Phase I and II Trials of a F genotype Live Attenuated Mumps Vaccine

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F genotype mumps vaccine

01 Mumps can cause inflammatory lesions of the parotid gland & inflammatory pathology

02 Attenuated mumps vaccines using A genotype S79 strain was developed in the 1960s and has been used In Mainland China in the 1990s

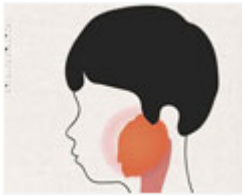
03 Mumps incidence and morbidity greatly reduced after use of the mumps vaccine.

04 Outbreaks of mumps re-emerged in the last 10 years in Europe and the US.

05 Mumps incidence increasing in recent years in Mainland China.

06 Pathogen monitoring suggests current circulating strain of F genotype since 2000

07 A new attenuated mumps vaccine developed F genotype SP viral strain + human diploid cells.



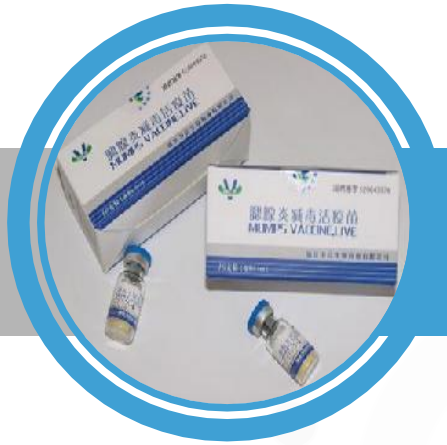
Phase I trial – Vaccines and placebos

Vaccine

Three doses containing A genotype SP virus:
A: 3.5 ± 0.25 logCCID50;
B: 4.3 ± 0.25 logCCID50;
C: 5.0 ± 0.25 logCCID50.

Placebo

D: identical to the vaccine, but did not contain the mumps virus.



Positive Control

E: A commercial, live attenuated mumps vaccine containing F genotype S79 virus manufactured by Zhejiang Weixin Biological Products Ltd. Corp

Phase I trial – Trial design

A randomized, controlled and observer-blind trial was designed to conduct in adults → children → preschoolers → infants with continuous clinical safety observation after A dose → B dose → C dose inoculation in Hebei CDC.

Primary objective
to assess the safety of immunization with different dose vaccines, placebo and positive controls in adults, children, preschoolers and infants.

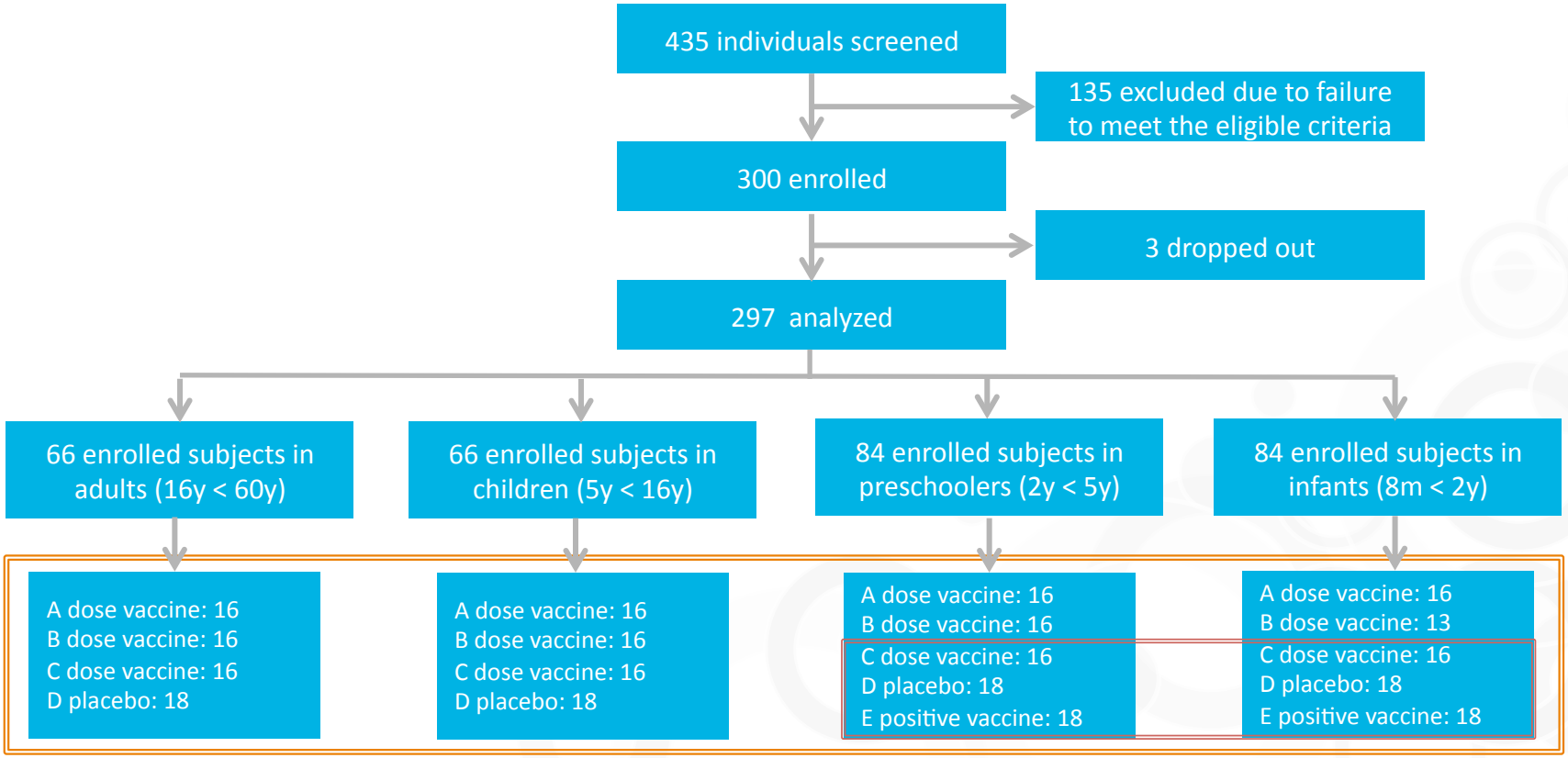
Primary safety endpoint
Systemic and local adverse reaction at day 0-14 p.i.
AEs rates associated with vaccine

