

Overview of Current Vaccine Manufacturing Capacity in Developing Countries: Existing Infrastructure

Current Status at SIIL/Pune for Pandemic Influenza Vaccine

**3rd Meeting with International Partners on Prospects for Influenza Vaccine
Technology Transfer in Developing Countries**

5-6 May 2010, Nha Trang, Vietnam

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*Sincere apologies from
Dr. R.M. Dhere for leave of
absence.*

Global Pandemic Influenza Action Plan: Historical Background

- **A World Health Assembly Resolution (WHA 58.5, Agenda item 13.9): WHO Secretariat to seek solutions for reducing global shortage of influenza vaccines for both epidemics and pandemics – 23 May 2005.**
- **WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply (GAP) – 2-3 May 2006, launched in November 2006.**
- **Vaccine production capacity building in developing countries : a GAP inspired approach to strengthen pandemic influenza preparedness and response – launched by IVR in February 2007.**

Global Pandemic Influenza Action Plan to Increase Vaccine Supply (GAP 2006)

Goal

- Developing enough pandemic vaccine to immunize the world's population (6.7 billion people in 6- 9 months)

Specific objectives

"By increasing the supply of a pandemic vaccine and thereby reducing the gap between the potential vaccine demand and supply anticipated during an influenza pandemic"

- Increase use of seasonal vaccine to drive market & production capacity
- Expand vaccine production capacity by building new production plants in both developing and industrialized countries.
- Encourage further research and development



SERUM INSTITUTE OF INDIA LTD. (SIIL)

PUNE, INDIA

Indigenous Influenza Vaccine Production

Considerations for vaccine development

Reported influenza vaccine technologies

• **Attenuated influenza vaccine for immunization through nasal route**

- Large number of doses in a short duration
- Small manufacturing setup
- Low cost

• **Inactivated vaccine containing whole virus/subunit virus preparations**

- Time tested technology



**Inactivated vaccine containing
whole virus/ subunit virus preparations**

Development laboratory

**Development of protocols for
virus growth, inactivation and
purification in**

- MDCK cells
- Vero cells
- Embryonated eggs

Analytical laboratory

**Establishment of testing
protocols**



Summary of activities

(Year 2007 to Feb 2009)

A/PR/8/34, A(H1N1)

Establishment of analytical tests protocols
Testing of virus growth and purification methods
(Quarter 1, 2)



Seasonal influenza vaccine strain

A(H1N1), A(H3N2), type B

Establishment of virus growth and purification methods
Comparison of yields in eggs and tissue culture
Generation of trivalent seasonal influenza vaccine
Immunogenicity studies
(Quarter 3, 4, 5)



Pandemic influenza vaccine strain A(H5N1): NIBRG-14

Generation of prototype whole and subunit vaccine
Immunogenicity studies with and without adjuvants
(Quarter 6)

