Sabin IPV Development

Institute of Medical Biology,
Chinese Academy of Medical Sciences

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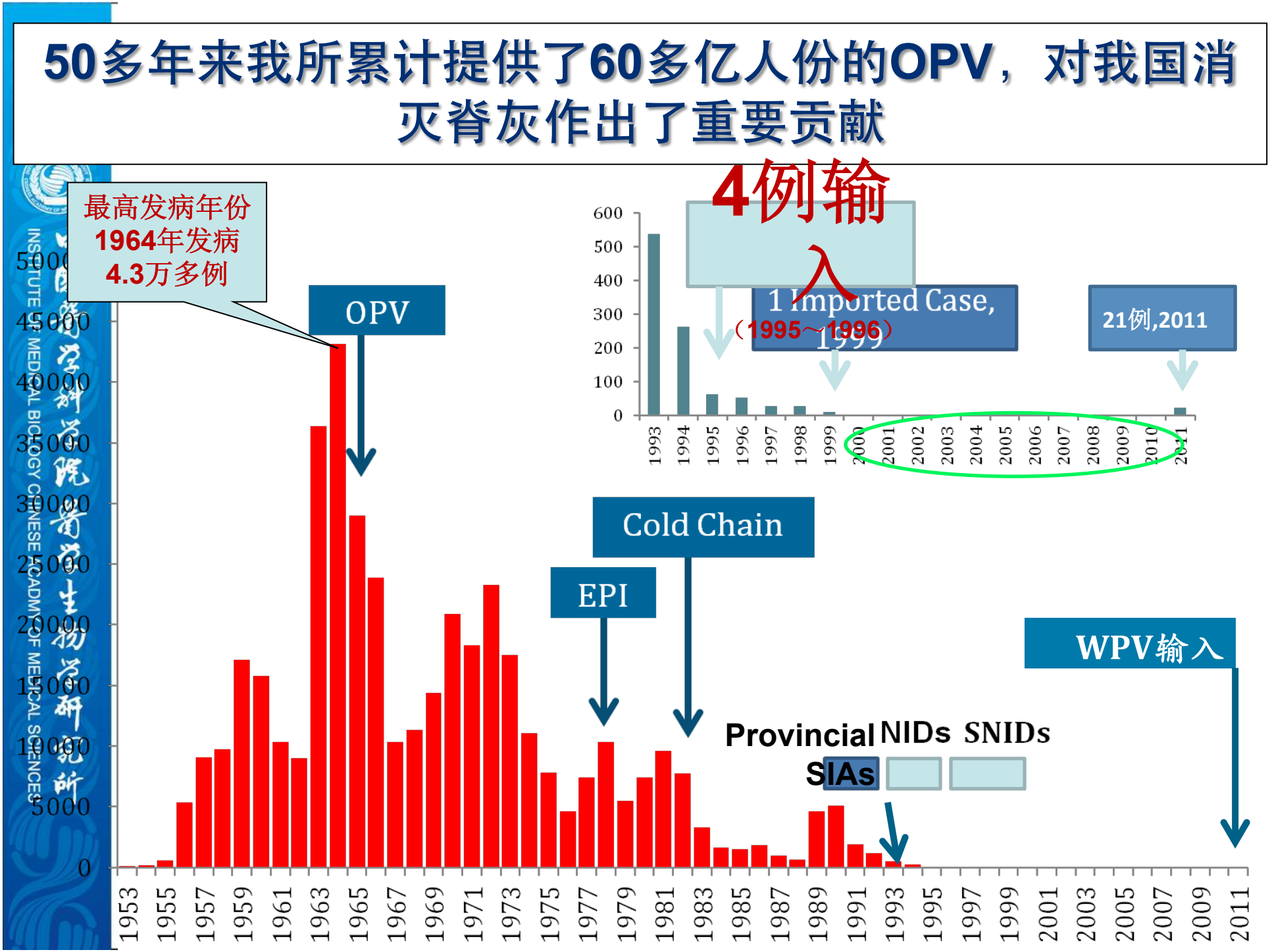
Oct.6, 2015

Outline

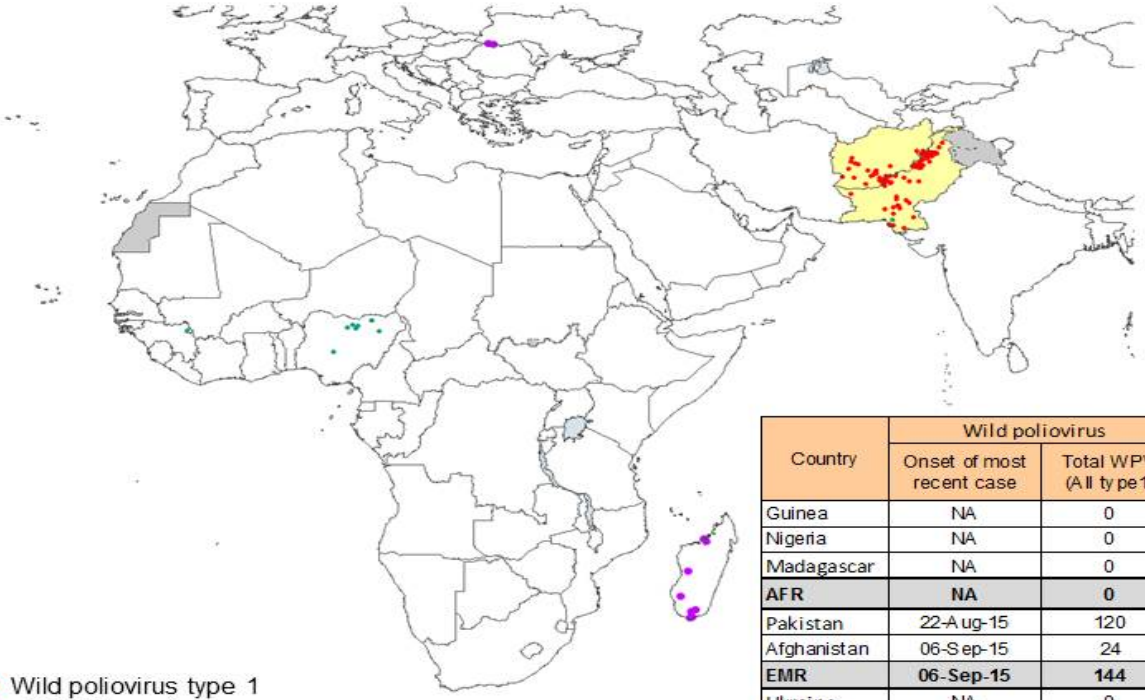
- Background
- Process and quality controls
- Phases Ⅰ, Ⅱ and Ⅲ clinical trials
- Production licensure
- Future consideration

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



Global Poliomyelitis (30 Sept. 2015)

Wild Poliovirus & cVDPV Cases[1], Previous 12 Months[2,3]



Country	Wild poliovirus		cVDPV	
	Onset of most recent case	Total WPV (All type1)	Onset of most recent case	Total cVDPV*
Guinea	NA	0	20-Jul-15	1
Nigeria	NA	0	16-May-15	8
Madagascar	NA	0	22-Aug-15	10
AFR	**NA**	**0**	**22-Aug-15**	**19**
Pakistan	22-Aug-15	120	13-Dec-14	1
Afghanistan	06-Sep-15	24	NA	0
EMR	**06-Sep-15**	**144**	**13-Dec-14**	**1**
Ukraine	NA	0	07-Jul-15	2
EUR	**NA**	**0**	**07-Jul-15**	**2**
Global	**06-Sep-15**	**144**	**22-Aug-15**	**22**

