INTERNATIONAL MEETING ON INFLUENZA VACCINE EFFECTIVENESS

Centre International de Conférences Genève (CICG),
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Meeting Summary

On 3-4 December, 2012, the Initiative for Vaccine Research (IVR) of the World Health Organization and the US Centers for Disease Control and Prevention (CDC) convened the “International Meeting on Influenza Vaccine Effectiveness”. The meeting was attended by approximately 100 international experts from industry, academia, governmental and non-governmental organizations who are interested in evaluating influenza vaccine effectiveness (VE). The context of this meeting was the need to better understand the performance of established and new influenza vaccines in different target groups and to support evaluation of influenza vaccines as use expands globally. The meeting was designed to review the current landscape of influenza VE evaluation; identify data pooling opportunities and develop consensus on best practices for VE studies. The following objectives were outlined for the meeting: to review currently available information; to discuss optimal study methods and determine critical knowledge gaps; and to identify specific challenges in pooling of data and communicating information regarding influenza VE.

The meeting began with a session on the global landscape of influenza VE, including the limited data available for VE in targeted populations, particularly in low- and middle-income countries. Although serological data may help in understanding protection afforded by vaccines, the correlation of serum antibody levels, as measured by current assays, to vaccine-related protective immunity is not sufficiently well understood. Assessment of VE is challenging when only non-specific outcomes are collected, highlighting the need for laboratory confirmation. Standardization of methods is also essential to improve comparability between studies for estimating the efficacy, effectiveness, and impact of influenza vaccines.

Partners shared updates from ongoing VE research and monitoring in Europe, Australia, the US, and Canada, as well as the Pan-American Health Organization (PAHO). Central issues for these programs, which often use existing surveillance systems to generate VE data, included the question of which outcome to measure, best methods for observational studies and the need to optimize resources and ensure financial sustainability. Case-control designs using influenza test-negative individuals as a control group are frequently used for influenza VE estimation in addition to more intensive population-based cohort studies in selected epidemiological settings as well as enhanced data collection for targeted risk groups for vaccination.

A number of efforts are underway to evaluate influenza vaccine performance in low- and middle-income countries through clinical trials. Vaccine manufacturers from Thailand, Vietnam, India, and Brazil shared progress to date on pandemic, seasonal, and avian influenza vaccine development, including live-attenuated seasonal influenza vaccines and vaccines with low-cost adjuvants. Researchers in South Africa, India, Bangladesh, and Thailand presented preliminary findings examining the efficacy of trivalent inactivated influenza vaccine (TIV) in pregnant women with and without HIV infection; the indirect effects of vaccinating children in limiting transmission at the household-level and the effect of quadrivalent vaccines in preventing
influenza-associated pneumonia, as well as upcoming plans for clinical trials of live-attenuated influenza vaccines (LAIV) in Thailand and other countries.

The second day of the meeting explored a number of methodological issues for VE studies, in particular looking closely at the challenges of case-control study design and the use of outcomes (e.g., influenza-like illness, pneumonia, all-cause mortality) that are not specific for influenza infection. For case-control studies, controls should be selected to match the exposure to influenza infection of the source population in relation to the selected cases. Test-negative controls are often used to match the healthcare seeking behavior of the controls to that of the cases. Additional issue for case-control design included the need to account for timing of specimen collection in order to correctly classify individuals as influenza infected cases or non-cases. Furthermore, systematic laboratory testing with a standardized case definition is essential for test-negative study designs in order to reduce bias, which has been a constant issue in observational VE studies. Vaccinees may be more likely to seek health care, or may have more or less underlying comorbidity than unvaccinated persons. This bias is especially acute when non-specific outcomes are used.

International data pooling is an important strategy for generating regional or global VE estimates. Data pooling can also increase sample size to allow greater statistical power to estimate VE among specific ages, risk groups, and other subsets of populations, as well as the generation of more timely mid-season VE estimates. Such information is important for vaccine policy development and implementation. International pooling of data is carried out by the I-MOVE network in Europe for influenza VE estimation across European countries as well as other participating countries outside Europe. However, barriers such as country-level data sharing policies and variability in healthcare utilization across settings can make pooling of data difficult. A clear objective for the use of pooled data as well as standardized operating procedures such as the use of standard protocol and joint interpretation of the data is essential for correct interpretation and use of information.

Estimation of VE among elderly populations was explored in a special session, where the overestimation of VE against all-cause mortality due to the “healthy vaccinee” effect was explored. Further strategies for identifying and minimizing this bias, such as functional status of subjects (frailty index), were discussed. Meta-analyses of published information have identified a number of issues relating to VE estimates in the elderly. Difficulties in interpretation of such analyses is also compounded by the methodological limitations of performing meta-analysis, resulting in an ongoing debate about the accuracy of pooled influenza VE in this age group.

The meeting concluded with a discussion of the critical need to communicate vaccine effectiveness findings appropriately, and the need to develop a guidance document for best practices for influenza VE studies. As vaccine advisory groups such as SAGE, ACIP, and others are using evidence-based methods (such as GRADE) to evaluate the data used to provide vaccine recommendations, influenza VE studies should be designed with standard outcomes that can be included into these evaluations. Such guidance should be operational for low- and middle-income countries, where influenza VE data are particularly needed as influenza vaccine coverage increases, as well as guidance on program monitoring and evaluation.