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International meeting on influenza vaccine effectiveness, 3–4 December 2012, Geneva, Switzerland

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Abstract

On December 3–4 2012, the World Health Organization convened a meeting of influenza vaccine effectiveness (VE) experts from over 25 countries in Geneva, Switzerland, to review recent developments in the global influenza vaccine landscape and evaluate approaches to determining the effectiveness of influenza vaccine products among target populations. Vaccine manufacturers from Thailand, Vietnam, India, and Brazil shared recent advances illustrating the expansion of influenza vaccine production worldwide. Randomized controlled trials are underway in several low and middle-income countries including India, Thailand, Bangladesh, and South Africa, to fill knowledge gaps in target populations such as children and pregnant women. National and international networks in the United States, Canada, Europe, Latin America and Australia are conducting multi-site observational studies with shared methodologies to generate national influenza VE estimates and pool data for regional estimates. Standardized VE estimation methods are key to generating point estimates that are comparable internationally and across different settings.

Keywords

Conference report; Influenza; Vaccines; Vaccine effectiveness

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Conflict of interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of their institutions or organizations. All authors reported no conflicts of interest.

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1. Introduction

On December 3–4 2012, the World Health Organization (WHO) convened a meeting of experts on studies of influenza vaccine effectiveness from over 25 countries in Geneva, Switzerland, to review developments in the global landscape of influenza vaccines and in particular, the measurement of the effectiveness of different influenza vaccines. In late 2012, WHO released a position paper on influenza vaccination, stating that, for countries considering the initiation or expansion of seasonal influenza vaccine programs, pregnant women should have the highest priority. WHO also stated that additional risk groups to be considered for vaccination, in no particular order of priority, are: children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and health-care workers [1]. A further development is the increasing number of manufacturers that are developing and producing influenza vaccines – expanding global manufacturing capacity that will make vaccines increasingly available and aid pandemic preparedness efforts [2]. The range of influenza vaccine products has also diversified to include additional inactivated vaccines (e.g., adjuvanted, high-dose formulations, intradermal, cell-culture-based vaccines), live attenuated vaccines, and recombinant protein vaccines, and the recent development of quadrivalent formulations. These newly licensed vaccines may provide increased clinical protection in groups that tend to respond poorly such as young children and the elderly. Further, in the last 5–10 years, the burden of seasonal influenza has been increasingly documented in settings where data had previously been limited [3–5]. This expanding evidence base is particularly valuable in low- and middle-income settings, where disease burden may be high and where risk factors for severe disease may differ from high-income locations.

Efforts to increase worldwide influenza vaccine availability have highlighted the need for ongoing data on the effectiveness of influenza vaccines in settings where influenza vaccination programs are conducted. In addition, measuring the relative and absolute effectiveness of newly licensed products by age group and setting, and the effectiveness of influenza vaccines newly introduced into a country’s immunization programs will be necessary data for evaluating the value of influenza vaccines in the next decade. Recent meta-analyses have highlighted the uncertainty of the protection afforded by traditional vaccines and have challenged the evidence for significant protection of the elderly [6,7]. Furthermore, certain knowledge gaps remain for current vaccines, including the relative effectiveness of live-attenuated and adjuvanted vaccines in young children versus older children and the availability of robust estimates of vaccine effectiveness (VE) among children with high-risk medical conditions as well as pregnant women and their infants. Multiple challenges in addressing these gaps include the inherent antigenic variability of the circulating influenza viruses as well as how best to classify “matched” and “mismatched” virus strains, and the differences in influenza seasonality between temperate and tropical locations.

These recent developments have generated a need for an international collaboration to review methods to measure vaccine effectiveness and to identify opportunities for international data sharing to provide the best informed conclusions. The objectives of the meeting were: to provide an update on advances in influenza vaccination in low- and

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middle-income settings; to summarize global efforts to better measure influenza vaccine effectiveness and efficacy; to identify best practices and determine critical knowledge gaps; to discuss opportunities for global collaboration such as for pooling of observational data; and to identify specific challenges in communicating data. This report provides an overview of the findings of this meeting, as well as several key areas of discussion.