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

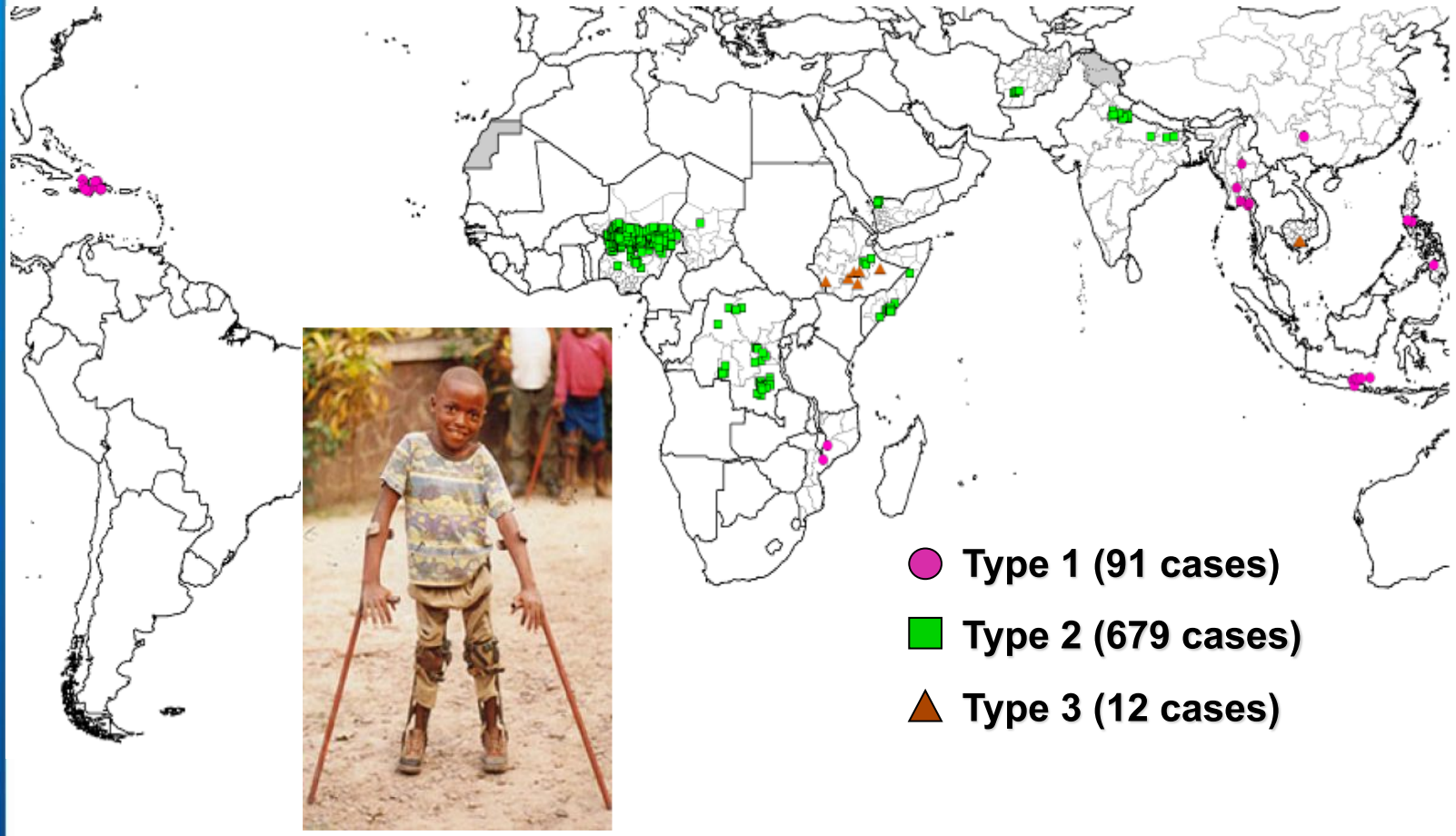
[1]Excludes viruses detected from environmental surveillance.
[2]Onset of paralysis 30 September 2014 – 29 September 2015
[3]Includes 1 case with onset of paralysis in Guinea but reported in Mali. Official reassignment to Guinea pending.

Data in WHO HQ as of 29 Sept 2015

Global Poliomyelitis in 2015(30 Sept. 2015)

Countries	Year-to-date 2015		Year-to-date 2014		Total in 2014		Onset of paralysis of most recent case	
	WPV1	cVDPV	WPV1	cVDPV	WPV1	cVDPV	WPV1	
Afghanistan	12	0	10	0	28	6	22-ASep-15	
Pakistan	32	0	173	19	306	22	22-AUG-15	
Nigeria	0	1	6	17	6	30	24-Jul-14	
Somalia	0	0	5	0	5	0	11-Aug-14	

Circulating Vaccine-Derived Poliovirus Outbreaks (cVDPVs), 2000-2015



Global eradication of wild poliovirus type 2 declared Sep. 20, 2015

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
Supamit Chunsuttiwat
Rose Gana F. Leke
Arlene King
Yagob Al Mazrou
David M. Salisbury

Bali, Indonesia

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.

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 (tOPV→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.

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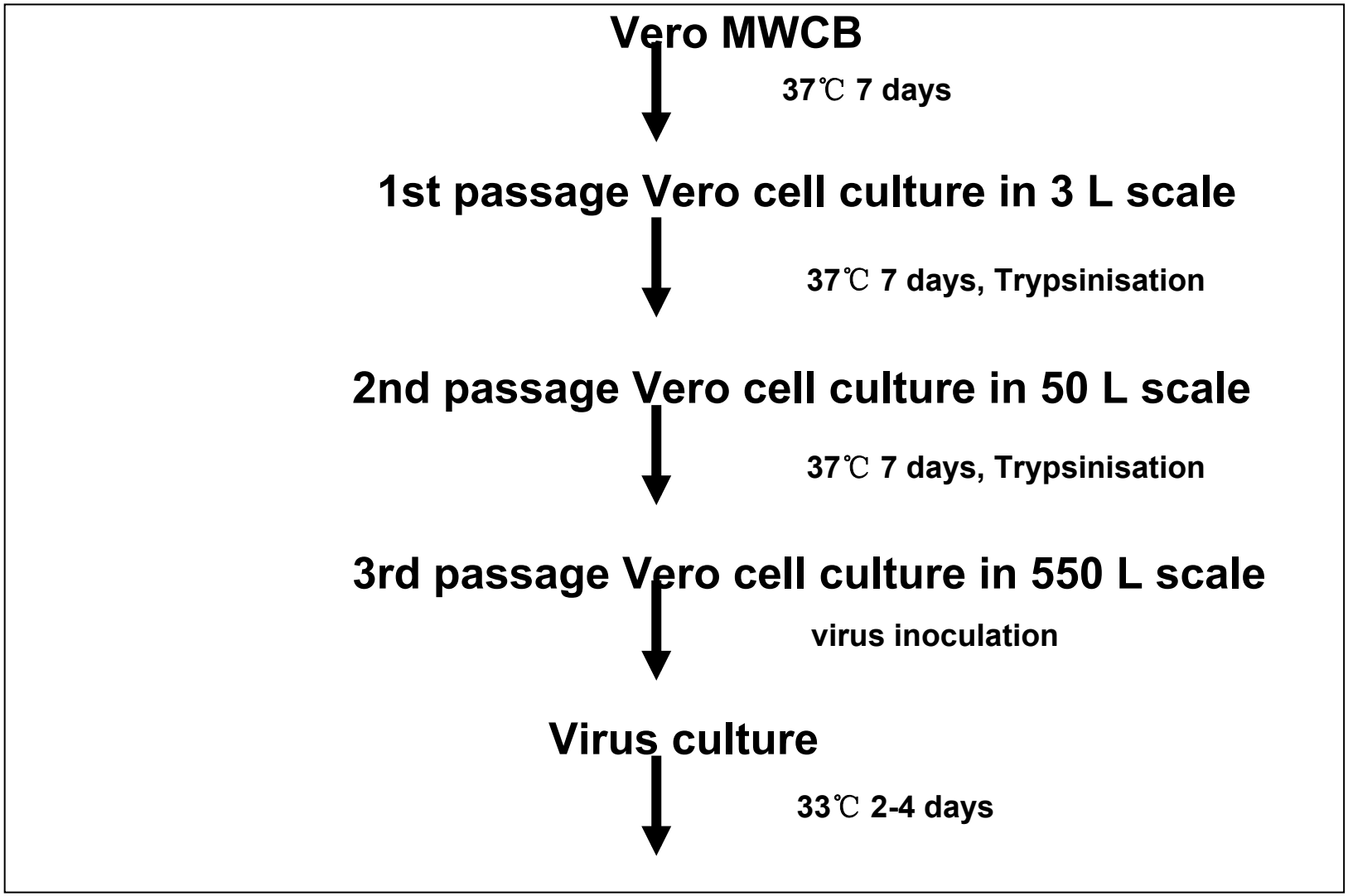
Developing Sabin IPV by Institute of Medical Biology in China

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
- Got new drug certification in Jan. 14, 2015
- Go into market in July 1, 21015

