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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.

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 middle-income settings; to summarize global efforts to better measure influenza vaccine effectiveness and

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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 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 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

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