compensation standards, including the actual amounts of compensation. Guidance should be strengthened, and the local government should be guided to timely adjust AEFI compensation standards, to further narrow the differences between regions.

NHFPC commissioned relevant research institutions to conduct a case study of international experience about three main compensation mechanisms, including financial compensation, insurance compensation, and foundation compensation. After several rounds of meetings, seminars, and on-site surveys, with suggestions collected from the Ministry of Finance and other relevant departments, some provincial Health and Family Planning Commissions, some CDCs, some insurance companies, and vaccine manufacturers recognized the need to establish a commercial insurance system to perfect a compensation mechanism for AEFIs. In 2016, as one of its priorities, NHFPC promoted a pilot project on compensation mechanism of AEFIs. The pilot project was conducted in Beijing, Hebei, and Shanghai to accumulate experience, so as to reduce patients' and family's economic burden through new sources of financing.

VAPP causes great harm to the health of children with many cases left with lifelong disability. In addition to compensation, the follow-up assistance and relief is a priority. The "guidance" requires local HFPC to designate one or two hospitals of Tier 2 or above to provide medical treatment and rehabilitation of high quality. The "guidance" also put forward requirements for relevant departments regarding follow-up care and assistance of AEFIs. For example, the Civil Affairs Department should include compensation-eligible AEFIs into the Urban and Rural Minimum Living Security System, the Poverty Support System, and the Temporary Relief

System. Individuals with severe disability should be considered as priority in local policy. The Federation of Disabled Persons should issue in timely manner Disability Certificates to people with compensation-eligible AEFIs, to protect their legitimate rights and interests. Those qualified should be provided with rehabilitation assistance. Disabled children aged 0–6 years should be a priority for rehabilitation assistance and should be provided with basic auxiliary equipment. The Red Cross should provide necessary humanitarian assistance to families with special difficulties due to AEFIs.

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Essays by International Experts Working on the Immunization Program in China

10

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10.1 Experiences with China EPI Evaluations

Alan Schnur

Evaluation has been an important component of the global Expanded Programme on Immunization since its inception in the 1970s. China emphasized evaluation from the very beginning of the national immunization program, with concurrent and retrospective evaluations given an integral role in the EPI and polio eradication efforts in China. At the start of the EPI program, three formal comprehensive evaluations were planned to identify successes and problems at each stage of the program and to make proposals for further improving activities. The first evaluation assessed achievement of the target of 85% immunization coverage at provincial level by 1988, the second 85% coverage at county level by 1990, and the third 85% coverage at township level by 1995. These evaluations included international experts and were comprehensive reviews of the EPI, going beyond just considering coverage, to look at program quality aspects such as cold chain, safe injections, disease surveillance (to assess impact of the program on the target diseases), training, and sustainability. The evaluation methodology adopted required international teams to make visits to all levels, including township and village levels, to review the work, which provided international experts with an opportunity to review the work, and see life in China, at all levels.

I first met EPI workers from China in 1987, during a Comprehensive EPI Programme Review in Myanmar, where a team had been sent to take part as observers. I was impressed with the knowledge and interest of the observers from China and also that China was sending a team to learn how EPI reviews were conducted in other countries. I later found that besides the team attending the EPI review in Myanmar, which was organized with the support of WHO SEARO where I was EPI Technical Officer, China also sent teams to observe EPI reviews in countries in other WHO regions. This reflected the priority placed on evaluation and the systematic way that China's EPI program was preparing for its first national EPI evaluation. I was surprised that some of the observers from China at this review were quite knowledgeable about EPI and evaluation but could not speak English. All questions and discussions had to be done through an interpreter. In most developing countries, senior staff speak excellent English (or French in French-speaking countries), while only junior staff at local level do not speak fluent English and need an interpreter to translate. It became clear to me that while the Chinese observers did not speak much English, their knowledge and interest was excellent, and they were capable of discussing high-level and complex issues and problems.

My next interaction with EPI evaluation in China was after my reassignment to the EPI unit at the WHO Western Pacific Regional Office (WPRO) in Manila. I was one of the WHO international team members who participated in the March 1989 national comprehensive evaluation of the EPI target of 85% immunization coverage at provincial level, assigned to work with the teams in two provinces: Jiangsu and Shandong (Fig. 10.1).

Fig. 10.1 Jiangsu EPI review record checking (March 1989)

For the first visit to Jiangsu province, Dr. Yihao Zhang (a member of the Global Commission for the Certification of Smallpox Eradication and also China's National EPI Advisory Committee) was a member of our team. As it was the first time I was working in China, I was not sure how much one could push to revise the schedule after arrival and to randomly select places to visit, as required by the standard EPI review methodology. The briefing at WPRO in Manila had indicated that there was almost no room to select places to visit at random or to change the schedule prepared by the host province. However, to my surprise, during the opening briefing in Nanjing, when the provincial EPI team laid out the proposed program to visit Wuxi City (including a visit to the famous tourist attraction of "Taihu") and another very advanced county and prefecture, Dr. Zhang very calmly and politely responded that we would not be visiting these places. He informed the provincial EPI team that according to the review methodology, the review team needed to select the counties to visit according to the data. We then selected two prefectures and counties (with high and low coverage) and proceeded to visit them. I was very impressed with Prof Zhang's spirit of looking at the actual work and his knowledge about evaluation and the EPI program. I had helped organize, and participated in, many country comprehensive EPI reviews while working in SEARO, and during the field visits, I enjoyed the many chances to discuss with Dr. Zhang the EPI review methodology and utilization of the review questionnaires and forms. I felt that the review in Jiangsu met international standards, with the findings reflecting the actual situation. This was my first of many experiences with enthusiastic and hardworking evaluation team members in China.

Dr. Zhang returned to Beijing after the visit to Jiangsu and did not accompany the team to Shandong province. Unlike Jiangsu, Shandong provincial officials did not permit any changes to the pre-arranged schedule. We did have full access to the data and could find at the very end of the visit, while reviewing in depth the disease incidence rates and the breakdown of rates by prefecture, that there was an ongoing polio outbreak in one prefecture that had not been highlighted in the briefing. At the time, I thought that if Prof Zhang had been with us, we might have changed the prepared schedule and visited this prefecture since a disease outbreak indicates low EPI coverage or a cold chain breakdown. But we did have a chance to discuss on the last day the reasons for the high number of polio cases in this prefecture and to include this in our findings. Since the target was 85% immunization coverage at province level, Shandong was able to meet the target, even with low coverage in one prefecture. I learned that the work was overall of a very high standard but that there were still pockets of low performance and low coverage. I also relearned the lesson that having a respected and capable team leader, such as Dr. Zhang, can greatly affect the success of a mission and of a program.

However, while participating in many evaluations and assessments in China, I learned that not all staff were content to let the evaluators observe random program performance. During a polio assessment in one county, I visited two randomly selected townships and was impressed by the high quality of the work and the welcome banner prepared for the evaluation team at each place visited, even when the visit was made with very short notice. I commented on this to the county health

officials, and they advised that they had requested all the townships to prepare carefully, since an evaluation team could visit any of them. I thought that while this could be seen as biasing the evaluation, by placing full emphasis on the county previously selected for the evaluation team's visit, it could also be viewed as "improving the work in all the townships in the selected county." On another occasion, during an assessment visit, I randomly selected the first house in a village to visit using the serial number of a currency note, where we found normal, basic conditions, and some problems with timely immunization. The township officials then offered to randomly select the second house, using the list of houses we had jointly prepared. The second house, while randomly selected, turned out to have a washing machine in the house and appeared quite well off compared to the first house, with the child immunized as per the schedule.

On another occasion, during a polio immunization day concurrent assessment in Yunnan province, I remember the evaluation team getting up early every day to travel to the selected places and working hard to visit as many immunization sites as possible to complete the assessment forms. One of the provincial team members was always enthusiastically getting everyone out to the transport in the morning, pushing everyone along with calls of "kuai-diar!," "kuai-diar!," or hurry up!

Following completion of assessment/evaluation missions, there were usually formal presentations of findings to senior MoH staff. I remember several of these presentation sessions in the traditional-style meeting room at the old MoH office near Houhai, attended by Vice Minister of MoH Dakui Yin. Vice Minister Yin, after carefully listening to the presentation of findings and recommendations by the international experts, would speak last to summarize the findings and what actions needed to be taken. He usually started off with some stories, and I could see some of the team members with less experience working in China puzzled about how the stories were related to the main issues presented. However, after starting his comments at the periphery of the main points, Vice Minister Yin would gradually move to issues closer to the center and by the end of his summation would succinctly address the key points and then explicitly talk about what would be done to address the recommendations. Those international experts who were familiar with his style simply waited for his comments to start edging closer to the center of the target until he reached "the bull's-eye." But all of the international experts left the presentation impressed that the main recommendations were understood and would be addressed.

Not only health workers were supportive of, and committed to, evaluation. On another occasion, during a polio immunization assessment in Qinghai province, a prefecture vice-governor accompanied the team during house-to-house visits to check whether children had received polio vaccine during the immunization day. We checked many houses and stayed out quite late, until it was almost dark. I requested that the vice-governor return, as we would take some time to carefully check all the required houses. She refused to return and stayed with us for the entire day, returning well after dark, energetically checking records and interviewing people in the villages about whether children had been immunized.

EPI evaluations provided international experts an opportunity to learn many things about the program, and about life in China, an interaction that I feel

privileged to have had the opportunity to experience. During evaluations, there were always usually formal banquets for lunch and/or dinner, at each level. While reminiscing about the polio assessment in Qinghai, it brings to mind one banquet experience with which I would like to close this vignette. I visited Qinghai several times on assessment missions. On one of my last visits, provincial staff informed me that they had arranged a special lunch but didn't mention where it would be. Toasts ("ganbei") with alcoholic drinks are important parts of banquets in China and serve to establish rapport between the local workers and visitors (both national staff from higher levels and international experts). I must admit that I am not an enthusiastic alcohol drinker and did not greatly enjoy this aspect of the interaction during visits. During my time in China, there were many provinces in China known for heavy drinking at banquets, where large amounts of very strong alcoholic drinks would be consumed at the banquet table. Several provinces had a good claim to the "heaviest drinking province," but I believe that Qinghai would have been included among the top five heaviest drinking provinces by all international experts. On this particular occasion, Qinghai provincial staff had organized an excellent lunch in a well-known Moslem restaurant in Xining. Provincial staff informed me on entering the restaurant that it did not serve alcohol. I remember many, many outstanding and memorable banquets during my evaluation and assessment work in China, but there is a special place for the very friendly interaction during that alcohol-free lunch in Xining.

10.2 The Foundation of Measles Case-Based Surveillance in China

Edward J. Hoekstra

I arrived in China early 1998 as a World Health Organization (WHO) medical officer, assigned to continue supporting the polio eradication efforts underway in the country since the early 1990s. I had been to China on several previous occasions to support the polio eradication effort while working at CDC but would now be residing in Beijing for 2 years to concentrate on that support, as the ongoing polio campaigns were successful and moving forward toward the goal of eradication.

At the same time, it was evident that measles outbreaks throughout the country remained problematic with a measles incidence of <10/100,000 population during 1991–2000, even though China had a two-dose policy at 9 months and 7 years of age, and the reported cases of measles had been drastically declining since the introduction of measles vaccine in China in 1965 [1, 2]. It was becoming clear that measles control, including upgrading the surveillance, should be simultaneously addressed with my polio mission.

So as it turns out, I would now have two main goals to focus on for the coming 2 years that I resided in China, the eradication of polio and the further control of measles. The following is the story of how the program of measles control and elimination was established.

On a cold spring day in early in 1998, Dr. Jingjin Yu, MoH; Dr. Zhiwei Yang, Chinese Academy of Preventive Medicine (CAPM); Dr. Steve Cochi, Centers for Disease Control and Prevention (CDC) Atlanta; and I, Dr. Edward Hoekstra from WHO, sat down in Beijing at the CAPM and discussed a collaboration between MoH, CAPM, CDC Atlanta, and WHO to start up a 3-year active case-based measles surveillance pilot project. The project was designed to establish the first step toward accelerated measles surveillance and control and included laboratory confirmation of cases, beginning in a limited area only, and building upon the systems used for polio eradication. While the polio infrastructure used laboratories at province level, the measles infrastructure needed laboratories at prefecture level because there would be too many cases to evaluate at the province level. It was intended that the operational experience obtained through this project would in the future be used nationwide.

In 1998, nationwide mass measles campaigns to eliminate measles were not politically feasible because polio eradication was ongoing, and the country had not yet been certified polio-free. Therefore, it was decided that the first step would be to develop case-based measles surveillance in the areas with a lower incidence of measles as it would be impossible to take blood samples from each case in areas with high incidence of measles. CDC Atlanta agreed to provide 500,000 USD annually for 3 years through WHO to support setting up province-wide surveillance in two provinces, and the Chinese government agreed to match the amount with 2 dollars for every dollar pledged.