Flow chart of production of Sabin IPV



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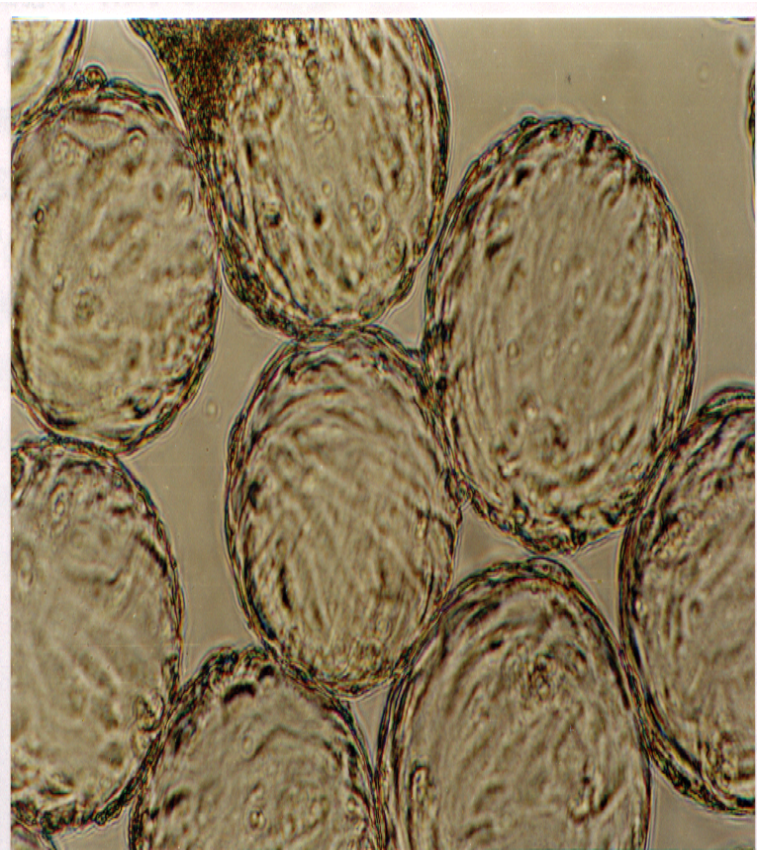
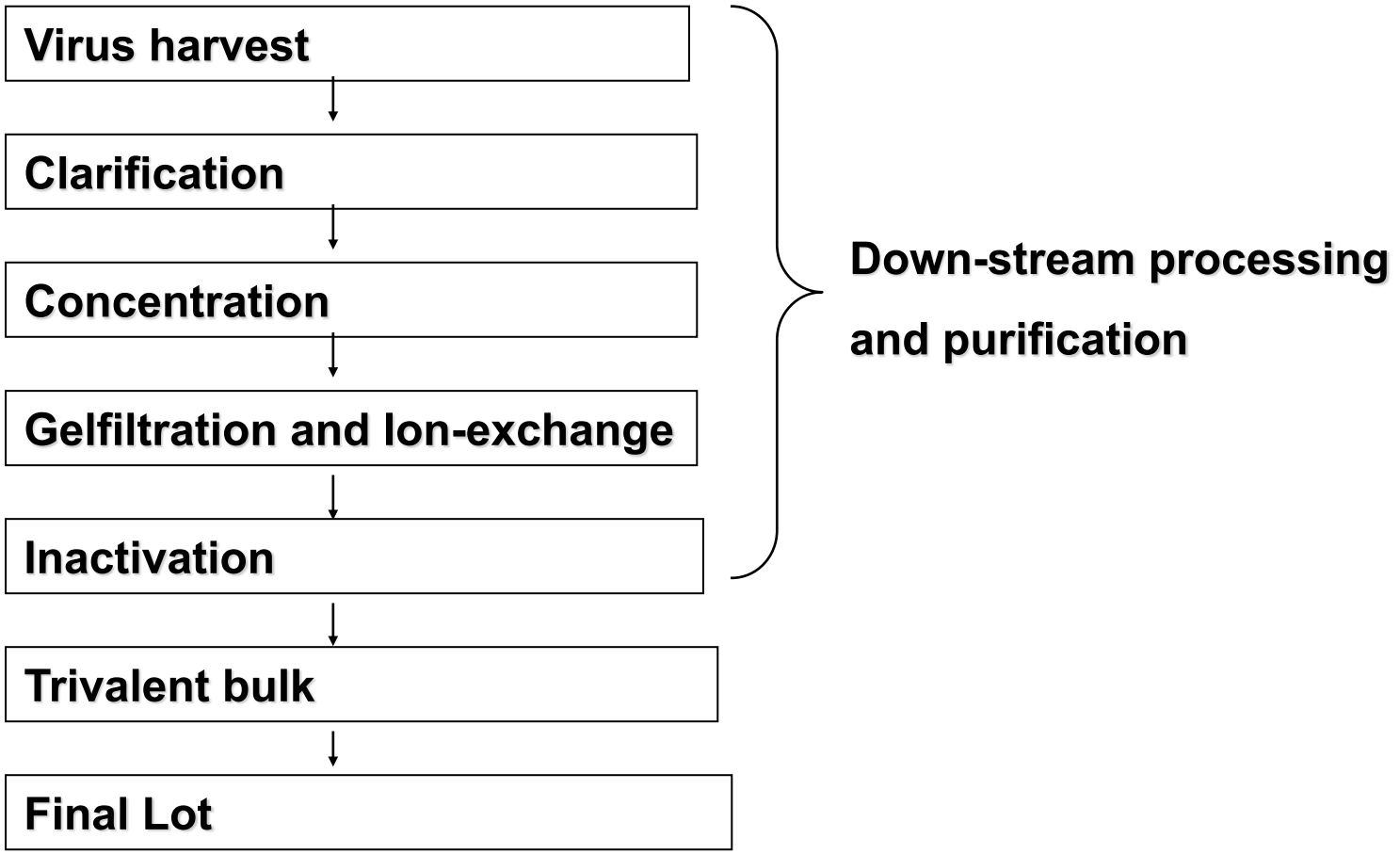
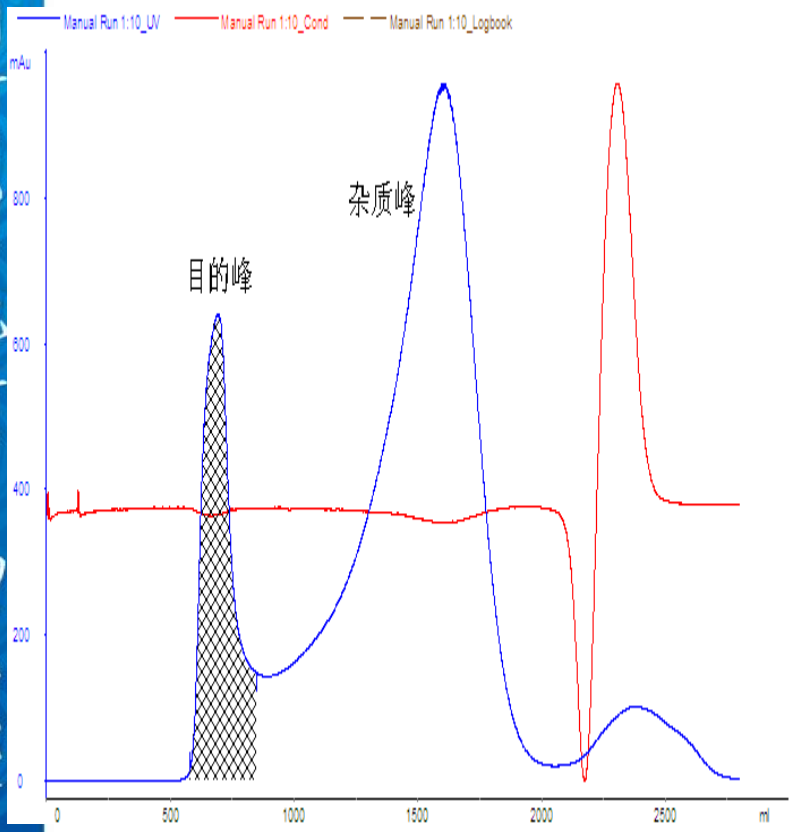
中国医学科学院医学生物学研究所

