

CLINICAL TRIALS OF LAIV H1N1

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PROTOCOL OF CLINICAL TRIALS (LAIV, A/17/CALIFORNIA/2009/38 (H1N1))

Population	Site	Vaccine	Infectivity (log ₁₀ EID ₅₀ /0.5 ml)	No. of Doses	No. of Volunteers	Interval (days)
Healthy adults * 18-50 years old	Moscow Institute of Military Medicine	Vaccine	6.5	2	25	10
		Placebo			5	
		Vaccine	6.5		25	21
		Placebo			5	
	St. Petersburg Institute of Influenza	Vaccine	6.5		25	10
		Placebo			5	
		Vaccine	6.5		25	21
		Placebo			5	
Children 12-18 years old	Perm Medical State Academy	Vaccine	7.0	2	30	10
		Placebo			0	
Elderly > 60 years old	Perm Medical State Academy	Vaccine	7.0	2	30	10
		Placebo			0	

* 46.7% - man

53.3% - women

Average age – 35 years old

7 days after 1st and 2nd vaccination volunteers stayed in clinic

Clinical trials continue among children 3-11 years old

REACTOGENICITY OF LAIV A/17/CALIFORNIA/2009/38 (H1N1)

Group (No. of volunteers)	Temperature (%)			Systemic reactions (%)*	Local reactions (%)**
	Low (37.1-37.5)	Middle (37.6- 38.5)	High (>=38.6)		
Vaccination					
Vaccine (N=100)	11 (11.0)	1 (1.0)	0	2 (2.0)	33 (33.0)
Placebo (N=20)	0	0	0	0	0
Revaccination					
Vaccine (N=100)	1 (1.0)				
Placebo (N=20)	0	0	0	0	0

Vaccination

Revaccination

*Systemic reactions:

Fatigue, headache

Headache

**Local reactions:

Sore throat, running nose, cough, dysphonia

Running nose

IMMUNE RESPONSE IN VOLUNTEERS VACCINATED WITH LAIV A/17/CALIFORNIA/2009/38(H1N1)

Preparation, Interval between 1 st and 2 nd vaccinations	Number of persons	Sample	Assay					Cumulative data from all tests (%) ***	
			HAI			ELISA sera	ELISA nasal secrets		
			≥ 4 fold rise (%)	GMT	Ab titers ≥ 1:20 (%)	Ab titers ≥ 1:40 (%)	IgG ≥ 4 fold rise (%)		IgA ≥ 4 fold rise (%)
LAIV 10 days*	46	I	4.3 %	5.5	0	0	10.9 %	6.5 %	13.0 %
		II		6.5	6.5%	1.8%			
		III	50.0 %	15.4	54.3 %	32.6%	45.7 %	56.5 %	
LAIV 21 days**	47	I	23.4 %	5.4	0	0	25.5 %	38.3 %	42.5%
		II		8.8	25.5%	2.1%			
		III	34.4 %	11.0	34.1%	17.0%	44.7 %	63.8 %	
Placebo	19	I	0	6.5	5.3%	5.3%	0	0	0
		II		8.4	10.5%	0			
		III	0	9.0	10.5%	0	0	0	

Volunteers with HAI serum Ab titers ≤ 1:10 before vaccination

* I – before first vaccination; II – 10 days after first vaccination; III – 21 days after second vaccination.

** I – before first vaccination; II – 21 days after first vaccination; III – 21 days after second vaccination.

*** % of volunteers with conversions detected in one or more tests.

Virus-specific CD8+ and CD4+ T-cells in volunteers vaccinated with LAIV A/17/California/2009/38 (H1N1)

