Typhoidal & Non-Typhoidal Salmonella Conjugate Vaccines in China

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Conjugate Vaccine Development at Lanzhou Institute of Biological Product (LIBP)

Salmonella conjugate vaccine	
Vi-rEPA	*Phase I, II/ III (2008-2012)*
S.Para A-TT	*Phase I (2009) Phase II (2012)*
S.Para B-TT	*Pre-clinical*
S.GpD-TT	*Pre-cliical*

Other conjugate	
Hib-TT	*Licensed 2003*
S .flexneri 2a and sonnei-rEPA	*Phase Ⅱ (2010)*
Men-TT (A,C,Y,W135)	*Phase Ⅰ (2014)*
Pn-TT (13 valent)	*Phase Ⅰ (2015)*

Typhoid vaccine development

- **Vi_{LIBP} vaccine:licensed in 1996**

- **Vi conjugate vaccine development: started in 2002**

  Carrier protein: rEPA(recombinant exoprotein A from *Pseudomonas aeruginosa)*

  ***Conjugate Scheme:* linker ADH**

Clinical study coordination in China including LIBP, FDA, CDC

- LIBP provide vaccine as an Investigational New Drug (IND)
- SFDA review and approval IND, Chemical, Manufacturing and Control (CMC) and Clinical protocol
- Clinical trial conducted and safety monitored by local CDC and report to SFDA
- Serology performed by SFDA
- Final code opened by SFDA, CDC and LIBP
- Regulatory pathway

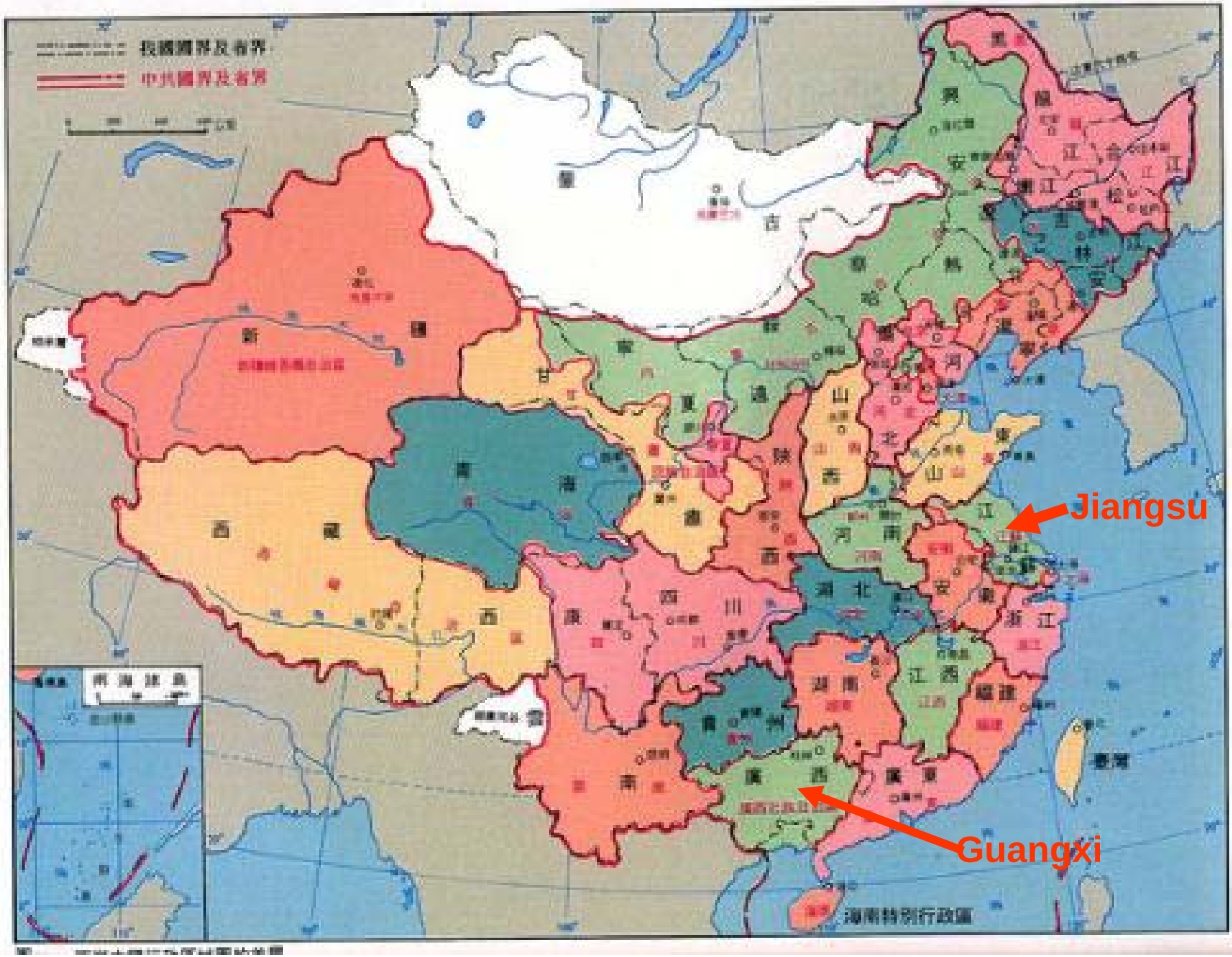
  -- New drug license will be applied in June, 2013

