New vaccine approaches for seasonal and pandemic influenza

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Abstract
Inactivated influenza vaccines have been available since the late 1940s for the prevention of influenza disease. Based on the available scientific evidence, many public health authorities, including the World Health Organization, recommend annual use of these vaccines for specific populations, including the elderly. Despite these recommendations, actual vaccination uptake rates are very limited in many countries. Influenza vaccine research is confounded by the variable nature of the influenza viruses and annual influenza epidemics and by non-specific clinical diagnostic criteria. These confounding factors complicate evaluation not only of overall vaccine effectiveness, but also of the relative efficacy and effectiveness of different vaccine formulations. This paper summarizes recent advances in the development of seasonal and (pre-)pandemic vaccines, discusses the methodologic constraints on influenza vaccine research, and proposes measures to reduce the level of potential bias and confounding in influenza vaccine research.

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1. Introduction
In recent years, global pandemic preparedness initiatives have stimulated the research and development of new influenza vaccines for the control of epidemic and pandemic influenza outbreaks. As a result, many new influenza vaccines have been submitted for license approval [1]. At the same time, however, currently available safe and effective vaccines are grossly under-utilized in many countries, resulting in annual serious morbidity and mortality that could be prevented [2]. In many countries, the target vaccination rates of 50% by 2006 and 75% by 2010 recommended for the elderly by WHO are not being met [3,4].

Recently, the scientific basis of public health authority recommendations for annual immunization policies and practices has been questioned [5]. This has led to a debate in the literature about the appropriateness of different methodologic approaches to evaluate the effectiveness of influenza vaccines [6–15]. This methodological debate has also highlighted the complexity of proving that one influenza vaccine is superior to another. Proof of superiority of a new influenza vaccine depends on the clinical study design used, the endpoints evaluated, and the assays used in the clinical development program. Many confounding factors associated with the methodologies used may result in biased observations or interpretations of clinical study outcomes. Ultimately, such biases can lead to confusion about the appropriateness of policy recommendations [5]. Despite these intrinsic methodological difficulties, influenza vaccines are licensed in Europe on the basis of clinical trials using serological antibody titers as surrogate markers of efficacy [16]. However, these relatively simple serologic studies also have intrinsic confounding factors [17,18].

This article describes recent advances in the development of seasonal, pre-pandemic and pandemic influenza vaccines and evaluates some of the methodologic difficulties associated with the development of new and improved vaccines. It also suggests ways in which the number of confounding factors may be at least minimized through a consensus among the scientific influenza vaccine community on methodologic approaches, influenza case definitions and laboratory tests and assays.

2. Globally available inactivated influenza vaccine types
The first convincing description of an influenza epidemic dates back to the late 12th century [19]. Since then, the burden of epidemic, and occasionally pandemic, influenza has been well documented. In general, influenza outbreaks and epidemics occur every year, though the seriousness and consequences may vary from year to year. Pandemics may occur occasionally when new influenza virus types are introduced into the human population and successfully transmit from human to human. Three pandemics have occurred in the 20th century, of which the one in 1918 had the most dramatic societal consequences. Since 1997, a new pandemic threat has arisen, due to avian influenza viruses, such as A-H5N1 strains, which are widespread in poultry and migratory birds and occasionally infect man.

Since the 1940s, inactivated influenza vaccines have been developed for the control of annual influenza epidemics. Early trials...
(1943–1945) with whole-virus vaccine preparations in the USA army indicated 70% efficacy for this type of vaccine [20]. In 1964, it was shown that neutralizing antibody was produced in response to an ether-split virus vaccine formulation, with few adverse reactions, in humans [21]. In 1976, surface antigen (subunit) vaccines were shown to be safe and immunogenic in humans [22,23].

At the present time, inactivated split-virus and subunit influenza vaccines are globally available and recommended for the prevention and control of influenza infections and its associated complications for certain populations [24].