2. Expanded global picture of influenza vaccination

2.1. Influenza vaccine production in middle-income countries

Vaccine manufacturers from Thailand, Vietnam, India, and Brazil shared recent advances that illustrated the expanding landscape for influenza vaccines production worldwide. In Thailand, the Government Pharmaceutical Organization (GPO) presented work to develop and produce an inactivated influenza vaccine (IIV) and a live-attenuated influenza vaccine (LAIV) for local use among recommended target groups. Their aims are to develop national capacity for seasonal vaccination with IIV and additionally produce a small volume of seasonal LAIV annually that could be scaled up rapidly in the case of a pandemic. VABIOTECH (Vietnam) influenza vaccine development is guided by similar priorities of protecting the population against potential pandemic influenza viruses such as influenza A(H5N1) and other avian influenza strains. A cell culture-derived inactivated H5N1 vaccine has completed Phase IIb trials, while production of seasonal influenza vaccines are being explored for 2014–2015. The Serum Institute of India (SII) developed a monovalent influenza A(H1N1)pdm09 LAIV that was licensed in India in July 2010, and their trivalent LAIV formulations have completed Phase I and II clinical trials for use in children (2–17 years) and adults. At time of presentation, the trivalent LAIV was under review for licensure by the national regulatory agency (Drug Controller General of India (DCGI).[1] In Brazil, where influenza vaccines for persons over 65 years and children under 5 years are provided by the federal government, Butantan produces southern hemisphere formulations of IIV, and it is currently exploring several options for low-cost adjuvants to improve immune response.

2.2. Vaccine efficacy research in low- and middle-income country settings

A systematic review of influenza VE studies from low- and middle-income countries published to date showed limited information on vaccine efficacy and effectiveness. Of the available published studies from lower-resource settings, a large proportion did not describe their methods for randomization and blinding. Insufficient randomization and blinding can introduce bias during ascertainment of outcomes, since study participants and/or investigators may be aware of which vaccines have been administered, thereby systematically altering who is tested for influenza. High-quality data from these settings are critical, since the effectiveness of influenza vaccines in a given setting may be influenced by a range of factors, including the prevalence of comorbidities, influenza seasonality and vaccine formulation used. In many low-to middle-income settings, age distribution and health conditions such as HIV, tuberculosis, malnutrition, malaria and other factors will

[1]The Serum Institute of India’s trivalent live attenuated influenza vaccine was licensed by the Drug Controller General of India in 2013.

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differ from that of the United States (US) and other settings that have traditionally conducted studies of influenza vaccine efficacy.

Although published literature is limited, summaries of randomized controlled trials in several low and middle-income countries were presented from researchers in India, Thailand, Bangladesh, and South Africa. In India, a multi-year household-randomized study began in 2009 to estimate the direct and indirect effects of vaccinating children 6 months to 10 years with IIV in three villages near Delhi. Also in India, a seasonal trivalent LAIV is in the process of obtaining licensure[1], and a new Phase IV study is being designed to evaluate the effectiveness of locally produced LAIV versus placebo or trivalent IIV among children 2–10 years of age once that vaccine is licensed. In Thailand, clinical research activities for influenza vaccines include safety and immunogenicity studies of monovalent A(H1N1)pdm09 IIV and avian A(H5N2) IIV as well as planning activities for seasonal IIV and LAIV evaluation, with clinical trials anticipated to start in 2014–2015. In Bangladesh, a maternal immunization trial found a VE of 63% of IIV administered to pregnant women in preventing lab-confirmed clinical influenza among infants through 24 weeks, as well as a 29% reduction in all-cause febrile illness in this group [8]. Additional ongoing studies include a randomized controlled trial of quadrivalent IIV in children 12–35 months of age, a probe study to quantify the effect of trivalent IIV on all-cause pneumonia, and Phase II/III trials of trivalent LAIV in children less than 5 years of age. In South Africa, the “SA Mat-Flu Study” was initiated in 2011 to determine the immunogenicity of IIV among HIV-infected and uninfected pregnant women, and to calculate the efficacy of IIV vaccination against influenza in their vaccine-exposed infants (up to 24 weeks of age). Initial results indicate only modest immunogenicity in HIV-positive pregnant women, which may suggest less passive transfer of antibody and decreased clinical effectiveness of IIV in newborns of HIV-infected women.