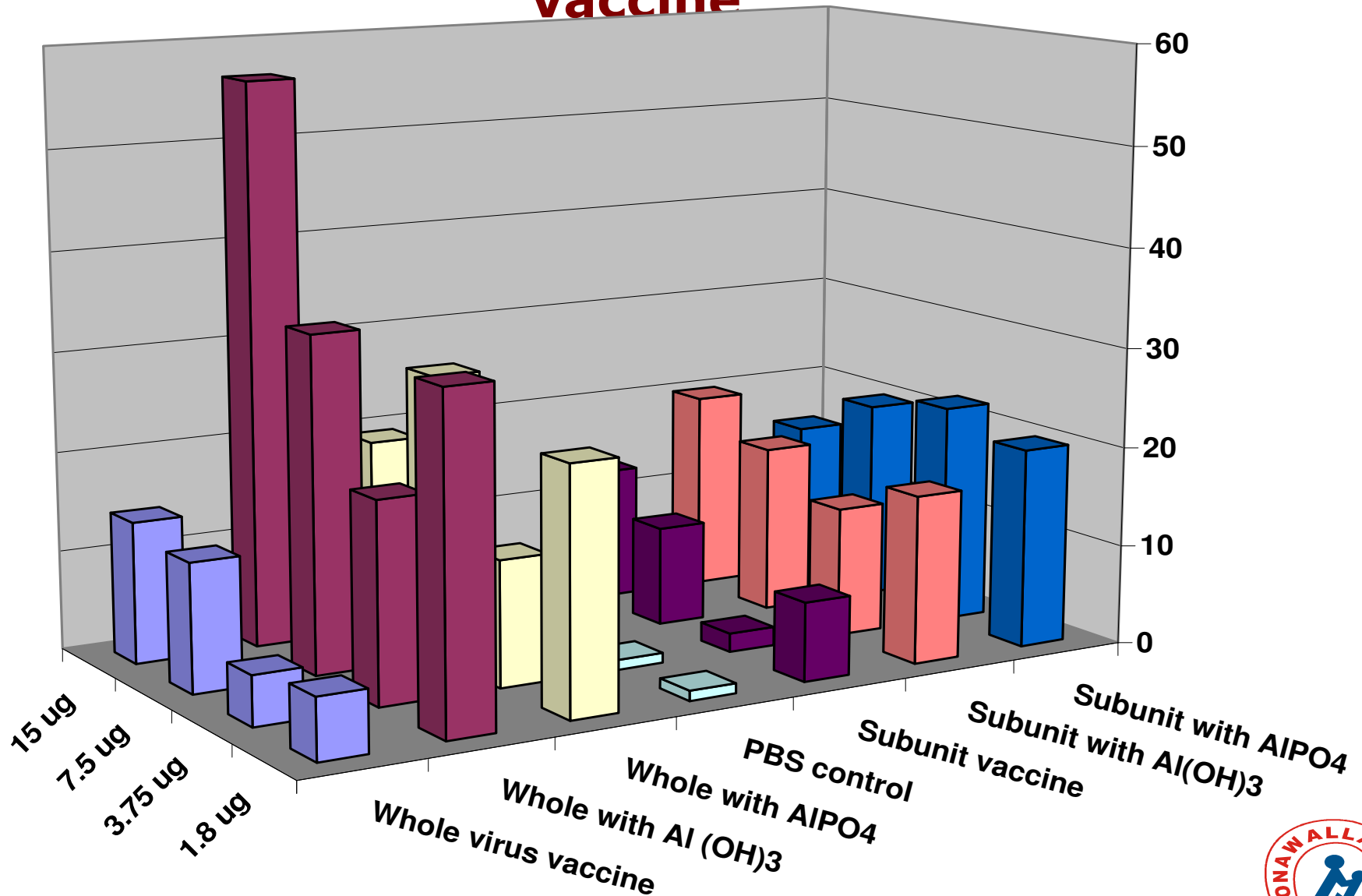


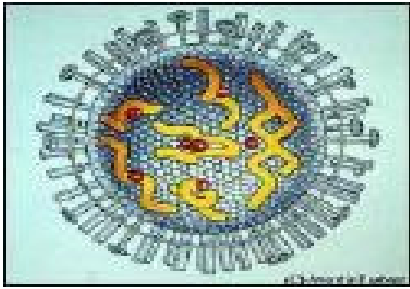
Attenuated influenza vaccine for immunization through nasal route

- **Nobilon has -by a license agreement of 15 January 2009- granted WHO a non-exclusive license to develop, register, make, use and sell egg-based, live attenuated influenza vaccines with the right to grant a sublicense to private companies or governmental or non-governmental organizations in developing countries working within the framework of the WHO Global Pandemic Influenza Action Plan.**
- **SIIL has signed an agreement with WHO for tech transfer of technology for the manufacture of live attenuated influenza vaccine.**



Comparative immune response to H5N1-NIBRG-14 whole virus vaccine and subunit vaccine





H1N1: Global Health Threat (April 2009)

- April 2009, spread of new influenza virus H1N1. Raised concerns for emerging pandemic.
- April 2010: At least 17853 deaths were reported in 214 countries globally.
- Vaccine manufacturers globally have prepared for pandemic flu vaccine.
- May 2009: SIIL was asked to undertake Swine Flu vaccine development to be ready by early 2010 for global use.
 - July 2009 : Strain for inactivated vaccine was received.
 - August 2009 : Strain for live attenuated vaccine was received.

