WHO Meeting on Live Attenuated Influenza Vaccine Effectiveness

20 - 21 September 2016

Executive Summary

WHO recommends that all countries vaccinate vulnerable high risk groups annually to prevent severe influenza illness and death. WHO also acknowledges that influenza causes considerable morbidity worldwide, even beyond high risk groups, and therefore represents a public health problem with significant socioeconomic implications.

Immunization with live attenuated influenza vaccines (LAIVs) can be an important intervention for the prevention of seasonal influenza illness and also as part of a global response to influenza pandemics. There are currently two different LAIV technologies in use: 1) Ann Arbor backbone-LAIV produced by AstraZeneca in the United Kingdom, licensed under the names FluMist® (United States / Canada) and Fluenz® (European Union / European Economic Area) which is used in North America and Europe respectively; and 2) Leningrad backbone-LAIV produced in Russia (Ultravac®) and India (Nasovac-S®) and used primarily in those two countries.

Based on evidence from randomized clinical trials showing that FluMist®/Fluenz® had superior efficacy as compared to non-adjuvanted inactivated influenza vaccines (IIVs) in children, several countries have previously recommended the product for preferential use in children. In recent years, there have been signals from some observational studies suggesting lower than expected effectiveness of LAIV from the United States. In particular, very low effectiveness has been found against the A/H1N1pdm09 virus in some studies over several seasons in the United States. Results from elsewhere have indicated moderate to good levels of protection against A/H1N1pdm09, though the protection has been lower than from IIV. Protection of LAIV against A/H3N2 and influenza B has generally been similar or better than IIV in many of these other settings. These signals have led some National Immunization Technical Advisory Groups to review their recommendations for the use of this product. These groups have made different recommendations for LAIV use within their countries. Examples include the United Kingdom which has continued its preferential recommendation for LAIV use in children, Canada and Germany which have discontinued preferential recommendations for LAIV use in children, and the United States which has recommended that LAIV should not be used for the coming 2016-17 influenza season.

In this context, WHO convened the Meeting on Live Attenuated Influenza Vaccine Effectiveness in Geneva, Switzerland on 20-21 September 2016. The objectives of the meeting were the following:

- To review past and recent data regarding LAIV performance
- To discuss potential virologic and immunologic explanations for recent data suggesting decreased LAIV performance in some sites
- To develop a learning agenda of hypotheses in need of investigation to better understand possible LAIV performance limitations and to propose a path forward to ensure LAIVs remain available for prevention of seasonal and pandemic influenza
- To discuss the policy and public health implications of whether previous influenza vaccination could modify LAIV or IIV effectiveness
Participants included influenza vaccine experts and public health officials from countries where LAIVs are used or manufactured. Manufacturers of LAIV products participated in sessions related to specific reviews of LAIV performance, but they were excluded from sessions in which policy and public health implications were discussed. The meeting agenda and list of participants can be accessed on the WHO website.\(^1\)

In the meeting, the clinical development of FluMist®/Fluenz® was discussed, as were recent observational vaccine effectiveness data among children from North America and Europe. Most studies from the 2015-2016 influenza season found significant protection of LAIV against influenza illness of any type (influenza A/B), although one study from the United States did not demonstrate significant LAIV effectiveness. However, most of the recent studies reviewed suggested that, even if significantly effective, the effectiveness of the influenza A/H1N1pdm09 component of LAIV was lower than that reported for IIVs in similar age groups and during the same influenza season.

The reasons for the lower than expected effectiveness of FluMist®/Fluenz® for influenza A/H1N1pdm09 are not clear, however a review of non-clinical and clinical data on product performance during the meeting revealed several potential explanations for this finding. These include methodological study differences, differences in vaccine handling, intrinsic characteristics of the live virus vaccine such as decreased receptor binding and replication of the A/H1N1pdm09 component, as well as population-specific characteristics such as levels of pre-existing immunity and rates of previous exposure to influenza vaccines. AstraZeneca scientists described their ongoing analyses, and experts in the meeting provided recommendations for further evaluation of the product.

The clinical development of the Leningrad -backbone LAIV was also discussed, as were recent non-clinical and clinical studies. Recent data from evaluations of Nasovac-S® were presented by the manufacturer, Serum Institute of India, and by PATH. The monovalent influenza A/H1N1pdm09 Nasovac-S® has been shown to be effective at preventing influenza illness during the 2009 pandemic in India. Phase III trials were conducted with Nasovac-S® during the 2012-13 influenza season in Bangladesh among vaccine-naive children and in Senegal among children with some prior exposure to IIV. There was significant vaccine efficacy found in Bangladesh but none in Senegal. Driving these findings was the efficacy against influenza A/H1N1pdm09 virus which was significant in Bangladesh but not significant in Senegal. Non-clinical data suggested decreased receptor binding and replication of the A/H1N1pdm09 component. Serum Institute of India scientists described efforts they are taking as part of their ongoing analyses, and experts in the meeting provided recommendations for further evaluation of the product.

It is unclear whether the findings from the FluMist®/Fluenz® evaluations and the Nasovac-S® evaluations are related.

After a review of the data for LAIV performance, WHO has determined that a change to current recommendations is not warranted, but that there is a need for continuing careful evaluation of LAIV

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programmes and further pre-clinical and clinical studies to better understand the reasons for recent variations in estimated effectiveness of LAIVs. WHO continues to recommend that countries immunize persons at high risk for severe influenza illness annually with influenza vaccines. Vaccines used by countries in public health programs should be chosen according product characteristics including safety, effectiveness, and programmatic aspects of delivery, among others. The current WHO position paper on influenza vaccines can be accessed on the WHO website.²

² http://www.who.int/wer/2012/wer8747.pdf?ua=1