3. Assessing the efficacy and effectiveness of influenza vaccines

3.1. Serologic criteria

Antigen-specific, anti-hemagglutinin (HA) antibody titers, measured in the hemagglutination inhibition (HI) assay, are generally accepted as a marker of efficacy for influenza vaccines [25]. Due to the natural and continuous variation in influenza viruses and epidemiology, individual comparative clinical trials to assess the relative immunogenicity of the various vaccine types give variable results. However, a literature review published in 1998 of head-to-head comparative clinical trials with different vaccine types in primed populations found that the different vaccine types were immunogenically similar [26].

In Europe, the licensing authorities require clinical testing of each season’s updated vaccine, using serologic criteria in subjects aged under 60 years as well as in subjects aged 60 years and older, before granting a product license [16]. However, some authors have pointed to methodological confounders in assessing vaccine efficacy based on these serological criteria [17,18]. Nevertheless, these serologic criteria are also used in Europe for registration of new seasonal vaccines, such as virosomal influenza vaccine [27] and MF59-adjuvanted vaccine [28].

There are several limitations to the exclusive use of anti-HA antibody titers as markers of efficacy. For example, other immunologic responses, such as cellular immunity [29], mucosal antibodies [30] and anti-neuraminidase antibodies [31], may all contribute to the protective efficacy of influenza vaccines, though no quantitative correlations with immunity have been established. Moreover, there are no harmonized and validated tests to measure these immunologic parameters. Even the golden-standard HI test shows significant inter-laboratory assay variability, and the variability for virus neutralizing assays may be even larger [32]. It is well known that the nature of the erythrocytes used in the HI test seriously influences the magnitude of the titer determination. Many clinical studies that report serologic results do not provide details of the HI test used to determine anti-HA antibody titers. These factors all complicate the pooling and interpretation of serologic data from clinical trials in the literature, and it might be argued that only comparative trials using the same laboratory using a standardized HI test for that particular laboratory allow reliable serologic comparisons between different vaccines rather than comparisons between different reported studies.

3.2. Clinical criteria

Although antibody titer is the generally accepted correlate of protection, the protective efficacy of influenza vaccines should ideally be established by randomized controlled trials with clinical outcomes, such as occurrence and seriousness of clinical illness, complications and death in vaccinated and control groups. However, as such studies are methodologically complex, have intrinsic risks for failure (e.g. the clinical influenza attack rate of true influenza infections may be low [33]; antigenic mismatch), need large group sizes and are very costly, they are not practical to perform.

As an alternative to randomized controlled trials, observational studies are often used to measure the efficacy and effectiveness of influenza vaccines [for reviews see Nichol [39], Demicheli et al. [34] and Villari et al. [35]). However, this type of study also has methodologic limitations [6–15,36], which should be taken into account when assessing or comparing the protective efficacy and effectiveness of influenza vaccines. In addition, it has been convincingly demonstrated that the case definitions used in clinical studies to determine ‘influenza’ or ‘influenza-like illness’ influence the outcome of the study [37]. A recent review of the literature found 16 different case definitions in 19 observational clinical trials [38]. Thus, as with serologic studies, caution is required in interpreting the literature, especially reviews and meta-analyses that combine and analyze results from different clinical studies reported in the literature.

3.3. Efficacy and effectiveness of current inactivated influenza vaccines

A review of the literature available to 2003 on the efficacy and effectiveness of influenza vaccine found that the clinical efficacy against laboratory-confirmed influenza illness ranged between 60% and 90% in children and adults below 65 years of age and 50–60% in the elderly population (Table 1) [39]. In agreement with these findings, other reviews in healthy younger adults have shown that laboratory-confirmed influenza illness occurs in 8.4 cases/100 unvaccinated subjects and in 2.3 cases/100 vaccinated subjects [10,40–42]. These observations lead to an overall relative risk reduction (RRR) of 69% and an absolute risk