Secondary safety endpoint
Total AEs and SAEs
Lab testing indicators and vital signs
Virus shedding

Secondary objective
to primarily analyze the immunogenicity of different dose vaccines.

Immunogenicity endpoint
Seroconversion rates and GMTs at 28 day p.i.

Phase I trial – Trial design



Phase I trial – Safety observation

Trial time (Oct.15 – Nov.23, 2012)

30 min after inoculation

Body temperature measurement
AEs observation

0 – 28 d

Diary & contact card record

The participants, or their parents/ guardians, were required to complete a diary card on the inoculation day, and day 4,7,10,14 post-inoculation, and a contact card on day 15-28 p.i. for recording any solicited, unsolicited AEs and SAEs for the evaluation of systemic and local AEs and SAEs.

0-28 d

Lab examination

Blood samples were collected at day 0, 4 p.i. for lab blood routine examination and routine urine analysis. Female adults were required to do the urine pregnancy test.

Phase I trial – Safety assessment

The safety evaluation of all 3 different dose vaccines, the positive and the placebo controls in the adults, children, preschoolers and infants groups showed similar AEs: 39% , 42%, 35%, 38% and 40%, respectively, with no statistical significance. The AEs were typically characterized by fever and cough. The cumulative local AEs mainly included mild pain, local swelling and scleroma at the injection site. The rate of AEs in C dose inoculators was a slight higher than the positive control. None of the AEs were more severe than a grade III. Furthermore, no SAE was reported throughout the trial, indicating that the vaccine is relatively safe.

Systemic adverse events, local adverse events and mumps-specific adverse events of each participant receiving vaccines, placebo or positive vaccine as controls

	Vaccine group						Control group (n = 36)		Placebo group (n = 72)	
	A dose (n = 64)		B dose (n = 64)		C dose (n = 64)					
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All local and systemic adverse events	25	39	27	42	23	35	14	38	18	40
Solicited systemic adverse events after injection										
Fever	18	28	16	25	13	20	10	27	19	26
Fever ≥ 3grades	1	1	0	0	0	0	0	0	0	0
Diarrhea	1	1	1	1	0	0	1	2	1	1
Diarrhea ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Nausea/vomiting/anorexi	1	1	3	4	0	0	1	2	2	2
Nausea/vomiting/anorexia ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Irritability/Drowsiness/acratia	0	0	4	6	4	6	0	0	1	1
Irritability/Drowsiness/acratia ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Allergy	1	1	0	0	0	0	0	0	0	0
Allergy ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Cough	7	11	9	14	6	8	4	11	9	12
Cough ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Muscle pain	0	0	0	0	1	1	0	0	1	1
Muscle pain ≥ 3grades	0	0	0	0	0	0	0	0	0	0

Solicited local adverse events after each injection										
Pain	0	0	3	4	5	7	1	2	2	2
Pain ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Redness	1	1	0	0	4	6	1	2	1	1
Redness ≥ 3grades	0	0	0	0	0	0	1	2	0	0
Swelling	1	1	0	0	1	1	1	2	0	0
Swelling ≥ 3grades	0	0	0	0	0	0	1	2	0	0
Itching	0	0	0	0	1	1	0	0	0	0
Itching ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Scleroma	1	1	0	0	5	7	0	0	0	0
Scleroma ≥ 3grades	0	0	0	0	1	1	0	0	1	1
Rash	0	0	0	0	0	0	0	0	0	0
Rash ≥ 3grades	0	0	0	0	0	0	0	0	0	0
Mumps-specific adverse events										
Orchitis	0	0	0	0	0	0	0	0	0	0
Parotitis	0	0	0	0	0	0	0	0	0	0
Meningitis	0	0	0	0	0	0	0	0	0	0
Pancreatitis	0	0	0	0	0	0	0	0	0	0

Phase I trial – Immunogenicity & virus shedding

Inoculation (Oct.15 – Nov.23, 2012)

Ethics

The study was approved by the IRB in HBCDC and registered at www.cliniclatrials.gov (NCT01712906). Written ICR was obtained from each participant or the parent/ guardian following an explanation of the purpose and potential risks of the study.

