

# Pandemic vaccine development in Japan

## Association of Biological Manufacturers of Japan

- Biken
- Denka Seiken
- Kaketsuken
- Kitasato

2005.11.02

# Concept of vaccine development in Japan

- Better immunogenicity
- Antigen sparing



**Alum-adsorbed whole virion vaccine**

# Vaccine development plans

- **Candidate formulations**
  - Alum adjuvanted whole virion vaccine or plain whole virion vaccine
- **Reference virus**
  - NIBRG-14
- **Preclinical safety testing**
  - Single dose toxicity
  - Repeated dose toxicity
  - Local irritation toxicity
  - Reproductive and developmental toxicity

# Seed Virus preparation

Virus	Kaketsuken (SPAFAS)	Kitasato (Japanese SPF eggs)	Biken (Japanese SPF eggs)
Vero1/E2 (NIBSC)	6.4	7.5	7.1
Vero1/E2/E1	6.6	7.5*	7.7
Vero1/E2/E2	6.4	-	7.9

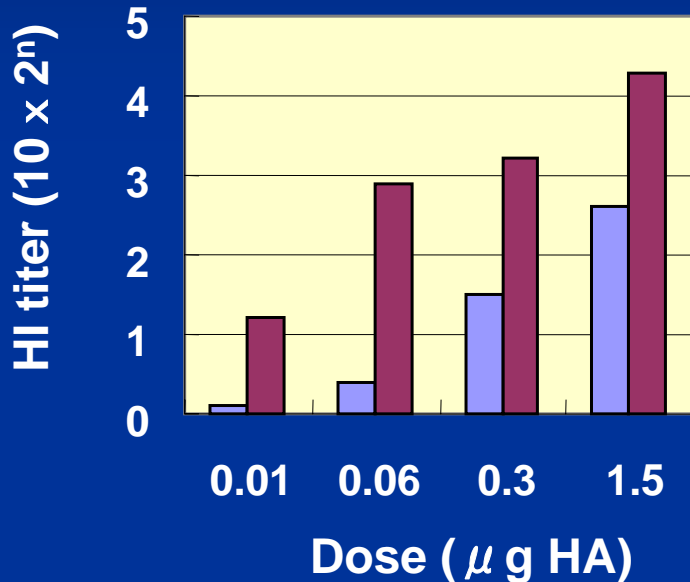
\*Selected as the seed virus

# Pilot vaccine productions

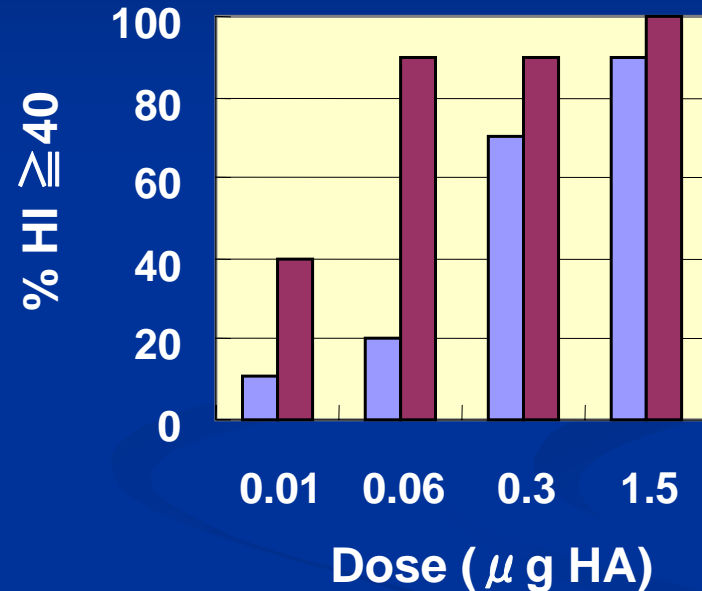
- Each manufacturer produced several batches of bulk solutions using conventional eggs
- Antigen yields were 1/5-1/10 of interpandemic viruses

