Immunogenicity and Seroconversion of Sabin IPV Schedules in China

1 Introduction and Background

The World Health Assembly approved the Polio Eradication & Endgame Strategic Plan 2013-2018 in 2013 to accelerate interruption of wild poliovirus transmission on the way to becoming polio-free by the end of 2018. Polio eradication has made tremendous progress since then, certifying eradication of type II poliovirus in 2015; WPV3 has not been detected since November 2012, and only 37 wild poliovirus type 1 (WPV1) cases were detected in 2016, the lowest annual count ever. The risk of wild poliovirus transmission is decreasing, and it is anticipated that wild polio virus transmission will be terminated globally in the next few years.

To eliminate all VDPV risk, global eradication of polio requires cessation of OPV in routine and supplementary immunization as soon as possible after eradication of wild poliovirus (WPV). In late-April to early-May 2016, all OPV-using countries switched from trivalent OPV to bivalent OPV to minimize risks associated with type 2 cVDPVs. As a part of global polio eradication endgame immunization strategy, WHO requested all OPV-using countries to introduce at least one dose of IPV into the routine immunization schedule to mitigate potential consequences should any re-emergence of type II poliovirus occur following the planned withdrawal of Sabin type II strains from OPV. The dose of IPV should be administered after 14 weeks of age to decrease interference by maternal antibodies, however an IPV-OPV sequential schedule is acceptable for countries concerned about VAPP.

In China, we stopped all use of trivalent OPV in May 2016 and introduced one dose of IPV into the routine schedule at 2 months, followed by three doses of type I/III bivalent OPV (bOPV) at 3 and 4 months and at 4 years. An IPV-only schedule is available in the private sector (paid for by parents), using a 4-dose schedule recommended by the manufacturer, at 2, 3, 4, and 18 months. However, an IPV supply shortage is a medium- and long-term challenge in China as well as globally.

A Sabin-strain IPV, developed and produced by the Institute of Medical Biology Chinese Academy of Medical Sciences (Kunming Bio institute), was the first domestic IPV developed in China, and was licensed by China FDA in January 2015. This vaccine is also the first standalone Sabin strain IPV licensed in the world. Kunming Bio’s Sabin IPV and an imported standalone Salk IPV produced by sanofi pasteur were in introduced into China’s National Immunization Program at the same time as the tOPV to bOPV switch. However, even with 2 sources of IPV, China remains in a shortage situation. A second domestic Sabin IPV, produced by Beijing Bio-Institute Biological Products Co., Ltd under China National Biotec Group Company Limited (CNBG), was approved by CFDA in August 2017, and will be available in the market in October 2017. Other Sabin IPV products developed by Chinese manufactures are still in the process of clinical trial testing. We anticipate that the IPV shortage will be resolved in 2018, and that the supply capacity will increase quickly in the next few years to meet the IPV demands not only for the one-dose IPV schedule of China, but also for two or more does for all infants in China.
A study comparing the immunogenicity and reactogenicity of a fractional dose of IPV (one fifth of a full dose) administered intradermally with a full dose administered intramuscularly in Cuban infants at the ages of 4 and 8 months, showed that vaccinating infants with two doses of either a fractional or full dose of IPV can induce a satisfactory immune response, and seroconversion reached nearly 100% of immunized infants after a two full-dose schedule. However, there are no direct data on the duration of protection following the receipt of 2 fractional or full IPV doses, although there is no evidence demonstrating waning immunity against polioviruses.

An observational study conducted by China CDC during 2015-2016 showed that among infants vaccinated with one dose of Sabin IPV at 2 months of age, the seroconversion rates against types I, II, and III polio were around 94%, 75% and 46% among seronegative infants before vaccination (no maternal antibody). Conversely, the seroconversion rates against types I, II, and III were around 50%, 27% and 30% among seropositive infants before vaccination (existing maternal antibody). The preliminary findings also showed that seroconversion rates reached higher levels (around 90% and above) by two doses of Sabin IPV at 2 and 3 months. (Data not published yet, see appendix 1)

Considering that risk of polio virus transmission is decreasing over time, and that IPVs, either domestic Sabin-IPV or imported Salk-IPV, are still expensive (6 USD/dose) for a program responsible for immunizing an 18-million annual birth cohort, an efficient two-dose IPV-only schedule would be very advantageous compared with the traditional 4-dose IPV schedule that is recommended by IPV manufactures for 2, 3, 4, and 18 month children. However, there are no seroconversion data available supporting a two-dose schedule at 4 and 8 months using standalone Sabin IPV.