Bioreactor 550L

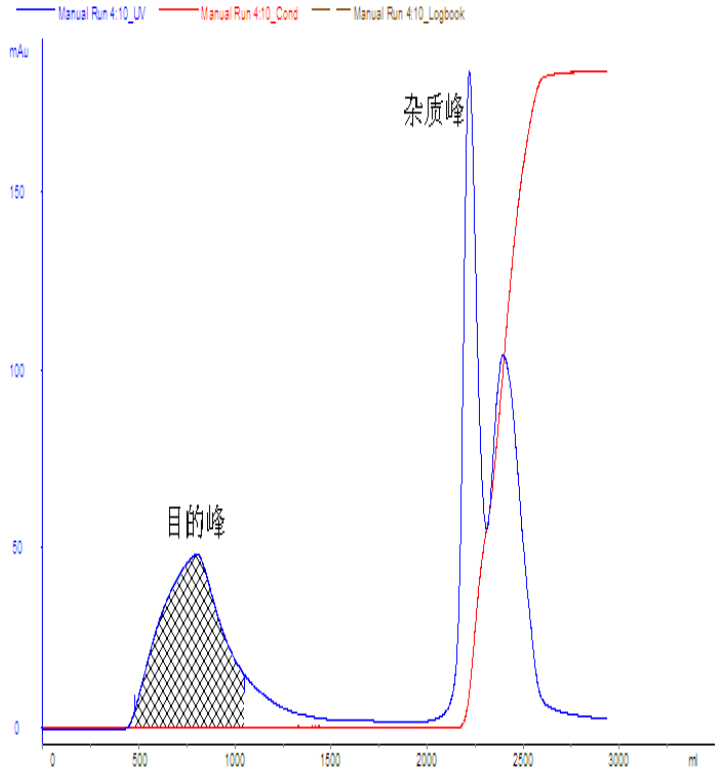




Prurification by Chromatography

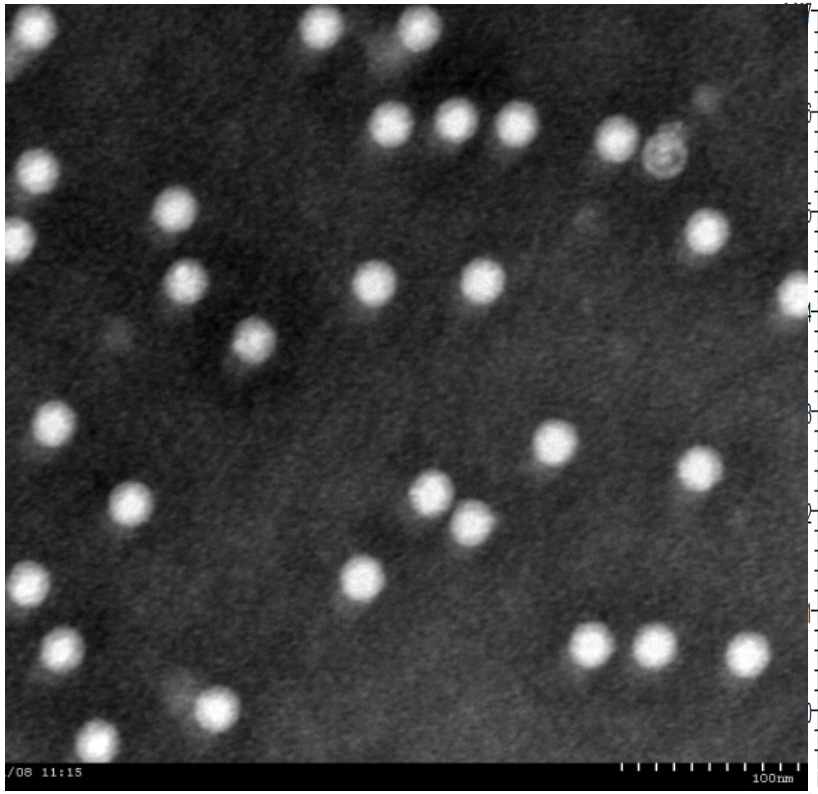


Sepharose CL6B

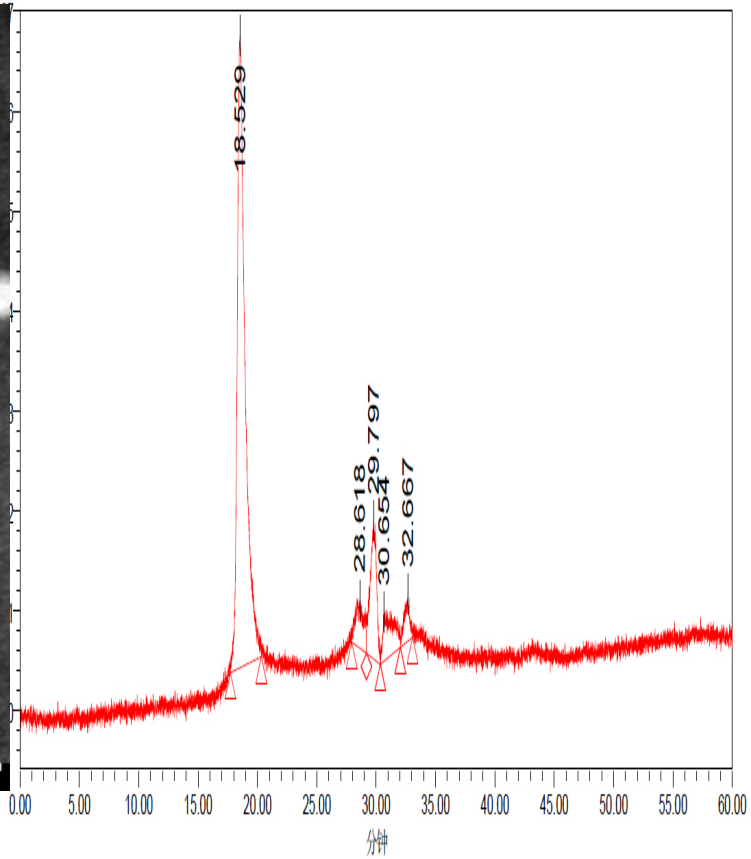


DEAE-Sepharose FF

Purified Poliovirus D Antigen

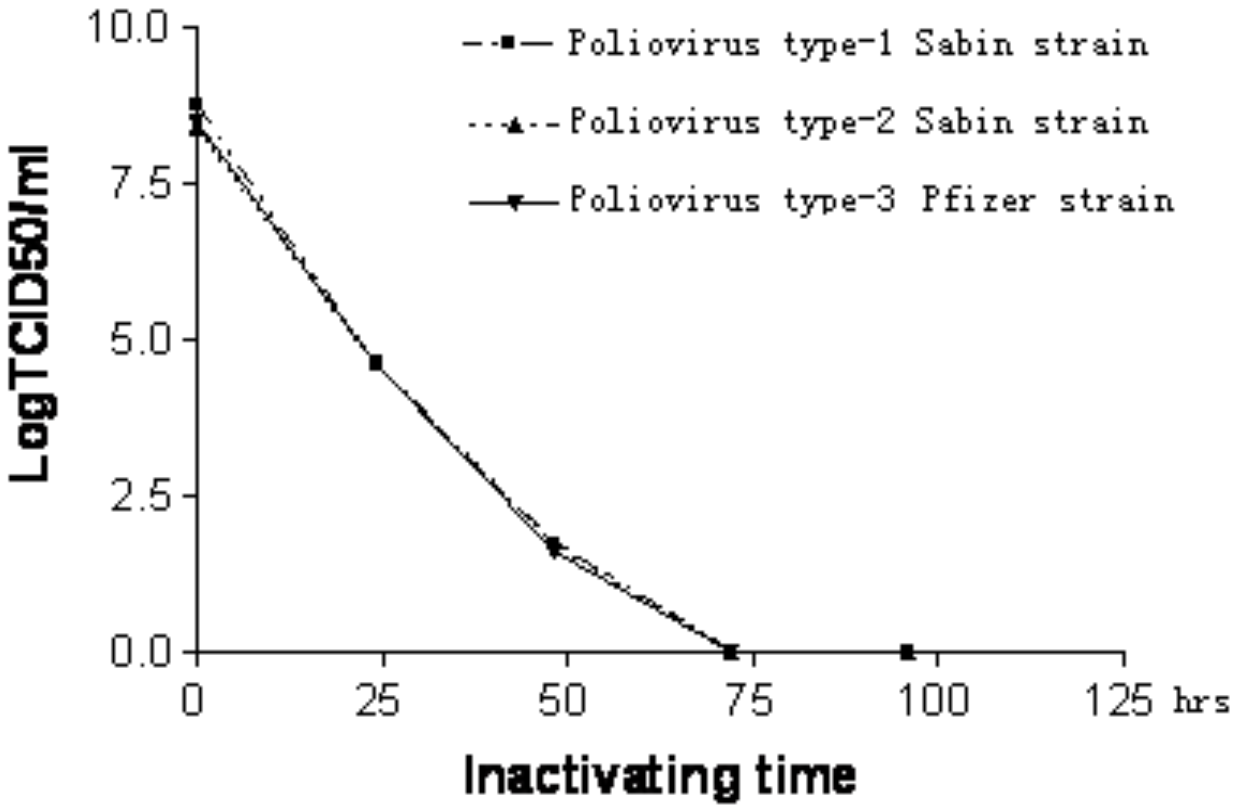


Virus particle

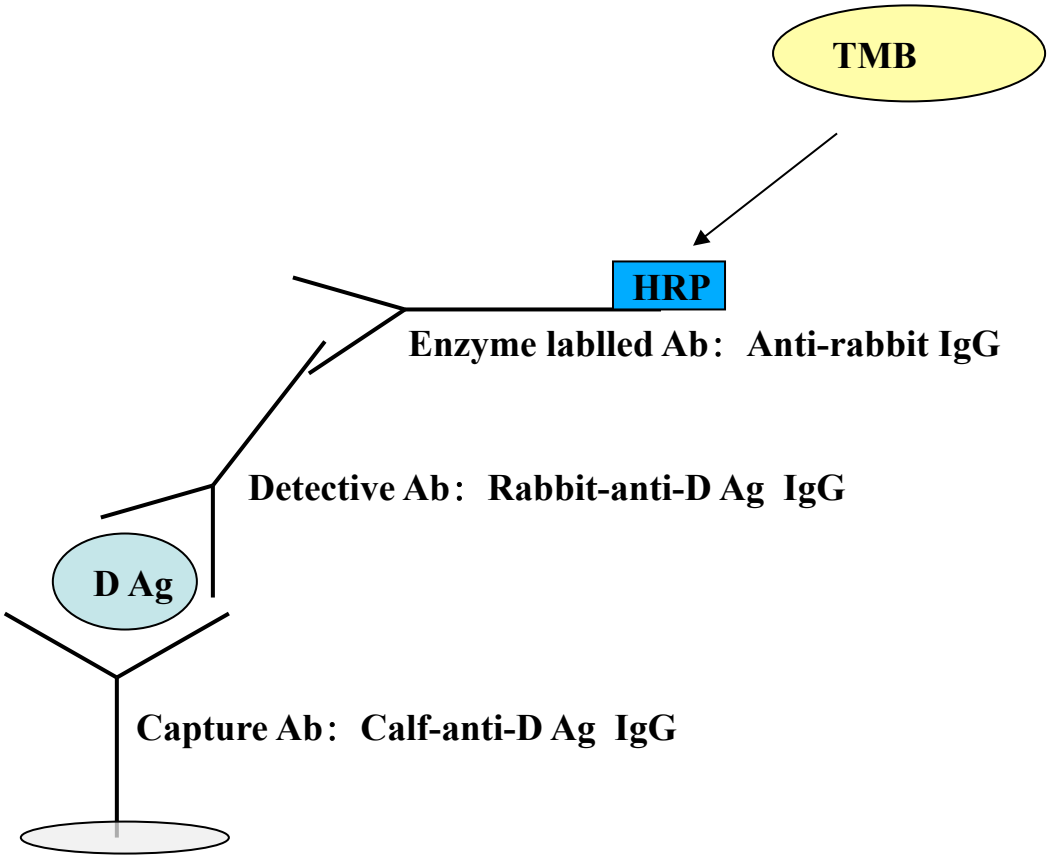


HPLC

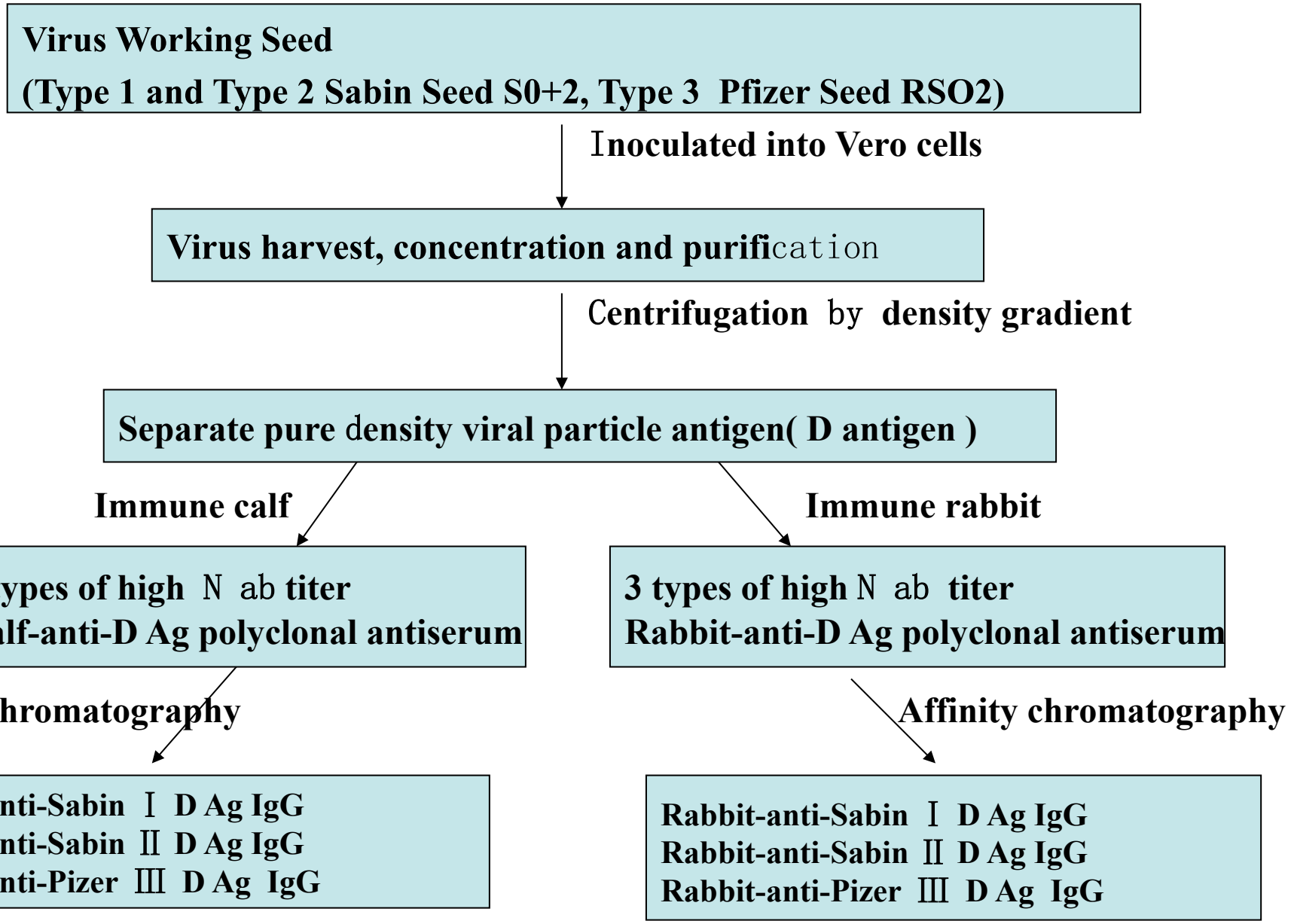
Inactivation by Formalin