Serology analysis

All blood samples of immunized subjects were collected on days 0 and 28 p.i. for measuring neutralizing antibody and hemagglutination-inhibiting antibody levels.

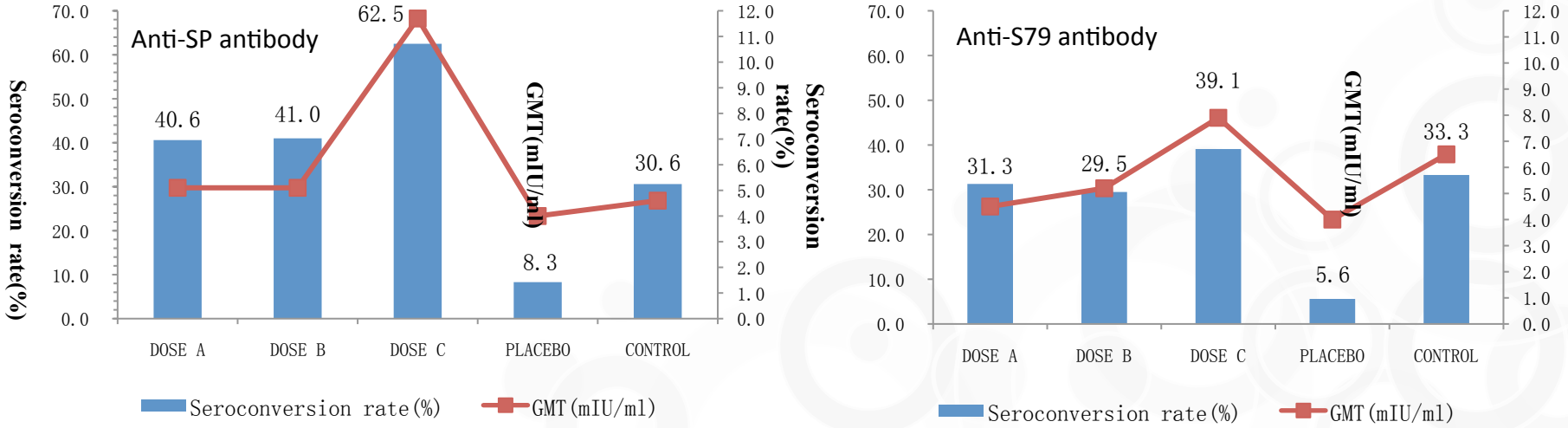
Detection of virus shedding

Throat swabs were collected from each immunized subjects at days 0, 4, 7, 10, 14, and 28 post inoculation for detecting the mumps virus shedding by routine RT-PCR amplification.

Phase I trial –Seroconversion & GMTs

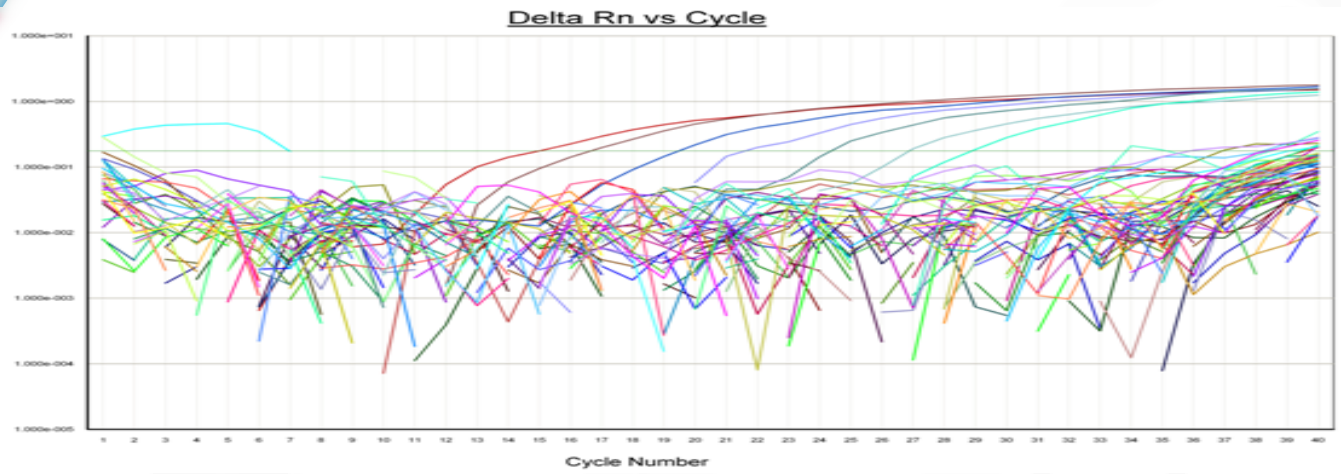
The S79 and SP virus were used for the neutralizing antibody assays. The results showed that seroconversion rates of anti-SP antibody were 40.6%， 41.0% and 62.5%,and seroconversion rates of anti-S79 antibody were 31.3%， 29.5%,39.1,respectively in A, B, C, placebo and positive control immunized subjects. There was no statistical difference in the A, B, C dose groups. GMTs for the anti-SP virus in the C dose inoculators was higher than, and GMTs for the anti-S79 virus in the C dose inoculators was similar to those in the positive and placebo controls.