While this pilot project was further designed, planned, and funded, the MoH with technical support form WHO and CDC Atlanta finalized and issued in 1998 the Plan for Accelerated Measles Control in China [3]. The plan grouped provinces into one of three control goals on the basis of average annual measles incidence. Provinces in group A had an average measles incidence of <2/100,000 population, and their goal was measles elimination. Provinces in group B had an average measles incidence of 2–15/100,000 population, and their goal was measles outbreak prevention (group B provinces are subdivided into groups B1 and B2, with measles incidences of 2 to <5 and 5–15 per 100,000 population, respectively). Provinces in group C had an average measles incidence of >15/100,000 population, and their goal was measles control.

China had reported measles data to the National Notifiable Diseases Reporting System (NNDRS) since 1954. However, the reporting is passive, and the cases were only clinically confirmed. To increase the sensitivity and specificity of measles surveillance, the MoH issued guidelines in 1999 for the introduction of a measles-specific surveillance system (MSS) [4]. Both the measles control plan and the national measles surveillance plan called for a phased approach, with different reporting requirements for provinces in different control groups. In Group A and B1 provinces, active surveillance for measles cases should be conducted every 10 days, and all suspected measles cases should be investigated, with blood samples obtained for serologic confirmation of acute measles infection. In group B2 and C provinces, the emphasis was on improving the timeliness of reporting and serologic confirmation of measles outbreaks.

Also in 1999, the 3-year case-based surveillance pilot project was initiated in Shandong (group A) and Henan (group B1) provinces to gain experience with implementation of intensified measles surveillance, laboratories were set up at prefecture level in both provinces, equipment was installed, health and laboratory staff were trained, and guidelines for monitoring of active case-based measles surveillance were distributed.

After starting the pilot project in the first eight prefectures in Shandong in 1999, the CDC Shandong became aware of the number of measles cases and the increased workload related to case-based surveillance for health-care workers and laboratory staff. So by summer 1999, a province-wide measles campaign for children 8 months to 7 years of age was successfully conducted. As expected, this instantly further reduced the number of susceptible measles cases reported to MSS.

At WHO we knew from experience around the world that first conducting a mass measles campaign followed by introduction of a case-based surveillance was the preferred strategy to control measles. The pilot project in Shandong province with the overwhelming number of cases identified created the political will to conduct a mass campaign. This process also led to the desired measles control.

After 3 years, in 2001, the active case-based measles surveillance was reviewed positively [5] and became the foundation of the nationwide measles surveillance as we know it today.

10.3 The World Bank (IDA)-Financed Disease Prevention Project

Enis Barış

The World Bank (IDA)-financed disease prevention project, also commonly called as “Health-7,” had as one of its two main objectives the prevention and control of vaccine-preventable diseases in the poorest ten provinces of China, including adding new vaccines to the Expanded Programme on Immunization. While I certainly enjoyed being the Bank’s lead in the implementation of this project which allowed me to visit some of the poorest and remotest areas of mostly Western China, what I like most was its simplicity in design, yet its huge potential for making real impact in reducing mortality among the poorest children. Indeed the design was a tribute to Einstein who famously said “Everything should be made as simple as possible but not simpler,” having the basic necessities for a successful EPA, with vaccines, cold chain, training, and supervision and management, but nothing else spurious, the implementation went as smoothly as one could imagine, corroborated by the Operations Evaluation Department’s (OED) independent evaluation as project with a satisfactory outcome a rare rating for health projects in general.

This being said, I would like to emphasize three features of this project. First, this project came about at a time when there was a policy and leadership vacuum in health care and public health in China with a rather “laissez faire” attitude at the national level and serious financial and capacity constraints in poorer provinces.

Many Chinese colleagues and their international partners were worried that the hard won past accomplishments despite extreme poverty in yesteryears are under serious threat by policies deferring financial responsibility for public health to provinces under the guise of encouraging financial autonomy and thus incentivizing them to introduce user fees for generating income even for essential services such as immunization. With this project, we were able to put a stop to it, at least in the 392 poverty countries in 10 poorest provinces.

Second, we were able to not only invest in cold chain and training but also were able to introduce some discipline in record keeping, and sound program management principles based on data and evidence, especially with regard to adverse event reporting, safe injection, and safeguarding the integrity of the cold chain for vaccine safety and efficacy. And this was done through one of the most exemplary partnership displays, at least in my record, the World Bank staff working hand in hand with WHO and US CDC colleagues, together with local, provincial, and national authorities in China at every field mission there was.

And finally, we were able to lay the groundwork for the introduction of hepatitis B vaccine, a first in China, and in my opinion, one of the greatest accomplishments of this highly successful project, at a time when about 10% of Chinese population were HBsAg positive. As a result, hepatitis B vaccine has been included in the EPI with the Ministry of Finance providing significant financing but also requiring provincial governments to bear the cost of purchasing vaccines while GAVI committing itself to finance the hepatitis B immunization in the interim, thus securing the sustainability of the EPI both in the medium and longer term.

These days, we do not talk much about immunization in China. This is so because there is not much to talk about, thanks to the incredible effort put by Chinese and international experts through our affectionately called Health 7 project.

10.4 Polio Eradication in the Middle Kingdom: The Early Era of the Mid-1990s

Jessie S. Wing

It was the 13th of December 1995… Beijing was a bright, sunny, dry, cold, dusty, and vibrant city of less than ten million official residents with a few cars but a sea of people weaving in and out in a synchronous wave of moving bicycles. Beijing was wonderful, amazing and thrilling. I was quite excited to start this new adventure as the second CDC Medical Officer assigned to China – the Middle Kingdom and the birthplace of my parents. There was so much history and so much work to do to eliminate polio that had exacted a heavy burden in China.

In the World Health Organization (WHO) Office in Beijing, there were only a few staff assigned at that time: Dr. Kingsley Gee (the WHO Country Director), Alan Schnur (WHO technical officer), and me as the medical officer from the Centers for Disease Control (CDC) for the Expanded Programme on Immunization (EPI). We had a few offices in a suite near the canal in the northeastern section of the city.

Along with millions of other workers, I easily rode to work each morning on my Flying Pigeon bike from my WHO-assigned apartment in the Sanlitun area of Beijing where you could still hear the hawkers sonorously calling their wares from bikes and donkey-drawn carts. While I was in Beijing, I also provided clinical services at the US Embassy Clinic near the colorful Russian Market, Friendship Store, Chaowai, the outdoor Silk Market, and the Dirt Market where many transactions were made under China's burgeoning economy.

Some of our activities and accomplishments

- Acute flaccid paralysis (AFP) data: An important milestone was the ability to obtain AFP data from every county in China every month. Dr. Mac Otten's work to help "data-fy" China was fundamental. Mac, as the first CDC Medical Officer seconded to Beijing, Robb Linkins (CDC consultant), and Chinese Academy of Preventive Medicine (CAPM) helped to install and train provincial staff on CDC's free Epi-Info software and electronic surveillance. With the support of the Chinese Ministry of Health (MoH) and CAPM, AFP data were submitted from each county in China to their province then forwarded to Beijing each month. These data laid the foundation for my work to transform the county-level AFP data into meaningful maps for subsequent immunization activities, and the numerous epidemiology and laboratory reviews that followed.
- Surveillance, epidemiology, and mapping: I had "dualing" computers on my desk at the WHO office – one computer was for Epi-Info analysis and the other was a renegade Macintosh computer for mapping data. Each month, provinces/cities would transmit their electronic AFP data to CAPM, where my CAPM counterpart would receive, clean, and compile the data into one file. CAPM would provide a cleaned data file, and I did the epidemiologic analyses and produced many maps to track the distribution of AFP cases in China each month.
- Any case suspected of having AFP was promptly investigated by local EPI staff, provincial officials, and national teams. Mopping up campaigns and Sub-National Immunization Days (SNIDs) were conducted, as needed. Several imported cases of wild polio virus reported in 1996 prompted a special visit to Yangon, Myanmar, by an international team. MoH also convened an international delegation for a rare visit to Tibet's Autonomous Region in 1997 to review their EPI data and processes for inclusion in China's polio certification application.
- Immunization activities: For polio vaccination, China used their domestically produced oral polio vaccine (OPV, a ¼″, ivory-colored, sweet dragee) that was crushed to administer to younger children. Diverse conditions throughout China necessitated special cold chain accommodations and various methods to target immunizations for the "floating population" (unregistered children). Some areas used horse-drawn carts and motor bikes to transfer OPV to remote areas to meet the ambitious goals of the NIDs. The level of cooperation, support, and effort throughout the provinces to vaccinate all NID-eligible children was remarkable. MoH led the NID efforts of the EPI staff along with CAPM, UNICEF, WHO, CDC, and Rotary, International. A record of 80 million children in China received OPV during the weeklong NIDs held during this time period.

- International reviews: We hosted a series of international epidemiology, laboratory, and immunization reviews each year. Working closely with Director General Zhao Wang and Jingjin Yu at MoH, specific provinces and counties were selected for site visits. We created special provincial profiles using the latest county-level AFP data, detailed epi/surveillance data files and maps, and laboratory data for the international consultants who came to China for the field visits, data reviews, and discussions. The status of laboratory specimens, laboratory processing, use of data (electronic and missing variables), analysis, and consolidation of wild virus specimens was discussed with Dr. Libi Zhang and other staff from CAPM, MoH, and the Western Pacific Regional Office (WPRO). This was the era that CDC consultants (Drs. Walt Dowdle, Steve Cochi, Olin Kew, Mark Pallansch) along with our WPRO colleagues from Manila (Drs. Rudy Tangermann and Ray Sanders) came to review China's local polio data in a series of special field visits.
- EPI training: In winter of 1997, we trained over 600 local EPI staff in Xinjiang, a large province in northwest China that was part of the venerated Silk Road. We also developed and hosted study tours to CDC/Atlanta for nearly 60 provincial EPI staff to receive advanced training in EPI, surveillance, and accelerated measles elimination methods.
- Public health infrastructure: Many of our field visits included provinces of north central and southwestern China, including Yunnan, Guizhou, Guangxi, and other areas with colorful but underserved minority populations. We calculated that I traveled in over half of this continental country, visiting EPI stations in many rural areas of China. At every level in China – village, township, county, prefecture, province, national level – we were well received and impressed with the commitment, hard work, and congeniality of the EPI and laboratory staff throughout the country. China's leaders and colleagues were sterling – including Director General Wang, Jingjin Yu (from MoH), Kean Wang, Libi Zhang, Xinglu Zhang, and Tao Xu (from CAPM) to name a few principal colleagues. We would not have been able to make progress in any of our polio work without their express support and dedication.
- Outcomes: Strong political support was illustrated by Jiang Zemin in posters distributed to many EPI stations in China and reminds us of the centralized, top-down infrastructure that facilitated the EPI work at that time. The collaboration among the partners (WHO, CDC, CAPM, MoH, UNICEF, Japanese International Cooperation Agency) illustrated the potential of a strong relationship and the outcome of the collective effort. With a strong mission and tenacity in the rank and file of resourceful and pragmatic staff at all levels in China, polio elimination (and eradication) progressed fairly quickly. After only 6 years, the widespread distribution of polio cases in China in 1990 decreased to only three cases of wild polio virus imported into southwestern China from Myanmar in 1996.

I think China demonstrated to the public health world that with an effective oral vaccine, reasonably good NIDs/SNIDs, good surveillance, electronic data, vigilance for clusters/outbreaks, development of a laboratory network, interventions as needed – in the context of an intact public health infrastructure – dedicated staff,

and political will, the world's most populous nation eliminated polio in a relatively short amount of time. With these important components in place, this mega country could ultimately eradicate polio along with the other smaller countries in the region. The last polio case in the region was reported in Cambodia in 1997, and the Western Pacific Region (including China) was certified polio-free in 2000. In his 2015 Mountain Lecture at CDC/Atlanta, Bill Gates recalled that the BMGF (now a major global health partner) joined the polio eradication effort in India (another large country) in 1998.

Polio eradication was the initial reason that CDC staff were seconded to China, but subsequent CDC staff came to China for measles and other public health work as the WHO/Beijing office evolved. I believe the numerous epidemiology and laboratory activities and reviews that we carefully planned and implemented with MoH, CAPM, WHO, and CDC during this era helped develop a good model for subsequent EPI work. These important partnerships and relationships continue now in the transition to the use of inactivated polio vaccine in the Polio Eradication Endgame in China.

Every parent wants the best for their child, which was especially true for the numerous single-child families in China's 1.2 billion population. The Chinese characters, "prevention first," are particularly poignant for immunizations. While my parents left China because of world events, I think they would have been very pleased that I chose to live in Beijing and work to help the Middle Kingdom end the chapter on a devastating disease that was halted using a simple, two cent polio vaccine. With good infrastructure and an effective vaccine, China's progress was proof positive that polio eradication could be done at the macro and micro levels in a mega country with 1/6 of the world's population – even in the early era of polio eradication of the 1990s.