Table 1

<table>
<thead>
<tr>
<th>Age group and outcomes assessed</th>
<th>Efficacy/effectiveness of vaccination [%]</th>
</tr>
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<tbody>
<tr>
<td>Children</td>
<td></td>
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<tr>
<td>Laboratory-confirmed influenza illnessa</td>
<td>60–90</td>
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<tr>
<td>Acute otitis media</td>
<td>30–36</td>
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<tr>
<td>Healthy adults &lt;65 years of age</td>
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<tr>
<td>Laboratory-confirmed influenza illness</td>
<td>70–90</td>
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<tr>
<td>Upper respiratory infections or influenza-like illness</td>
<td>25–34</td>
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<tr>
<td>Work loss due to upper respiratory infections or influenza-like illness</td>
<td>32–43</td>
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<tr>
<td>Healthcare provider visits due to upper respiratory infections or influenza-like illness</td>
<td>42–44</td>
</tr>
<tr>
<td>Community-dwelling elderlyb</td>
<td></td>
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<tr>
<td>Laboratory-confirmed influenza illness</td>
<td>50–60</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
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<tr>
<td>Pneumonia (all causes)</td>
<td>33 (95% CI, 27–38%)</td>
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<tr>
<td>Respiratory conditions (all causes)</td>
<td>32 (95% CI, 29–40%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>27 (95% CI, 15–39%)</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>50 (95% CI, 45–56%)</td>
</tr>
<tr>
<td>Elderly nursing home residents</td>
<td></td>
</tr>
<tr>
<td>Respiratory illness</td>
<td>56 (95% CI, 39–68%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>53 (95% CI, 35–66%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>48 (95% CI, 28–63%)</td>
</tr>
<tr>
<td>Death</td>
<td>68 (95% CI, 56–76%)</td>
</tr>
</tbody>
</table>

Modified with permission from Nichol [39].

a Effectiveness for very young children may be somewhat lower.
b Effectiveness levels for high-risk elderly persons have been reported to be similar to those for healthy elderly persons.
reduction (ARR) of 6.1 cases/100 patients [10]. When using less specific influenza diagnostic criteria based on clinical symptoms only without laboratory confirmation, influenza-like illness was found in 44.1 cases/100 unvaccinated subjects and 30.6 cases/100 vaccinated subjects. These observations lead to an overall relative risk reduction of 22% and an absolute risk reduction of 13.5 cases/100 subjects [10]. In other words, the 69% reduction in laboratory-confirmed influenza illness translates into a 22% reduction in all influenza-like illness, because many of those infections are caused by other pathogens [10,33]. Thus, based on the currently available literature, influenza vaccination will on average prevent 6–14 cases/100 people.

The available vaccine efficacy and effectiveness data, together with the excellent safety profile of the currently available inactivated vaccines documented over many years [43], confirm the position of inactivated split-virus and subunit influenza vaccines as the gold standard for influenza vaccination and justify the annual influenza vaccine recommendations issued by many health authorities [24,43].

These efficacy and safety data can be considered the baseline for defining ‘better’ seasonal influenza vaccines. Better influenza vaccines should provide greater, and possibly broader, protection for those who need it, where current vaccines fall short of the desired performance. The superiority of any improved influenza vaccine should ideally be demonstrated in active-controlled clinical trials. It is desirable that the scientific influenza community agrees on study design, case definitions for influenza and influenza-like illness, and assays for serologic testing, so that in due course, study outcomes from reported clinical trials in the literature will be more comparable for confounding factors. Because of the documented excellent safety profile of the current vaccines, such improved vaccines should be at least as safe as the current vaccines.

4. The influenza paradox

The effectiveness of a vaccine depends on the intrinsic biologic protective efficacy of the vaccine, on the attack rate of true influenza infections with clinical symptoms [33], and also on the vaccination practices adopted for disease control and management. Thus, even a highly effective vaccine for a widespread disease will only provide limited benefits on population level if the vaccine is grossly under-utilized. On the other hand, modest effective vaccines might still provide considerable benefits on population level if widely used for the target populations. This concept was described for influenza and pneumococcal vaccination in 1994 [44].