Seroconversion rates and GMTs of anti-SP and anti-S79 antibodies induced by inoculation of A, B, C dose vaccine, placebo and positive vaccine



Phase I trial – Virus shedding

Viral nucleic acid detection in throat swabs collected at days 0, 4, 7, 10, 14, and 28 post-inoculation from all the immunized subjects were performed. Negative results were obtained at all of the tested time points as compared with positive control, in which, the digital viral genome was capable of being identified in detection and quantitation by the qRT-PCR (data not shown), implying no virus shedding from the vaccine-immunized subjects.



Phase I trial – Summary

It is suggested that B and C dose be considered in phase II trial for further observing dose-effect association.

Immunogenecity

The immunogenicity analysis showed higher seroconversion rate in C dose than that in A and B dose negative immunized subjects. There was no statistical significance in immunized subjects with A, B, C dose.

Safety

The identified solicited and unsolicited AEs showed no significant differences among the 3 dose vaccine, and the positive and placebo control groups. The rate of identified AEs associated with vaccine was not seen to increase with the dose increasing. No SAEs were noticed. A favorable safety profile for the new F genotype mumps vaccine was suggested in this trial.

Phase II trial – Vaccines and placebos

Vaccine

Two doses containing SP virus (lyophilized):
High dose:4.5–5.0 logCCID50
Low dose:3.5-4.0 logCCID50

Positive Control

A commercial live attenuated measles and mumps combined vaccine containing S79 virus manufactured by Shanghai Biologic Co. Ltd., CNBG

Phase II trial – Trial design

A randomized, double-blind noninferiority trial was designed to conduct in healthy 8-24-month-old children in 2 county centers of Hubei CDC

Primary study objective

to analyze the seroconversion rates of anti-SP and anti-S79 neutralizing antibody, and hemagglutination-inhibiting antibody at day 28 p.i. in all the groups immunized with vaccines and positive control vaccine.

The endpoint for immunogenicity and safety was designed to be on day28 p.i.

Secondary study objective

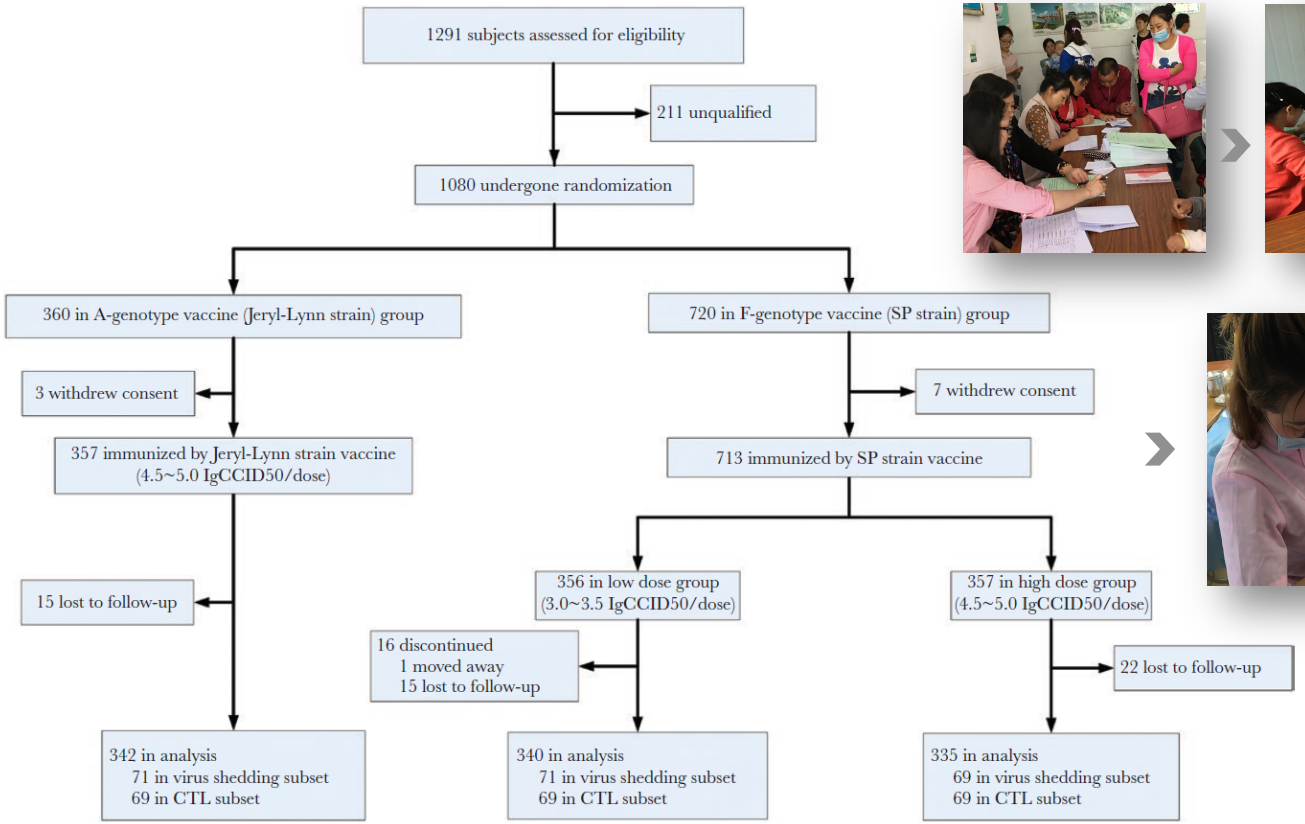
To analyze the anti-SP and anti-S79 neutralizing antibody GMTs and hemagglutination-inhibiting GMTs on day 28 p.i.

