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Development and approval of live attenuated influenza vaccines based on Russian master donor viruses: Process challenges and success stories

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ABSTRACT

Influenza is a viral infection that affects much of the global population each year. Vaccination remains the most effective tool for preventing the disease. Live attenuated influenza vaccine (LAIV) has been used since the 1950s to protect humans against seasonal influenza. LAIVs developed by the Institute of Experimental Medicine (IEM), Saint Petersburg, Russia, have been successfully used in Russia since 1987.

In 2006, the World Health Organization (WHO) announced a Global action plan for influenza vaccines (GAP). WHO, recognizing potential advantages of LAIV over the inactivated influenza vaccine in a pandemic situation, included LAIV in the GAP.

BioDiem Ltd., a vaccine development company based in Melbourne, Australia which held the rights for the Russian LAIV, licensed this technology to WHO in 2009. WHO was permitted to grant sub-licenses to vaccine manufacturers in newly industrialized and developing countries to use the Russian LAIV for the development, manufacture, use and sale of pandemic and seasonal LAIVs. To date, WHO has granted sub-licenses to vaccine manufacturers in China (Changchun BCHT Biotechnology Co., Ltd.), India (Serum Institute of India Pvt. Ltd.) and Thailand (Government Pharmaceutical Organization). In parallel, in 2009, IEM signed an agreement with WHO, under which IEM committed to supply pandemic and seasonal candidate vaccine viruses to the sub-licensees.

This paper describes the progress made by collaborators from China, India, Russia and Thailand in developing preventive measures, including LAIV against pandemic influenza.

1. Introduction

Influenza is a life-threatening viral infection that may affect up to 40% of the world's population each year [1]. Vaccination remains the most effective means of preventing seasonal influenza epidemics, which are associated with significant morbidity and mortality worldwide.

Long-term observations have shown that live attenuated influenza vaccine (LAIV) has some major advantages over inactivated influenza vaccine (IIV). These advantages include ease of needle-free delivery, extremely low rate of adverse reactions, smaller infrastructure requirement for manufacturing, limited downstream processing and significantly higher yield in eggs (nearly 15 doses of LAIV can be produced from one embryonated egg). These factors make LAIV especially attractive for developing countries with a large population. Furthermore, the concept of replicating the vaccine virus in the nasal cavity and thus generating a specific immune response at the site of infection appears to be the most appropriate mode of immunization.

All these features of LAIV become even more relevant with the emergence of potentially pandemic influenza viruses of different serotypes. The World Health Organization (WHO) recognized the advantages of LAIV over IIV in the event of a pandemic and therefore included LAIV in its Global action plan for influenza vaccines [2,3].

In Russia, LAIV has a long history of development, stage-wise improvement, licensing and use in public health. Since 1987, Russian LAIV has been used for the prophylaxis of influenza in children aged over three years, in adults and in the elderly. Currently, reassortant viruses for Russian LAIV are prepared by classical reassortment in eggs of wild-type influenza A and B viruses with two cold-adapted master donor viruses (MDVs) as a backbone: A/Leningrad/134/17/57 (H2N2) and B/USSR/60/69, respectively. Russian LAIV has been shown through studies to consistently provide superior effective protection, especially in children, compared to IIV.

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Table 1
List of seasonal LAIVs prepared by IEM on A/Leningrad/134/17/57 (H2N2) and B/USSR/60/69 backbone, which were transferred to WHO.

Vaccine strain designation (LAIV candidate)	Wild-type parental strain	Influenza season[a]
B/56/Brisbane/60/2008	B/Brisbane/60/2008 (Victoria lineage)	2009–2010
		2010–2011
		2011–2012
		2016–2017
A/17/California/2009/38 (H1N1)pdm09[b]	A/California/07/2009 (H1N1pdm)	2009–2010
		2010–2011
		2011–2012
		2012–2013
		2013–2014
		2014–2015
A/17/Perth/2009/87 (H3N2)	A/Perth/16/2009 (H3N2)	2010–2011
		2011–2012
B/60/Wisconsin/2010/125	B/Wisconsin/1/2010 (Yamagata lineage)	2012–2013
A/17/Victoria/2011/89 (H3N2)	A/Victoria/361/2011 (H3N2)	2012–2013
		2013–2014
A/17/Texas/2012/30 (H3N2)	A/Texas/50/2012 (H3N2)	2013–2014
		2014–2015
B/60/Massachusetts/2012/10	B/Massachusetts/2/2012 (Yamagata lineage)	2013–2014
		2014–2015
B/60/Phuket/2013/26	B/Phuket/3073/2013 (Yamagata lineage)	2015–2016
A/17/Bolivia/2013/6585 (H1N1)pdm09	A/Bolivia/559/2013 (H1N1) pdm2009	2015–2015
A/17/Hong Kong/2014/8296 (H3N2)	A/Hong Kong/4801/2014 (H3N2)	2016–2017

IEM – Institute of Experimental Medicine; LAIV – live attenuated influenza vaccine; WHO – World Health Organization.
[a] Northern hemisphere influenza season.
[b] Vaccine is registered in Russia.

