MEETING TO ASSESS LIVE-ATTENUATED INFLUENZA VACCINES TO PREVENT PAEDIATRIC INFLUENZA DISEASE IN LOW AND MIDDLE INCOME COUNTRIES: DECEMBER 16-17, 2014

EXECUTIVE SUMMARY

Background

In the context of the Global Action Plan for Influenza Vaccines (GAP), a multidisciplinary group of vaccine experts came together for 2 days to discuss the history and clinical evaluation of live-attenuated influenza vaccines (LAIVs), both the Ann Arbor-backbone LAIV (e.g. Fluenz, FluMist) and the Leningrad-backbone LAIV (e.g. Ultravac, Nasovac). Also discussed was the context of possible LAIV use in low- and middle-income country settings, including the burden of influenza disease and programmatic considerations of LAIV vaccine use. A potential unmet need of LAIV vaccines is that there is no product licensed for use among children <2 years of age. Therefore, a plan for age de-escalation trials of LAIV to include evaluation in children <2 years was discussed. On the second day, the relevance of LAIV was discussed in the broader agenda of paediatric influenza immunization. Research data for paediatric influenza immunization (both inactivated vaccines and LAIVs) were presented.

The objectives of the consultation were:

- Review available evidence of the public health benefits and potentially associated risks of the use of LAIV in children and infants
- Discuss scientific, regulatory, and ethical perspectives of clinical studies to be conducted with LAIV in children under 2 years of age
- Review relevant data on influenza vaccines in children to better identify data gaps and implementation issues for future introduction of influenza vaccines, in particular LAIV, in pediatric immunization programs

The agenda and participant list can be found at: https://www.dropbox.com/sh/m20lheqagsx0k23/AAC1c-a6L3d_wFLd5S_y50Ba

A closed session was held at the end of the meeting and included regulators, the WHO secretariat, and its consultants. No participant of the closed meetings had declared interests relevant to the topic discussed.
Outcome

While the burden of disease due to influenza is recognized to be significant in developing countries, there remain many challenges in assessing influenza disease burden and its relative importance compared to other vaccine preventable diseases. During the meeting, a vaccine probe study approach was proposed as the best way to provide anchoring data for interventions.

Wheezeing illness as a safety signal

Wheezeing illness in children less than 2 years of age has previously been reported as a safety signal in clinical trials of Ann-Arbor backbone LAIV. Several speakers addressed the assessment of wheezeing illness and its clinical significance. A recent systematic review of wheezeing illness definitions and severity assessment from randomized clinical trials showed that current definitions of wheezeing illness are heterogeneous and that there is a need to standardize these definitions in paediatric clinical trials.

In a UK cohort, most wheezeing illness is caused by rhinovirus C, and preschool wheeze is a heterogeneous condition. The prevalence of wheezeing illness in young North African children is 4 to 5%, but this burden and the global burden in general may be underestimated. The role of influenza as a trigger for wheezeing illness is unclear. There is a need to better investigate the mechanisms of wheezeing illness as a vaccine-related adverse event and a need to understand whether the wheezeing signal is product-specific.

Lessons that can be drawn from rotavirus vaccine development to inform plans for LAIV age de-escalation are that risk/benefit decisions will vary by location, that vaccine safety fears have the potential to significantly endanger the overall program, and, since it is impossible to design a trial to detect an unanticipated rare adverse event, that postlicensure surveillance is critical.

Unexpected 2013-2014 effectiveness findings with LAIV

In recent phase II and phase III trials with Leningrad-backbone LAIV in Bangladesh and Senegal, influenza virus infection was common and the vaccine was safe and well tolerated. Both trials were conducted during the same year and used, used a single dose of vaccine, and used the same vaccine lot of the 2012-13 NH LAIV formulation. However, efficacy estimates for the H1N1 strain diverged between Bangladesh and Senegal from very significant to not significant respectively).

The low overall efficacy point estimates found in Senegal were driven by vaccine performance against H1N1, which was the predominant circulating subtype.
Explanations for this discrepancy may include drift in circulating H1N1 strains at either site, population differences, including prior history of influenza infection or vaccine use, nutritional differences, and differences in the ecology of the nasopharynx. Differences in potency at the time of administration can also be considered. The investigators were unable to identify a cause for the discrepant results.

During 2013-14, several independently conducted observational studies in the US with Ann Arbor derived LAIV yielded unexpected low LAIV effectiveness against H1N1 virus strains, similar to the results obtained in Senegal (but not in Bangladesh). There is presently no clear explanation for this lack of effectiveness against H1N1 in the US. The manufacturer (AstraZeneca) found that lot shipment timing was a strong effect modifier for vaccine effectiveness. Current attention is being paid to issues related to storage conditions as the cause for low vaccine effectiveness, as the H1N1 component of the vaccine may be particularly vulnerable to temperature disturbances. One cannot assume that Ann Arbor LAIV and the Leningrad backbone LAIV will have identical efficacy and safety profiles, and they are different products with different dosing.

**Conclusions**

Participants agreed that a major priority should be to try to find a convincing biologically plausible explanation for lack of vaccine effectiveness during the 2013/14 influenza season in vaccines that used the Leningrad and the Ann Arbor LAIVs.

Despite these current unknowns about vaccine effectiveness, the meeting recognized overall the current unmet need for influenza prevention in young children. Participants agreed that a cautious stepwise age de-escalation study with LAIV in children under 2 years of age would address a need in that high burden age group. As with all vaccine trials, there must be a favourable relationship between potential benefit of vaccine receipt and potential risks of vaccine-related harm. Clinical studies should not be pursued without expectation of benefit to participants. It was noted that de-escalation plans to study the safety and immunogenicity of 2 doses of LAIV among children aged 12 - 23 months are considered in a country (Bangladesh) where the vaccine was shown to be effective during a recent randomized trial. There was general agreement that children less than 1 year of age should not be studied until there are strong data from the 1-2 year-old population.

Some participants stated that adjuvanted-inactivated influenza vaccine may also turn out to be a favourable solution for influenza prevention in children <years. While inactivated influenza vaccines are generally less effective in the youngest children than LAIV, adjuvants increase the immunogenicity and efficacy in this age group.

Finally, as in all vaccine trials, efforts should be made to ensure that informed consent process is rigorous and according to global standards.