  -- Product Registration License will be in 2015

Clinical lot of Vi-rEPA conjugate vaccine

- **Formulation: single dose vial, liquid in PFS, no preservative**

- **Dosage: 25ug Vi ploysaccharide in 0.5ml per dose, intramuscular injection**


Jiangsu
Guangxi

Vi-rEPA$_{LIBP}$ phase II trial

Age years	Injection times	Injection number		total
		conjugate	controle※	
2-5years	2	250	250	500

※:First injection:influenza vaccine, second injection:Vi vaccine.

Injection and blood sample schedule

- Two injections, 8 weeks apart
- Blood samples taken on day 0, and 4, 26 weeks post second injection
- Anti-Vi IgG determined by ELISA, titer assigned according to NIH human reference serum in EU or ug/ml

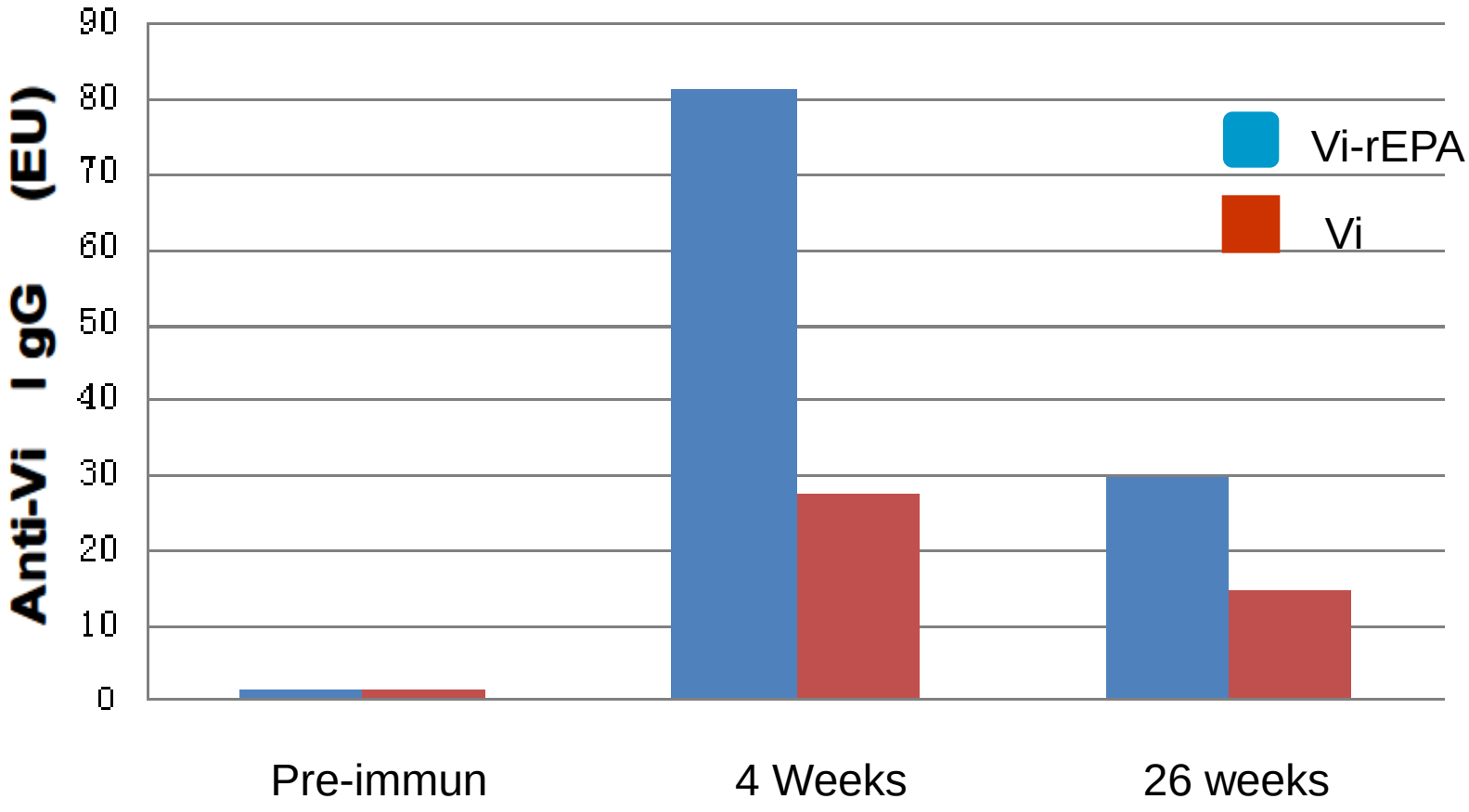
Anti-Vi IgG in 2-5 years old children received 2 injections of Vi-rEPA (LIBP)