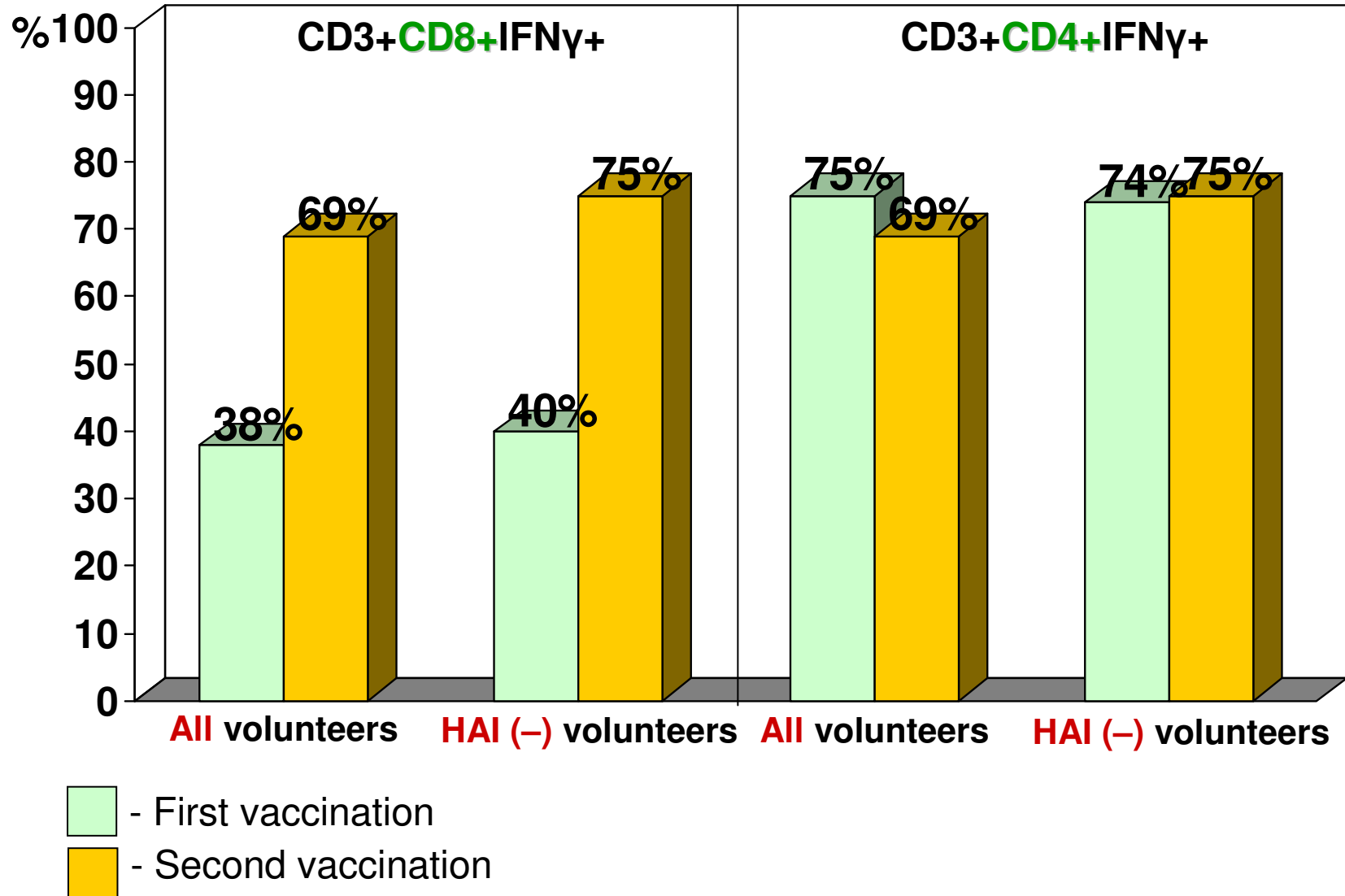
Group	n	Fold changes of CD8+ and CD4+ levels			
		CD3+CD8+IFN γ + cells		CD3+CD4+IFN γ + cells	
		First vaccination	Second vaccination	First vaccination	Second vaccination
LAIV interval - 21 days	9	3.5	4.3 *	16.0*	32.5*
LAIV interval - 10 days	7	1.4	2.0 *	5.6 *	12.0*
Placebo	9	0.9	0,7	1.0	0.8

Virus-specific cells were detected by cytokine test (intracellular IFN- γ +). CD3+ molecules are present on T-lymphocytes only.

$$\text{Fold change} = \frac{\% \text{ of cells before vaccination}}{\% \text{ of cells after vaccination}}$$