SAGE recommends a poliovirus vaccine seroconversion target of 90% for routine immunization in the post-eradication period. Since one dose of IPV cannot reach the 90% seroconversion target, at least 2 doses of IPV will be needed in all countries’ schedules. There is little or no benefit to exceeding the 90% seroconversion target in the post-eradication period, implying that the minimum schedule that reliably attains 90% seroconversion optimizes value in the post-eradication period. Since at least 2014 and currently, GAPIII requires countries like China that have poliovirus-essential facilities to use a 3-dose schedule. However, it is not clear if the current GAPIII requirements may be changed in the future, as GAP is evolving with new polio-related knowledge. Thus, any study for a post-eradication polio schedule should consider GAPIII, while recognizing that the requirements may change in scope or geography.

Use of reduced IPV schedules has significant public health implications. First, it will save vaccine costs for the national immunization program, and the budget savings might be helpful for other new vaccine introductions. In China, we still have several important vaccines, which are not in the program, including Hib vaccine, pneumococcal conjugate vaccine, varicella, rotavirus, and HPV vaccine. Second, if a two-dose or three-dose IPV schedule is acceptable, we may be able to shift to an IPV-only schedule earlier than if we had to attain the manufacturing capacity for a 4-dose schedule. This would and eliminate risk of VDPVs and VAPP in China as early as possible, even before global polio eradication. Third, a reduced schedule can decrease the number of clinic visits and injections for childhood vaccination and support optimizing the overall national immunization schedule. Thus, it is important and
necessary to determine whether a two-dose or a three-dose Sabin IPV-only schedule is suitable for Chinese infants and China’s immunization program.

Because the Sabin IPV products were developed by different manufacturers, the antigen contents are different between Sabin IPV and Salk IPV, also different among Sabin IPVs. For example, the D-antigen of type I, II and III are 40DU, 8DU, and 32DU respectively in Salk IPV; are 30DU, 32DU and 45DU respectively in Kunming’s Sabin IPV; are 15DU, 45DU and 45DU respectively in the CNBG Sabin IPV; and are 15DU, 45DU, and 45DU respectively in Sinovac’s Sabin IPV.

2 Research Questions and Main Objectives

The overall objective of the research project is to determine the seroconversion rates of two reduced Sabin IPV schedules in Chinese Children.

The specific objectives of the study are to:

1) Determine whether the seroconversion rate is above 90% using a two-dose Sabin IPV alone schedule with the first dose Sabin IPV given at 4 months and the second dose Sabin IPV given ≥4 months after the first dose.

2) Measure neutralizing antibody titers against poliovirus type I, II and III among two-dose Sabin IPV-only schedules, compared with three-dose Sabin IPV alone schedule.

The secondary objectives are to:

1) Evaluate reactogenicity and adverse events between two-dose IPV-alone schedule compared to three-dose IPV alone schedule.

2) Evaluate reactogenicity and adverse events for concurrent administrated IPV with other program vaccines based on China immunization routine schedule, including DTaP, measles-containing vaccine, Japanese encephalitis vaccine, and meningococcal meningitis group A vaccine.

3) Keep the study cohort available for the potential next two follow-ups at 18 months and 4 years of age to evaluate the duration of protection by those ages (although additional funding will be sought for this follow-up).

3 Methodology

3.1 Study design

This will be a multi-center, randomized, open-label, seroconversion/immunogenicity study. Investigators at study sites will be aware of group assignment since different schedule will be used in different arms. Laboratory investigators will be unaware of group assignment. No placebo will be used.

● Study vaccines

We will select one Sabin IPV produced by Kunming Bio institute, which is available for China’s National Immunization Program in the selected study sites. Study vaccines will be provided free of charge for participants.