Duration	Anti-Vi IgG (GM)	Vi-rEPA N=231	Vi N=234	Vi-rEPA (USA) N=52
Pre-immu	ELISA units	1.71	1.76	0.18
	ug/ml	2.12	2.18	0.23
	P	NS		
4 weeks	ELISA units	81.36	27.75	95.4
	ug/ml	100.9	34.41	118.3
	P	0.0001		
26 weeks	ELISA units	30.02	14.96	30.6
	ug/ml	37.22	18.53	37.9
	P	0.001		

S. paratyphoid A conjugate vaccine clinical evaluation

- **Bacteria source: NTP-6**
- **LPS detoxified**
- **Conjugated with tetanus toxoid (TT) by CDAP**
- **25ug/dose, intramuscular injection**
- **one injection, blood sapple taken on 0, and 4 weeks post injection**

Antibody response in 2-5 years children injected with Vi-rEPA or Vi vaccine



Proportion of 2-5 years old children elicited higher than protective level antibody (≥3.52EU/ml)

		Pre-vaccination		4weeks		26weeks	
groups	items	conjugate	control	conjugate	control	conjugate	control
2-5	⩾3.52EU/ml	8.66%	5.56%	100.00%	94.44%	98.70%	86.32%
	P	0.193		⟨0.001		⟨0.001	

Conculsion of Phase II clinical trial of Vi-rEPA (Lanzhou)

- **Vi-rEPA is safe and immunogenic in 2-5 years old children**
- **Vi-rEPA elicited significantly higher level of antibodies than Vi**
- **26 weeks post immunization, 98% volunteers had anti-Vi IgG level ≥3.52 EU (est. protective level)**

S. Paratyphoid A LPS antibody response in volunteers injected with one dose SPA-TT or Hib-TT

Age (Yr)	*S.parat A-TT (GM,EU) N=30/group*			*Hib-TT (GM,EU) N=10/group*		
	pre	post	*fold increase*	*pre*	*post*	*fold increase*
> 17	*13.3*	*242.4*	*18.2*	*12.2*	*11.4*	*1*
6-17	*9.67*	*471.1*	*48.7*	*19.5*	*17.1*	*1*
2-5	*3.94*	*219.6*	*55.8*	*5.1*	*5.24*	*1*

Serum bactericidal titers against S. para A in volunteers injected with SPA-TT or Hib-TT

Age (Yr)	*SPA-TT (GMT)*			*Hib-TT (GMT)*		
	Pre	*Post*	*fold rise*	*Pre*	*Post*	*fold rise*
> 17	*881*	*6932*	*7.9*	*1253*	*1439*	*1*
6-17	*836*	*6719*	*8.0*	*964*	*749*	*1*
2-5	*437*	*5748*	*13.1*	*421*	*272*	*1*

Phase II clinical trial group

Age group	Dosage group	one injection	two injection	total
18-59	25.0ug	110	110	220
	12.5ug	110	110	220
6～17	25.0ug	110	110	220
	12.5ug	110	110	220
2-5	25.0ug	110	110	220
	12.5ug	110	110	220
total	\	660	660	1320

1.blood sample taken on day 0, and 4, 26 week post one or two dose injection

2.anti-LPS IgG antibody concentration will be determined by ELISA

3.SBA(serum bactericidal activity) will be determined

Future plans

- **Licensing application of Vi-rEPA conjugte vaccine**
  - **New Drug license (2013)**
  - **Production and Marketing license (2015)**
- **Antibody persistence study – 2 and 3 years after Vi-EPA immunization**
- **Infants safety and immunization study of Vi-rEPA and SPA-TT administered with EPI vaccines**
- **Combination vaccine with other infants vaccine**
- **Combination vaccine with other Salmonella conjugate vaccines**

acknowledge

Dr. Zengming, NIFDC, SFDA,China

Dr. Rongchen Li, Guangxi CDC,China

Dr. Fengcai Zhu, Jiangsu CDC,China

Dr. Shousun Szu, NIH, USA