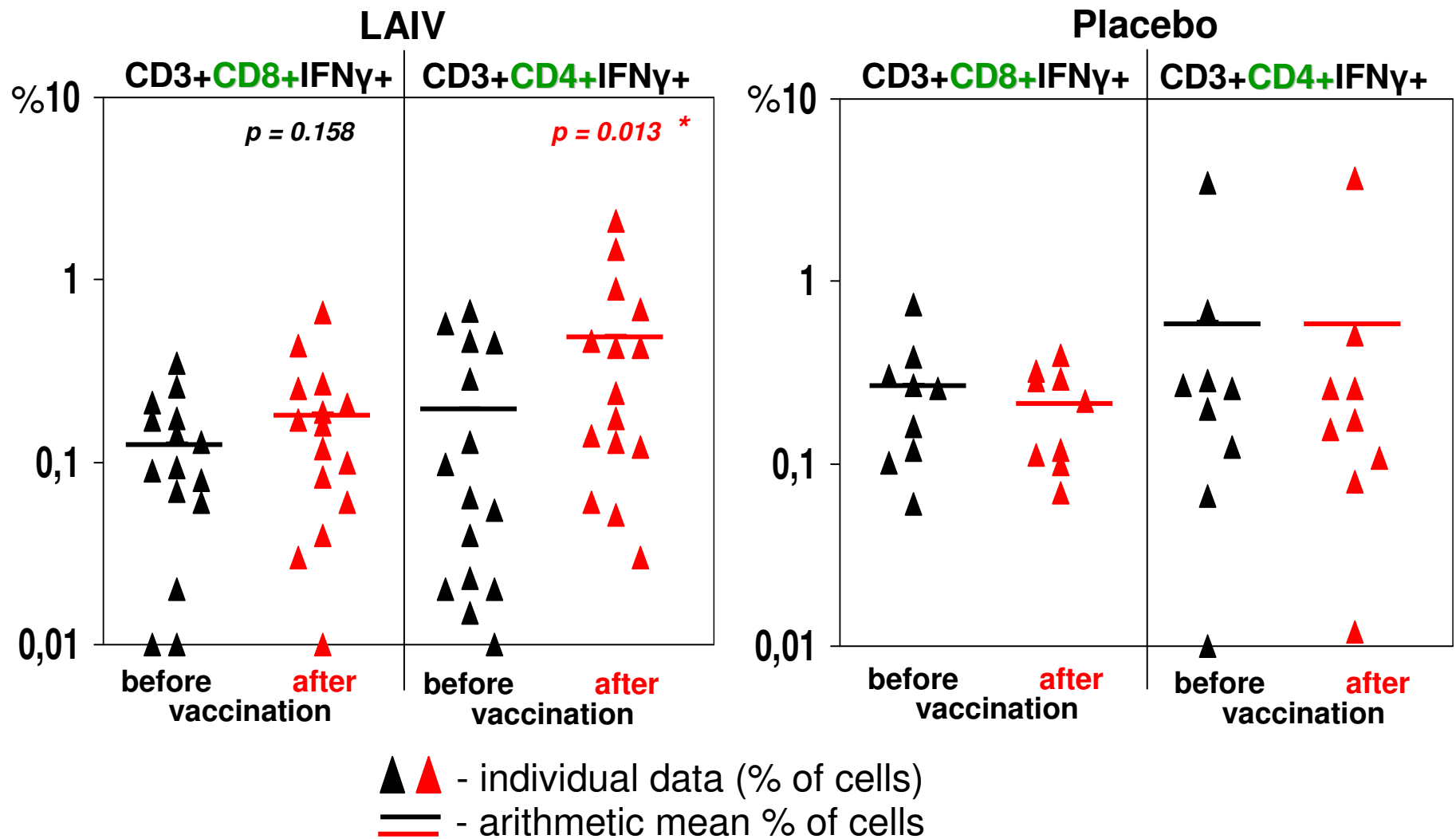
* Results were adjusted with P value <0.050, compared with Placebo group.

Percentage of volunteers with reliable increase* (RI) of virus-specific CD8+ and CD4+ T-cells after vaccination with LAIV A/17/California/2009/38 (H1N1)