2.3. Vaccine effectiveness networks

A number of national and international efforts have also been established to generate pooled VE estimates. In the US, the US Flu VE Network has generated annual estimates of influenza VE through a case-control design using influenza-positive cases and influenza-negative controls (“test-negative” design, or TND) at four to five sites using a case definition of medically attended acute respiratory infection (MAARI). In Europe, the I-MOVE network (Monitoring Influenza Vaccine Effectiveness in Europe), established in 2007, conducts VE research using both case-control and cohort-based approaches at 15 sites across the region, taking advantage of computerized national registries where feasible. In Latin America, a multinational research effort, REVELAC-i (“Red para la Evaluación de la Efectividad de la Vacuna en Latino América y el Caribe – influenza”) was initiated in 2011 to evaluate influenza VE in children and older adults, initially in four countries. The REVELAC-i approach is also based on a test-negative case-control design, using a case definition of severe acute respiratory illness (SARI) and building on sentinel surveillance in hospitals. In Australia, several networks collect data to generate annual VE estimates, including FluCAN among adult inpatient populations, WAIVE among pediatric inpatient and outpatient populations, and the VIDRL outpatient influenza surveillance system, all of which utilize a test-negative case–control design. In Canada, national VE estimation is integrated with

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sentinel surveillance activities across five provinces, also utilizing a test-negative case-control design.

3. Methodological considerations for estimating vaccine effectiveness

As the diversity of manufacturers and vaccine products increase globally, along with increased uptake and new global recommendations and the ethical and financial challenges of conducting randomized control trials (RCT) to evaluate VE, observational research is a valuable tool for monitoring the effectiveness of these vaccines. Moreover, the variability and sometimes limited effectiveness of traditional trivalent IIV highlights the importance of robust methodological approaches that allow comparison of data among different studies to quantify the public health benefit of influenza vaccines under different epidemiological settings [7].

3.1. Observational study designs for influenza vaccine effectiveness

Observational estimates of influenza VE are typically conducted in countries where influenza vaccination recommendations make RCT difficult to conduct for ethical reasons, or to evaluate public health programs due to relative ease, lower cost, and other feasibility concerns. In recent years, influenza researchers have increasingly utilized a test-negative case–control design for estimating VE, although case–control studies with community controls and cohort/screening designs have also been implemented. TNDs enroll laboratory-confirmed influenza-positive and negative patients meeting a pre-defined case definition such as influenza-like illness (ILI) or SARI from the same healthcare facility, to attempt to control for healthcare-seeking behaviors. This design may also provide a comparable source population in terms of vaccination coverage (typically higher than among the community, due to care-seeking behavior). Additionally, existing SARI surveillance networks can serve as a platform for TND VE studies, with adaptations to best collect essential data for vaccine effectiveness studies–a concept being piloted in several Latin American countries by REVELAC-i. One limitation of test-negative case-control VE studies is their potential for misclassification of influenza cases with clinical specimens that do not test positive for influenza. Despite the diagnostic sensitivity of influenza testing by reverse transcription polymerase chain reaction (RT-PCR), delays in care seeking and testing, especially among adults and hospitalized individuals of any age can result in low virus yield and misclassification of true influenza cases as non-influenza controls. By using eligibility criteria that restrict specimen collection to a time window of a few days after onset when viral shedding is highest, this reduces the risk of misclassifying cases, although larger sample sizes will likely be needed.

3.2. Measures of effect and study outcomes

Understanding the differences in vaccine study designs is important in the interpretation and comparing findings among VE studies. In the context of vaccine research, a study can measure a vaccine’s efficacy, effectiveness, or impact. “Efficacy” refers specifically to the direct effect of vaccine generated from an RCT. “Effectiveness” refers also to a direct effect, but is generally calculated in an observational (usually post-marketing) setting. “Impact” includes indirect, total, and overall effects, ideally in two populations or a before and after

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study. “Overall effect” describes the population-level effects of vaccination (among both vaccinated and unvaccinated), while “total effect” is the combined (direct and indirect) effect among the vaccinated population. For group-randomized study designs, it can be challenging to separately define direct and total effects among vaccinated individuals. Additionally, if vaccine coverage in study population is high, this can increase indirect effects, resulting in an increased total effect seen through a higher VE than in a community with lower vaccine coverage.

