Sabin IPV Development

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Outline

- Background
- Process and quality controls
- Phases I, II and III clinical trials
- Production licensure
- Future consideration
50多年来我所累计提供了60多亿人份的OPV，对我国消灭脊灰作出了重要贡献

最高发病年份
1964年发病
4.3万多例

4例输入

21例，2011
Global Poliomyelitis (30 Sept. 2015)

Wild Poliovirus & cVDPV Cases\(^1\), Previous 12 Months\(^2,3\)

![Map showing distribution of wild poliovirus and cVDPV cases](image)

<table>
<thead>
<tr>
<th>Country</th>
<th>Wild poliovirus</th>
<th>cVDPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset of most recent case</td>
<td>Total WPV (All types)</td>
</tr>
<tr>
<td>Guinea</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Nigeria</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Madagascar</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>AFR</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Pakistan</td>
<td>22-Aug-15</td>
<td>120</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>06-Sep-15</td>
<td>24</td>
</tr>
<tr>
<td>EMR</td>
<td>06-Sep-15</td>
<td>144</td>
</tr>
<tr>
<td>Ukraine</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>EUR</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Global</td>
<td>06-Sep-15</td>
<td>144</td>
</tr>
</tbody>
</table>

\(^1\) Excludes viruses detected from environmental surveillance.
\(^2\) Onset of paralysis 30 September 2014 – 29 September 2015
\(^3\) Includes 1 case with onset of paralysis in Guinea but reported in Mali. Official reassignment to Guinea pending.

* cVDPV1 in Madagascar & Ukraine, cVDPV2 in all other countries. NA: most recent case had onset of paralysis prior to rolling 12 months.

Data in WHO HQ as of 29 Sept 2015
## Global Poliomyelitis in 2015 (30 Sept. 2015)

<table>
<thead>
<tr>
<th>Countries</th>
<th>Year-to-date 2015</th>
<th>Year-to-date 2014</th>
<th>Total in 2014</th>
<th>Onset of paralysis of most recent case</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WPV1</td>
<td>cVDPV</td>
<td>WPV1</td>
<td>cVDPV</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>12</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Pakistan</td>
<td>32</td>
<td>0</td>
<td>173</td>
<td>19</td>
</tr>
<tr>
<td>Nigeria</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Somalia</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>
Circulating Vaccine-Derived Poliovirus Outbreaks (cVDPVs), 2000-2015

Type 1 (91 cases)
Type 2 (679 cases)
Type 3 (12 cases)
Global eradication of wild poliovirus type 2 declared Sep. 20, 2015

The Global Commission for the Certification of Poliomyelitis Eradication (GCC) has concluded that wild poliovirus type 2 (WPV2) has been eradicated worldwide. With WPV type 3 not being seen anywhere in the world for nearly three years, the programme is seeing exciting strides towards ending polio for good.

Declaration

We, the members of the Global Commission for the Certification of Poliomyelitis Eradication, conclude today, 20th September 2015, that indigenous wild poliovirus type 2 has been eradicated worldwide.

Anthony Adams, Chair
Supasit Chumsuntivat
Rose Gama F. Leke
Arlene King
Yagob Al Mazrou
David M. Salisbury

Bali, Indonesia
Big Eradication progress

This announcement marks a major landmark.

1) WPV1, WPV2 and WPV3. WPV2 has been disappeared from 1999.

2) WPV3 has not been detected globally since November 2012 (in Nigeria);

3) the only remaining endemic WPV1 strains are now restricted to Pakistan and Afghanistan.

The WPV2 eradication is also a significant step in preparation for the phased removal of oral polio vaccines (OPVs), beginning with the removal of type 2 oral polio vaccine requiring a switch from using trivalent, planned for April 2016 \( (\text{tOPV} \rightarrow \text{bOPV}) \).
To prepare for the switch in April 2016, require introducing inactivated polio vaccine (IPV, including type I, II, III antigen) in all routine immunization programmes to maintain immunity levels to type 2 polio.
Biosafety requirement is more stringent

At the final stage of eradication of poliomyelitis, the requirement for biosafety is more stringent. **GAP III** WHO global action plan to minimize poliovirus facility-associated risk in the post-eradication/post-OPV era has been drafted.
Resolution WHA 61.1: WHO calls for expressions of interest in developing Sabin-IPV.