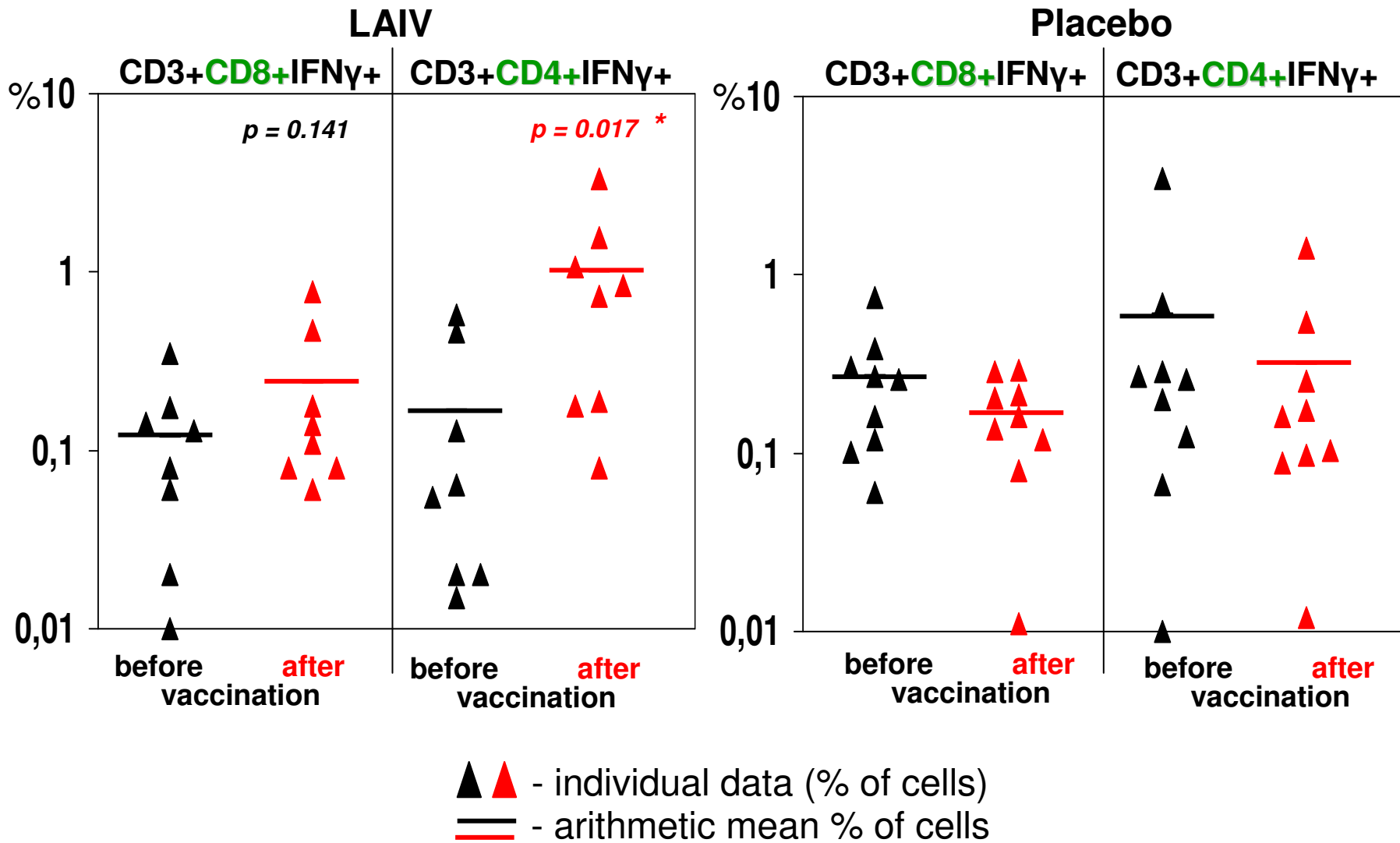
* RI were estimated as results exceeding 2 Standard Deviations of placebo mean value.

VIRUS-SPECIFIC CD4+ AND CD8+ MEMORY T-CELLS IN VOLUNTEERS WITHOUT SERONONVERSIONS TO PANDEMIC A (H1N1) *FIRST DOSE*



* Results were adjusted with P value <0.050

VIRUS-SPECIFIC CD4+ AND CD8+ MEMORY T-CELLS IN VOLUNTEERS WITHOUT SEROCONVERSIONS TO PANDEMIC A (H1N1) *AFTER TWO DOSES*



* Results were adjusted with P value <0.050

**Cumulative data of post-vaccination immune response in
volunteers (n=16) after vaccination with LAIV
A/17/California/2009/38 (H1N1)**

Immunological tests	Number of volunteers with reliable immune responses		
	First vaccination	Second vaccination	Long-term immune response (42 days after second vaccination)
HAI test	12.6 %	50.0 %	56.3 %
All tests - cumulative data *	56.3 %	87.5 %	100 %

* Cumulative data – reliable increases in one or more tests (HAI-test or local IgA-antibodies or serum IgG-antibodies or cellular immune responses: virus-specific CD8⁺IFN γ ⁺ and CD4⁺IFN γ ⁺ T-cells).