● Study Arms

Sabin IPVs will be administered in two schedules, making this a 2-arm study. IPV will be co-administrated with other vaccines in the routine schedule.
Arm 1: three-dose schedule, vaccinate at 2, 3, and 4 months.
Arm 2: two-dose schedule, first dose IPV vaccinate at 4 months, and the second dose IPV given between 8 and 11 months of age.

Table 1. Study arms.

| Group | Vaccine          | Age 0m | Age 2m | Age 3m | Age 4m | Age 5m | Age 8m | Age 9m | Age 10m | Age 18m | Age 4yr |
|-------|------------------|--------|--------|--------|--------|--------|--------|--------|---------|---------|--------|
|       | Routine Vaccine  | HBV    | DTaP   | DTaP   | DTaP   | MR     | JE     | Men-A  | MMR     | DTaP   | HAV    |
| A1    | Sabin-IPV A      | B+V    | V      | V      | B      |        |        |        |         |        |        |
| A2    | Sabin-IPV A      | B+V    | V, 1m  | B      |        |        |        |        |         |        |        |

Note: B= blood collection; V=IPV vaccination; HBV=hepatitis B vaccine; DTaP=diphtheria, tetanus, acellular pertussis combined vaccine; MR=measles and rubella combined vaccine; JE=Japanese encephalitis vaccine; MMR=measles, mumps, and rubella combined vaccine; HAV=hepatitis A vaccine; Men-A=meningococcal meningitis group A vaccine.

- Blood specimen collection
  In group A1, we will collect blood specimens twice - right before the first dose of IPV, and one month after the 3rd dose of IPV.
  In group A2, we will also collect blood specimens twice - right before the first dose of IPV, and one month after the 2nd dose of IPV.

3.2 Data collection techniques
- Sample size estimation
  We calculated the sample size by setting 90% seroconversion as the minimum required for the program, and assumed a 95% seroconversion rate against all three types of poliovirus in both groups. We use a power of 0.80, and significance level of 0.05 (alpha, two-side), estimating that no more than 15% of subjects may become lost to follow-up. Therefore, in each arm, we will need 281 subjects, for a total of 562 infants in the study.

Study site and target population
We plan to conduct this study in all townships of one or two counties in China. The target population will be all infants reaching 2 months of age, living in the selected county, having the potential for follow-up at 18 months and 4 years.
All participants at each site will be assigned at random into one of two study arms – the 2-dose schedule arm or the 3-dose schedule arm.

- Study duration
  The study, as supported by this proposal, will continue for 2 years from the first enrollment; allowing 6 months to enroll participants at 2 months of age and following subjects for the next
10 months, until the last specimens are collected. The next 4 months will be for laboratory testing, and the final 4 months will be for data analysis and writing a technical report of the study results.

The study cohort will be followed up at 18 months of age and 4 years of age to monitor persistence of antibodies. Additional funding will be sought for the follow-up blood specimen collection and laboratory work.

- **Inclusion and exclusion criteria**
  Eligible study subjects will be healthy 2-month old infants at enrollment.

  **Inclusion Criteria:**
  1) Parent or legal guardian agree to participate in our study.
  2) The family is living locally with legal residency status.

  **Exclusion Criteria**
  1) Parent or legal guardian does not agree to participate in our study.
  2) The potential subject has received IPV or OPV before 4 months of age in group A2.
  3) The potential subject has one or more contraindications to IPV (although we will note the contraindications).

3.3 Laboratory methods
Titer of 1:8 dilution is considered positive for neutralizing antibody against Sabin poliovirus type I, II and III.
Seroconversion is defined as either from seronegative of the 1st specimen to sero-positive of the 2nd specimen, or seropositive of 1st specimen but ≥4 fold increasing for the 2nd specimen. If the baseline antibody level is positive at 2 months of age before the 1st polio vaccination, we will use an adjusted titer for calculating seroconversion, considering the biological half-life per month of maternal antibodies.

3.4 Data analysis and Interpretation
Statistical analyses will be performed with the use of the SAS statistical package. Comparisons of proportions of infants that seroconvert in the study groups will use chi-square tests (with the Yates-corrected test, or with Fisher’s exact test if the number of data in a cell is 5 or fewer). Differences in the distribution of antibody titers will be tested with the Kolmogorov–Smirnov nonparametric method.