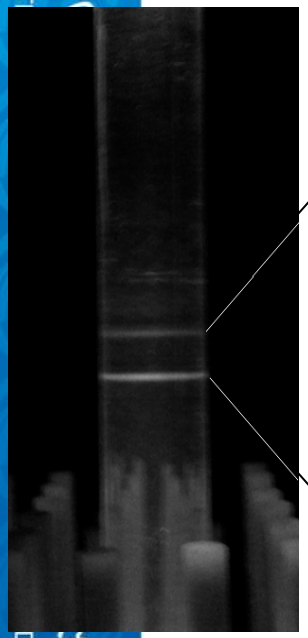
Sandwich ELISA for our sIPV D antigen detection



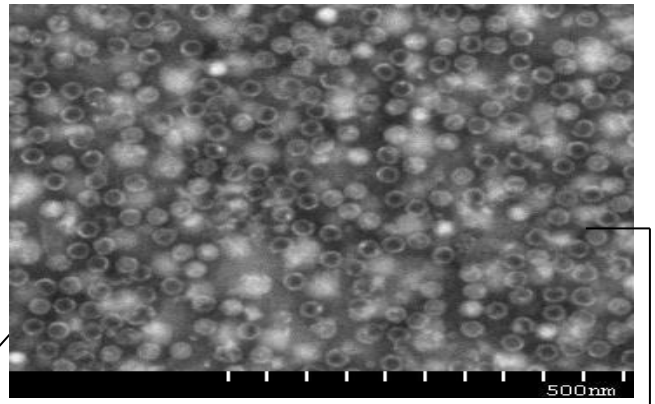
Antisera production



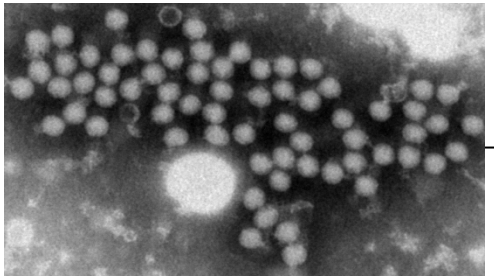
Pure Density viral particle antigen (D antigen) by density gradient centrifugation



Electron microscope

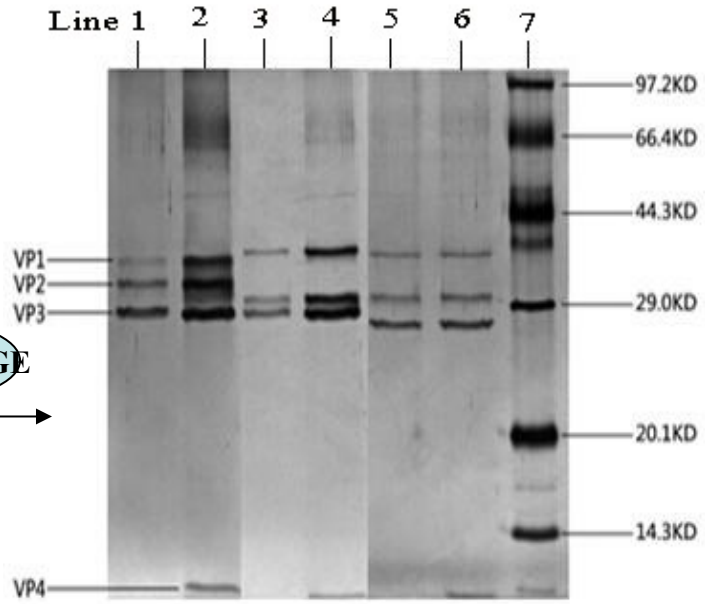


Upper zone: Capsid viral partical antigen (C Antigen)