Highly specific study endpoints with laboratory confirmation of influenza reduce bias in vaccine effectiveness estimates. VE estimates for non-specific outcomes, including influenza-like illness, pneumonia or all-cause hospitalizations or deaths, will be much lower, and are difficult to interpret, especially if co-circulation of other respiratory pathogens such as respiratory syncytial virus that may affect one age group more than others. Of particular concern for VE estimates among the elderly that use all-cause mortality as an outcome is that frail health is linked to both lower vaccine coverage and high mortality in this population, resulting in biased estimates of VE – also known as the “healthy vaccinee” effect. Before, during and after-season studies with less specific outcomes can be used to demonstrate the impact of influenza on pneumonia hospitalizations in a defined population, looking at the “ratio-of-ratios”. This method compares the actual and expected vaccination coverage among influenza-positive cases both when influenza is and is not circulating, in order to identify confounding due to “healthy vaccinee” status. However, this approach is computationally intensive, requiring multiple years of data and a larger number of observations [9].

Understanding VE against severe outcomes, however, has great value for policy makers as the approach measures the potential impact against a serious and costly public health problem. Moreover, it is possible that the effectiveness of some vaccines will vary by outcome severity, so that measuring the effectiveness of vaccination against one outcome will provide an incomplete picture on the value of vaccination. Large sample sizes are required to detect influenza-associated pneumonia or other influenza-associated severe diseases. Although high-quality data on the effects of different influenza vaccines on severe outcomes are needed, there is no clear consensus on best practices for assessing VE for severe outcomes.

3.3. Potential sources of bias and confounding

Several important sources of bias should be considered in estimating VE in both observational study and RCT settings. First, test-negative studies require a systematic approach to laboratory testing with a standard case definition, as clinician selection of participants can result in bias if clinicians decide who to test for influenza based on clinical suspicion and assumed vaccine status. Additionally, calendar time may act as a confounding variable if cases and controls are not selected at the same time or distributed similarly throughout the influenza season and if the vaccine coverage changes during the season. This effect can be controlled in case–control studies by matching of cases by epidemiological week, and by adjusting for time in analyses. Time from vaccination can also act as an effect modifier in any VE study, due to potentially decreasing VE as a result of waning immunity

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and/or virus antigenic drift over time. However, virus antigenic drift may not always be accurately measured by the standard HI assay-based definitions of “matched” and “mismatched” influenza strains [10]. Although there is no single best way to adjust for all sources of bias and confounding, some standard techniques include collecting basic information on healthcare-seeking of the source population, careful selection of controls in case–control studies, and ensuring that all VE estimates adjust for key confounders. Also needed is a continued validation of approaches to classify “matched” and “mismatched” viruses.

4. Communication of vaccine effectiveness estimates

Variability in influenza viruses, and therefore in influenza vaccine effectiveness, presents a challenge for public health communication for health professionals and lay population. Further, even when circulating viruses are well matched to the vaccine, host factors may influence VE estimates, resulting in a lower VE. One key message is that although influenza VE may not always be satisfactory in different populations, vaccination is still the most effective intervention for preventing infection. Evidence from health communication studies suggest that perceived risks are more critical than perceived benefits in the decision-making process for vaccination [11,12]. Among pregnant women, vaccines lower the likelihood of infection and potential progression to severe disease, but influenza may not be perceived as severe in this population, who may instead perceive a higher risk from influenza vaccine-related side effects than from infection [13]. Among a survey of healthcare workers, lack of perceived risk and fear of adverse events were also more important reasons than doubts about the vaccine’s effectiveness [14].