# Immunogenicity in mice

## GMT

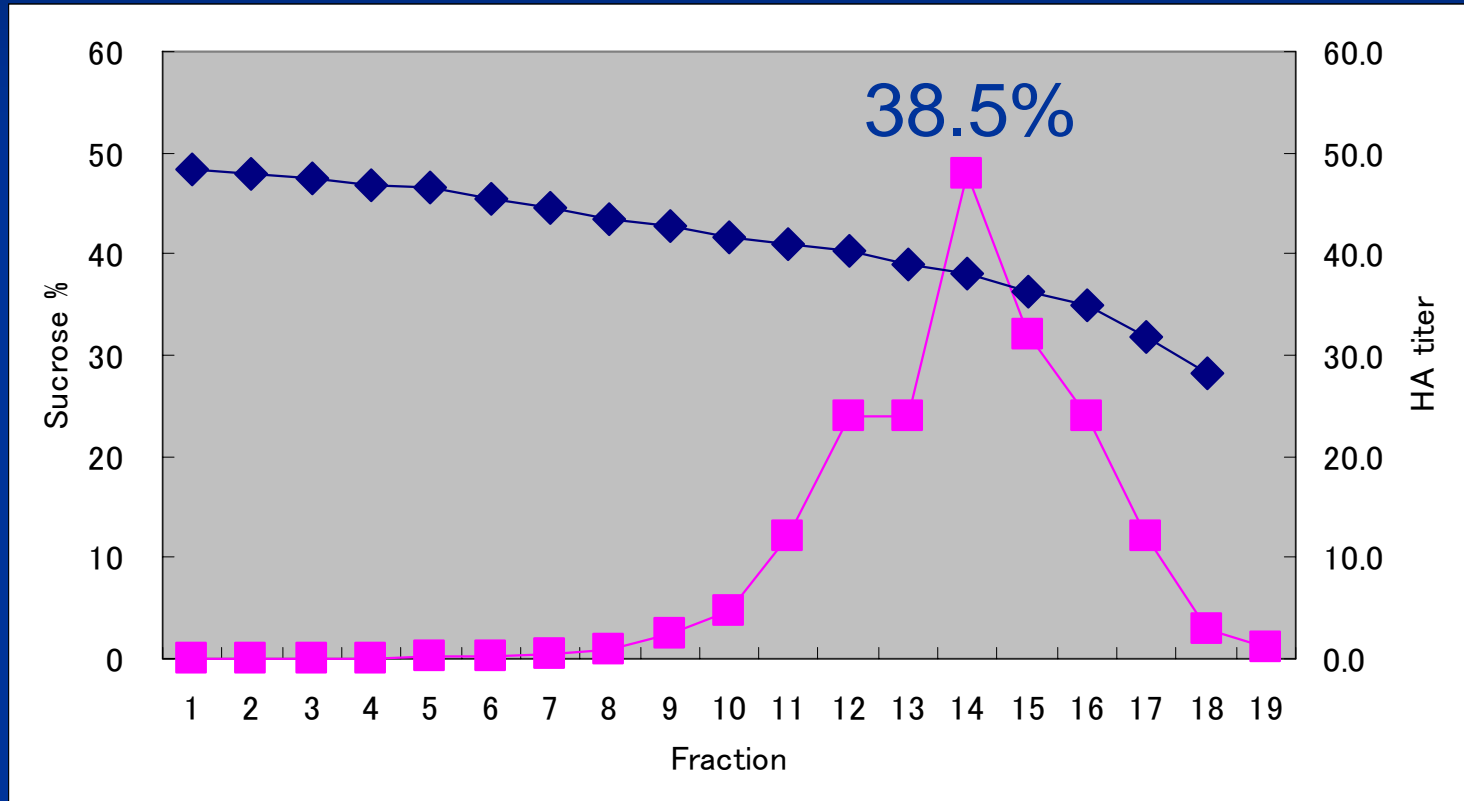


## Sero-conversion

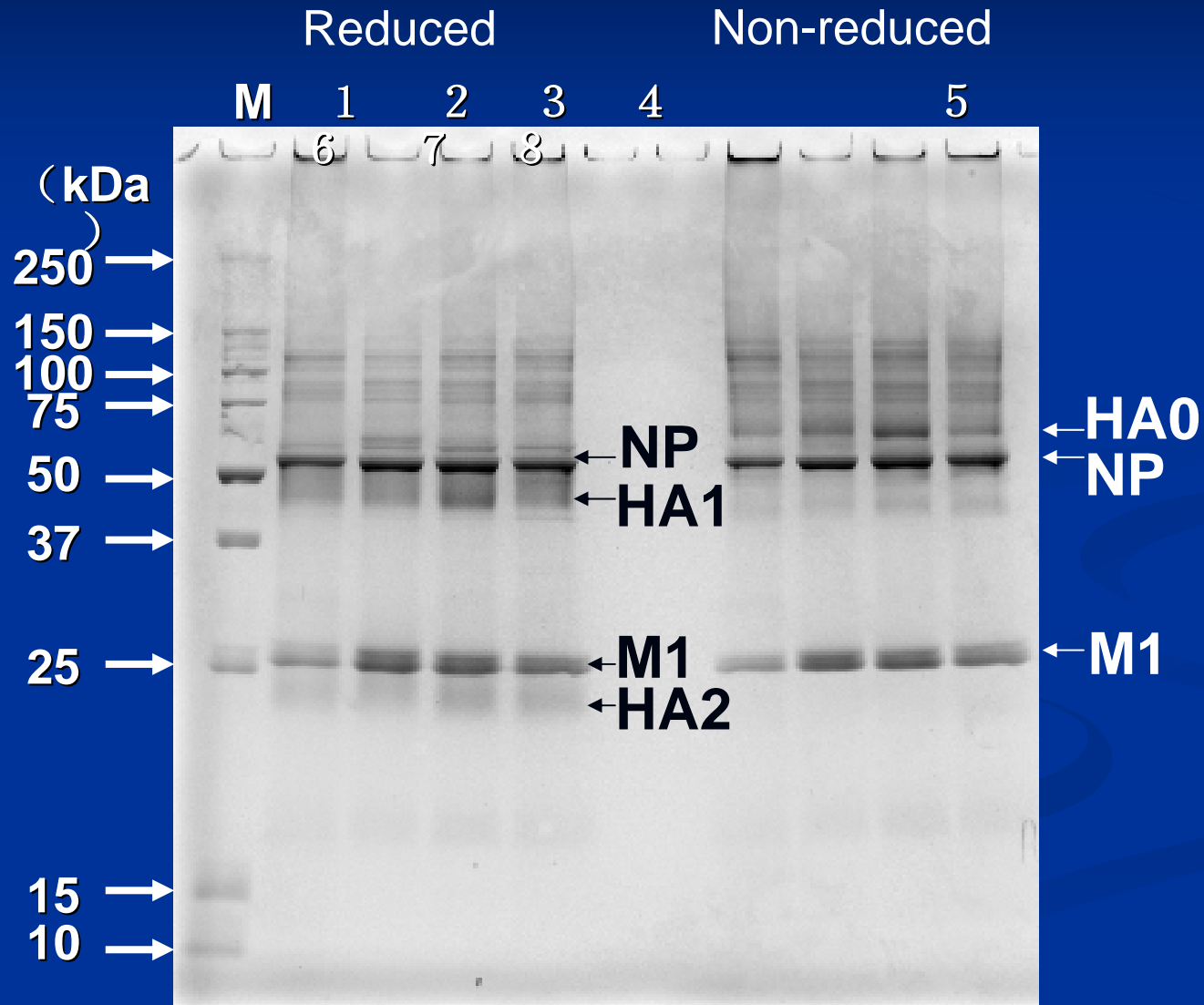


- Plain vaccine
- AL adjuvanted

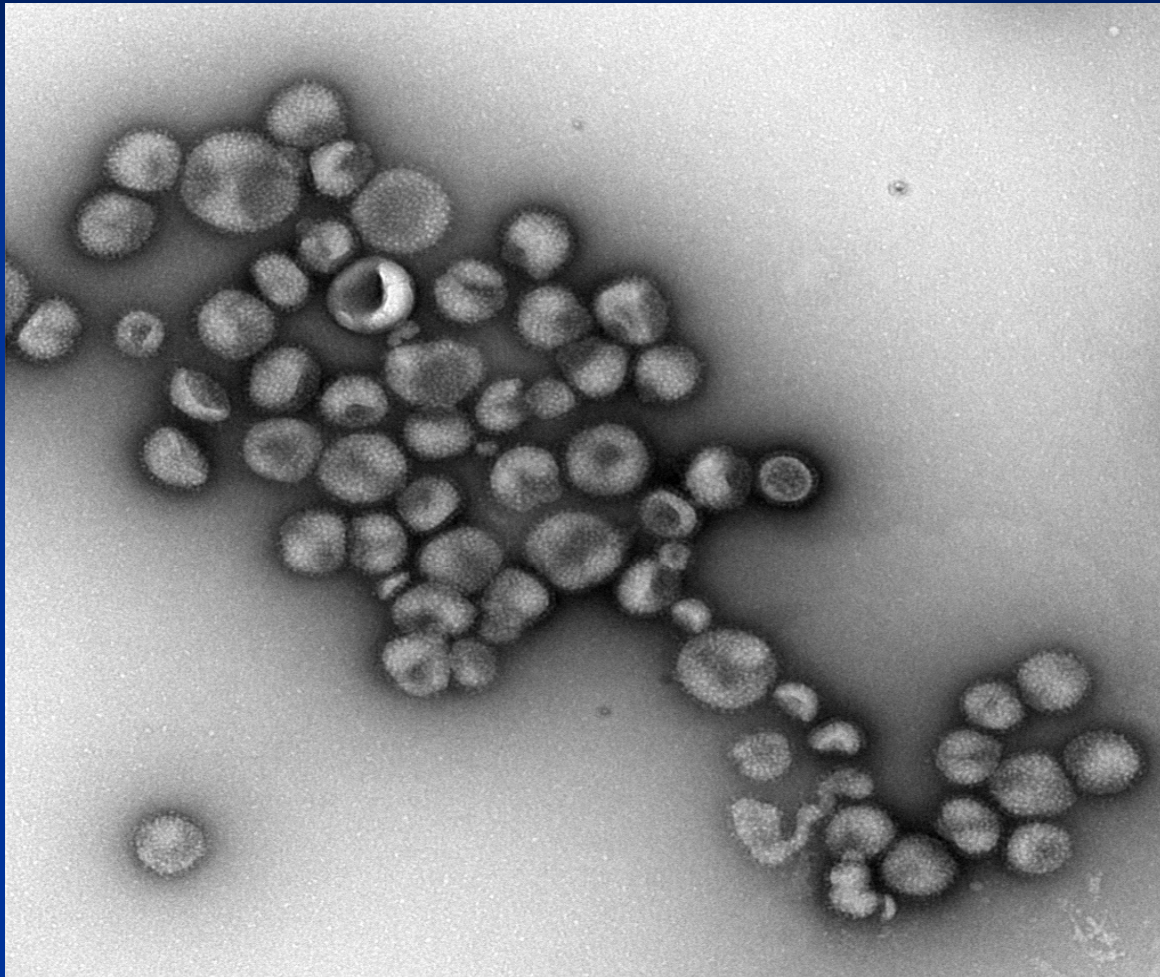
# Zonal centrifugation pattern



# SDS-PAGE patterns of bulks



# EM picture



Z0401 filtration ( )-09.tif  
Z0401 filtration ( )  
Print Mag: 88800x @ 7. in  
10:59 01/11/05

100 nm  
HV=100kV  
Direct Mag: 10000x  
X:-307 Y: -408.9 T:-0.0  
AMT Camera System

# Samples used for the toxicity studies

- Whole virion antigen, 30ug HA/mL, with 0.3mg AL/mL aluminum hydroxide gel
- Plain vaccine sample, 30ug HA/mL, without aluminum hydroxide gel
  - An alternative when strong toxicities are found with the adjuvanted vaccine

# Single dose toxicity

Animal Used	Samples	Route	Dose	Results
Rats	AL+/- Whole	Sc	2, 10mL/Kg	LD50: >10mL/Kg
Dogs	AL+/- Whole	Sc	1, 5mL/Kg	LD50: >5mL/Kg

# Local irritation (sc, im)

Sample	Injection	Dose	Results
■AL+/- Whole ■DTaP	1 2	0.5mL/site	■There are no differences among AL+, - and DTaP in observations upon autopsy
■AL+/- Whole ■DTaP	1 2	0.5mL/site	■Histopathology is ongoing

# Repeated dose toxicity in rats

<b>Sample</b>	<b>■Route</b> <b>■Number of injection</b>	<b>Dose</b>	<b>Results</b>
<b>AL+ only</b>	<b>■Sc</b> <b>■5 times at 1 week intv.</b>	<b>0.25, 0.5 mL/Kg</b>	<b>Results will be obtained shortly</b>