Despite the well-documented annual burden of influenza disease, the availability of safe and effective inactivated influenza vaccines, and published recommendations from the World Health Organization and many national health authorities, in many countries annual vaccination coverage rates for recommended target populations, including the elderly, are still low. A recent survey of vaccination coverage in 11 member states of the European Union showed that in many of these states, influenza vaccination coverage will fail to reach the WHO target of 75% in the elderly by the year 2010, and reaches less than halfway to this target in three of the 11 states [34]. In addition, coverage of younger at-risk adults is below 50% in almost all states, and coverage of healthcare workers is 25% or less in all the member states surveyed. Overall, these vaccine coverage rates demonstrate the serious under utilization of currently available influenza vaccines and represent many missed opportunities to prevent people at risk for the potential serious complications associated with influenza infections. In 2006, it was estimated that across the 25 countries of the European Union (excluding Romania and Bulgaria), nearly 800,000 hospitalizations and nearly 70,000 deaths could be prevented annually if vaccination coverage were to be increased from the existing level of 35.4% of the target population to 100% coverage [2].

While the data presented in Table 1 indicate a need for improved influenza vaccines for at least some population groups, in particular the elderly, it is also evident that increasing the annual uptake rates of the currently available influenza vaccines in these populations would provide considerable benefit for these population groups. William Schaffner of Vanderbilt University, writing in the New York Times on 21 February 2006, stated that: “waiting for perfection is the greatest enemy of the current good”. Improved control of seasonal influenza outbreaks should therefore be approached in two ways: in the short term by increasing annual vaccination coverage rates [45], and in the longer term by developing vaccines with improved efficacy [45].

5. New influenza vaccines

5.1. Research concepts for new influenza vaccines

Many approaches to developing new influenza vaccines with improved efficacy/effectiveness are being explored. One important approach is the development of vaccine adjuvants, which should improve the immune response to vaccine antigens. Particularly for the elderly and those with some degree of immunocompromise, new influenza vaccines are needed that will elicit increased levels of protective antibodies, and preferably also other immune responses [29–31], in order to increase the overall protective efficacy of the vaccine.

Influenza vaccines are known to be optimally effective if there is a good antigenic match between the viral antigens in the vaccine and those in the influenza virus circulating in the population and causing influenza infections. Vaccines providing a greater degree of cross-reactivity and protection would be advantageous from a public health perspective, because their efficacy in a particular year would be less dependent on the antigenic match. The ultimate goal would be the existence of a ‘universal influenza vaccine’ that would protect vaccines against ‘any’ influenza strain. Research is currently in progress to develop influenza vaccines that will elicit protective antibodies against highly conserved viral proteins such as M2 [46].

Another approach to improving influenza vaccines is to induce antibodies at the mucosa of the respiratory tract by administering the vaccine intranasally. Live-virus influenza vaccine as well as inactivated influenza vaccine have been developed as intranasal formulations. A cold-adapted, live-virus intranasal vaccine is available in the USA for individuals aged 2–59 years. This vaccine is particularly effective in children [47]. Another inactivated, intranasal, virosomal influenza vaccine and NasalFlu, was withdrawn from the Swiss market in 2002 after its initial market authorization for the 2000/2001 influenza season. Toxicity, associated with the heat-labile toxin from Escherichia coli that was used as an adjuvant was observed after market introduction [48].

5.2. Seasonal influenza vaccines

Two novel seasonal vaccines, MF59-adjuvanted subunit vaccine (Fluad®, Novartis) and a virosomal vaccine (Inflexal V®, Crucell), were licensed some years ago in some countries. Serologic studies with these vaccines have shown inconsistent results. In some studies, improved anti-HA titers were observed [27,49], whereas in other studies, no such improved titers were demonstrated [50,51]. So far, no studies have shown superior efficacy or effectiveness on clinical parameters for these vaccines compared with the non-adjuvanted, split-virus or subunit seasonal vaccines.

Market authorization has recently been sought for a seasonal influenza vaccine administered intradermally using microneedles.
In addition to its simpler administration, the vaccine seems to provide an enhanced immune response in elderly patients [52]. In early studies, reduced doses of trivalent inactivated vaccine given intradermally were reported to produce a similar immunogenic response as full doses of vaccine given by the normal intramuscular route in adults aged 18–60 years [53]. More recently, low doses of influenza vaccine given intradermally were reported to produce a similar response to low doses given intramuscularly, but induced significantly more local inflammatory response [54].