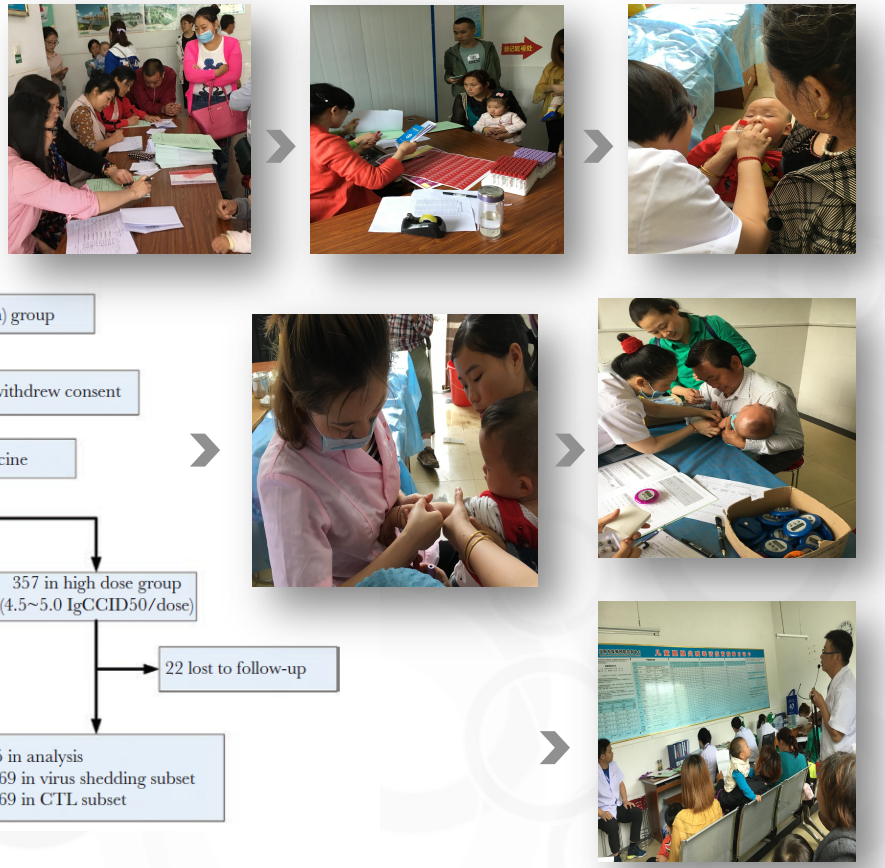
To assess the adverse reaction rates in all the enrolled subjects immunized with vaccines and positive control vaccine.

To observe the virus shedding at day 0,4,8 p.i.