The other LAIV used in the world, based on Ann-Arbor backbone has likewise been shown to provide superior protective efficacy in children, compared to IIV, through randomized controlled trials. Some recent studies have however suggested that since 2011 there has been a reduction in the comparative efficacy of the Ann-Arbor based LAIV compared to IIV. The cause is still unknown however efforts to understand this sudden loss of efficacy are focusing on the role of the A/California H1N1 component as well as the inclusion of a second B-strain, and it is expected that this issue will be successfully addressed.

2. Transfer of Russian LAIV technology

BioDiem Ltd. (Melbourne, Australia), holding the rights for use of the Russian MDVs, licensed Russian LAIV technology to WHO [4]. The agreement with BioDiem permitted WHO to grant sub-licenses to vaccine manufacturers in the newly industrialized countries (NICs) and developing countries within the framework of the WHO influenza vaccine technology transfer project. Since 2009, WHO has signed agreements with the Changchun BCHT Biotechnology Co., Ltd. (BCHT, Changchun, Jilin, China), the Serum Institute of India Pvt. Ltd. (SIIPL, Pune, India) and the Government Pharmaceutical Organization (GPO, Bangkok, Thailand) for the development, manufacture, use and sale of the egg-based LAIV using Russian MDVs.

At the same time, the Institute of Experimental Medicine (IEM), Saint Petersburg, Russia – the sole developer of reassortant strains for Russian LAIV – signed an agreement with WHO. Under this agreement, there were two main areas of work: development of seasonal LAIV candidates according to biannual WHO recommendations for influenza vaccine compositions, and Development of LAIV candidates against potentially pandemic influenza viruses.

During the period 2009–2015, IEM developed and transferred to WHO nine seed-LAIVs for seasonal vaccines and one H1N1 pandemic seed-LAIV for further distribution to manufacturers (Tables 1 and 2). All of these LAIV candidates were accompanied by strain certificates drawn up in accordance with international standards, which included detailed descriptions of the seed-LAIV generation and the quality-control attributes; that is, antigenicity and identity tests, phenotypic and propagation characteristics, genetic stability data, full genome sequencing, sterility control and safety preclinical testing in laboratory animals.

In 2012, the increased international demand for the Russian LAIV prompted the establishment of an additional (back-up) laboratory facility at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America (USA) for parallel preparation of the LAIV candidates based on Russian MDVs for international use. The organizations responsible for this were WHO, the Biomedical Advanced Research and Development Authority (BARDA), USA, and IEM. This decision made it possible to reduce the unpredictable risks associated with the production of LAIV candidates in one laboratory and in one country alone. The back-up laboratory has been working successfully [5–8] and a number of reassortants have been used to produce the LAIV in India and China (Table 4).

3. Creation of a modern high-tech pathogenic agent's laboratory facility and development of potentially pandemic LAIV candidates

To meet the demand for high-quality LAIV seed viruses for further distribution between dedicated manufacturers, it was necessary to reconstruct and build a new state-of-the-art facility at IEM to work with pathogens of biosafety level BSL-2 and BSL-3 groups, in compliance with all international biosafety standards. For this purpose WHO, in collaboration with BARDA, allocated all necessary funds, and the construction was completed in 2014. Since then, the facility has been fully operational and has been certified by the Russian Ministry of Health. This laboratory occupies a

Table 2
List of potentially pandemic LAIVs prepared by IEM on A/Leningrad/134/17/57 (H2N2) backbone, which were transferred to WHO.

Vaccine strain designation (LAIV candidate)	Wild-type strain	The stage of the study	Ref.
A/17/turkey/Turkey/05/133 (H5N2)	NIBRG–23 (H5N1), clade 2.2	Phase I clinical trial completed	[7,19]
A/17/Vietnam/04/65107 (H5N2)	IDCDC–RG1 (H5N1), clade 1	Preclinical trials completed	[7]
A/17/California/66/395 (H2N2)	A/California/1/66 (H2N2)	Phase I clinical trial completed	[8,18]
A/17/Anhui/2013/61 (H7N9)	A/Anhui/1/2013 (H7N9)	Phase I clinical trial completed	[9,20]
A/17/mallard/Netherlands/00/95 (H7N3)	A/mallard/Netherlands/12/2000 (H7N3)	Phase I clinical trial completed	[10,17]

IEM – Institute of Experimental Medicine; LAIV – live attenuated influenza vaccine; WHO – World Health Organization.