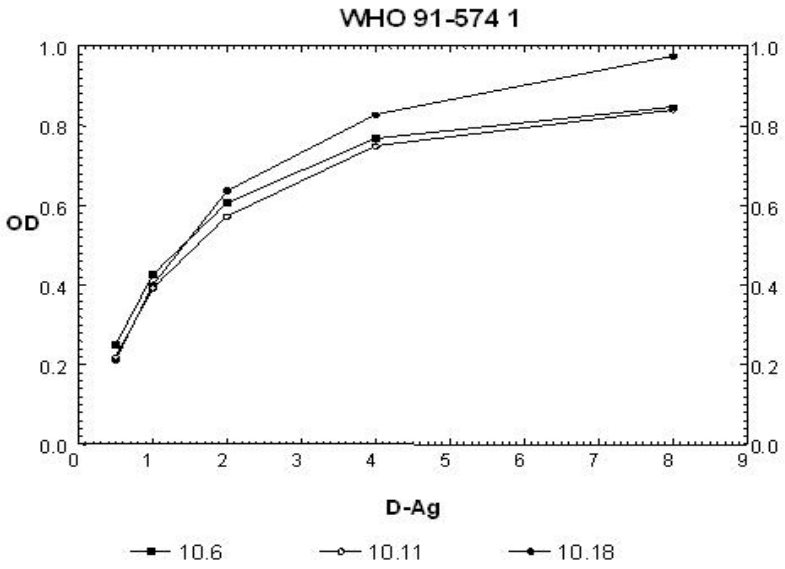
Lower zone: Density viral partical antigen (D Antigen)

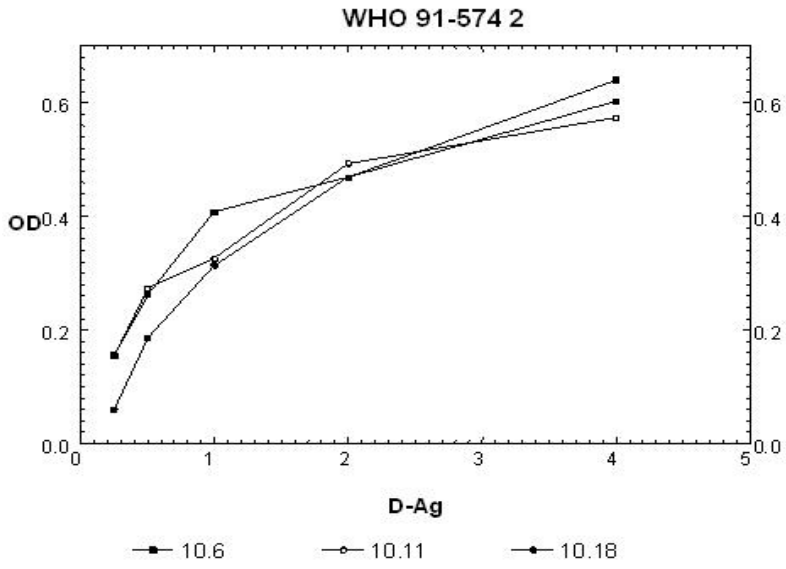
SDS-PAGE

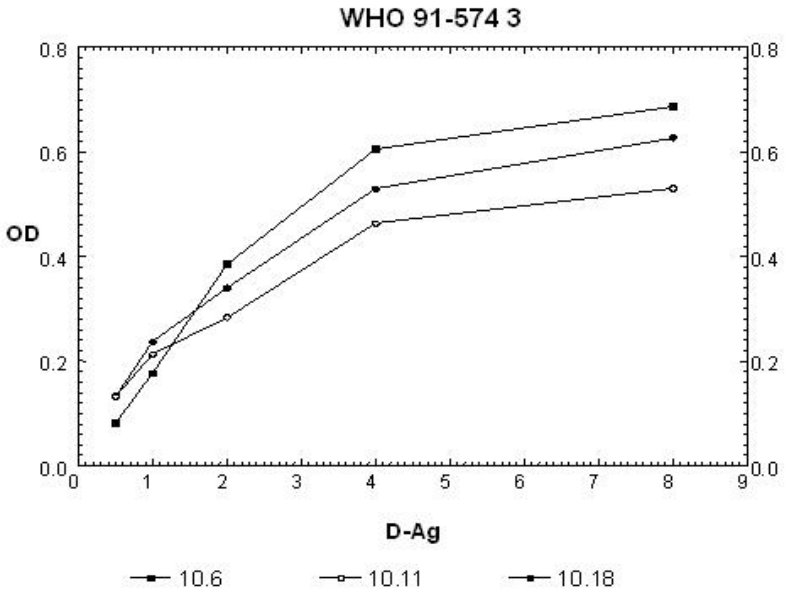


Line 1: type Ⅰ upper zone; Line 2: type Ⅰ lower zone;
Line 3: type Ⅱ upper zone; Line 4: type Ⅱ lower zone;
Line 5: type Ⅲ upper zone; Line 6: type Ⅲ lower zone;
Line 7: Protein marker.

Standard curve of WHO reference 91/574



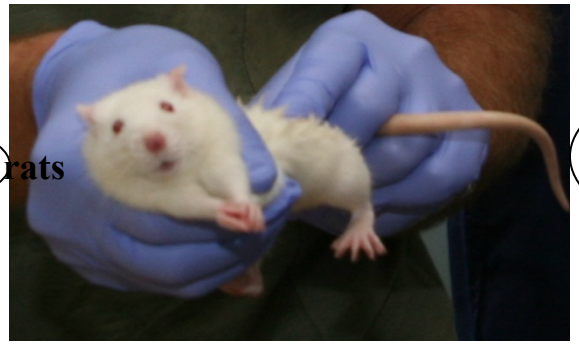




These pictures showed individual result from 3 experiments.