10.5 Answering Questions for a Nationwide Measles Supplementary Immunization Activity in China, 2010

K. Lisa Cairns

In 2010, China conducted the largest measles supplementary immunization activity (SIA) which had ever been held in the world. At that time, I was serving as the team leader for the World Health Organization's (WHO's) Expanded Programme on Immunization team and as such had been actively involved in conceptualizing and then planning for this massive effort. The SIA aimed to vaccinate all children in targeted age groups regardless of previous vaccination history. Planning for the SIA had been an enormous undertaking – from ensuring adequate vaccine supply to enlisting the support of provincial health bureaus and preparing for adverse events following immunization. The SIA was accompanied by extensive social mobilization, which in turn generated many questions, particularly from the educated elite in China's large cities. The recommendation that all children be given a dose of measles vaccine, regardless of previous vaccine history, received particular scrutiny.

WHO had coordinated the participation of a number of foreign observers eager to learn from China's ability to vaccinate so many children in such a short time. Several observers from the Pan American Health Organization, famous for spearheading measles elimination, were present. I listened in amazement as one of them mentioned to me that many people in the Americas had likely been vaccinated against measles five or six times as a result of nonselective SIAs and outbreak response activities. I could not help but think of the concern that we heard repeatedly expressed from Chinese parents that children who had already received two doses of measles vaccine might, as a result of the current SIA, receive three doses and marvel at differences in parental attitudes.

Dr. Peter Strebel, responsible for WHO's global measles program, also arrived to act as an observer. He and I were invited to participate in an open question-and-answer session for the public to be held in China's Centers for Disease Control and Prevention's (CCDC's) new communication center a day or two before the beginning of the SIA. We drove together through Beijing's car-jammed roads, moving slowly beyond the city to where fields opened up and traffic thinned, arriving eventually at CCDC's new, large, and ultramodern complex. We went through an enormous and impressive lobby into the state-of-the-art communication center. Individuals from CCDC were already there. Peter and I were directed to one side of the amphitheater where we waited patiently, albeit with the trace of anxiety which always accompanies such unscripted events. Shortly after, the questions began to arrive. The public e-mailed or phoned in queries which were translated for us into English. Peter and I would confer briefly, craft an answer, and have it translated to Chinese and sent out. As I sat surrounded by advanced electronics answering questions in real time from across the country, I thought of the remote villages in Sichuan that I had traveled to, and the contrasts of modern China seemed particularly striking. They were encapsulated for me in the two questions which I remember best: one seeking to verify that no imported vaccine would be used during the SIA, and the other, shortly after, asking why imported vaccine was not being used.

The SIA went on to vaccinate over 100 million children in China, demonstrating amazing planning and coordination. I visited many sites and gave a number of radio and television interviews. Nonetheless, my clearest memory of the SIA is sitting in the amphitheater, answering questions with Peter.

10.6 Expanded Programme on Immunizations, WHO/China, January 1999 to May 2006

Lisa Ann Lee

I spent 4 years as a Medical Officer and 2 years as Team Leader at WHO/China supporting the Expanded Programme on Immunizations. I had worked in many countries prior to my China posting and was very impressed and inspired by the dedication of counterparts at the Ministry of Health, China CDC and local health departments, and the Biological Product Institutes who worked tirelessly and over

many years to build the EPI. The opportunity to contribute to China's development also had personal resonance as my parents emigrated from China as teenagers when the country was still impoverished and torn by war.

It was difficult choosing what to write about with so many good memories of working in China. When I arrived, Jingjin Yu was the Director of the EPI Division and Zhao Wang was the Director of the Department of Communicable Diseases. Both showed great leadership and skill in facilitating the effective collaboration between national and international experts on many priorities. Much of my first year in China was spent working at the China Academy of Preventive Medicine, later China CDC, on the China's documentation to present to the Regional Committee on Certification of Poliomyelitis Eradication. I spent a memorable week at the Rainbow Hotel working with national experts and EPI directors from all the provincial CDCs, many of whom I worked with in subsequent years. We all put a lot of effort into making the document of the highest quality since we knew it would be an important historical record of China's poliomyelitis eradication efforts, which began well before the start of the Global Poliomyelitis Eradication Initiative.

Two areas that I worked on which I felt had important impacts were advocacy for increased public funding for EPI and strengthening routine immunizations in Guizhou Province. When I arrived in 1999, much of the costs of vaccine delivery was financed by parents through out-of-pocket user fees, a result of market reforms which had extended to public health. While this worked in many areas, there was inadequate incentive to deliver vaccines to the poor, with vaccine-preventable disease burden higher in Western China and urban floating populations. An experience in one village where I found several unvaccinated young children made a strong impression. Their parents said they couldn't afford to pay the user fee and even though the village doctor had offered to vaccinate the children for free, they had refused because they felt that the village doctor was just as poor as they were. We started collecting more information on immunization financing in China and other countries in the region. In 2003, we had the opportunity to highlight financing constraints to delivery of public health services, with EPI as an example, in a high-level report "Public Health Options: Lessons Learned from SARS," submitted by WHO/China to the government as the epidemic ended. In the report, we also recommended that EPI be a benchmark program for monitoring the effect of recommended public health reforms. We were able to describe the health system and financing constraints faced by EPI in the 2004 EPI International Review Report, which included the results of a detailed immunization costing and financing field study supported by GAVI. In 2006, the State Council passed comprehensive new immunization laws making EPI vaccines and vaccinations completely free while at the same time greatly increasing central government funding for EPI. There is good evidence that inequities in access to recommended immunizations have greatly narrowed, and currently, the delivery of expanded preventive health services through the New Rural Cooperative Medical System is building on the foundation established by EPI.

The EPI in Guizhou province was also facing many challenges when we started a project there in 2003 to accelerate measles control and strengthen routine immunizations. At that time Guizhou had the highest measles incidence in China and accounted for the majority of measles deaths nationwide. Three-fourths of the

counties had no budget for EPI, and over half of the village doctors received no government payment. Average per capita income was less than USD 200, and most of the province is mountainous and difficult to access. Despite these challenges, the project set ambitious goals of reducing measles deaths to near zero and measles incidence to very low levels through a measles catch-up campaign, increased government funding, increased accountability for EPI performance, and enforcement of existing school entry immunization laws that had yet to be fully implemented in any province.

When the project started, EPI staff seemed demoralized after years of being ranked at or near the bottom on most measures of EPI performance. Rankings are common and important in China, and provincial rankings are quite competitive. At the project inauguration meeting, we committed ourselves to moving Guizhou to the top of the national rankings and ensure that they stayed there. I felt there were initial doubts, but after the catch-up campaign in 2004, which benefited from careful support and planning by Yoshihiro Takashima, a Medical Officer on the EPI team, measles incidence in Guizhou fell dramatically and was even lower than Beijing's. This attracted a lot of positive attention and gave a huge boost to the program. The challenge was sustaining this achievement. In this we were very fortunate to have the strong support of Heng Bai, the Director of Disease Control at the Guizhou Health Bureau, who adroitly negotiated increased provincial funding for more immunization cards and vaccine supplies, the inclusion of EPI performance measures in the evaluation of political appointees, and the complex coordination between the Health and Education Bureaus needed to successfully implement school entry immunization requirements.

Alan Hinman, who was previously head of the Immunization Division at US CDC, was on the baseline project evaluation team and recommended "No shots, no school." It took almost 4 years to work out how to effectively operationalize those four words due to other laws mandating compulsory education. However, once operationalized, it turned out to be very effective given the high status of teachers in China. We conducted many training courses and supervision visits, and the project greatly benefited from continued involvement of Shuyan Zuo, a National Programme Officer on the EPI team. It's very encouraging to see that measles incidence in Guizhou province years after the project ended is still among the lowest nationwide.

10.7 The Remarkable Progress of the Chinese Measles and Rubella Laboratory Network

Paul Rota

The Measles Laboratory at US CDC was started in 1989 under the leadership of Dr. William Bellini. The laboratory was formed in response to a global resurgence of measles in the late 1980s. When I joined the Measles Laboratory in 1991, the laboratory already had a global reputation for being a leader in measles diagnostic methods and the genetic characterization of measles viruses. At that time, we were

receiving many inquiries from international scientists who were interested in training at the US CDC. One of the first international trainees to visit us was Dr. Wenbo Xu. Dr. Xu had been working in China's national polio laboratory and was asked to initiate laboratory activities for measles in China. Dr. Xu arrived in 1995 and quickly became a productive member of our laboratory. Within a few months, he had mastered most of the laboratory methods and was making great progress in characterizing measles viruses isolated from China. Dr. Xu was the first to describe genotype H1 which we now know has been the endemic genotype in China since at least 1993. In fact, we are continuing to monitor the circulation of genotype H1 viruses which is limited almost exclusively to China.

Before Dr. Xu returned to China in 1998, we sat together at my desk at US CDC and outlined a plan for a measles laboratory network in China. The plan called for reference laboratories in each of the 31 provinces with the basic serologic testing performed at the prefecture level. This network of laboratories would be supervised by the National Measles Laboratory at the China CDC in Beijing. At the time, I thought that this was a bold and very ambitious plan especially considering the limited resources available at the time.

My first trip to China was in 1999 as part of a review team for a CDC/WHO/China CDC demonstration project. I was able to visit laboratories at all levels in China, and I remember that the prefecture laboratories were quite basic. There were a number of significant challenges including an inconsistent supply of commercial IgM test kits, ageing equipment, and substandard facilities. However, the demonstration project was successful in showing the case-based surveillance for measles with laboratory confirmation could be conducted in three, very populous Chinese provinces, Henan, Shandong, and Anhui.

Since 1998, I have traveled to China almost every year to either participate in the national laboratory training workshops or to conduct accreditation of the national and provincial laboratories. I have had the pleasure of visiting 12 provinces so far and have very fond memories of the outstanding hospitality of my Chinese colleagues. Over these visits, I witnessed a tremendous expansion and improvement of the Chinese National Laboratory Network. The SARS outbreak in 2003 hit China especially hard, but China made a major investment in laboratories following this outbreak resulting in substantial improvement in the capacity of the provincial laboratories. Under Dr. Xu's leadership, the China Measles and Rubella Laboratory Network made great use of these additional resources. Each province now has a modern, accredited laboratory; there are laboratories in 331 prefectures. Most of the provincial laboratories are capable of performing the full range of serologic and molecular tests, and many prefecture laboratories perform real-time RT-PCR in addition to testing for IgM. Through the efforts of the national laboratory, the provincial and prefectural laboratories have access to high-quality commercial kits for both IgM testing and real-time RT-PCR. The national laboratory provides annual training and proficiency testing for both serologic and molecular assays. The Chinese Measles and Rubella Laboratory Network was one of the first national networks to include testing for rubella virus in the standard laboratory protocols. The Chinese laboratory network now submits thousands of measles sequences and hundreds of rubella sequences to the WHO global sequence databases, MeaNS and RubeNS.

China still has endemic measles, and the endemic genotype is H1. However, the Chinese Measles and Rubella Laboratory Network has been able to detect a handful of imported genotypes in a tremendous background of genotype H1. This is an amazing level of surveillance sensitivity in a country as large as China.

Of course, Dr. Xu could not accomplish all of this by himself, and one of his outstanding achievements has been mentoring the next generations of Chinese scientists. US CDC has had continual scientific exchange with China CDC. Over the years, many scientists have visited the US CDC in Atlanta to work on measles, rubella, and mumps, and we have published a large number of papers. Chinese scientists have also worked with the other Global Specialized Laboratories at Public Health England and the National Institute on Infectious Disease in Tokyo. In addition to supervising the extensive Chinese Measles and Rubella Laboratory Network, these now senior scientists are making contributions to the entire WHO Measles and Rubella Laboratory Network. They regularly attend WHO meetings and are serving in numerous advisory and supervisory capacities.

In summary, the progress of the Measles and Rubella Laboratory Network has been nothing short of remarkable. The network is fully capable to provide the high-quality laboratory surveillance needed to document the elimination of measles in China in the near future. I am honored to have been part of this outstanding program, and I look forward to the day when genotype H1 is no longer detected anywhere in the world.

10.8 Notable Experiences: The China-GAVI China Project and Hepatitis B Immunization

Yvan J. Hutin, Craig Shapiro, Stephen Hadler

The China Ministry of Health-Global Alliance for Vaccines and Immunization Hepatitis B Project (China-GAVI Hepatitis B Project) was a multi-year project initiated in 2002 with the primary focus of increasing routine infant hepatitis B vaccination coverage in China. The project ultimately accomplished that objective and also improved hepatitis B vaccine birth dose timeliness and the general status of safe injections within the country. A unique aspect (compared with GAVI-supported activities in other countries) was that the project was overseen by a team that included an in-country international co-project manager in addition to a national co-project manager. This brief vignette contains observations from the three international co-project managers who served over the course of the project: (1) Craig Shapiro, who was involved in project conception and initial implementation (2001–2003); (2) Steve Hadler, who continued project implementation (2004–2007); and (3) Yvan Hutin, who continued project implementation with an emphasis on improving birth dose timeliness (2007–2011). All of us were inspired by the dedication and enthusiasm of the Chinese counterparts at all levels with whom we worked, and we feel privileged to have had the opportunity to be part of an activity that ultimately had such a broad impact in helping to change policy and improve public health.