3.5 Monitoring and Evaluation
1) **Monitoring and Evaluation of field work**
   **Training:** We will conduct a unified technical training for all staff involved in the study prior to the study start.
   **Supervision:** During the study, we will send supervisors at least monthly to determine whether the vaccination units strictly implement research plan and find important questions and common problems timely feedback to higher level feedback management, to share the related information and solve problems in time.
Vaccination: Vaccination practices will follow national guidelines for the immunization program. We will record the vaccination unit, and the type, quantity and lot number of the vaccine used in this study. After each vaccination, the infants will be monitored for 30 minutes for immediate adverse events. We will design AEFI recording cards and following up tables to facilitate parents and visitors recording of adverse events. AEFI monitoring will be active, with parents of subjects being asked to complete an AEFI card at 1 week and 1 month after each vaccination.

Blood collection and handling: The collection of blood samples will be carried out by trained and experienced professionals. Blood samples will be kept in a safe laboratory in locked and temperature-controlled and monitored storage conditions. Serum sample handling will be minimized to avoid repeated freezing and thawing.

Vaccines used in this study will be distributed and managed in accordance with the requirements of national immunization guidelines.

2) Data Management and Quality Assurance

Quality control measures: To ensure the quality of data, we will ask China CDC professional statisticians to help design and pre-test the questionnaire.

Laboratory: All laboratory testing will be conducted by the National Institute of Food and Drug Control (NIFDC), which is under the China Food and Drug Administration. NIFDC has done the laboratory work for the licensure clinical trials for all Sabin IPV products in China. They developed the national standard to measure the D-antigen of Sabin IPV.

Data entry and cleaning: To ensure accuracy of data entry, all original data will double-entered by provincial CDC staff. After verification, the database will be submitted to China CDC. Cleaning and compilation of the data will be carried out by China CDC’s professional analysts.

Data Completeness: To ensure the completeness of data, we will send quality controllers at the start of the study to monitor questionnaire completion and blood sample collection.

3.6 Ethical review

We will obtain approval from China CDC’s Ethical Review Committee for this study.

3.7 Study Limitations

It is possible that some subjects will be exposed to OPV during the study. We will minimize exposure by using only IPV products in the selected counties that are included in the study.

We do not include a Salk IPV arm because data on 2-dose Salk IPV schedules are available globally. A non-inferior comparison between vaccines would require a larger sample size. Increasing the sample size or adding a Salk IPV arm will significant increase the budget cost but will add little benefit for achievement of our primary objectives.

We did not include the follow-up period into this proposal to evaluate the duration of persistence of antibody because follow up at 18 months of age and 4 years of age will exceed the 2 years duration of grant supported study and will significantly
increase the budget. However, we believe that the follow up period is important and should be part of the overall study. We will keep the study cohort available for follow-up in the meantime and will seek resources for the follow-up.

4 Expected Outcomes and Benefit to the GPEI

We understand that there are no data on the seroconversion rates of two-dose Sabin IPV schedules; this study will provide seroconversion and immunogenicity data for 2- and 3-dose Sabin IPV schedules. The data from this study will be made available to China’s National Immunization Technical Advisory Committee for consideration of the polio vaccination schedule.

GPEI will benefit from this study to help resolve the global shortage of IPV in 2 ways - a reduced IPV schedule in China will make more IPV available for other countries, and the clinical trial of the 2-dose schedule can help with prequalification of China-manufactured Sabin IPV for use in other countries. Depending on the evolution of GAPIII requirements for polio vaccination schedules in the final poliovirus containment period (into the post-eradication period) of countries with polio-essential facilities, both the 2-dose and the 3-dose IPV schedules will be relevant for China and for prequalification for export of Sabin IPV to the UNICEF/Gavi markets.

5 Timeframe

The study will continue for 2 years, which includes field work for study participant enrollment, blood collection, IPV administration, laboratory testing, data analysis and writing the final report. The timeframe is shown in the following Gantt chart.