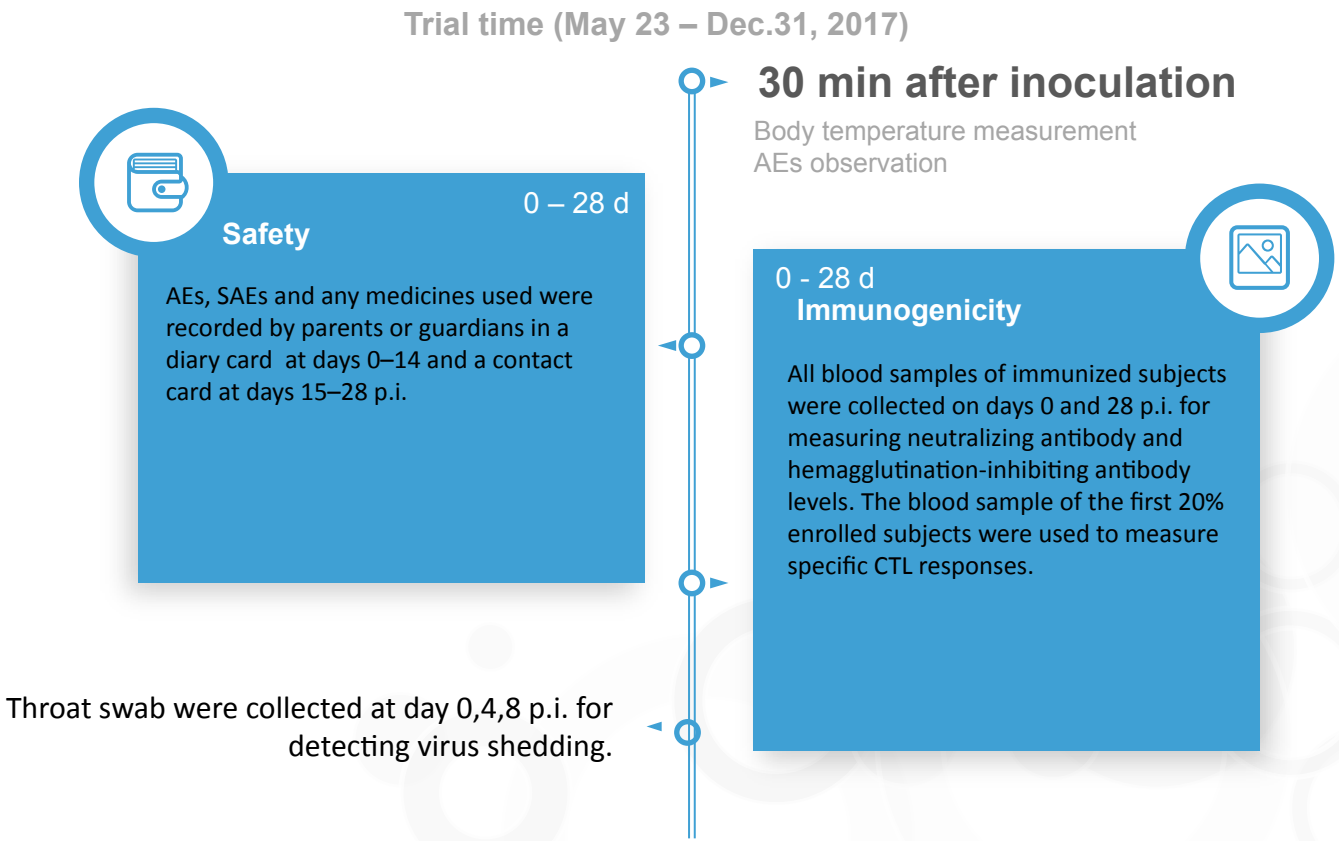
To investigate the specific cytotoxic T lymphocyte (CTL) responses at day 0,28 p.i. in the first 20% of the enrolled subjects.

Phase II trial – Trial design





Phase II trial – Safety & immunogenicity observation



Phase II trial – Noninferiority of seroconversion

Both vaccines were capable of inducing seroconversion of neutralizing and hemagglutination-inhibiting antibodies at rates of approximately 90% except for the low-dose SP vaccine. The high dose SP vaccine showed noninferiority to the S79 vaccine in terms of anti-SP neutralizing antibody as the lower bound of the 95% CI for the risk differences (Riff) of seroconversion rates was greater than −10%.