When Dr. Shapiro first arrived to Beijing in 1999 to work as a special consultant from the US Centers for Disease Control and Prevention (US CDC) to the China CDC (then referred to as the Chinese Academy of Preventive Medicine), the situation with respect to hepatitis B immunization was much different in China than it is today. It was before the SARS epidemic, which was a turning point in China in terms of investing dramatically in its public health system. It was also before the establishment of GAVI, which was a turning point in the world for prioritizing and investing in the introduction of new vaccines. Chinese leaders certainly recognized how important hepatitis B was as a public health problem in China (and given China's contribution to the worldwide burden of hepatitis B, global public health experts considered controlling hepatitis B in China as critical for global hepatitis B control). And Chinese health officials desired to provide hepatitis B vaccine to all infants. However, at that time in China, hepatitis B vaccine was available only if the vaccine was purchased by the family (often with a substantial markup), and an administrative fee was also charged – such markups and fees were an important source of revenue to cover the operating costs of clinics and the salaries of immunization providers. With such significant financial barriers to changing policy, the way forward, to make hepatitis B vaccine a routine immunization provided at no cost, was not entirely clear.

A variety of work activities and events came together in the early 2000s that enabled changes that ultimately led to hepatitis B vaccine being made a routine infant immunization in China. One was the completion of a World Bank immunization project, which had a component in which hepatitis B vaccine was provided to infants in several provinces at a lower price, through a subsidy. The World Bank study showed that even with the subsidy, hepatitis B vaccine coverage rates remained much lower than those of routinely provided vaccines such as DPT – vaccine price and user fees were significant barriers to receiving vaccine, especially among poor populations. Also around that time, a national immunization coverage survey showed wide disparities in hepatitis B vaccine coverage, with much lower coverage in poorer western provinces.

So with these lessons learned, and with the national desire at that time (and present to this day) to improve the general economic situation of the western provinces, conditions were primed for some type of change, and that is where GAVI played an important catalytic role. GAVI was in its initial stages and had the express purpose of promoting introduction of new vaccines, including hepatitis B, into countries around the world. However, while China in that era met the GAVI country eligibility criterion of per capita GDP less than USD 1000 (and certainly each of the western provinces – individually larger than many countries receiving GAVI support – met that criterion by wide margins), GAVI had not yet decided how to address China, India, and the Philippines, which had such large birth cohorts that providing support in the way that it was providing support elsewhere (essentially purchasing vaccine for a period of 5 years) would deplete GAVI's budget.

Several international teams visited China during 2001 and met with MoH official and country-based international staff at WHO, UNICEF, DFID, and the World Bank and the US Centers for Disease Control and Prevention to see if any type of

collaborative activity could be put together that would help improve hepatitis B coverage. A pivotal moment was a meeting at the MoH, at which GAVI representatives reviewed how hepatitis B vaccine was being provided in China, and remarked that such a mechanism (which involved generating profit) might be appropriate for "consumer products such as cars or refrigerators" but not for a public health intervention such as hepatitis B vaccination. Such a statement, recognized by all but never so clearly communicated to high-level MoH officials (with Ministry of Finance officials present), helped moved the agenda forward.

Over an ensuing series of visits and discussions, GAVI representatives worked with Chinese counterparts to devise the China-GAVI project as a subnational project focusing on providing support for western provinces and poverty-designated counties in the rest of the country and involving matching funding from China to purchase vaccine, syringes, and safety boxes. Hepatitis B vaccine would be provided free of charge to all infants in the target area and with a minor administrative fee that was to be phased out by the end of the project.

Several unique things were part of the project design:

The China-GAVI project was the first for which counterpart funding was provided by the recipient country to purchase vaccine. Because of this matching fund arrangement, an agreement, accompanied by a detailed project implementation plan, was signed by China and GAVI/vaccine fund representatives that spelled out the financial and operational commitments of all involved parties. An implementation plan of such detail with high-level agreement had not been a feature of previous GAVI-supported work in other countries.

The vaccine provided for the project was not through UNICEF, as GAVI had done for all other countries; instead, GAVI provided funds to China for domestic vaccine procurement. The reason for this was that China itself produced hepatitis B vaccine, and provision of UNICEF vaccine would impact the domestic market. However, China vaccine was not WHO-prequalified, and the national regulatory authority was only in the process of demonstrating that it was fully functioning. There were concerns that GAVI would be providing funding for the purchase of a vaccine that was not WHO-requalified. The GAVI project was one factor among others that helped to move forward the approval of the national regulatory authority.

Previously, vaccine procurement had been at the provincial level, but the project moved this for hepatitis B vaccine to the national level, increasing the capacity of the MoH and the China CDC National Immunization Program to conduct such activities for vaccine and injection equipment.

One of the criteria for receipt of GAVI support was formation of an interagency coordinating committee (ICC), which included representatives of the MoH, China CDC, WHO, UNICEF, DFID, the World Bank, the China Foundation for Hepatitis Prevention and Control (an NGO led by former MoH official Wang Zhao which also played an important advocacy role in the project), PATH, and others. Committees addressing general immunization issues with such broad participation had not existed before in China, and the ICC facilitated progress related to the project and larger topics (including immunization financing).

The project was a stimulus for conducting studies and demonstration programs in China to address other issues related to routine hepatitis B immunization, including improving timeliness of the birth dose and catch-up immunization.

From 2002 to 2011, the project progressed with the input of a number of generations of GAVI co-managers. First, Dr. Craig Shapiro and Dr. Xiaojun Wang were involved with project inception and initial implementation. Second, Dr. Steve Hadler saw major progress in three-dose vaccine coverage, which allowed them to focus more attention on the timely birth dose. Third, Dr. Yvan Hutin and Dr. Fuqiang Cui dealt with the final evaluation, which included a large mission throughout China for data collection in three strata of 80 clusters in October 2010.

Among many enlightening and delightful experiences while working in China, what stood out most strongly was the ability to plan and successfully execute public health programs, ranging from hepatitis B vaccination in least developed provinces and counties, to enhanced surveillance for meningitis and encephalitis, to measles and polio vaccination campaigns. During the tenure of Dr. Steve Hadler, his major responsibility was to help guide implementation of the GAVI-funded hepatitis B vaccine project, aimed at reaching high coverage with timely birth dose and full 3-dose series of hepatitis B vaccine among 12 less advantaged western provinces and poorest counties in 10 middle provinces. Ultimately, this project was remarkably successful, bringing coverage indicators in western provinces from 49% to 85% on time birth dose and from 68% to 89% HepB3 by 2009 [6].

Several factors were key to this success, most notably the co-leadership of the China MoH and China CDC nationally and at each administrative level reaching down through province, prefecture, and county. China CDC brought the scientific expertise and basic strategies, as well as monitoring, and the MoH and bureaus of health at provincial and lower levels brought the authority to assure work would be effectively implemented in each hospital and clinic. Hence, the basic strategies for giving timely birth dose – first assuring hospitals took responsibility for providing the birth dose "he who delivers the infant gives the vaccine dose" – were systematically implemented in every hospital, reaching 98% coverage with timely birth dose among children born in hospitals. This success was based on training conducted jointly by China National and Provincial CDC technical experts and Health Bureau leaders; intensive monitoring including vaccine registers in the delivery room and at county health clinics, using key indicators; and biennial reviews in selected areas, with feedback reasons for low coverage (unstable at birth and transferred to pediatrics, low birthweight, etc. – none of which were actual contraindications). Assurance of high coverage in each hospital is owed in large part to the authority of the leaders of health bureaus and provincial and county CDCs.

Another key factor which contributed to the success was a concurrent national policy to reduce maternal mortality, through promoting births in hospital, especially in rural areas where these had previously occurred at home. This had been established as a national initiative and rigorously implemented through subsidies to expectant mothers in rural areas to give birth in hospitals and resulted in dramatic increase in births in hospitals in all areas. This coincided with efforts to achieve high on-time birth dose coverage in every hospital and hence drove remarkable increases

in timely birth doses in project counties [7]. At the same time, the GAVI team had worked hard to learn how to deliver birth doses for rural births while improving coverage in hospital births – promoting registration of pregnant women, tracking prenatal care, assuring vaccine could be brought to the village in time for the birth, trying to get vaccine licensed for use off the cold chain (scientifically valid), and achieving high coverage in demonstration projects in Qinghai, Gansu, and Ningxia [8]. Yet this work was ultimately superseded by the national initiative to bring deliveries into hospitals, to the greater health benefit of mother and child – and so that by project end, an estimated 84% of births were in hospitals in these least advantaged counties in China.

A third factor that contributed to the success was the ability to track progress at all levels. Although China has always excelled at compiling statistics, a persistent challenge was the unavailability of exact denominators at any level, due primarily to out-of-plan births and migration. In general, tracking of immunization coverage relied on locally determined denominators for each vaccine dose and resulted in coverage usually exceeding 95% at each level – not unusual for administrative vaccination systems in any country but relatively useless for tracking progress. For the GAVI project, we instead chose to compare HBV3 and on-time birth dose coverage to those of other EPI vaccines due at roughly the same time – DTP3 and DTP1. This provided measures and achievable targets for each dose, which could be tracked at each level. Ultimately, these indicators were also used to help guide choice of districts in which to do evaluations, allowing selection of high, middle, and low performers to compare strategies and progress. Although these indicators did overestimate total coverage (not including children who did not receive DTP1 or DTP3), they presented the best approach for this project based on timeliness and providing information at each level.

During our tenures, there was occasionally tension, particularly with the opportunities to do direct monitoring in the project provinces (usually only annually except in special WHO-funded projects). However, with the system of feedback and oversight, even the periodic field supervisions were ultimately converted into strong progress in improving the project. Although field opportunities were not always as often as hoped, these were always both eye-opening and delightful. It was a privilege to work with talented and conscientious colleagues at national, provincial, and local levels and their ability to convert plans into action even in the most remote and challenged areas. Seeing the scope of the Chinese geography, the various peoples and ethnic groups were fabulous. And of course every field visit had its nonwork attractions, from the inevitable sightseeing trips to such historical places as Yan'An, Shaanxi, where Chairman Mao and the communist party spent the several years after the Long March; districts in Sichuan where Long March fighting occurred; the high plateaus and Buddhist monasteries of Qinghai; and the beautiful mountains and rural areas of Yunnan, Ningxia, Gansu, and Guizhou. And not to mention the inevitable banquets, with the rich variety of local dishes, bai jiu contests, and sange nege tournaments.

While the success of the GAVI China in terms of hepatitis B vaccine coverage and reduction of prevalence of chronic hepatitis B virus infection was widely disseminated through scientific communications and publications, the results in terms

of injection safety had not been documented so systematically. Hence, in 2010, as part of the final evaluation of the project, China CDC evaluated immunization injection safety using the standardized WHO assessment tool. Results of this observational assessment indicated that over 10 years, major progress had occurred. Glass syringes had disappeared, and locally produced auto-disable syringes had become the norm [9].

Aside from the direct output of the GAVI project, the achievement of uniformly high coverage for the third dose of hepatitis B vaccine, the birth dose, and the injection safety, the GAVI project was a tremendous learning opportunity on all sides. First, we all learned through trial and error what was the best way to make the program work in a country as large and complex as China. In fact, the spirit of these pilot projects for the timely birth dose was exactly about that: let's try together, plan it together, monitor it together, and troubleshoot issues that come up together until we succeed. Second, on the side of the Chinese counterparts, many China CDC staff got professional development opportunities that allowed them to further apply their skills in other challenging settings afterward, in China or internationally. Dr. Fuqiang Cui actually used the experience acquired with the final evaluation of the project to defend a PhD at the University of Basel. Third, while the project was wrapping up, WHO and China CDC thought that it would be important to review practices in terms of viral hepatitis surveillance. A joint mission was then organized that formulated recommendations in the field of surveillance of acute hepatitis and chronic infections. Fourth, on the side of the international colleagues, everyone worked hard on his Chinese, each with its own focus. Dr. Steve Hadler was very much into characters, numbers, and proper nouns, so he was rapidly able to read the tables and figures in Chinese, and Dr. Yvan Hutin invested in the HSK, the Hanyu Shuiping Kaoshi, the Chinese language exam, after Dr. Fuqiang Cui has ambitioned for him to try to graduate from the Chinese primary school exam before he would leave China. Last but not least, following an idea from Dr. Mark Kane and active editorial work by Dr. Steve Hadler, the entire GAVI China experience was recorded as a special issue of the *Vaccine* journal (Vaccine 2013;31 (Suppl 9)) so that public health officials working to increase hepatitis B vaccine and timely birth dose coverage in other countries could get inspiration from the positive experience in China.