- Sabin polioviruses pose less of a threat in the event of an intentional or unintentional release from the production facility. This is a particular concern in low-income countries where the transmissibility of polioviruses is high.
Developing Sabin IPV by Institute of Medical Biology in China
Overeview of Sabin IPV development in IMB

- Started in 1983 by Dr. Shude Jiang
- Used microcarrier technology since 1994
- Got approval for clinical trials (phase I & II) in 2007
- Started phase I clinical trial in Aug. 2008
- Finished phase II clinical trial in Aug. 2010
- Finished phase III clinical trial in March, 2013
- Go into market in July 1, 2015
Flow chart of production of Sabin IPV

Vero MWCB
37°C 7 days

1st passage Vero cell culture in 3 L scale
37°C 7 days, Trypsinisation

2nd passage Vero cell culture in 50 L scale
37°C 7 days, Trypsinisation

3rd passage Vero cell culture in 550 L scale
virus inoculation

Virus culture
33°C 2-4 days
Bioreactor 550L
Virus harvest

Clarification

Concentration

Gelfiltration and Ion-exchange

Inactivation

Trivalent bulk

Final Lot

Down-stream processing and purification
Prurification by Chromatography

Sepharose CL6B

DEAE-Sepharose FF
Purified Poliovirus D Antigen

Virus particle

HPLC
Inactivation by Formalin

-- Poliovirus type-1 Sabin strain
--- Poliovirus type-2 Sabin strain
- Poliovirus type-3 Pfizer strain

Log TCID50/ml vs Inactivating Time
Sandwich ELISA for our sIPV D antigen detection

Capture Ab: Calf-anti-D Ag IgG
Detective Ab: Rabbit-anti-D Ag IgG
Enzyme labelled Ab: Anti-rabbit IgG

TMB
HRP
Antisera production

Virus Working Seed
(Type 1 and Type 2 Sabin Seed S0+2, Type 3 Pfizer Seed RSO2)

Inoculated into Vero cells

Virus harvest, concentration and purification

Centrifugation by density gradient

Separate pure density viral particle antigen (D antigen)

Immune calf

3 types of high \( N \) ab titer
Calf-anti-D Ag polyclonal antiserum

Affinity chromatography

Calf-anti-Sabin I D Ag IgG
Calf-anti-Sabin II D Ag IgG
Calf-anti-Pizer III D Ag IgG

Immune rabbit

3 types of high \( N \) ab titer
Rabbit-anti-D Ag polyclonal antiserum

Affinity chromatography

Rabbit-anti-Sabin I D Ag IgG
Rabbit-anti-Sabin II D Ag IgG
Rabbit-anti-Pizer III D Ag IgG
Pure Density viral particle antigen (D antigen) by density gradient centrifugation

Upper zone: Capsid viral particle antigen (C Antigen)

Electron microscope

Lower zone: Density viral particle antigen (D Antigen)

SDS-PAGE

Line 1: type I upper zone; Line 2: type I lower zone;
Line 3: type II upper zone; Line 4: type II lower zone;
Line 5: type III upper zone; Line 6: type III lower zone;
Line 7: Protein marker.
These pictures showed individual result from 3 experiments.

Repeatability and clear dose-response relationship between D antigen concentration and OD value can be seen in these pictures.
The potency of sIPV in vivo assay

Test vaccine groups: sIPV Final bulk
1:1 1:3 1:9 1:27

10 rats per groups
Intramuscular injection into the hind limbs, 0.5ml/rat

Reference vaccine groups
1:1 1:3 1:9 1:27

10 rats per groups
Foster in Clean Animal Facility for 21 days

Clean Wistar rats
About 250g
The weight of individual rats varied ≤20% of group mean

Bleed and separate serum. Neutralizing antibody titres in the serum to all three poliovirus types were tested by using Hep-2 cells.
The ED50 of the vaccine should not be less than that of the reference.
Formulation Selection of Sabin IPV by rat immunogenicity in vivo assay

In vivo assay results

Formulation 1: 40 32 60 DU
Formulation 2: 20 16 30 DU
Formulation 3: 10 8 15 DU

We choose formulation as sIPV: 30, 32, 45 DU for Type I, II, and III
Brief summary of phases I, II and III
Protocol of clinical trial phase 1