Seroconversion Rates of Serum on the 28th Day After Vaccination in Three Groups

Outcome	Negative population pre-immunization †			Positive population pre-immunization ‡			Whole population §		
	A*	F-Low*	F-High*	A	F-Low	F-High	A	F-Low	F-High
Hemagglutination inhibition antibody— % (95% CI)									
Against S79	97.5 (95.7 to 99.2)	84.1 (80.1 to 88.2)	93.4 (90.5 to 96.2)	53.6 (33.9 to 72.5)	29.2 (12.6 to 51.1)	25.0 (11.5 to 43.4)	93.9 (91.3 to 96.4)	80.2 (76.0 to 84.5)	86.8 (83.1 to 90.4)
Riff. ¶ (95% CI)		-13.3 (-17.7 to -8.9)	-4.1 (-7.4 to -0.8) ‖		-24.4 (-50.3 to 1.5)	-28.6 (-52.4 to -4.8)		-13.6 (-18.6 to -8.7)	-7.1 (-11.5 to -2.6)
Against SP	89.5 (85.7 to 93.4)	83.7 (78.9 to 88.5)	95.3 (92.6 to 98.0)	40.0 (21.1 to 61.3)	37.0 (19.4 to 57.6)	63.6 (40.7 to 82.8)	84.9 (80.5 to 89.2)	78.7 (73.7 to 83.8)	92.6 (89.4 to 95.8)
Riff. ¶ (95% CI)		-5.8 (-12.0 to 0.3)	5.8 (1.1 to 10.5) ‖		-3.0 (-29.4 to 23.5)	23.6 (-4.2 to 51.4) ‖		-6.1 (-12.7 to 0.5)	7.8 (2.4 to 13.1) ‖
Neutralizing antibody— % (95% CI)									
Against S79	73.6 (68.9 to 78.3)	21.7 (17.3 to 26.1)	64.4 (59.2 to 69.5)	0.0 (0.0 to 97.5)	66.7 (9.4 to 99.2)	50.0 (1.3 to 98.7)	73.4 (68.4 to 78.0)	22.1 (17.8 to 26.9)	64.3 (58.9 to 69.4)
Riff. ¶ (95% CI)		-51.9 (-58.3 to -45.5)	-9.3 (-16.2 to -2.3)		66.7 (13.3 to 100.0) ‖	50.0 (-19.3 to 100.0)		-51.3 (-57.7 to -44.8)	-9.1 (-16.1 to -2.2)
Against SP	86.9 (83.3 to 90.6)	72.8 (68.0 to 77.7)	89.4 (86.1 to 92.8)	61.5 (31.6 to 86.1)	13.3 (1.7 to 40.5)	72.7 (39.0 to 94.0)	86.0 (82.3 to 89.6)	70.2 (65.3 to 75.1)	88.9 (85.5 to 92.3)
Riff. ¶ (95% CI)		-14.1 (-20.2 to -8.0)	2.5 (-2.4 to 7.5) ‖		-48.2 (-79.8 to -16.7)	11.2 (-26.1 to 48.5)		-15.8 (-21.9 to -9.7)	2.9 (-2.1 to 7.9) ‖

Phase II trial – Noninferiority of GMTs

In the neutralizing antibody assay with the S79 virus, the S79(positive) vaccine immunization showed higher GMTs than the SP vaccine groups, and followed a dose-dependent effect. In the assay with the SP virus, an inverse correlation was observed between the positive and the high-dose SP vaccine group. The hemagglutination-inhibiting antibody assay with the 2 genotype viruses indicated the same tendency. Further analyses indicated the noninferiority of the SP high dose vaccine to the positive vaccine, with a lower bound of the 95% CI for the GMT ratios higher than 0.67 .

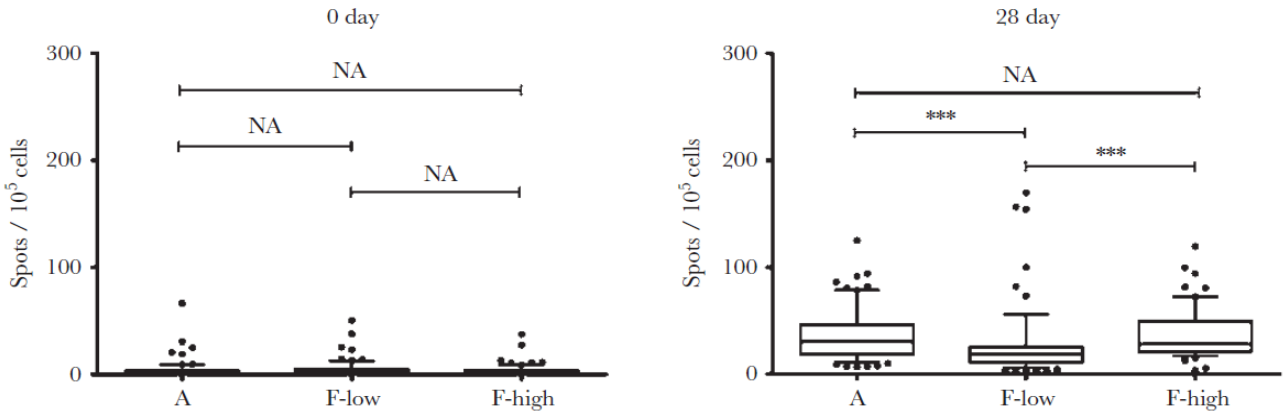
Geometric Mean Titers of Serum on the 28th Day After Vaccination in Three Groups