5.3. (Pre-)pandemic influenza vaccines

In response to the important public health challenge of preparing for a potential new pandemic that may arise from avian influenza viruses infecting humans, a number of research concepts for new influenza vaccines have been thoroughly explored in order to develop potential (pre-)pandemic influenza vaccines [1,55]. One of the main objectives for the development of influenza vaccines against avian influenza viruses in general, and influenza virus A/H5N1 in particular, is to stimulate an adequate immune response at a low antigenic dose (‘antigen-sparing’ strategy), in order to relieve the enormous gap between currently available global vaccine production capabilities and potential demand during a pandemic [45].

At a recent WHO briefing, the International Federation of Pharmaceutical Manufacturers and Associations International Task Force on Influenza Vaccine Supply presented information on the progress that has been made over the last few years in developing pre-pandemic and pandemic influenza vaccines [11]. Several vaccine formulations, including alum-, MF59- and AS03-adjuvanted vaccines, have been shown to have antigen-sparing capacity. Two vaccines (A/H5N1 whole-virus, alum-adjuvanted vaccines (Biken and Kitasato)) have received approval from the Japanese Ministry for Health, Labor and Welfare (MHLW) as pre-pandemic and mock-up pandemic influenza vaccines. A similar whole virus, alum-adjuvanted vaccine (GlaxoSmithKline) has received approval from the European regulatory authorities (EMEA) [56,57], while an A/H5N1 non-adjuvanted, split-virus vaccine (Sanofi Pasteur) has received FDA approval in the USA as a mock-up pandemic vaccine. In addition, an MF59-adjuvanted, subunit A/H5N1 mock-up pandemic vaccine (Novartis) has also been approved in Europe by the EMEA [58]. Alum-, AS03- and MF59-adjuvanted vaccine formulations are currently at different stages of review by the European and USA regulatory agencies as pre-pandemic vaccines [1].

Another research innovation for influenza vaccines is the development of different cell culture techniques for the production of vaccines [59–63]. Apart from other advantages, a vaccine production technology which does not depend on fertilized chicken eggs might prove of crucial importance in a pandemic situation when chicken farms may be affected by highly pathogenic avian influenza viruses. In 2003, such a situation occurred in the Netherlands [64].

The research and development efforts on this new production technology for influenza vaccines have resulted in a market authorization for a cell-culture seasonal influenza vaccine by the Dutch Authorities in 2001 (Solav) and by EMEA in 2007 (Novartis). Also (pre-)pandemic vaccines based on the cell culture technology have been developed [1] and are going to be evaluated shortly by the regulatory agencies.

In summary, driven by the threat of a pandemic, much progress has been made over the last 5 years by collaborative efforts by industry, in partnership with the scientific-regulatory- and public health community, in developing new seasonal and (pre-)pandemic influenza vaccines.

6. Discussion

In essence, nature has given humankind the time to prepare for a potential public health catastrophe due to the next influenza pandemic. The licensing of (pre-)pandemic vaccines represent the successful initial phase of developing tools in the time nature has given us. The next challenge is to develop and implement effective public health strategies that optimize the use of these tools to the best of our knowledge. Due to an intrinsic degree of uncertainty associated with the nature of an unpredictable next influenza pandemic, the implementation of any strategy will require long-term financial commitments, strong political will and leadership. In every scenario and strategy, it is essential to increase annual vaccine uptake rates of currently available vaccines [45]. This approach will undoubtedly reduce the number of influenza-associated hospitalizations and deaths on an annual basis in a cost-effective manner [39,65]. At the same time, it is also important to continue and strengthen the development of new and better seasonal and (pre-)pandemic vaccines. The superiority of new influenza vaccines should be demonstrated on solid scientific- and methodological grounds so that these efforts will be beneficial for everybody, including the patients [66].

By achieving these objectives, the world population will obtain the maximum benefit from global efforts to control seasonal- and pandemic influenza.

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