Preparation and quality control of High middle and low doses of trivalent Sabin IPV

After getting qualified report issued by NIDBC and clinical trial protocol approved by Ethic committee

Phase 1: 130 persons

Infants 90, test group 45 each
15 for low, middle and high doses 3 times
immunization at 2, 3, and 4 months
Control group 45

Children 20 each 10
for middle and high doses sequentially

Adult 20 each 10 for middle and high doses sequentially

Safety evaluation and antibody detection in infant groups

Antibody detection before and after immunization

Determination of serum normal values and function of liver and kidney

Placebo control
The rate of adverse events in phase I (%)
## Primary Immunogenicity of Sabin IPV in Phase II

<table>
<thead>
<tr>
<th>Group</th>
<th>No of infants</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GMT</td>
<td>Seroconversion (%)</td>
<td>GMT</td>
</tr>
<tr>
<td>sIPV-H</td>
<td>85</td>
<td>6335</td>
<td>100.00</td>
<td>339</td>
</tr>
<tr>
<td>sIPV-M</td>
<td>92</td>
<td>2981</td>
<td>97.83</td>
<td>155</td>
</tr>
<tr>
<td>sIPV-L</td>
<td>89</td>
<td>1789</td>
<td>96.63</td>
<td>101</td>
</tr>
<tr>
<td>OPV</td>
<td>92</td>
<td>3315</td>
<td>100.00</td>
<td>410</td>
</tr>
<tr>
<td>cIPV</td>
<td>91</td>
<td>386</td>
<td>90.11</td>
<td>192</td>
</tr>
</tbody>
</table>
Phase III Clinical Trials

**Trial Plan:** Random, Blind, Positive control

**Number:** 1200 infants in 2 months old

**Group:**
- sIPV 600 infants 581 at end
- wIPV 600 infants 573 at end

**Blood:**
- Before immunization
- 1 month after third dose

**Lab. Test:** Neutrilizing antibody by NIFDC of China
Cross Neutralization

Understand why selected the formulation:

30, 32, 45 DU
Conclusion of clinical trial

The formulation of sIPV with 30/32/45 DU per dose for type I/II/III showed good safety and immunogenicity in clinical trials, which was not inferior to Salk IPV.
GMP Production and new drug certification
Production and Quality Control in the production scale
The First Inoculation of Sabin IPV in the World
Future Consideration

1. Production capacity
2. Reducing DAg content by intradermal delivery
3. DTaP-sIPV or DTaP-sIPV-Hib
1. Capability of production in first phase

- **Present Scale:** 10–12 millions doses each year

- **Second phase:** phase: 60 millions doses each year and do WHO PQ.
2. Reducing DAg content

The DAg needed for types 2 and 3 are more than that for wIPV, therefore need to improve production process to increase yield

Study reducing DAg content per dose through different ways:

1) Reducing volume per dose (intradermal delivery);
2) Using adjuvant;
3) Reducing number of doses.
Advances in ID of Sabin IPV
(Bill-Mellinda Gates Foundation OPP1049425)
Three Needle free injector

Bioject Zetajet
PharmaJet Tropis
MIT Med-Jet H4
MIT Device training
May 26, 2013
Biojet

Choosing the appropriate injection site.

Training our colleagues to inject the pig.
Pharmajet
Reducing DAg content by intradermal delivery
(Protection rate after 3rd dose in rats)

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle ID sIPV 1/3</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Needle ID cIPV 1/3</td>
<td>70%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Needle ID sIPV 1/5</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Needle ID cIPV 1/5</td>
<td>65%</td>
<td>100%</td>
<td>90%</td>
</tr>
<tr>
<td>Needle free Injex sIPV 1/5</td>
<td>100%</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Needle free Injex sIPV 1/3</td>
<td>103%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Needle IM sIPV whole dosage</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Needle IM cIPV whole dosage</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(IM NS) control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
Summary

- Established production process and quality controls.
- Phases I, II and III clinical trials indicated good safety and immunogenecity.
- Got the certifications of GMP, production and new drug and success into market.
Acknowledgements

Guangxi CDC in China
National Institute for Food and Drug Control
WHO
Bill-Melinda Gates Foundation
USA CDC
NIBSC
RIVM

Thanks