Vaccine-related public health messages should be directed at healthcare providers in addition to target populations, in order to best communicate risks and benefits of influenza vaccines. Surveys in Europe, Australia, and the US, of pregnant women and other groups indicate that recommendation from health-care providers is an important factor in the decision to be vaccinated [15–17].

5. International data pooling

The advantages of VE data-pooling projects include increased statistical power and precision for VE analysis, and generalizable results that can be applied across locations. Increased statistical power may also result in earlier determination of VE for mid-season estimates, or improved subgroup analyses for key research questions and rare outcomes. Pooling data also provides opportunities for additional research, such as correlation of VE with new molecular markers or phylogenetic findings. In the European I-MOVE network, for example, key objectives of data pooling are to improve sample size and generate regional estimates for Europe. I-MOVE also has a pilot project underway to estimate VE against influenza hospitalizations. This effort combines data from 21 hospitals at four sites and was able to generate age group-specific estimates for 2011–2012, showing a decreasing VE with age [18].

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However, data pooling introduces a number of scientific and programmatic challenges that must also be considered. Pooling data requires the assumption of a single true VE for any one product, which may not be the case. One primary concern is the heterogeneity between populations in different settings, including healthcare-seeking behavior, age distribution, underlying health conditions, available vaccine products (including usage of northern or southern vaccine formulations), local epidemiological conditions and other potential sources of bias. The I-MOVE data from 2010 to 2011 identified an outlier VE estimate from one country, raising a key question for when to exclude certain sources from pooled estimates. There are also methodological concerns such as agreeing on a common protocol, ensuring compliance with privacy laws, local ethical considerations and optimizing the use of limited financial resources. Given the challenges, preliminary data sharing and consensus on the scope of any data-pooling project are necessary before full data pooling can take place. Other approaches that should be considered as alternatives to international data pooling include rapid sharing of early VE results across hemispheres and meta-analysis of existing studies using similar designs.

Standardized VE estimation methods will assist in generating point estimates that are comparable internationally. Study design that incorporates test-negative controls is a valid standard for VE estimation in observational settings, although studies using community controls or cohort design can also provide valuable VE data. Standard outcomes should be laboratory confirmed as influenza-associated, preferably by RT-PCR. Mild disease such as influenza-like illness or medically attended acute respiratory infection, and more severe presentations such as WHO-defined SARI are useful outcomes to measure, if laboratory confirmed. Measurement of VE against SARI may have more public health meaning in countries implementing programs for the first time, but also may present challenges such as smaller numbers of participants and therefore statistical power. Pooling of data from multiple studies with defined protocols can enhance the accuracy of VE estimates in this respect.

6. Conclusions and next steps

Key points of the two-day meeting encompassed discussions on a wide range of methodological and operational issues related to estimating the effectiveness of influenza vaccines. Expanded influenza vaccine production and efficacy research in tropical and lower-income countries demonstrate an increased focus on influenza vaccination in these settings, although some data gaps remain among target populations. The inherent antigenic drift of circulating influenza viruses also presents unique scientific questions, such as how antigenic match among virus strains relates to immunological protection, and optimal timing of vaccination of pregnant women, particularly in tropical settings with ongoing virus circulation. Observational studies in Europe, the US, Canada, and Australia, often using test-negative design methodology, are benefiting from multi-site collaboration and data pooling, which allows for increased analytic power but also presents challenges in harmonization, data comparability, and long-term sustainability. Improved communication of the value of influenza vaccination and clear messaging on the effectiveness of different vaccine products in different populations are essential.

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A key next step for global influenza VE estimation is the production of a guidance document outlining best-practice approaches to observational approaches for VE estimation. The meeting concluded that this guidance document would provide researchers with standard case definitions and options for different methods in different settings, including choices in selection of controls, as well as minimum sample size for key analyses and monitoring and evaluation for impact assessment of vaccine programs. VE estimates from low- and middle-income countries are especially needed, so any VE research guidance should be operational in these settings. Such a document could also serve to identify VE data gaps in countries with new introduction or expansion of vaccine recommendations. Agreement on methodologies can also generate new opportunities for pooling data, in order to increase the impact of individual efforts for quantifying the effectiveness of influenza vaccines.

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