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Live attenuated pandemic influenza vaccine: Clinical studies on A/17/California/2009/38 (H1N1) and licensing of the Russian-developed technology to WHO for pandemic influenza preparedness in developing countries

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ABSTRACT

In February 2009, Nobilon granted the World Health Organization (WHO) a non-exclusive licence to develop, register, manufacture, use and sell seasonal a pandemic live attenuated influenza vaccine (LAIV) produced on embryonated chicken eggs. WHO was permitted to grant sub-licences to vaccine manufacturers in developing countries within the framework of its influenza vaccine technology transfer initiative. In parallel, the Institute of Experimental Medicine (IEM), Russia, concluded an agreement with WHO for the supply of Russian LAIV reassortants for use by these manufacturers.

Also in 2009, IEM carried out a study on a novel A/17/California/2009/38 (H1N1) pandemic LAIV candidate derived from the pandemic-related A/California/07/2009 (H1N1) influenza virus and the attenuated A/Leningrad/134/17/57 (H2N2) master donor virus, using routine reassortant technique in embryonated chicken eggs. Following successful preclinical studies in eggs and in ferrets, a double-blind, controlled, randomized clinical trial was carried out in immunologically naïve study participants between 12–18 and 18–60 years old. Collectively, the immunogenicity data (haemagglutinin inhibition test, ELISA and cytokine tests for the detection of memory T cells) support the use of a single dose of the pandemic H1N1 LAIV in 12–60 year olds. The outcome of the studies showed no significant adverse reactions attributable to the vaccine, and suggests that the vaccine is as safe and immunogenic as seasonal influenza vaccines. Importantly, it was clearly demonstrated that reliance on the HAI assay alone is not recommended for testing LAIV.

To date, via the licence agreement with WHO, the H1N1 LAIV has been transferred to the Government Pharmaceutical Organization in Thailand, the Serum Institute of India, and the Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd. in China.

1. Introduction

The Institute of Experimental Medicine (IEM), founded in 1890, is one of the oldest scientific institutes in Russia. It was here in the Department of Virology that Academician Smorodintsev first developed live viral vaccines against polio, measles, mumps and influenza.

Live attenuated influenza vaccines (LAIVs) generated by IEM have been used in Russia in adults since 1980 and in all age groups since 1987. To date, more than 100 million doses of LAIV have been used in the country for protection against seasonal influenza.

Production of LAIV is based on the classic reassortment methodology, i.e. six genes from an attenuated donor backbone strain are combined with the genes coding for the haemagglutinin (HA) and the neuraminidase (NA) of circulating influenza virus strains. LAIVs are temperature sensitive with limited growth at 39–40 °C *in ovo* and thus cold adapted (ca) "donor strains" are used due to their growth ability at reduced temperature such as occurs in the human upper respiratory tract. Currently, all licensed LAIVs are produced in embryonated eggs, although some manufacturers are in advanced stages of new generation cell-based LAIV development [1].

From 1997, when highly pathogenic avian influenza viruses began to circulate in Asia, IEM concentrated on the development of candidate pandemic LAIV. The first pandemic candidate H5N2

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Table 1
Virus isolation data from ferrets infected with A/17/California/2009/38 pandemic LAIV or pandemic A/Netherlands/602/09 (H1N1) virus.

Animal no.	Group	Day 1		Day 3	
		qPCR[a]	MDCK[b]	qPCR[a]	MDCK[b]
Nasal turbinates					
1	A/Netherlands/602/09 (H1N1)	5.8	3.0	6.8	3.3
2		6.7	4.8	6.7	5.3
3		3·8	3.0	6.7	4.0
4	A/17/California/2009/38 (H1N1)	a[c]	nd[d]	2.1	nd
5		a	nd	2.2	nd
6		a	nd	a	nd
Throat swabs					
1	A/Netherlands/602/09 (H1N1)	7.5	5,5	6.4	4.8
2		7.3	5,5	5.9	4.3
3		9.6	5,5	5.7	3.5
4	A/17/California/2009/38 (H1N1)	a	nd	1.6	nd
5		a	nd	a	nd
6		a	nd	a	nd
Lungs					
1	A/Netherlands/602/09 (H1N1)	na[e]	na	9.4	5.1
2		na	na	8.0	5.1
3		na	na	8.8	5.4
4	A/17/California/2009/38 (H1N1)	na	na	a	nd
5		na	na	a	nd
6		na	na	a	nd

[a] Data is presented as $\log_{10}$ CDU/mg.
[b] Data is presented as log $TCID_{50}$/mg.
[c] Below detection limit.
[d] Not determined.
[e] Not applicable.

Table 2
Average immunogenicity of LAIV A/17/California/2009/38 (H1N1) in ferrets after single dose immunization.

HAI assay	Average HAI titre (6 ferrets)		
	HAI serum day 0	HAI serum day 20	
Group/testing viruses	A/California/EURRG4/09	A/California/EURRG4/09	A/Netherlands/EURRG02/09
Negative control	5	5	5
IEM clinical trial grade PLAIV[a]	5	533	593

Data from ViroClinics, the Netherlands.
HAI, haemagglutination inhibition.
[a] Pandemic LAIV.

Table 3
Reactogenicity of A/17/California/2009/38 (H1N1) LAIV for adult volunteers 18–60 years of age within 7 days of vaccination.

Reactogenicity event	Treatment group, *n* (%)			
	Vaccination		Revaccination	
	Vaccine (*n* = 100)	Placebo (*n* = 20)	Vaccine (*n* = 100)	Placebo (*n* = 20)
Febrile reactions 37.1–37.5 °C	11 (11%)	0	1 (1%)	0
Febrile reactions 37.6–38.5 °C	1 (1%)	0	0	0
Febrile reactions ≥38.6 °C	0	0	0	0
Headache	2 (2%)	0	1 (1%)	0
Vomiting	0	0	0	0
Muscle ache	0	0	0	0
Chills	0	0	0	0
Running nose	9 (9%)	0	1 (1%)	0
Nasal congestion	4 (4%)	0	0	0
Cough	5 (5%)	0	0	0
Sore throat	8 (8%)	0	0	0
Hyperaemia of the fauces/arches	31 (31%)	0	0	0
Fatigue	2 (2%)	0	0	0
Systemic reactions	12 (12%)	0	1 (1%)	0
Local reactions	33 (33%)	0	1 (1%)	0
Total	35 (35%)	0	1 (1%)	0