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



Clean Wistar rats

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

Test vaccine groups: sIPV Final bulk

Reference vaccine groups

1:1	1:3	1:9	1:27	1:1	1:3	1:9	1:27

10 rats per groups

Intramuscular injection into the hind limbs, 0.5ml/rat

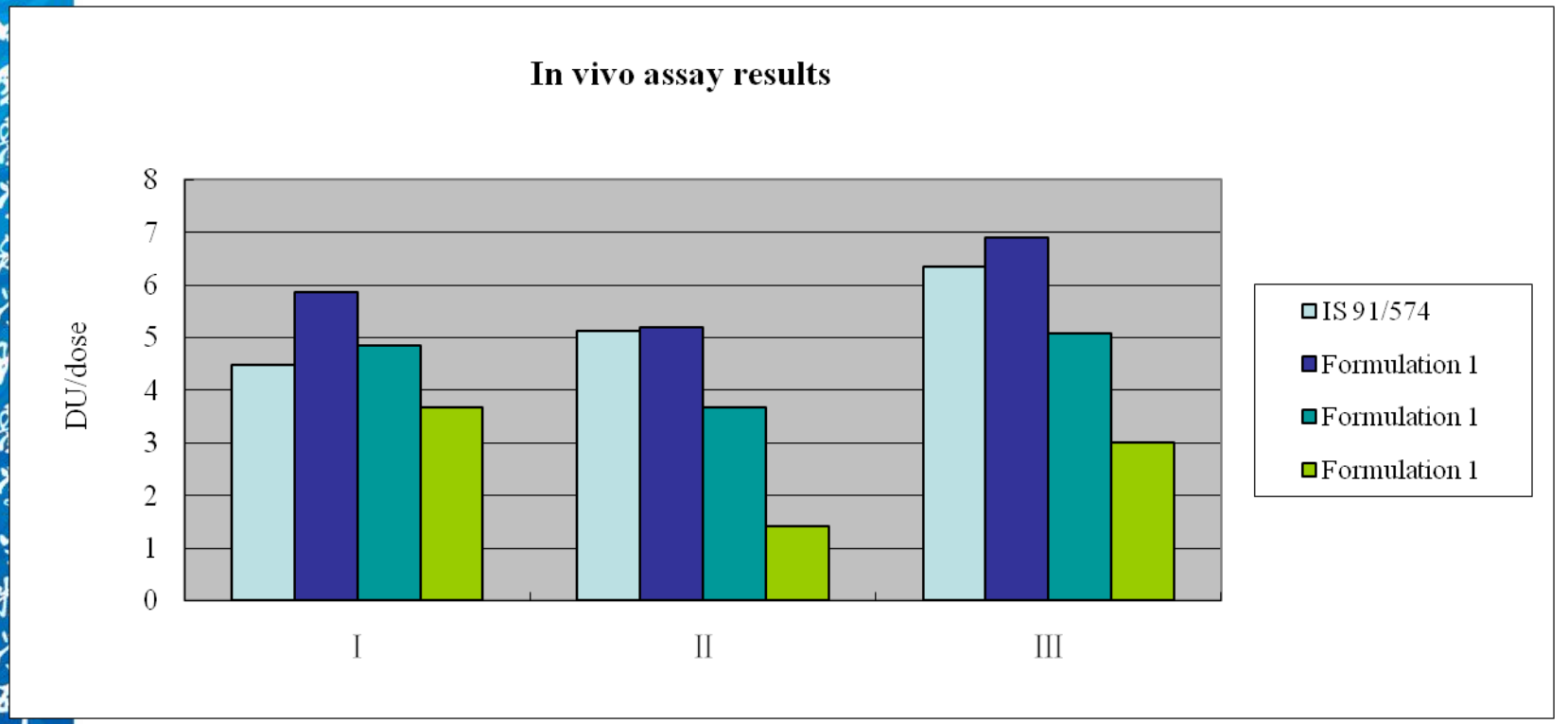
10 rats per groups

Foster in Clean Animal Facility for 21 days

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



Formulation 1 : 40 32 60 DU

Formulation 2 : 20 16 30 DU

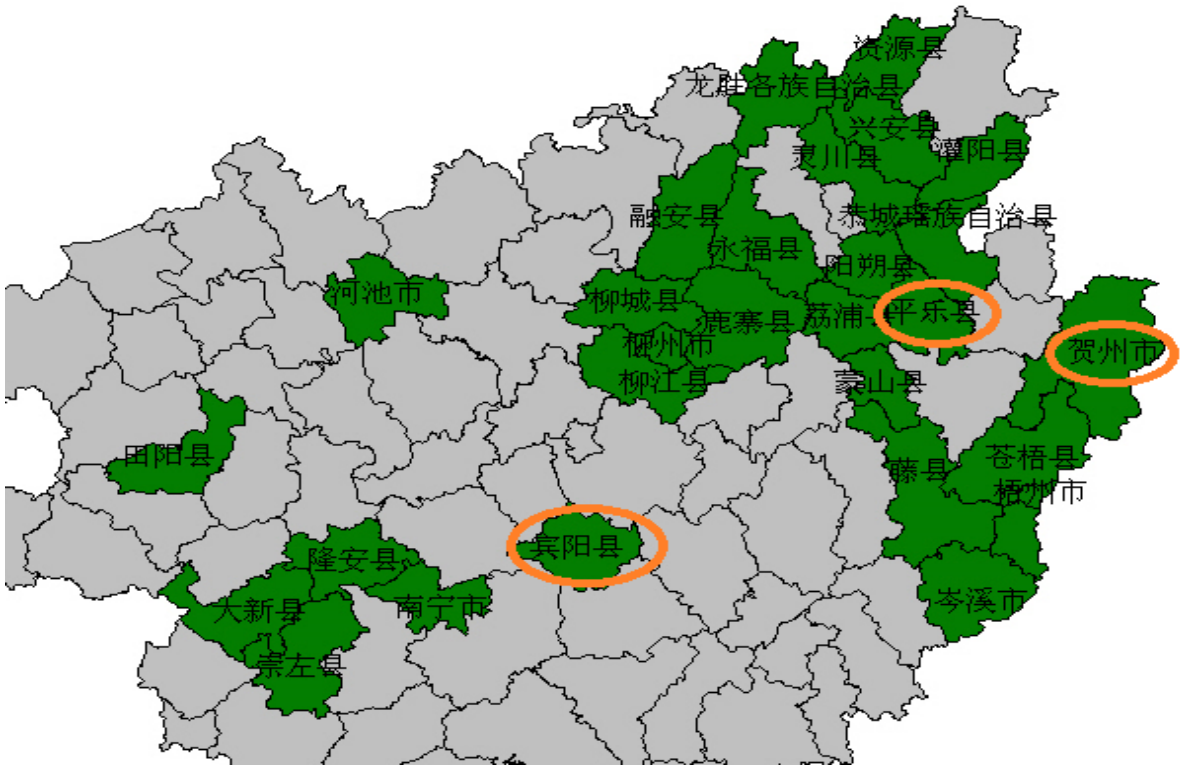
Formulation 3 : 10 8 15 DU

wIPVReference: 40 8 32DU

We choose formulation as sIPV:

30, 32, 45 DU for TypeI, 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

Adult 20 each 10 for middle and high doses sequentially

Children 20 each 10 for middle and high doses sequentially

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

Safety evaluation and antibody detection in infant groups

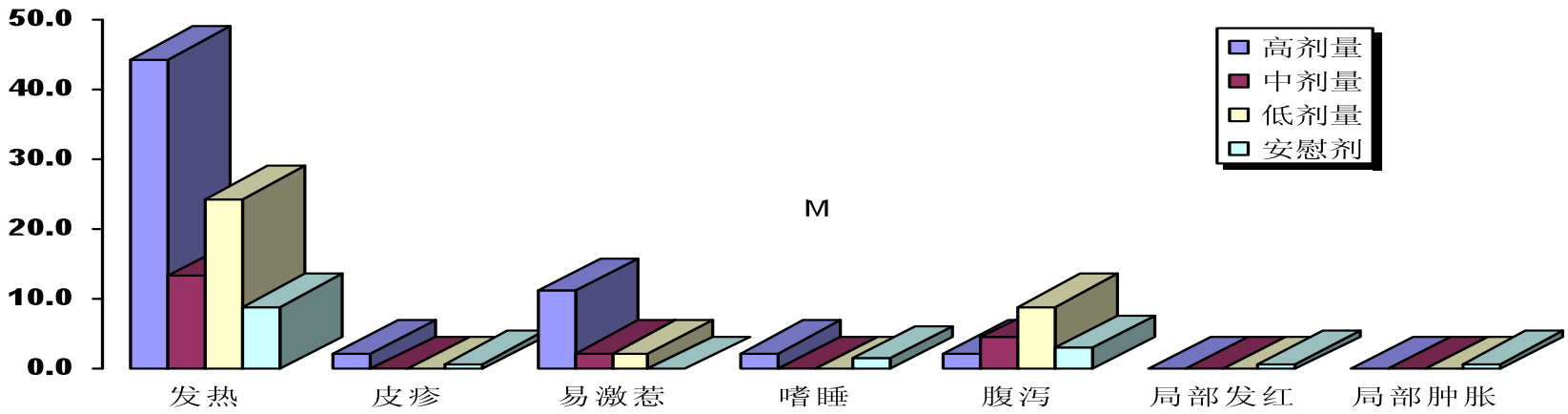
Antibody detection before and after immunization

Determination of serum normal values and function of liver and kidney

Placebo control

Adverse events in phase Ⅰ

Groups	sIPV-L		sIPV-M		sIPV-H	
	Test	Placebo	Test	Placebo	Test	Placebo
Adult	/	/	1/10	/	2/10	/
Children	/	/	5/10	/	3/10	/
Infants	9/15	9/15	6/15	6/15	11/15	3/15
SAE	0	0	0	0	0	0



The rate of adverse events in infants of phase Ⅰ（%）

Primary Immunogenicity of Sabin IPV in Phase II

Group	No of infants	Type Ⅰ		Type Ⅱ		Type Ⅲ	
		GMT	Seroconversion（%）	GMT	Seroconversion（%）	GMT	Seroconversion （%）
sIPV-H	85	6335	100.00	339	97.65	884	98.82
sIPV-M	92	2981	97.83	155	95.65	492	98.91
sIPV-L	89	1789	96.63	101	78.65	307	93.26
OPV	92	3315	100.00	410	100.00	545	100.00
cIPV	91	386	90.11	192	90.11	706	97.80

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

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Cross Neutralization

Understand why slected 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.**

中國醫學科學院醫學生物學研究所
INSTITUTE OF MEDICAL BIOLOGY CHINESE ACADEMY OF MEDICAL SCIENCES

GMP、Production and new drug certification

国家食品药品监督管理总局
药品 GMP 认证审批件

编号：国药认字 20150013

企业名称	中国医学科学院医学生物学研究所		
生产地址	昆明新城高新技术产业基地 A1-2		
认证范围	Sabin 株脊髓灰质炎灭活疫苗（Vero 细胞）		
受理编号	GMP140135	受理日期	2014 年 04 月 30 日
检查时间	2014 年 12 月 27 日-12 月 28 日	检查人员	孙东，英志芳，张华
认证结论	经审核，符合药品 GMP 认证管理有关规定，同意发给《药品 GMP 证书》。		
证书编号	CN20150012	证书有效期	2015 年 02 月 10 日至 2020 年 02 月 09 日
附件	药品 GMP 认证检查缺陷项目		
主送	中国医学科学院医学生物学研究所		
抄送	云南省食品药品监督管理局，国家食品药品监督管理总局食品药品审核查验中心		
备注			

国家食品药品监督管理总局
二〇一五年二月十日

中华人民共和国
药品GMP证书
CERTIFICATE OF GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS
PEOPLE'S REPUBLIC OF CHINA

证书编号：CN20150012
Certificate No.

企业名称：中国医学科学院医学生物学研究所
Manufacturer: Institute of Medical Biology Chinese Academy of Medical Sciences

地址：昆明新城高新技术产业基地 A1-2
Address: Xincheng High-tech Industrial Base A1-2, Kunming

认证范围：Sabin 株脊髓灰质炎灭活疫苗（Vero 细胞）
Scope of Inspection: Inactivated Poliomyelitis Vaccine, Sabin Strains（Vero cell）

经审查，符合中华人民共和国《药品生产质量管理规范》要求。特发此证。

This is to certify that the above-mentioned manufacturer complies with the requirements of Chinese Good Manufacturing Practices for Pharmaceutical Products.