Considerations for vaccine development

Reported influenza vaccine technologies

• **Attenuated influenza vaccine for immunization through nasal route**

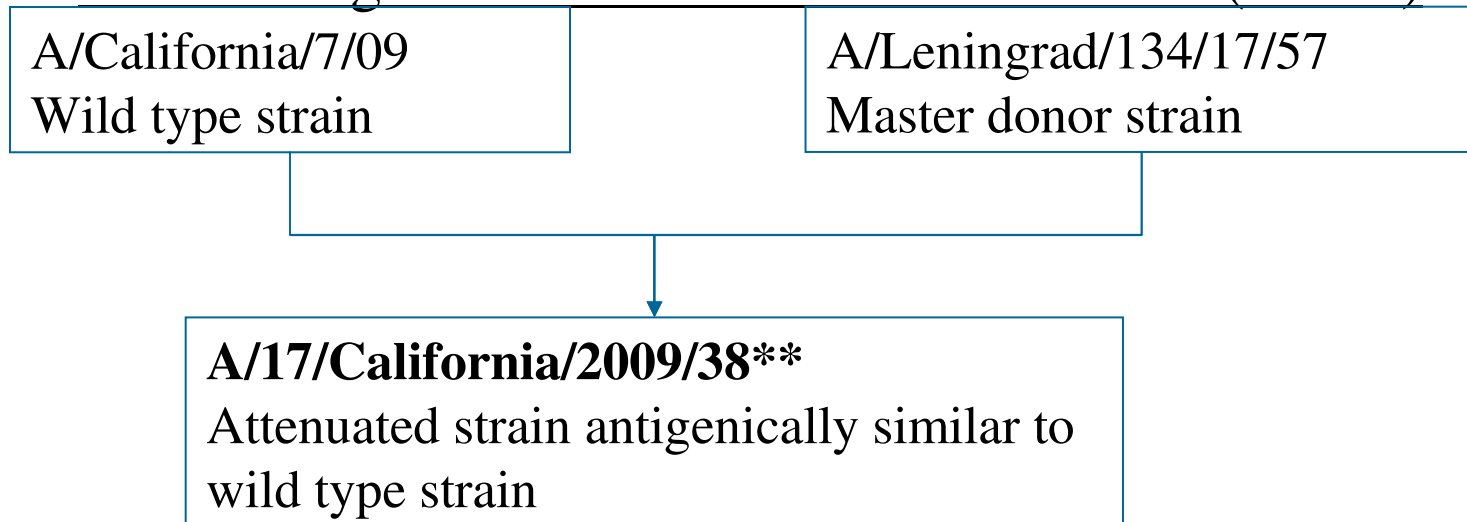
- Large number of doses in a short duration
- Small manufacturing setup
- Low cost

• **Inactivated vaccine containing whole virus/subunit virus preparations**

- Time tested technology

Live attenuated Influenza Vaccine

Strain designation: *A/17/California/2009/38* (H1N1)



** [A/17/California/2009/38](#) refers to

A-Type A strain

17- A/Leningrad/134/17/57 master donor strain

California/2009- A/California/7/2009 recommended strain

38- Laboratory number of attenuated strain

Intranasal delivery

Egg Based Live Attenuated Influenza Vaccine (LAIV): Salient Features

SUMMARY

- Extensive community experience with LAIV in Russia.
- Proven safety and efficacy.
- No evidence of either genetic reversion or new mutant formation.
- Community immunity benefits – particularly with children.
- No evidence of increased allergic reaction in children or adults.
- Vaccine capable of being produced in either eggs or mammalian cell culture.
- Protective value of mucosal immunity and functional antibody levels associated with LAIV.
- Ability of vaccine to protect (substantially) in face of antigenic drift.
- Immediate level of protection with LAIV (1st 7 days).
- LIV H5/17 virus reassorted with avian H5N2 displayed high levels of protection in mice challenged with H5N1 viruses isolated in 1997 – 2003.

LAIV Vaccine



Lyophilized Vaccine 5 dose per vial



Diluent: Sterile Water for Inhalation USP

The components (Multi-dose-5)



Supply
configuration

Details of Live Attenuated Influenza Vaccine Production and Vaccine Capacity

- Dedicated setup for bulk production
- Dedicated setup for filling and freeze drying
- Estimated to generate substantial quantity of vaccine



Details of Inactivated Influenza Vaccine Production and Vaccine Capacity

- Dedicated setup for bulk production
- Dedicated setup for filling
- Vaccine to be delivered as an intra-muscular route
- Estimated to generate substantial quantity of vaccine.
- Strain used: NYMCX-179A received from NIBSC, UK
- Reassortant between A/PR/8/34 and A/California/7/2009v developed using classical method
- Influenza vaccine (inactivated, whole virion) adjuvanted using Al(OH)₃

Status report of influenza vaccine development and production as of 3rd May 2010

	LIVE ATTENUATED INFLUENZA VACCINE (LAIV)
Production and testing	<ol style="list-style-type: none">1. Production process and analytical testing completely established.2. Process validation and analytical process validation and stability is in progress.
Animal tox studies	<ol style="list-style-type: none">1. Acute and Sub-Acute toxicity studies completed.2. Teratogenic effect studies are in progress.
Clinical evaluation	<ol style="list-style-type: none">1. Clinical Trial Application for LAIV was filed in last week of Dec'092. Permission obtained in 1st week of January 2010.3. Phase I Clinical Trial completed4. Phase-II/III: Ongoing

Phase I study

- Double-blind, randomized, placebo-controlled study
- 50 healthy Adults of 18-49 years of age
- Lambda Therapeutic Research Limited, Ahmedabad.
- Vaccine: live attenuated influenza virus re-assortant of the pandemic (H1N1) 2009 virus: A/California/7/2009 (H1N1)
- Dose: Not less than $10^{7.0}$ EID₅₀ in 0.5 ml
- 40 subjects are male.
- Mean age was 31 ± 11 yrs
- Study visits: Day -7, 0, 1, 3, 7, 14, 21 and 42.
- Route- Intra nasal spray