The ultimate success of the project can be attributed to the vision of public health leaders and Chinese hepatitis experts in generating the data to stimulate the need and to the dedication of the many individuals within the MoH, the national and local CDCs, the immunization providers, and international partners. Making hepatitis B a routine immunization likely would have happened eventually without GAVI support, but at a later time, with the massive changes brought about by the SARS epidemic and the overall economic development in China. The China-GAVI project, consistent with the overall goals of GAVI, served as a catalyst to make this happen earlier and set the stage for full implementation. The thousands of children who are protected from hepatitis B virus infection, and therefore will not develop liver cancer or cirrhosis due to the hepatitis B, are the direct beneficiaries of the work of all involved.

10.9 China's EPI and Measles Elimination Programme Looked Back in the JICA Project's Point of View

Yasuo Chiba, Hiroshi Yoshikura

Japan's cooperation for poliomyelitis eradication, the China Polio Control Project, JICA, launched in 1990, and it aimed at establishing its activity model in Shandong province (Fig. 10.2). We collaborated with provincial epidemics prevention station (present CDC) to begin AFP surveillance, supplemental immunization, and poliomyelitis laboratory diagnosis. As to the laboratory, the National Institute of Infectious Diseases, Japan, has provided technical support, and it has also contributed to build national laboratory network system. Two years later, the cooperation expanded to four neighboring provinces, Hebei, Henan, Anhui, and Jiangsu, and from 1995, it shifted to southern five provinces, Sichuan including Chongqing City, Yunnan, Guizhou, Guangxi, and Jiangxi. In these provinces, we have visited more than 300 major medical institutions, where we reviewed their implementation of AFP surveillance. We also collaborated with the provinces of Xinjiang, Qinghai, and Gansu, which have been facing polio importation from polio-endemic neighboring countries. The JICA project continued in the several phases of similar activities even after China achieved polio free as a member state of WHO Western Pacific Region in 2000.

China's public vaccination service, the Expanded Programme on Immunization (EPI), began in the late 1970s, and by the middle 1990s, the most provinces had achieved high (≥85%) coverage at township level with four classic vaccines, BCG,

Fig. 10.2 Door-to-door survey about a polio case in a farmhouse in rural Shandong province (February 1992)

DPT, polio, and measles. Despite this overall success, polio outbreaks have recurred from the end of the 1980s, mainly in eastern provinces including Shandong. In order to figure out the various causes behind the outbreaks, we have visited and investigated widely rural agricultural areas where cases with polio were reported. This action uncovered as-yet-unrecognized problems of EPI as well as conditions responsible for the polio outbreaks, and it has also provided information about other vaccine-preventable infections, such as measles.

During the 1990s, China was in the developmental stage of economy, and provinces which can afford EPI services satisfactorily were rather rare. Budget amounts to maintain or replace cold chain equipment were generally small at any administrative level, and, therefore, in prefecture and subprefecture units, for example, vehicles for vaccine transportation, walk-in cold rooms, and other cold storages appeared extremely old. Similarly, in rural vaccination posts, ice packs and injection syringes often run short relative to the size of target population, suggesting that the vaccinations in such posts might have resulted in unsafe and unsuccessful ones. Two other factors, rapid increase of floating families and high childbirth rate, further negatively affected EPI activities by leaving a number of children out of vaccination services. Village health workers appeared to have been insufficiently trained for accomplishing their duties and have received only a small amount for their work. Nevertheless, they had to bear all the burden derived from these problems. Indeed, the coverage of routine as well as supplemental vaccinations seemed to depend to a great extent on their motivations. Village health workers did a wide range of jobs, from registration of newborns, vaccine transportation, preparation, and sterility of injection equipment, till house-to-house visits for vaccination. These amounts of duties might have exceeded their capability particularly at a time when the supervision and support were insufficient. However, the progress of EPI in China was remarkable after the middle of the 2000s, when the government further increased commitment and financial support.

In October 2014, we visited several new vaccination posts, so-called vaccination clinic, in the townships of Shandong and Gansu. Vaccinations in a fixed site started in the early 2000s, replacing gradually the old practices which had been carried out in villages for a long period. Shandong is one of the provinces which played an important role for the promotion of such a system in China. Vaccinations in the clinics have been improved significantly than before. Once, an ampule containing multiple doses of vaccine was cooled on ice until finishing several injections, a procedure which might affect sterility and cooling of the preparation. But today the most preparations are for single use and have been kept in a small refrigerator on the desk just until injections. Vaccinations have been done by trained EPI staff. It was not until recently that parents were requested to sign a consent form after EPI staff's explanations about their child's vaccination. Administrative works also appeared to be improved since EPI registration, and the recording of vaccinations has been done on personal computers in many clinics. Further efforts, however, should be made to reach to children who are out of vaccination service, including those of migrant worker families, in order to close immunization gaps.

Having achieved remarkable vaccination services as well as polio free, measles elimination would be the next target of China's EPI. In the year 2005, WHO in the Western Pacific Region proposed an initiative to eliminate measles by 2012, and for this purpose, the JICA project also has collaborated on the activities of this country.

In 2010, China conducted national-scale supplemental immunization activities (SIAs) of measles-containing vaccine (MCV), although many provinces have been strengthening vaccinations by their own policies. As a result, a historic low of about 6000 measles cases were reported nationwide in 2012. The outbreaks, however, resurged in 2013, and it increased to over 40,000 cases in 2014. In Shandong province, about 2000 measles cases were reported in the same year, with the age being distributed widely, involving infants before vaccination age, adolescents, and young adults. A number of patients in the older age groups had a history of vaccination by MCV, and it was therefore assumed that the previous weakness of cold chain systems might be related to the vaccination failure in those patients.

The elimination of measles is more challenging than that of polio. In the poliomyelitis eradication, National Immunization Days campaigns with oral polio vaccine (OPV) successfully interrupted the transmission of wild poliovirus in China. Children were administered with OPV in every corner of the country, including even the marketplace, railway station, etc., while MCV has to be administered only by injection in the well-equipped clinics. In addition, measles virus is so contagious that transmission to others would occur easily if susceptible subjects remained in the population. The chance of infection increases as the population become larger, which is really the case in China with population 1400 million, equivalent to 19% of the total world population. Thus, the interruption of measles virus transmission by SIAs may be more difficult than that of poliovirus. It would be better to focus more on subjects who have no definite evidence of vaccination with the second dose of MCV rather than to target certain age range as a sole requirement. This policy might be practical and cost-effective in reducing measles susceptible population further.

Measles elimination in Japan also took time until it was verified as "measles endemic transmission free" (though 299 cases were reported in 2013 and 482 in 2014 [as of January 2016], which were considered imported or importation-related). It was accomplished by the introduction of routine second dose of MCV and achieving its high coverage in broad age range including adolescents. Although China's measles vaccination coverage seems high, continuous efforts would be needed to promote and secure vaccinations with the second dose of MCV. As a long-term policy, strengthened collaboration with Maternal Child Health (MCH) programs may worth consideration. In Japan, Pediatric Association and other groups related to MCH played an important role for the promotion of public awareness about measles elimination and the vaccinations for it. Ultimately, such a collaboration will be useful for further development of overall EPI programs as well. In any event, the measles elimination program in China, as my hope, should be the one which can raise further the quality of routine immunization services in the future.

10.10 Experience from Andrea Gay

Andrea Gay

Prior to China's decision in 2005 to eliminate measles, my knowledge of China's immunization system was very superficial despite 40 years of intermittent, varied experience with Chinese in the United States and in China, including 5 years

involving primary health care, that previously shaped my understanding of China's immunization program.

Beginning in the 1970s, my experience working with the Chinese population in San Francisco, California, to provide primary health care to this community indirectly formed my expectations about health care in China. For instance, I believed that once a public health intervention (e.g., vaccination) was required by the national government in China, it was expected to be followed with full support from Chinese people. As the community health center program in San Francisco was funded by the US Federal government, the Chinese community expectation was that the health services offered would be for their protection and should be accepted and used. Most of the program administrators and community residents were immigrants from China accustomed to having a government collect data so this health center always met the US Federal government requirements for timely and complete data. The health outcomes achieved and measured by the data ensured that this health center continued to have their annual grant requests fully funded.

During this same period in China, vaccination was viewed as one important preventive health activity. Recent Chinese immigrants in San Francisco brought this acceptance for vaccination with them. In China, despite high demand, the vaccine supply was often insufficient so many people in remote rural areas simply did not have opportunities for vaccination, creating a significant cohort of older Chinese immigrants without vaccine protection against various diseases. This led to a strong vaccination program in San Francisco's Chinatown to protect both children and adults.

When I taught in China in the mid-1980s, rapid changes to every aspect of life were just beginning, and optimism for change was high despite the unimaginable scale of effort required to develop a very populous poor country with a mostly rural population. In conversations with my students (all college graduates) coming from over half of China's provinces, I learned that many of them were not vaccinated because the vaccine supply had not been sufficient to reach distant rural areas, in many of their provinces. Health workers and doctors worked hard to vaccinate all children, but without vaccines, this was an impossible task. I gathered from these discussions that China's immunization program was highly valued in a population who valued prevention and were compliant with public health goals set by government. Yet even with a well-organized program which included collection of detailed data, the constant lack of sufficient resources (vaccines, supplies, health workers, finances) to provide needed vaccinations for a rapidly growing population would jeopardize attainment of national disease elimination goals. Discussions with my students led me to believe that when a goal was established in a national 5-year plan, there was intense pressure on officials to achieve this goal. To set and achieve a national goal, collecting data to measure the achievement was an approach to problem-solving that the Chinese population understood and is still used effectively today.

It was not until 2006 that I actually was able to work with the Chinese government's Ministry of Health, the China Centers for Disease Control, and the China offices of WHO and UNICEF on China's immunization program. I was then working at the United Nations Foundation (UNF), one of five (World Health Organization, UNICEF, American Red Cross, US Centers for Disease Control,

UNF) founding member organizations of the Measles Initiative, a global effort to eliminate measles worldwide. China's success in eliminating measles is key to the regional and global elimination of measles, and international organizations wanted to support China's efforts in whatever way possible. Measles elimination became a goal in the 2006 National 5-year plan with financial resources allocated to various levels of government to achieve elimination. However, measles is stubborn, and, 3 years past the original target date for the goal, measles still lingers in various provinces.

In 2006 at one of the WHO regional meetings, I was surprised to learn that vaccination data from China was incomplete, or at least the data shared with international agencies at that time was incomplete. I expected to find detailed data from all parts of China analyzed to determine what had been achieved and what still needed to be done to eliminate measles. I assumed the capability for data collection existed and that Chinese followed vaccination requirements for their one child before or by registration for preschool. Coordination of data between clinics and schools was established to ensure all children received vaccinations. The impact of China's many simultaneous and rapid development changes over a short time strained the health system leading to uneven progress among provinces as they developed. The one-child policy and increase in early school registration might logically be expected to increase vaccination rates, while the growing floating migrant population might decrease vaccination rates as the rural population increasingly migrated to township and urban areas without always registering their move. Ensuring accuracy of data became increasingly critical and difficult with these developments. However the measles elimination goal with a target date made accurate and timely data more critical than previously.

When, in 2008, I began to make field visits to Chinese provinces to understand the capacities and specific problems, I found that detailed data was indeed available and coordinated at various levels between health and education ministries, that recent technology being used was more advanced and wider spread than in most developing countries, and that the problems were more focused on the floating migrant population and the sparsely located minority populations in rural areas.

These supervisory visits to provinces were fascinating. In virtually every site we visited over several years, the data available was very detailed, and the analysis noted both strengths and weaknesses. The most common weakness was the surveillance system in timeliness of sample collection and lab capacity. In meetings with various health officials – at provincial, county, and prefecture levels and in hospitals, clinics, and schools – it was possible to better understand each situation but very difficult to be useful in suggesting possible solutions, particularly where both human and funding resources were insufficient to support increased technical activities.

These field visits to provinces, where data was shared and discussed openly in detail, were crucial to a clearer, more detailed understanding of the challenges and constraints facing public health officials at all levels of government in China. These visits also provided the only opportunity international colleagues have to interact directly and informally with Chinese colleagues who must implement solutions,

often without adequate training or exposure to alternative solutions used successfully in other places.

In my previous experiences with young Chinese, I often sensed a lack of confidence in what they think they know because of limited exposure to and interaction with other countries' immunization programs. Simultaneously they have great confidence in their individual ability to achieve solutions if given the opportunity (including resources). International colleagues are most useful when encouraging Chinese colleagues to feel confident in their ability to find solutions to specific problems by regularly sharing experiences among colleagues in different provinces (both what has and has not worked). International colleagues can share experiences from other countries, especially countries with similar issues such as highly mobile populations and diverse ethnic populations. International colleagues can also be useful working with Chinese colleagues to increase various uses and forms of communication, including messages about immunization data, goals, and the value of prevention. I found Chinese colleagues to be strong technically and well ahead of most countries in using the newest technology to manage data at all levels in their immunization program. One of the most useful roles international colleagues can do is bring global attention to and appreciation for the really significant immunization achievements in China. This attention can be used to encourage the Chinese government to increase support for the immunization program as a leader in disease control for vaccine-preventable diseases.