IMMUNE RESPONSE IN ELDERLY VACCINATED WITH LAIV A/17/CALIFORNIA/2009/38(H1N1)

Preparation, Interval between 1 st and 2 nd vaccinations	Number of persons	Sample	Assay						Cumulative data from all tests (%) ***
			HAI*			ELISA Ig G			
			≥ 4 fold rise (%)	GMT	Ab titers ≥ 1:20 (%)	Ab titers ≥ 1:40 (%)	≥ 4 fold rise (%)	GMT	
LAIV 10 days*	30	I	-	5.7	0	0	-	729.4	16.7%
		II	6.7 %	6.3	10.0%	0.0%	10.0 %	746.4	
		III	40.0 %	12.3	43.3 %	16.7%	26.7 %	919.0	56.7%

- **Volunteers with HAI serum Ab titers ≤ 1:10 before vaccination**

Immunogenicity of LAIV A/17/California/2009/38(H1N1) among children 12-18 years old

Antigen	Vaccination ²	Total No.	No. (%) with ≥ 4 -fold rise	GMT ³	GMT - rise	No. (%) with HAI titer $\geq 1:40$
A (H1N1) ¹	1st	29	12 (41.4)	20.5	3.1	13 (44.8)
	2 nd	18	15 (83.3)	44.9	6.7	15 (83.3)

¹A (H1N1) - A/17/California/2009/38 (H1N1) Source of erythrocytes: human

²Interval – 10 days

³GMT (Geometric mean titer) before 1st dose: 6.7

Immunogenicity of H1N1 LAIV A/17/CALIFORNIA/2009/38 (H1N1) in ferrets after a single-dose immunization

		HAI Serum					HAI Serum		
		Day 0	Day 20				Day 0	Day 20	
Group	Number	A/California /EURRG4/'09	A/California /EURRG4/'09	A/Netherlan ds/EURRG02 /'09	Group	Number	A/California /EURRG4/'09	A/California /EURRG4/'09	A/Netherlan ds/EURRG02 /'09
Negative control	1	5	5	5	Thai GPO clinical trial grade pandemic LAIV	13	5	640	640
	2	5	5	5		14	5	960	960
	3	5	5	5		15	5	1280	1280
	4	5	5	5		16	5	640	640
	5	5	5	5		17	5	400	320
	6	5	5	5		18	5	1120	1120
	Average:	5	5	5		Average:	5	840	827
Russian registered pandemic LAIV	7	5	400	400	Indian SII clinical trial grade pandemic LAIV	19	5	640	640
	8	5	640	640		20	5	280	320
	9	5	320	280		21	5	280	320
	10	5	560	640		22	5	800	960
	11	5	640	640		23	5	200	280
	12	5	640	960		24	5	400	400
	Average:	5	533	593		Average:	5	433	487

SUMMARY

- Safety of pandemic H1N1 LAIV was demonstrated in randomized, double-blind clinical trials among adults, elderly and children 12-18 years old.
- Study of 10-days and 21-days regimen between two doses of LAIV have shown that 21-days interval was optimal for immunogenicity.
- HAI, IgG ELISA, IgA ELISA (nasal washes) and cytokine tests were used for evaluation of immunogenicity of LAIV.
- HAI test results among different age groups reveal that LAIV is the most effective in children.
- Immunogenicity data based on cumulative data of different assays such as HAI, ELISA IgG, ELISA IgA and cytokine test have shown the possibility to recommend single dose vaccination with LAIV for different groups of population.
- Immunization of ferrets with H1N1 LAIV induces high titer of HAI.

ACKNOWLEDGEMENTS

PATH

Kathy Neuzil

Rick Bright

Institute of Influenza

O. Kiselev

M. Erofeeva

A. Sominina

E. Voyzheovskaya

IEM RAMS

N. Larionova

I. Kiseleva

A. Naykhin

S. Donina

“MICROGEN”

A. Mironov

I. Sakaeva

CDC

A.Klimov

Swine influenza? – Get LAIV!