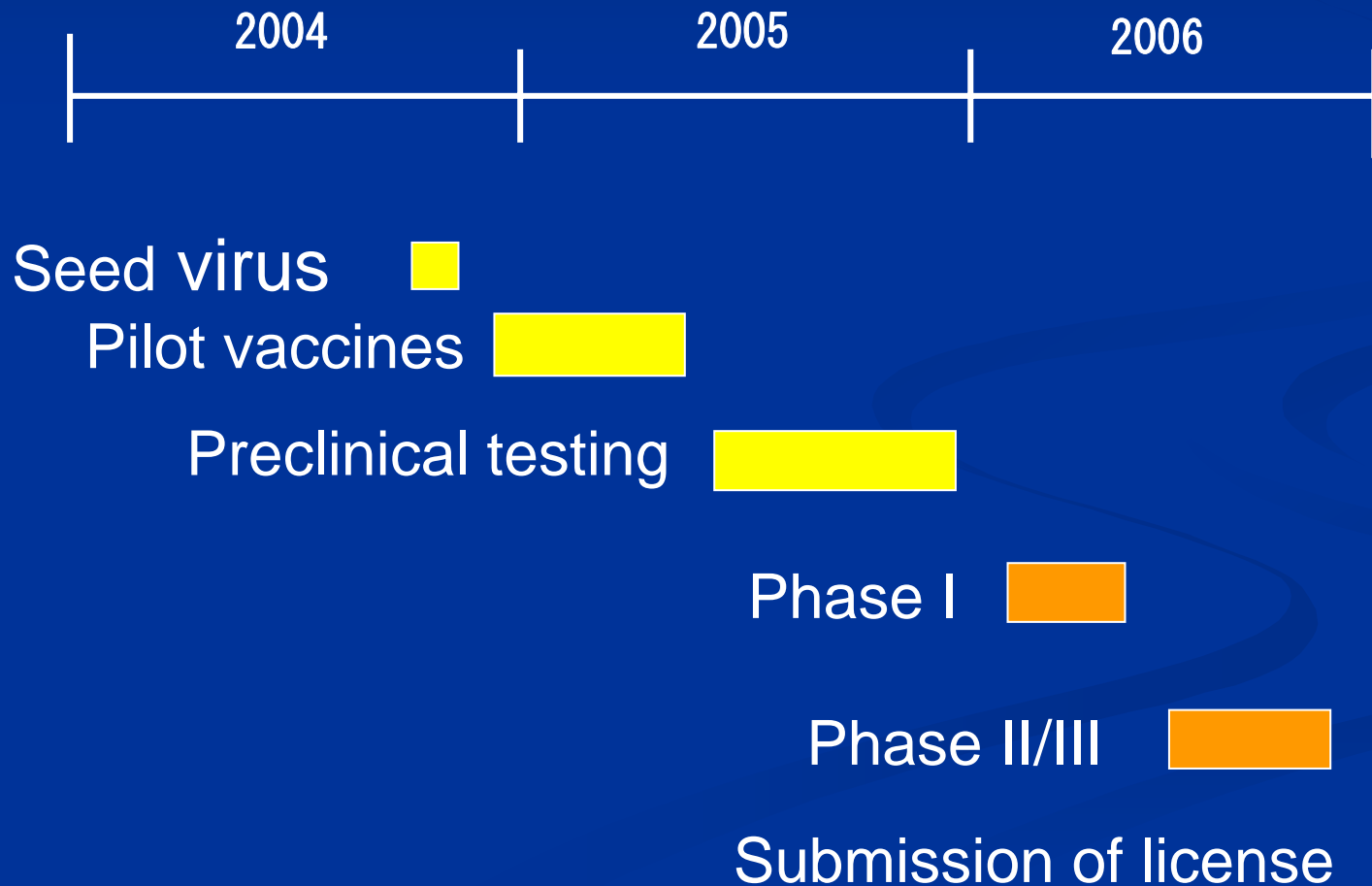
# Developmental toxicity

- **The testing is planned to be conducted before initiating phase II/III studies.**

# Conclusions

- Antigen yields of NIBRG-14 were 1/5-1/10 of interpandemic viruses
- Immunogenicity of NIBRG-14 in mice was enhanced by adding aluminum hydroxide gel
- Toxicity of the alum-adjuvanted whole virion vaccine was comparable to that of DTaP vaccine

# Tentative schedule



# Recommendation

- **SRD reagents may not be available in timely fashion at the beginning of a pandemic situation.**
- **Alternative methods, e.g. SDS-PAGE, should be standardized.**
- **Low yield of RG strains should be overcome.**