Outcome	A[a]	F-Low[a]	F-High[a]
Neutralizing antibody			
Against S79, GMT (95% CI)			
0 Day	1.01 (0.99 to 1.04)	1.02 (1.00 to 1.04)	1.02 (0.99 to 1.05)
28 Days	3.23 (2.92 to 3.57)	1.37 (1.26 to 1.48)	2.50 (2.27 to 2.75)
GMT ratio (95% CI)[b]		0.42 (0.37 to 0.48)	0.77 (0.67 to 0.89)[c]
Against SP, GMT (95% CI)			
0 Day	1.04 (1.01 to 1.07)	1.05 (1.02 to 1.08)	1.04 (1.01 to 1.07)
28 Days	5.06 (4.54 to 5.63)	2.83 (2.56 to 3.13)	6.52 (5.81 to 7.33)
GMT ratio (95% CI)[b]		0.56 (0.48 to 0.65)	1.29 (1.10 to 1.51)[c]
Hemagglutination Inhibition Antibody			
Against S79, GMT (95% CI)			
0 Day	1.09 (1.06 to 1.13)	1.07 (1.04 to 1.10)	1.13 (1.08 to 1.18)
28 Days	6.59 (6.07 to 7.15)	2.78 (2.59 to 2.99)	3.99 (3.70 to 4.33)
GMT ratio (95% CI)[b]		0.42 (0.38 to 0.47)	0.61 (0.54 to 0.68)
Against SP, GMT (95% CI)			
0 Day	1.07 (1.04 to 1.10)	1.08 (1.05 to 1.12)	1.08 (1.04 to 1.11)
28 Days	4.40 (3.99 to 4.84)	3.51 (3.21 to 3.83)	6.41 (5.75 to 7.16)
GMT ratio (95% CI)[b]		0.80 (0.70 to 0.91)[c]	1.46 (1.26 to 1.69)[c]

Phase II trial – CTL response

A significant increase in CTL response was observed in the immunization sera of the first 20% of the enrolled subjects in each group, whereas that of the S79 positive vaccine group was slightly higher than that of the SP experimental vaccine group.

CTL responses induced by purified mumps virus isolated from the recent pandemics and grown in Vero cells (identified as F-genotype)



***, $P < .001$. Abbreviation: NA, no differences between 2 groups

Phase II trial – Safety

No local or systemic AEs were observed in 30 min p.i.. There is no differences in local AEs, including slight pain, redness, and itching, or SAEs, such as slight fever, in 3 study groups for 14 days p.i.. The unsolicited AEs, such as moderate fever, occurred equally in the 3 groups at 14–28 days p.i. The rate of identified SAEs in the high-dose group was identical to that in the positive control group.

Adverse Events and Serious Adverse Events

Event	All Adverse Events				Adverse Events of Grade 3 or Higher			
	A[a]	F-Low[a]	F-High[a]	*P* Value	A	F-Low	F-High	*P* Value
	No. of Participants With Event (%)				No. of Participants With Event (%)			
Adverse Event ≤14 Days After Innocation								
Total	150 (42.0)	162 (45.5)	145 (40.6)	.40	15 (4.2)	24 (6.7)	16 (4.5)	.24
Systemic event	146 (40.9)	161 (45.2)	144 (40.3)	.35	15 (4.2)	23 (6.5)	16 (4.5)	.32
Fever	126 (35.3)	142 (39.9)	122 (34.2)	.24	13 (3.6)	19 (5.3)	16 (4.5)	.55
Cough	25 (7.0)	32 (9.0)	19 (5.3)	.16	1 (0.3)	1 (0.3)	0 (0.0)	.78
Allergy	3 (0.8)	8 (2.2)	8 (2.2)	.26	1 (0.3)	6 (1.7)	0 (0.0)	.008[b]
Diarrhea	16 (4.5)	15 (4.2)	14 (3.9)	.93	0	0	0	—
Nausea, vomiting	4 (1.1)	5 (1.4)	1 (0.3)	.24	0	0	0	—
Fatigue, weakness	0 (0.0)	2 (0.6)	0 (0.0)	.11	0	0	0	—
Local event	7 (2.0)	2 (0.6)	3 (0.8)	.26	0	0	0	—
Redness	6 (1.7)	1 (0.3)	2 (0.6)	.16	0	0	0	—
Pain	1 (0.3)	0 (0.0)	2 (0.6)	.78	0	0	0	—
Itching	0 (0.0)	1 (0.3)	0 (0.0)	.33	0	0	0	—
Swelling	2 (0.6)	0 (0.0)	0 (0.0)	.33	0	0	0	—
Rash	1 (0.3)	0 (0.0)	0 (0.0)	1.00	0	0	0	—
Scleroma	4 (1.1)	0 (0.0)	0 (0.0)	.04[c]	0	0	0	—
Adverse Event <28 Days After Injection								
Total	74 (20.7)	87 (24.4)	75 (21.0)	.41	25 (7.0)	23 (6.5)	19 (5.3)	.64
Serious adverse event	16 (4.5)	16 (4.5)	12 (3.4)	.68	16 (4.5)	16 (4.5)	12 (3.4)	.68

Phase II trial – Conclusions

01 **The F-genotype attenuated mumps vaccine (SP) is safe and offers good immunogenicity against a homologous virus through the detection of neutralizing and hemagglutination-inhibiting antibodies and the CTL response.**

02 **This vaccine is noninferior to the currently used vaccine made from A-genotype viral strain (S79) in 8- to 24-month-old children.**

03 **Since the current predominant circulating strain in China is F genotype, it is suggested that high dose F genotype vaccine should be used for phase III trial.**

Thank you very much for your kind attention!

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