China's historical inexperience with sharing data internationally sometimes made it difficult for international staff to offer useful ideas/approaches except in general terms. In the past 5 years, this has changed considerably, and currently the MoH publicizes measles data by province on monthly basis through MoH website. China now has a well-functioning immunization system valued highly by the Chinese population with mostly accurate and complete data available to analyze and use to improve immunizations. Work to strengthen surveillance is underway to make it more sensitive and timely to verify absence of endemic measles virus in China.

Public health community open and willing to identify and discuss key technical and programmatic issues increase political commitment and provide sufficient financial and human resources. Health officials at all levels of government know the problems and work hard to rapidly solve problems.

I would like to acknowledge the tremendous efforts undertaken by all Chinese people to protect their children from diseases by vaccinating them. The scale of China's national vaccination program is staggering and continuous with each new birth and despite occasional setbacks continues to improve and expand as new vaccines or combinations of existing vaccines become available. China has already eliminated several diseases by protecting their population with vaccination. My admiration for China's public health work continues to grow each time I experience the energy, competence, and dedication of government staff responsible for ensuring the quality and acceptance of China's immunization program. China's public health officials open sharing of data and appreciation for support from the international public health community encourages everyone involved to help achieve immunization goals set by the Chinese government as rapidly as possible.

10.11 Building National Regulatory System to Protect Public Health in China and Opening Pathway for Vaccine Industry to Contribute to WHO Expanded Programme on Immunization

Lahouari Belgharbi

China is one of the main vaccine producers of vaccines with a set of 41 vaccine manufacturers (as of 2013) producing yearly more than one billion of doses of vaccines (as of 2013) and is 100% self-sufficient for its own national immunization program. The production has increased significantly from 700 million and 38 types of vaccines to over 900 million of doses with 55 types of vaccines. The lot release data shows also that the quality of the domestic production had increased as the number of lot rejected failed from 30 in 2009 to 4 in 2013. It is expected that the next vaccines that will be prequalified will be soon an influenza vaccines that will contribute significantly to secure the global vaccine supply in case of epidemic. Moreover other vaccines are also expecting to increase the portfolio of WHO-prequalified vaccines and that can be produced in large volume to satisfy the export market.

Since 1998, the Chinese government has aimed to build up a stronger and modern national regulatory system; this was documented through the different national strategic plans that emphasized the need for the government to strive to meet the highest WHO standards of quality, safety, and efficacy for all health products and technologies. In 2001, WHO has proposed to the Government of China to develop a specific program for strengthening the national regulatory authority (NRA) represented by the Chinese Food Drug Administration (CFDA) and its affiliated institutions in the area of vaccines. Knowing the potential impact of Chinese production on the global supply of vaccines and the decrease of vaccine-producing countries from 63 in 1990 to 44 in 2013, WHO has made special efforts since 2001 to assist the Government of China to strengthen the vaccine regulatory capacity with a long-term objective to prequalify Chinese vaccines and contribute to sustain global vaccine production. Since 2001, WHO conducted regular formal and informal assessment (2001, 2003, 2005, 2007, 2009, and 2011) with development of institutional development plans (IDPs) and several road maps. This has led to an intensive capacity building efforts that successfully helped to bring the NRA to become functional in April 2011 following the assessment of December 2010 and allowed the prequalification of the first Chinese vaccines (JE vaccines) in October 2013. This has now open the pathway for the Chinese vaccine industry to become a major manufacturer of WHO prequalified for traditional EI and new vaccines knowing the important portfolio of domestic vaccines produced. It is expected that about ten new products will be submitted between 2016 and 2020 to be WHO-prequalified vaccines from China (e.g. hep.A, bOPV, seasonal influenza, typhoid Vi conjugate sIPV*, measles, oral cholera vaccine, HPV (1), HPV (2), PCV 13, LAIV).

Prior to this program, some in-country training activities were conducted mainly in the area of good manufacturing practices and quality control laboratory testing. WHO/HQ planned and organized the first NRA assessment in July 2001 for which

a road map and institutional development plan were developed to bring the CFDA to functionality against the WHO-published indicators. CFDA was reorganized twice during the period 2001–2007 that led to several changes in the management and regulation. WHO noted that the regulatory system despite some improvement was still meeting some constraints: several regulatory functions needed much improvement such as system for the governance and transparency part, the lot release and laboratory access functions, the pharmacovigilance, and oversight of clinical trials. Only two functions had improved slightly: regulatory inspections and marketing authorization functions. Finally, late August 2007, the CFDA expressed the desire to be reassessed for meeting the WHO vaccine prequalification and requested WHO to develop a road map to meet these expectations. As a matter of fact, the convergence of Bill and Melinda Gates Foundation investment in regulatory systems and the wish of the Government of China to get prequalified vaccines from China with the availability of the WHO technical leadership in this area did build an opportunity for a long and fruitful collaboration. This also helped to obtain the needed resources from Government of China for making this happen.

The first road map developed with these new supports aimed primarily to bring the Chinese NRA to become functional by the end of 2009, and then a second road map (2010–2014) aimed to get the first prequalified product for JE vaccine; this was done in close collaboration with the JE PATH project in the Chengdu Institute of Biological Products (CDIBP). The road map planned for the WHO NRA assessment to take place in 2009 or early 2010. It included a series of learning and training activities including self-assessment and WHO and CFDA field visits targeting all domestic vaccine manufacturers. Several WHO follow-up visits were organized to monitor the road map (17 visits). A review of the pharmacovigilance and GMP enforcement was done for selected provinces and all eight major vaccines producers (mainly CNBGs institutes) and several private companies producing with potential priorities vaccines produced or to be produced such as influenza or EPI vaccines. The WHO NRA assessment was conducted in December 2010, and an official announcement of the NRA functionality was announced in early March 2011 once the compliance report was considered as fully implemented. The WHO team was composed of regulatory and immunization experts from all WHO regions (the USA, Indonesia, Mexico, Egypt, Portugal, Thailand, WHO WPRO and HQ assessors) (Team leader: Lahouari Belgharbi).

Initially the official agency in charge of medicines regulation, including biologicals, traditional medicines, diagnostics, and medical devices was established in 1998 and named the “State Drug Administration (SDA),” and then in 2005 the name was changed to “Chinese Food Drug Administration (CFDA)” and was moved under the supervision of the MoH (NHFPC). Finally it was renamed the “Chinese Food Drug Administration” (CFDA) since mid-2013. These changes were because the food area was merged again with the drug and cosmetic area, and the institution was removed from the NHFPC (MoH equivalent) supervision to become one institution led by one minister seating at the State Council (Chinese government). The CFDA is supervising 18 affiliated institutions and has a decentralized enforcement power through 32 provinces that have 196 affiliated institutions, while at

sub-provincial level and municipality level, there are 356 administrative institutions and 560 affiliated institutions, and at county level, there are 2594 administrative institutions and 1134 affiliated institutions. The total staffing of all these institutions is 103,597 persons including 61,544 persons assigned to administrative organizations and 42,053 persons in the affiliated institutions. The scope of their work covers pharmacy, medicine, food, medical devices, public health, chemistry, law, economics, management, and related activities. The main affiliated institutions are the National Institutes for Food and Drug Control, Center for Medical Device Standardization Administration, Chinese Pharmacopoeia Commission, Center for Drug Evaluation, CFDA Center for Food and Drug Examination and Inspection, CFDA Center for Drug Reevaluation, CFDA National Center for ADR Monitoring, National Committee on the Assessment of the Protected Traditional Chinese Medicinal Products, CFDA Evaluation Center for Health Food, Center for Medical Device Evaluation, CFDA Center for Complaint and Report, CFDA Service Center, Information Center of CFDA, Chinese Food and Drug Supervision Data Center, CFDA Institute of Executive Development, CFDA Safety Emergency Drill Center, CFDA Center for the Certification of Licensed Pharmacists, China Center for Pharmaceutical International Exchange, CFDA Southern Medicine Economic Research Institute, CFDA 146 Warehouse, Chinese Medicine Information News, Chinese Medical Science, and Technology Press, Chinese Pharmaceutical Association.

The findings clearly indicated that the regulatory system has addressed several constraints and improved gradually and consistently since 2001. More progress and achievements were documented between 2009 and 2014. Moreover all WHO recommendations issued during the last WHO assessment had been implemented and thoroughly followed by one Vice Minister Mr. Zhen Wu who had been critical in the success of the first and the second assessment. WHO also continued to provide an extensive technical and substantial financial support together with BMGF since 2009, and the two road maps that were developed were achieved by meeting all expected objectives. The recent assessment also found that all regulatory functions were implemented, and performance varies between 95% and 100% of indicators met.

Some recommendations were issued to allow the Chinese system to ensure strong sustainability specially in the area of human resources where it was found that there was a need to hire urgently about 1000 staff over a period of 5 years to maintain the current workload and quality as well as to optimize the current product evaluation process by reducing timelines (more than 2–10 years for a product to be registered as more than 5000 products are submitted for registration) and also by exchanging reports (assessment and GMP inspection reports) and decentralizing or reducing redundant steps to speed up reviews. The system is already well computerized and using electronic application for all applications. Additional recommendations were made to continue the expansion of the quality management system (QMS) to all medicine areas and to all provinces to ensure consistency of regulation interpretations and decisions. Additional training is of course required, and stronger coordination was recommended to ensure a smooth decentralization decided by the state council. Serious efforts had been documented to increase the number of GMP inspections, and

all vaccine manufacturers had been certified against the new code of GMP issued in January 2011. It is expected and planned that all medicine manufacturers should comply against the new code of GMO by the end of 2015. The pharmacovigilance had raised its detecting and reporting capacity and its reaction to address major AEFI as it was documented during the last hepatitis B events last December. There is a greater coordination and cooperation, and intensive training and communication efforts were made to cover gradually all provinces, still two provinces seem not reporting well, but the government commits to expand quickly its efforts to these provinces. WHO will help to move on this area. Additionally the oversight of clinical trials had improved, and GCP inspections were conducted as recommended by WHO with revision of the regulations to avoid conflict of interest and comply with the WHO GCP.

Finally, the assessment process was closed on 18 April 2014 with the participation of Minister Mr. Yong Zhang, the two vice ministers (Mr. Zhen Wu and Mr. Jiacai Teng), all director generals (Lin Yuan, Lifeng Wang, Guoqing Li, Wei Zhang, Jiaqi Xu, Xiaoxi Du, Xiashun Hong, Wei Yang), and all key staff members involved in the assessment, including the WHO representative and his team.

This road map was developed following the WHO NRA assessment that was conducted end of 2009; it was aimed to sustain the functionality and to ensure prequalification of the JE vaccines. The main findings indicated that the system continued to improve its performance, and it has secured its eligibility status for vaccine prequalification. Previously the Chinese regulatory system was assessed with the previous version of the indicators revised in December 2007, but another revision took place in October 2011 that endorsed revised indicators that were more stringent with additional critical indicators. This assessment was also testing a new WHO-developed software (initially tested in Mexico in March 2014) that is aimed in the near future to conduct joint assessment (harmonized) for all health product areas or technologies (medicines, blood, traditional medicines, medical devices, and diagnostics).

This road map was the consequence of the WHO NRA assessment. It leased to a joint declaration of intent that was signed between WHO and CFDA on the 3rd of July 2014. In this declaration, it was agreed during the preliminary discussion when preparing the WHO DG's visit to China that in parallel and after the signature of the declaration that WHO and CFDA will continue developing the road map and detailed action plan and an MOU or Technical Cooperation or Collaboration Agreement (both terms being used interchangeably in WHO) would be concluded as soon as feasible for the purpose of defining the respective roles and responsibilities of WHO and CFDA in implementing the road map and action plan. Then the relevant document is expected to be signed by at ADG level in WHO.

The declaration highlighted the "Mutual Intentions for Continued and Expanded Cooperation" such as to:

- Improve the regulatory system and increase appropriate capacity building activities aimed at strengthening China's regulatory capacity for food safety and medical products.

- Promote convergence of Chinese standards with international standards and facilitate elevating the contributing role of China to the development of global norms and standards of interest to WHO.
- Increase awareness about good regulatory practices and share relevant best practices on strategic medical products.
- Foster further collaboration between CFDA and WHO on the management of food safety and the regulation of medical products.

10.12 Experiences in China Eradicating Polio

Mac W. Otten Jr

In the 1970s and 1980s, Brazil and the PAHO countries started the paradigm of using large (often nationwide) mass campaigns with tOPV in children <5 years to eliminate polio in the Americas.

In the early 1990s, WHO, CDC, Rotary, and the global polio community wanted to try to eliminate polio from another part of the world to see if the same strategies of mass campaigns and strong case-based surveillance worked outside of the Americas. WHO's Western Pacific Region (WPRO) was the region that was selected for the "trial." In 1992, three CDC former EIS officers were loaned from CDC to WHO WPRO – to Vietnam (Bernard Morniere), WPRO office (Rudi Tangermann), and China (Mac Otten) – to strengthen the effort with additional person power. Shiguru Omi (future RD of WPRO) was the WHO WPRO EPI chief at the time. I believe that I was the first CDC officer that had ever been assigned to China.