Day 42 follow up completed

Safety findings

- Most of the reactions were mild.
- All reactions resolved within 3 days without any sequelae.
- no unsolicited adverse event/SAE.
- No changes in hematology, biochemical, electrolyte and urine parameters.
- no protocol deviation or violations

Phase II/III

- Double-blind, randomized, placebo-controlled, multi-centric study
- Population: 330 subjects (110 children, 110 adults and 110 elderly).
- 10 study centre across India
- Randomization: 1:1
- Study visits: Day 0, 7, 21, 28, 42, 60 and 90.
- Two Doses of LAIV/placebo at 21 days apart intra-nasally
- Immunogenicity
 - HAI
 - Microneutralization
 - Serum IgG
 - Mucosal IgA

21 day follow up study has been completed.

Status report of influenza vaccine development and production as of 3 May 2010

	INACTIVATED INFLUENZA VACCINE (IIV)
Production /Testing	<ol style="list-style-type: none">1. Production process standardized, scale up and consistency batches are being produced.2. Batch for animal toxicity produced, tested and used for animal toxicity studies.
Animal tox studies	<ol style="list-style-type: none">1. Acute and Sub-Acute toxicity studies completed.2. Teratogenicity studies are ongoing
Clinical evaluation	<ol style="list-style-type: none">1. Filling of clinical (human) trial batch completed and under QC testing.2. Permission for clinical trial obtained on 9th Jan'10.3. Phase I study: completed4. Phase II/III: Study Ongoing

Phase I study

- Double-blind, randomized study
- 50 Adult subjects of 18-49 years of age (40 males and 10 females in mean age group of 31.04 ± 7)
- Inactivated Influenza A (H1N1) virus vaccine
- Two doses of 10 mcg and 15 mcg will be used
- Day -7, 0, 1, 3, 7, 14, 21 and 42.
- Route- intramuscular

Status: 42 day follow up completed

Safety findings

- All were mild in severity.
- All reactions resolved within 3 days without any sequelae.
- no unsolicited adverse event / SAE.

Phase II/III study

- Double-blind, randomized, multi-centric study
- Population: 330 subjects at 10 study centre across India (110 children, 110 adults and 110 elderly)
- Study visits: Day 0, 7, 21, 28, 42, 60 and 90.
- Two doses of 10 mcg and 15 mcg will be used 21 days apart intramuscularly
- Immunogenicity assessment: HAI titres
- 21 day follow up completed.

Conclusions

- Phase I study of LAIV & IIV suggest excellent safety of both the vaccines in healthy adults.
- 21 day data of Phase II/III studies of LAIV and IIV suggests safety of both vaccines in adults, elderly and children.
- Immunogenicity analysis in Phase II/III studies is ongoing.

Existing production capacity (Annual)

LAIV Monovalent , H1N1 (2009)	
Bulk	40 million doses/year
Filling/ Lyophilization	30 million doses (1 dose) 150 million doses (5 dose)
IIV Monovalent, HINI 2009	
Bulk	0.36 million doses/year
Filling and Lyophilization	15 million dose/year

Future plans

- Submission to Drug Controller General of India for license by second week of May 2010.
- Expected to make vaccine available by second week of June 2010.

Thank You

Solicited local reactions LAIV

Local reactions	LAIV vaccine		Placebo	
	N	%	N	%
Nasal discomfort	2	8 %	2	8 %
Sneezing	7	28 %	1	4 %
Stuffy nose	2	8 %	1	4 %
Runny nose	2	8 %	1	4 %

Solicited systemic reactions: LAIV

Systemic reactions	LAIV vaccine		Placebo	
	N	%	N	%
Headache	5	20 %	2	8 %
Chills	2	8 %	-	-
Fatigue	3	12 %	1	4 %
Sore throat	4	16 %	1	4 %
Cough	3	12 %	-	-
Myalgia	2	8 %	-	-
Arthralgia	2	8 %	-	-
Irritability	2	8 %	-	-
Loss of appetite	-	-	1	4 %
Nausea	2	8 %	-	-
Diarrhoea	-	-	2	8 %

Solicited reactions: IAIV

Reaction	N	%
Local pain/tenderness	6	12%
Headache	4	8%
Body ache	2	4%
Nausea	1	2%
Fatigue	2	4%
Myalgia	4	8%
Chills	2	4%
Malaise	1	2%

Immunogenicity assessment

- HAI will be used.
 - The proportion of subjects in each group with HI titres $\geq 1:40$ on day 0, 21 and 42.
 - The proportion of subjects in each group with a four-fold rise in HI antibody titres on day 21 and 42.
 - Geometric Mean of serum HI antibody titre in each group on day 0, 21 and 42.