有效期至 2020 年 02 月 09 日
This certificate remains valid until 09/02/2020

发证机关：
Issued By

Date for Issuing 10/02/2015 2015 年 02 月 10 日

国家食品药品监督管理总局制
CHINA FOOD AND DRUG ADMINISTRATION

国家食品药品监督管理总局
药品注册批件

原始编号：53130013
受理号：CXSS1300011滇
批件号：2015S00011

药品名称	药品通用名称：Sabin株脊髓灰质炎灭活疫苗 英文名/拉丁名：Inactivated Poliomyelitis Vaccine, Sabin Strains 商品名称：拔必维		
主要成份	本品含有脊髓灰质炎病毒 I 、II 型Sabin株和III型Pfizer株3个型的灭活病毒抗原。		
剂型	注射剂	申请事项	国产药品注册
规格	每瓶0.5ml，每剂量0.5ml。每剂量含病毒抗原量应不低于：I型30DU、II型32DU、III型45DU。	注册分类	预防用生物制品1类
药品标准编号	YBS00022015	药品有效期	24个月
审批结论	[illegible]		
药品生产企业	企业名称：中国医学科学院医学生物学研究所 生产地址：昆明高新区马金铺街道办事处打盏花街168号		
药品批准文号	国药准字S20150002	药品批准文号有效期	至2020年01月13日
监测期	5年，至2020年01月13日	新药证书编号	国药证字S20150002
新药证书持有者	中国医学科学院医学生物学研究所		
附件	注册标准、说明书及标签		
主送	中国医学科学院医学生物学研究所		
抄送	云南省食品药品监督管理局，云南省食品药品检验所，中国食品药品检定研究院，国家药典委员会，国家食品药品监督管理总局药品审评中心，国家食品药品监督管理总局信息中心，国家食品药品监督管理总局食品药品审核查验中心，国家食品药品监督管理总局药化监管司，国家食品药品监督管理总局稽查局。		
备注			

2015年01月14日

新 药 证 书

原始编号：53130013
证书编号：国药证字S20150002

根据《中华人民共和国药品管理法》，经审查，下述药品符合新药的有关规定，特发此证。

药品名称：Sabin株脊髓灰质炎灭活疫苗
主要成份：本品含有脊髓灰质炎病毒 I 、II 型Sabin株和III型Pfizer株3个型的灭活病毒抗原。
持有者：中国医学科学院医学生物学研究所

国家食品药品监督管理总局
2015 年 月 日

No.1302230

Prodution and Quality Control in the production scale

INSTITUTE OF MEDICAL BIOLOGY CHINESE ACADMY OF MEDICAL SCIENCES

中国医学科学院医学生物学研究所

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.

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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.

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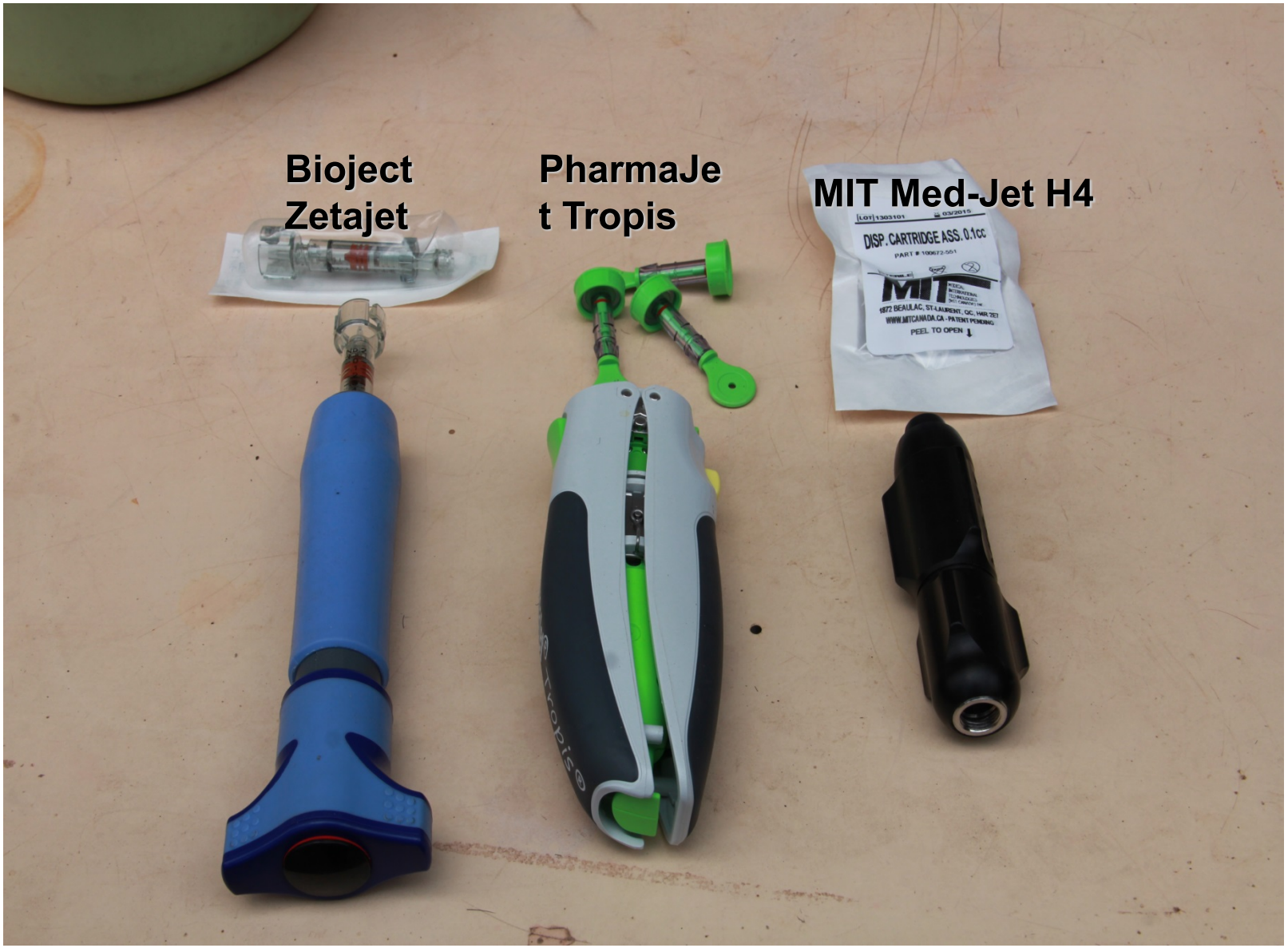
Advances in ID of Sabin IPV

(Bill-Mellinda Gates Foundation OPP1049425)

Three Needle free injector



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MIT Device training

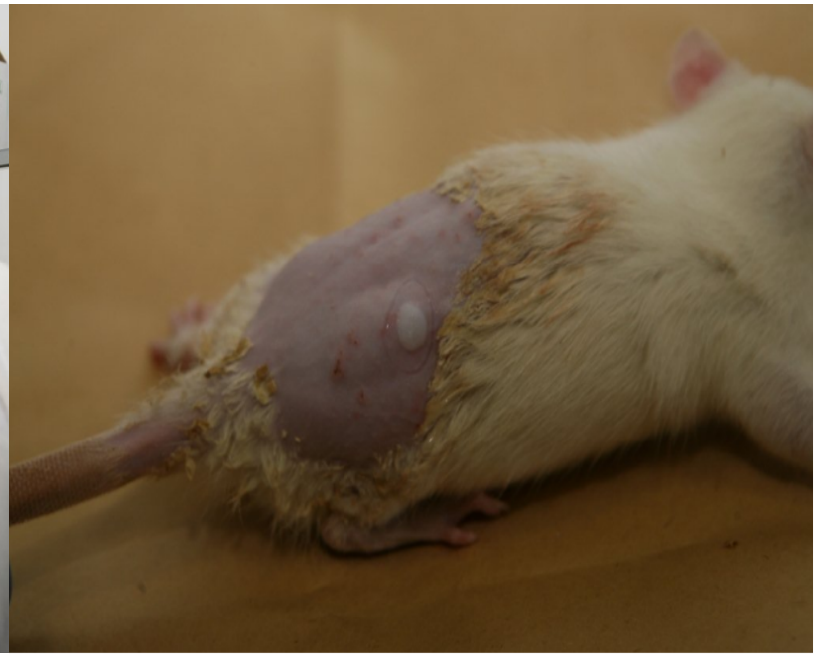
May 26, 2013

Biojet

Choosing the appropriate injection site.

Training our colleagues to inject the pig.

Pharmajet



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Reducing DAg content by intradermal delivery (Protection rate after 3rd dose in rats)

	Type 1	Type 2	Type 3
Needle ID sIPV 1/3	100%	100%	100%
Needle ID cIPV 1/3	70%	100%	90%
Needle ID sIPV 1/5	100%	100%	100%
Needle ID cIPV 1/5	65%	100%	90%
Needle free Injex sIPV 1/5	100%	75%	80%
Needle free Injex sIPV 1/3	103%	90%	100%
Needle IM sIPV whole dosage	100%	100%	100%
Needle IM cIPV whole dosage	100%	100%	100%
(IM NS) control	0	0	0

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**
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- NIBSC
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