In China, my primary focal point was Bao Ping Yang, who was the MoH EPI chief. Dr. Dai was Bao Ping Yang's boss. Tao Jiang was a young computer specialist with the MoH. Li Bi Zhang was the chief polio laboratory focal point who worked with Olen Kew and Mark Pallansch at CDC. Ke-An Wang was the chief of CAPM (Chinese Academy of Preventive Medicine).

A nationwide outbreak of 10,000 polio cases occurred in China in the 2 years prior to 1991; therefore, China was very motivated to eliminate polio. The first order of business was to establish case-based surveillance with laboratory specimens. To my knowledge, this was the first nationwide case-based surveillance system in China.

Every year starting in 1992, we had an international polio program and surveillance review. Approximately 20 "foreigners" came to the review including approximately 5 persons per year from CDC. We sent them to the 20 lowest-performing counties. For some, it took 2 days to reach the county that was assigned. Many of these counties had not seen a foreigner ever or at least for many years (20–30 years). These counties were the most rural and hard to reach. This method greatly raised the political visibility of those counties which soon had high surveillance (non-polio AFP) rates.

Prior to my arrival, China's relationship to the outside public health world through WHO was very formal. However, I was an "activist" epidemiologist that would produce reams of AFP and laboratory data every week. At first, MoH was

Fig. 10.3 Dr. Otten participating in a polio campaign

hesitant to share data, but trust was built over time. Bao Ping Yang was surprised to come in most mornings and find that were ten pages of analysis by county sitting on the MoH fax machine. This type of detailed technical collaboration had never happened between MoH and WHO before.

We built a computerized map of China's 2400 counties and used it extensively for public health action. It was the first county-level computerized map ever used by a health program in China to my knowledge.

A high-quality nationwide computerized AFP surveillance system was developed within 18 months, in no small part because of Tao Jiang, the MoH computer specialist. We established a decentralized provincial-level Epi-info case-based system alongside the provincial computerized EPI aggregate data system, the provincial computer files being sent to the national level every month.

The last indigenous wild poliovirus was detected within 18 months of starting the polio elimination program after just two nationwide mass campaigns. The key factors were the political will and structures to have two successful national mass campaigns, excellent case-based surveillance system, mapping of non-polio AFP rates and wild polio cases by county, and placing political attention on the low-performing counties. The highly effective nationwide computerized case-based surveillance system with laboratory specimens showed the enormous epidemiological power of that public health paradigm.

Many, many persons at the national, provincial, and other levels can be very proud of the excellent work that they did in quickly eliminating wild poliovirus. It was a privilege to have worked on one of the earliest and largest detailed technical collaborations between China and WHO/CDC that resulted in enormous public health impact (Fig. 10.3).

10.13 A Short History of Measles Elimination in China: Explore Feasibility of and Prepare for Measles Elimination in China

Yoshihiro Takashima

Since launching the Expanded Programme on Immunization in 1974, countries in the WHO's Western Pacific Region made tremendous achievements in controlling infectious diseases using vaccines and immunization programs, which include achievement of the regional polio eradication certified in 2000 and reduction of measles cases and deaths by 90% and 95%, respectively, compared with the pre-vaccine era.

Despite the impressive results produced by the measles immunization programs in the Western Pacific, measles remained the leading cause of vaccine-preventable death among children in the region. There were still an estimated 170,000 cases and 32,000 deaths due to measles in the region in 2002. In addition, it was found that, with only moderate-to-high immunization coverage, there would eventually be a large measles epidemic through the build-up of susceptibles after low measles incidence or interruption of measles transmission for a certain length of time.

Right after the certification of regional polio eradication in 2000, countries in the Western Pacific Region started more actively considering and discussing "measles elimination" as the appropriate option for combating measles so as to further reduce measles morbidity and mortality and prevent such periodic large-scale measles epidemic in the region. Then, in 2003, the WHO's Regional Committee for the Western Pacific decided that measles elimination should be one of the two new pillars with accelerated hepatitis B control to strengthen the EPI in the Western Pacific Region and confirmed that measles elimination should be a regional goal and "establishment of a target date should be made at the earliest opportunity."

How can a target date for measles elimination be established for Western Pacific Region when it encompasses the country with the largest population in the world, namely, China?

This was one of the fundamental questions that member states, WHO, and partner should answer before and even in 2003 when the region started the measles elimination initiative.

Guizhou province, with 39 million population, was one of the poorest provinces with the highest reported measles incidence of 360 per million population and 65% of all measles deaths in China in 2002. To develop a successful model for measles elimination, strengthen routine immunization program through measles elimination activities, and explore feasibility of measles elimination in a province with low level of economic development, weak immunization program, and highest measles mortality and morbidity in China, the Ministry of Health developed and conducted a large-scale demonstration project in Guizhou Province, so-called Guizhou Measles Project, from 2003 to 2009 with the support of the World Health Organization (WHO), UNICEF, US Centers for Disease Control and Prevention (CDC), and Japan International Cooperation Agency (JICA).

I joined the EPI team of WHO China Office in July 2003 and worked there until February 2009 as Medical Officer and focal point for measles elimination,

accelerated hepatitis B control, and immunization safety surveillance. On my first day at work, I was told by the Team Leader of EPI in WHO China Office, Dr. Lisa Lee, that I should act as the WHO focal person for the "Guizhou Measles Project." I was introduced a few days later to Dr. Zuo Shuyan, Medical Officer of China CDC, responsible for measles elimination and Guizhou Measles Project. Since then, I worked with him very closely in Beijing in developing and updating the annual implementation plans of the Guizhou Measles Project and in Guizhou in testing and evaluating strategies and implementation plans for the project.

"Guizhou Measles Project" consisted of four major strategic components: (i) conducting measles supplementary immunization activities (SIA); (ii) developing and improving case-based measles surveillance with laboratory confirmation; (iii) strengthening routine immunization services; and (iv) enforcing school entry immunization requirements at kindergarten and primary school for the purpose of achieving (a) at least 95% immunization coverage in SIA at county level, (b) at least 85% coverage of the 1st and 2nd doses of measles vaccines at county level, (c) measles and polio surveillance meeting national performance standards, (d) sustained reduction in measles incidence to less than five cases per 100,000 populations, (e) near-zero measles deaths, and (f) zero poliomyelitis cases due to wild or circulating vaccine-derived poliovirus.

What we stressed most for the successful conduct of the Guizhou Measles Project was to ensure as high quality of implementation of these strategies as possible. For instance, all the effort was made by village health volunteers and frontline health workers and provincial, national, and international supervisors and monitors in the field before and during implementation of SIA in order to reduce the number of target children who would be missed from SIA.

All frontline health workers and village health volunteers were asked to identify and register all eligible children before SIA through door-to-door visits to all houses in all communities. Schools and teachers were asked to prepare lists of all school-children eligible for SIA. Provincial, national, and international EPI experts aggressively carried out supervision and monitoring of completeness and quality of pre-intervention registration of eligible children before and during SIA. They conducted interviews to parents with eligible children in markets, checked preciseness of their knowledge on the SIA, visited communities from which people without precise knowledge on SIA had come, and checked whether or not the pre-intervention registration of eligible children and social mobilization activities had been properly carried out in these communities and any eligible child had been missed from the pre-intervention registration. They also visited as many schools as possible and reviewed completeness and quality of pre-intervention registration of eligible school-children before and during SIA. These efforts were made to improve the quality of denominator of vaccination coverage.

The practice of working with frontline health workers in the field; watching, listening, and learning from reality; and adjusting the strategies were repeatedly conducted and adopted for implementation of other strategies such as strengthening routine immunization services and enforcing school entry immunization requirements at kindergarten and primary school.

In June 2005, the Technical Advisory Group of the Expanded Programme on Immunization and Poliomyelitis Eradication of Western Pacific Region (TAG) held its 15th meeting in Beijing, concluding that the regional measles elimination by 2012 was feasible. With this, it was recommended the WHO Regional Director for the Western Pacific to propose 2012 as the target date for regional measles elimination at the 56th session of the Regional Committee for the Western Pacific. It was then in September 2005 that the Regional Committee decided that the Western Pacific Region should aim to eliminate measles by 2012.

The China Ministry of Health took actions swiftly and organized a consultation meeting from 18 to 19 October 2005 with China CDC, National EPI Expert Committee, domestic vaccine manufactures and WHO China Office to discuss feasibility of measles elimination in China by 2012. They further invited international EPI experts on 14–18 November 2005 to prepare a draft Framework for National Plan of Measles Elimination in China, 2006–2012, and organized the second consultation meeting on 17 November 2005 to review the draft prepared by the international EPI experts. The Framework for National Plan of Measles Elimination in China, 2006–2012, was finalized and submitted to China Ministry of Health on 09 February 2016. Then, "2006–2012 National Plan of Action for Measles Elimination in China" was developed and officially issued all over the country by the Ministry of Health on 10 November 2006.

Guizhou Measles Project provided the China Ministry of Health, China CDC, and national and international EPI experts with a lot of critical lessons learned and ideas while they worked on the development of the Framework for National Plan of Measles Elimination in China, 2006–2012, and finalization of the "2006–2012 National Plan of Action for Measles Elimination in China."

Toward the end of 2012, the national and regional target year for measles elimination, China has substantially reduced measles incidence. In particular, achievements made by Guizhou Province in measles elimination were remarkable: the annual incidence rate of measles per one million population declined from over 300 before and in 2003 to under 5 in and after 2010. Experiences and lessons learned from Guizhou Measles Project were also shared with other countries in the Western Pacific Region in several annual TAG meetings.

In 2012, the Western Pacific Region marked the historically lowest incidence of measles (5.9 per 1 million population). However, in 2013–2014, the Western Pacific experienced a region-wide measles resurgence (17.7 and 43.8 per 1 million population in 2013 and 2014, respectively). Some countries, including China, experienced resurgence of endemic measles transmission while others, a nationwide measles outbreak following importation after a certain period of low measles transmission. Several countries, including some provinces in China, experienced increased infection and transmission of measles virus among people out of the target of current immunization strategies for measles elimination (i.e., infants aged <8 months, adolescents, and adults).

To make further progress toward the regional measles elimination in the Western Pacific, we should revisit the achievements made in the provinces of China that we have seen from 2003 to 2012.

10.14 Letter to My Successor at WHO China

Lance Rodewald

Congratulations being selected as the WHO China EPI team lead! I am sure that you will find this job incredibly rewarding, as have all the international immunization experts in the past three decades. This job has been an incredible high point of my life – I would not trade my experience working in China for anything. During your time in WHO China, you will have the privilege of working with some of the most impressive and dedicated immunization leaders, scientists, and program professionals you will ever meet – they are the guiding force and public health army in the world's largest immunization program.

Perhaps a good way to introduce the WHO EPI team lead job is to describe the events of 1 year – so in this letter, I'll go over the most recent year – 2016, my fourth year in China. Let's get started.

The year started off with a meeting between our WHO EPI team and the MoH EPI division and China CDC NIP leadership to discuss priority activities for the year. We already knew that 2016 would be eventful because it was the year of the globally synchronized Switch of poliovirus vaccines and introduction of IPV – scheduled for April. However, the work plan for 2016 included workshops on vaccine safety and regulatory strengthening, vaccine prequalification, coverage assessment, and communication strategic planning, and measles/rubella elimination. There was also renewed interest in adding new vaccines to the EPI system, which was great news because vaccines in the program are used much more effectively than nonprogram, private sector vaccines. An exciting year lay ahead.

The polio Switch loomed large. Changing 50 years of polio vaccination policy can't be easy, and for China, the challenges were monumental. Two new polio vaccines had to be developed, tested, and licensed in time to be manufactured, procured, and distributed before the Switch date – a Sabin-strain IPV 25 years in development and a bivalent OPV; the safety monitoring system had to be able to identify emerging safety signals from the new vaccines; AFP and polio environmental surveillance had to be strengthened because polio immunity would change; the coverage monitoring system had to be set to rapidly identify any drops in polio vaccine coverage; communications and educational materials for the new vaccines had to be prepared and tested; over 200,000 clinics of vaccination had to be ready to manage the new polio vaccines, and the EPI doctors had to be able to educate parents about the new polio vaccination policy; and 1 billion RMB (!!) had to be identified to pay for the new, more expensive polio vaccines.

These challenges were monumental enough, but the rigid time line made the Switch into a pressure cooker. The Switch deadline had been agreed upon by the World Health Assembly in 2012 – all 155 OPV-using countries were to make the Switch during the same 2-week period in April 2016. The Switch deadline was not a political deadline – it was a biological and epidemiological deadline, as any country continuing to use tOPV after the Switch could infect other countries by exporting type 2 vaccine poliovirus.

In China, polio is a disease of the highest priority, and taking on risk of outbreaks was anathema. During February, our discussions with the program concerned the safety of the Switch in terms of population immunity and outbreak risk. Would one dose of IPV provide adequate protection against a type 2 virus, should one be unknowingly circulating? This was not an easy question to answer, and to make matters worse, it was becoming increasingly clear that the IPV supply situation in China mirrored the global situation – not enough IPV would be available to provide one dose per child, probably for months to more than a year, leaving some newborns with no type 2 protection.

In March, our discussions were about what might happen if China delayed the Switch for a few months to give enough time to accrue more IPV and bOPV. Asking this question sent shudders up and down all three levels of WHO, since a delay had potential to jeopardize the polio eradication effort. Globally, WHO and SAGE were holding fast to Switch deadline. Delaying the Switch would not be feasible because tOPV was no longer made anywhere in the world. China's immunization program thus faced a Hobson's choice – either switch vaccines in the face of polio vaccine shortages or break with the country's longstanding, steadfast participation in the Global Polio Eradication Initiative.

At this point in late March, it was difficult for me to think of anything worse than the possibility of a delayed polio vaccine Switch in China. But only 5 weeks before the Switch deadline, something worse did happen – the Shandong Vaccine Event. There is never a good time for a high-profile crisis, but this timing was incredibly bad. The Shandong Vaccine Event involved a criminal ring profiting from illegal sales of short-dated private sector vaccines, which were stored in a garage and eventually administered to children in hospitals and clinics. The international and national mainstream and social media were all over this story, but they had the biology wrong, as they stated with conviction and outrage that the implicated vaccines were toxic and poisoning or even killing children. Parents were frightened, confidence in vaccines and immunization plummeted, and vaccine use declined in lockstep with declining confidence.

The Shandong Vaccine Event reached the attention of top levels of government, which required forensic, remedial, and health investigations. China CDC, with other government partners, led a comprehensive and perfectly conducted health investigation of the implicated vaccines, including their stability, safety, potency, and effectiveness. Everyone in China's immunization program became involved in the health investigation, traveling to various provinces, examining records and surveillance systems looking for any health impact from the vaccines. In the meantime, parents continued to be frightened by media and social media reports. The WHO China office worked to get accurate information about vaccines and immunization to the media. Our key messages were (1) that improperly stored vaccines do not become toxic – rather, they may lose potency and become less effective and (2) that WHO is confident that vaccines that are made and used in China start out as safe, pure, and effective, based on our knowledge of vaccine regulatory oversight and safety monitoring. Additional messages included that WHO is confident in the EPI vaccine distribution system, based on evidence from effective vaccine management studies,

and that five of the private sector, non-EPI vaccines (Hib, pneumococcal conjugate, rotavirus, IPV, and influenza vaccines) are recommended by WHO for all national programs and would be more effectively used if they were EPI vaccines rather than private sector vaccines.

MoH, the State Council, and the program were now dealing with two simultaneous vaccine crises: the polio Switch and the Shandong vaccine event. The pressure was intense, since both were important and both were time sensitive.

China CDC's health investigation showed what had been seen in other countries' vaccine storage crises – there was no evidence that anyone was harmed by improperly stored vaccines; there was no evidence of increased VPD risk from ineffective vaccines; and there was no need to revaccinate anyone. The State Council needed to implement remedies to prevent similar occurrences, and this involved updating China's immunization legal framework – which they did in less than 1 month of the initial media reports. The rapidity with which the law was updated was possible because the immunization program had been planning for an update to the law for a few years. Indeed, there had been a publication in the Chinese Journal of Vaccines and Immunization by immunization program leadership in 2014 that outlined a vision to strengthen the program, which included improving the management of the private sector vaccines [10]. The updated law required changes in the distribution of private sector vaccines and adding additional security measures to ensure proper management of all vaccines used in China.

However, for polio, the pressure had only increased with the approaching global deadline. On the last workday before the global deadline, the State Council and the Health Commission approved stopping use of tOPV and procuring bOPV and IPV. This was the first update of the polio vaccination schedule in more than 50 years. What a month!

WHO/HQ wanted all 155 OPV-using countries to verify that they stopped using tOPV, and so China CDC and the WHO China EPI team organized a Switch monitoring site visit to two provinces, with the objectives of looking for appropriate quarantine and destruction of remaining tOPV. Monitors from UNICEF/HQ, WHO/HQ, and WPRO participated in site visits to either Zhejiang or Guangdong provinces. Knowing the precision of China's immunization program and its ability to move in synchrony, I didn't expect that we would see a single dose of tOPV – and we didn't, except for quarantined tOPV readied for appropriate destruction. A pleasant surprise was that the clinics we visited had IPV in stock, which they obtained prior to the Switch by borrowing from the manufacturer, as official procurement hadn't started by that time.

The Switch monitoring team had the opportunity to present our findings to Dr. Jingjin Yu, the Director General of the MoH Bureau of Disease Control – the government's top technical leader over the immunization program. After we gave a glowing report about the success of the Switch in the areas we visited, Dr. Yu wasted not a nanosecond on self-congratulation. His very first question was about the global IPV supply and what WHO and GPEI are doing to minimize risk of importations and outbreaks. The message was very clear – although China stopped using tOPV,

the global stage had not been perfectly prepared for the Switch, and this was no time to relax or let one's guard against polio down.

With the high drama of the Switch in the rearview mirror, the program was left managing an IPV shortage that would exist for more than a year – similar to the global situation. A policy move that was particularly poignant was that MoH moved all private sector IPV to the EPI system, which meant that more children would be able to receive their first dose of polio vaccine as IPV rather than bOPV. This policy move almost certainly spared some children from getting vaccine-associated paralytic polio (VAPP) and showed that the program will do what is needed to protect children. During the summer, I saw another example of government work to stretch the IPV supply. Kunming Institute, the manufacturer of Sabin-IPV, was asked to find a way to increase their IPV production beyond the capacity of their new facility. They decided to refurbish and reopen their facility that made Sabin-IPV for the licensure clinical trials – not an inexpensive decision, but one that will spare several million children from risk of VAPP in 2017.

Polio is one thing; hepatitis B is another. It is difficult to overstate the magnitude of China's accomplishments with reduction of chronic hepatitis B among children. Through a more than 25-year effort of escalating interventions to stop transmission of HBV, the immunization program has enabled the current generation of children to be the first generation in China to be virtually free of hepatitis B – a 97% reduction – and protected for life. This is a gift to children that keeps on giving, because stopping vertical transmission through China's laser-like focus on the timely birth dose means that when today's children grow up and have children, their children will not be at nearly the same risk. I believe that the way that HBV transmission was interrupted in China should serve as a model and inspiration to other countries. China made childbirth safer by moving delivery from homes to birthing centers and hospitals, making childbirth safer and more hygienic, and providing a platform for HBV vaccination. As a result, tetanus was eliminated, and HBV transmission was interrupted.

During the summer, the China CDC and US CDC directors decided to have the two agencies work together on health projects in Africa. Both directors have expertise in hepatitis and know that HBV is a major health problem in Africa. During the summer and rest of the year, a project to support Sierra Leone to introduce the birth dose of hepatitis B vaccine is taking shape. If this project moves forward, the China model of preventing chronic HBV will find its way to a continent where currently only 10 of 45 countries are using the birth dose of hepatitis B vaccine and where neonatal tetanus continues to take a toll.

Too much happened in fall and winter to cover in this letter, so I'll only mention two more activities – strengthening technical policy making to add new vaccines to the program and measles/rubella elimination.

EPI vaccines are expertly guided, managed, and implemented by China's program – expertly enough to not only provide individual protection but to also accomplish public health goals like control, elimination, and eradication. But private sector vaccines don't enjoy the nurturing and guidance by the program – instead, they are often more like commodities that are sold to parents, untethered to national

public health recommendations and goals. In contrast to the uniformly high coverage of EPI vaccines, private sector vaccine coverage is low and varies by provincial and parental wealth. And in the 39-year history of EPI in China, there have been only three occasions when vaccines were moved from the private sector into the program: in 2002 for hepatitis B vaccine; in 2007 for rubella, mumps, hepatitis A, Japanese encephalitis, and meningococcal vaccines; and this year for IPV.

We had been excited to learn at the beginning of the year that there is considerable interest in MoH for adding vaccines to the EPI system through a strong National Immunization Technical Advisory Group (NITAG). This interest led directly to an international workshop on adding new vaccines to immunization programs that was co-hosted by the WHO China office, the Chinese Preventive Medicine Association, and China CDC. We took advantage of a meeting of the International Association of Immunization Managers meeting, which brought leaders from many countries to Beijing to discuss program management.

Immunization leadership from the United Kingdom, Germany, Malaysia, the United States, and China presented their countries' systems for making evidence-based, NITAG-supported decisions to include new vaccines into their programs. Workshop participants included MoH leadership and China NITAG members (Fig. 10.4). The most important thing that we learned is that China CDC is developing a proposal for a strengthened mechanism to add new vaccines to the EPI system. This has tremendous potential to enable China's program to have more vaccines to protect Chinese children from even more vaccine-preventable diseases – another gift from the program that can keep on giving. As a side note, we had the exciting

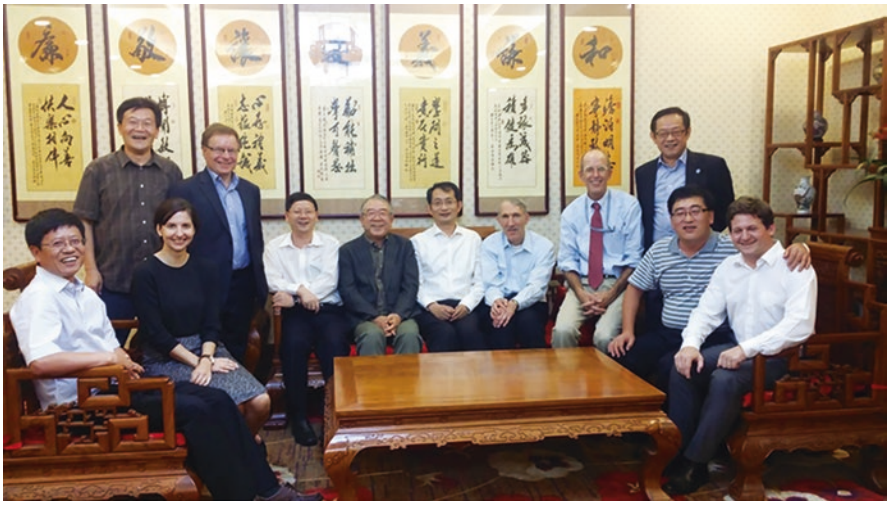

Fig. 10.4 Participants in the 2016 international workshop on adding new vaccines with a strong technical advisory group. From left to right are Drs. Huaqing Wang, Xu Zhu, Laura Davison, Anthony Harnden, Weizhong Yang, Chiba Yasuo, Jingjin Yu, Alan Schnur, Lance Rodewald, Zijian Feng, Aiqiang Xu, and Ole Wichmann

opportunity to visit Canada and Atlanta with China's top EPI leadership in a study tour of the Canadian and US systems for adding vaccines to their programs.

And finally, the year ended with a national and international consultation on measles and rubella elimination in China. For over 10 years, China has had a goal to eliminate measles, and during this time, a huge amount of progress was made, including conducting the world's largest SIA in 2010 when over 100 million children were vaccinated in a 2-week period. China's measles/rubella laboratory network is world class, as is China's measles and rubella surveillance. Coverage with measles and rubella vaccines is very high, and the program has used a two-dose measles vaccination policy for 30 years. Measles incidence is down by over 99.5% compared with the pre-vaccine era. Rubella vaccine has been universally used for less than 10 year, but the incidence of rubella is already quite low in China.

Despite strong program and progress, elimination of measles remains elusive, and there is a feeling of frustration in the program that the elimination effort has not yet succeeded. The questions for the consultation were whether China is on a track that will eliminate measles; if so, when; if not, what additional efforts will be necessary to hasten measles elimination. We brought international experts on measles and rubella elimination and mathematical modelers to help address these questions. It was clear to the international experts that the challenges in China, with such a large and concentrated population, are considerable. The measles and rubella work for 2017 is becoming clear – reinvigorate the measles elimination effort with national- and province-level plans that use all available data to identify and fill gaps in immunity; synergistically integrate rubella into measles elimination work; learn as much as possible from every measles or rubella outbreak; and use research and evaluation to identify program innovations to finish the job of eliminating measles and rubella. The measles/rubella elimination effort is going to take time, and this is going to be a significant part of your work as you assume the job of WHO EPI team lead.

As you can see, I am enthusiastic about China's immunization program. My feeling that China's program is one of the very best in the world – it is simply a national treasure. But in this letter, I've talked about the program as if it is an abstract entity. Of course, that is not the case at all. The program is composed of individuals who you will get to know during your time in the WHO office – and they are the best part of the job. You will get to work with dedicated, smart, and caring scientists, leaders, and professionals who will inspire you, just as they have inspired me and other international experts for more than 30 years. Enjoy!

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